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Early disturbances of gamma band dynamics in mild cognitive impairment

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Abstract Recent studies have indicated that gamma band oscillations participate in the temporal binding needed for the synchronization of cortical networks involved in short-term memory and attentional processes. To date, no study has explored the temporal dynamics of gamma band in the early stages of dementia. At baseline, gamma band analysis was performed in 29 cases with mild cognitive impairment (MCI) during the *n*-back task. Based on phase diagrams, multiple linear regression models were built to explore the relationship between the cognitive status and gamma oscillation changes over time. Individual measures of phase diagram complexity were made using fractal dimension values. After 1 year, all cases were assessed neuropsychologically using the same battery. A total of 16 MCI patients showed progressive cognitive decline (PMCI) and 13 remained stable (SMCI). When adjusted for gamma values at lag −2, and −3 ms, PMCI cases displayed significantly lower average changes in gamma values than SMCI cases both in detection and 2-back tasks. Gamma fractal dimension of PMCI cases displayed significantly higher gamma fractal dimension values compared to SMCI cases. This variable explained 11.8% of the cognitive variability in this series. Our data indicate that the progression of cognitive decline in MCI is associated with early deficits in temporal binding that occur during the activation of selective attention processes.

Keywords Brain rhythms · Electroencephalography (EEG) · Linear regression model · Mild cognitive impairment · Working memory

Abbreviations

EEG	Electroencephalography
ERO	Event-related oscillations
MCI	Mild cognitive impairment
SMCI or PMCI	Stable or progressive mild cognitive impairment
MMSE	Mini-mental state examination
HAD	Hospital anxiety and depression scale
IADL	Lawton's instrumental activities of daily living

Introduction

Electroencephalography (EEG) is an easily accessible, high temporal resolution procedure that may be

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particularly efficient for the identification of subtle functional changes before the occurrence of significant brain damage in Alzheimer disease (AD). Among the different EEG markers that have been studied in this context, frequency analysis is thought to provide a good indication of the integrity of cortical connectivity. Classically, AD is associated with a power increase in the lower delta and theta band frequencies and decrease in the alpha and beta frequencies (Huang et al. 2000; Jelic et al. 1996; Jeong 2004). In mild cognitive impairment (MCI), these EEG parameters showed intermediate values between those of controls and AD patients with substantial inter-individual variability (Wolf et al. 2003). Earlier and more recent contributions reported significant changes in power and event-related synchronization of the very high gamma band frequency (30–100 Hz) that occur in both MCI and AD cases (Driver et al. 2007; Jiang et al. 2008; Koenig et al. 2005; Ribary et al. 1991; Rossini et al. 2006; Stam et al. 2002, 2003; Teipel et al. 2008; van Deursen et al. 2008). The exact significance of this phenomenon remains a matter of debate (Basar-Eroglu et al. 2007; Haig et al. 2000; Naatanen and Alho 1995; Ruusuvirta and Huotilainen 2005; Tallon-Baudry and Bertrand 1999; Tallon-Baudry et al. 1998). Overall, high oscillatory activities are thought to reflect the selective assembly of neurons into functional groups needed for the temporal coding supporting fast selection and multiregional cortical binding (Bressler et al. 1993; Engel et al. 2001; Fries et al. 2007; Gruber et al. 2004; Jensen and Colgin 2007; Llinás and Ribary 1992; Salinas and Sejnowski 2001; Tallon-Baudry and Bertrand 1999; Uhlhaas et al. 2008; Varela et al. 2001). It has been proposed that gamma band oscillations play a key role in the synchronization of the cortical networks involved in short-term cognitive processes (Babiloni et al. 2004; Daskalakis et al. 2008; Kaiser and Lutzenberger 2003; Rodriguez et al. 1999; Schneider et al. 2008; Tao and Tian 2005). Appropriate synchronization depends on the ability of neural networks to self-organize and form stable EEG patterns at the initial stages of cognitive activation (Stam 2005). A well-organized network displays a temporal memory in that its current state may be predicted on the basis of an earlier one. According to this recent conceptualization, it is crucial to investigate not only gamma power or event-related synchronization, but also the temporal evolution of the gamma band in early stages of cognitive decline. Using an *n*-back working memory activation paradigm, we report here that changes in gamma band temporal dynamics at baseline may predict further cognitive decline after 1 year with MCI.

Methods

Inclusion procedure and follow-up

Mild cognitive impairment participants were recruited in a large acute and intermediate care geriatric hospital. Subjects with MMSE scores between 25 and 28 underwent an additional clinical evaluation, which included the Hospital Anxiety and Depression Scale (HAD, Zigmond and Snaith 1983) and Lawton's Instrumental Activities of Daily Living (IADL, Barberger-Gateau et al. 1992). Depressive co-morbidity was excluded on the basis of a HAD score consistently <8. Extensive neuropsychological testing was performed including attention (Wechsler 1981), orientation (MMSE items), short-term memory [Mattis Dementia rating scale items (DRS)] (Gardner et al. 1981), digit span forward (Wechsler 1981), Corsi block-tapping test (Milner 1971), episodic memory (Buschke double memory test, Buschke et al. 1997; Shapes test, Baddeley et al. 1994), executive functions (verbal fluency test, Butters et al. 1987), trail making test (Reitan 1958), language (Boston naming test, Kaplan et al. 1983), ideomotor (Schnider et al. 1997), reflexive (Poeck 1985) and constructional praxis (Welsh et al. 1994), and visual gnosis (Ghent overlapping figures) (Ghent 1956). Global cognitive function was assessed by the clinical dementia rating scale (CDR, Hughes et al. 1982) and the Mattis DRS. Subjects having a test score of more than 1.5 SD below the age-appropriate mean in any of the above tests and a CDR score of 0.5, but no dementia, were diagnosed with possible MCI (Petersen et al. 2001). Among these cases, 8 had single domain amnestic MCI (decreased performance in the Buschke double memory test) and 21 had multiple domain amnestic MCI (impaired performance in the Buschke double memory test and either the trail making test or the Corsi block-tapping test (Petersen and Morris 2005). These cases were reviewed independently by two highly experienced clinicians blinded to each other's findings and included in the MCI group only if both clinicians concurred on this diagnosis. The final sample included 29 MCI cases (mean age 82.5 years, age range 77–91) who underwent a detailed neuropsychological follow-up evaluation 1 year after inclusion using the same neuropsychological battery. On follow-up, subjects were considered to have progressed and were included in the PMCI group if: (1) they exhibited a significant deterioration (defined as $\geq$0.5 SD compared to inclusion values) in the Buschke double memory test and at least $\geq$1.0 SD among the other neuropsychological tests, and (2) they were considered to have clinically deteriorated based on the review of all the neuropsychological tests by an independent physician highly experienced in cognitive

disorders, who was blinded to all other data. Subjects were considered stable and included in the SMCI group if (1) they exhibited no or marginal changes in their neuropsychological performances on follow-up (test result improved or decreased to <0.5 SD compared to inclusion values), and (2) they were considered to be clinically stable by the independent physician described above.

All participants had normal or corrected-to-normal visual acuity, and none reported a history of sustained head injury, or other neurological or psychiatric disorders. All participants with regular use of neuroleptics, antidepressants, anti-epileptic medications, stimulants, opioids and β-blockers were excluded from the present study. In contrast, regular use of low doses of hypnotics was tolerated. After formal approval of the local ethics committee, informed written consent was obtained from all participants included in this study.

Design

Subjects watched a computer-controlled display screen at a distance of 57 cm. They viewed pseudo-random sequences of consonants and vowels common to the French alphabet and pressed a computer-controlled button with their right index finger as soon as a target appeared (response trials). For non-target stimuli, no motor response was required (no-response trials). Targets were defined either according to the oddball (rare event) or to the *n*-back design.

Stimuli consisted of white letters, arial font (2° × 2.5° visual angle), with 10% gray noise, embedded in a 50% random noise gray rectangular background patch (6° × 6.7° visual angle). They were presented for a duration of 0.5 s, separated by 5-s intervals (onset to onset) during which a dot helped subjects maintain fixation. In addition, subjects were instructed to remain quiet and to only move their right index finger in accordance with the nature of the task to minimize any muscle artifacts during the EEG recording.

Two different tasks were used: in a simple detection task (control), sequential letters or background patches without letters were presented. Subjects responded as fast as possible when background patches without letters appeared; in the 2-back task, the target was any letter that was identical to the one presented two trials back. Thus, working memory load increased from control (memory free-condition) to 2-back task (highly demanding).

Each task was tested in three stimulus sequences of 30 images each (7 targets), adding up to 90 trials (epochs) per task (21 targets). Before each sequence block, subjects were informed about the nature of the task, and several warm-up trials were performed for MCI patients. A control task block was followed by three blocks of the 2-back condition, and two blocks of the control task. Reaction time (RT) and performance were systematically recorded, but no feedback on performance was provided. The absence of difference in RT and performance between blocks of the same task indicated that learning, habituation and fatigue effects were minimal during the recording session. Before and after the experimental paradigm, an open and close eye EEG session without task was realized during a period of 3 min. Electrophysiological and neuropsychological assessments were all performed in the morning.

Electrophysiological recordings

Continuous EEG (Micromed, Brain Quick system 98, Treviso, Italy) was recorded, using 20 surface electrodes placed over the scalp according to the 10–20 international electrode placement system (Homan et al. 1987), with linked earlobes as reference. Skin impedance was kept below 5 kΩ. Electrophysiological signals were software filtered and digitized (sampling rate 1,024 Hz), with a lower cutoff of 0.33 Hz and an upper cutoff of 120 Hz (DC amplifiers Micromed). The electrooculogram (EOG) was recorded using two pairs of bipolar electrodes in both vertical and horizontal directions. Single pulses (TTL) synchronized with stimulus onset (letter or background patches) were recorded and used off-line to segment the continuous EEG data into epochs time-locked to stimulus onset.

Data processing

Electroencephalography data were analyzed using the NeuroScan software (NeuroScan Inc., Herndon, VA, USA). EEG signals were corrected for ocular artifacts using an off-line threshold reduction algorithm (NeuroScan Inc.). This method operates by subtracting EOG signals from EEG channels using linear derivation approach with a spatial filter transform. The EEG signals were automatically cleared of movement artifacts in which voltage exceeded 100 μV criteria and the remaining trials were inspected visually to control for minor artifacts. EEG data were detached into epochs of 1,050 ms, starting 525 ms before the stimulus onset. To eliminate effects from manual responses and exclude the confounding effect of motor processing, correct answers without motor response were analyzed according to the task condition (detection, 2-back). Then, the EEG data were analyzed using two distinct types of electrophysiological analysis: (i) spectral power analysis and (ii) event-related oscillations (EROs).

Spectral power analysis

Artifact-free close and open eyes EEG recordings at rest were converted into the frequency domain using an FFT function computed on overlapping 2-s windows (10%

Hanning filter). For resting EEG data, gamma frequency band power was measured at the frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrode sites as the average power between 35 and 45 Hz, respectively.

Event-related oscillations

Event-related oscillations were averaged over a window of 1050 ms with a 525-ms pre-stimulus onset and band-pass filtered at 35–45 Hz (−48 dB/octave). They were also averaged for artifact-free open eye EEG recordings at rest. Analyses of the segment-evoked oscillations included the frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrodes. Additionally, to study the possible group and task effects on visual sensory processing, we performed an analysis restricted to the occipital (O1, Oz, O2) electrodes. Over a maximum of 90 epochs, on average for SMCI subjects, the percentage of artifact-free trials was 65 ± 14, and 61 ± 16 in control and 2-back tasks, respectively. Similar percentages were obtained for PMCI cases with 61 ± 10 and 61 ± 13, respectively.

Statistical analysis

Demographic, clinical characteristics at inclusion, differences in *n*-back performance, as well as neuropsychological values at baseline and on follow-up were compared between the PMCI and SMCI groups using the Mann–Whitney non-parametric *U* test. Cognitive changes over time were assessed using the Wilcoxon matched-pairs signed-ranks test. RT differences were assessed using two-way repeated measures ANOVA.

To normalize the variance of the EEG data (i.e., magnitude of gamma power at rest), a logarithmic transformation was used to perform parametric two-way repeated comparisons. The normality of data distribution was verified with skewness and kurtosis tests. Statistical analysis was performed to compare EEG measures between groups, using a two-way repeated measures ANOVA, with task condition (detection, 2-back) and electrode site (frontal, central, parietal, occipital) as within-subject factors. The significance values were determined using the Greenhouse–Geisser correction. Post hoc analysis was performed using Fisher's least square difference test (Milliken and Johnson 1984).

As the time series were not stationary (as assessed with run tests), we explored the association between the temporal evolution of gamma oscillations and cognitive decline using the following procedures. First, phase diagrams were used to explore the best time lag to discriminate between PMCI and SMCI. Phase space represents all the possible states of a dynamic system. A phase plot corresponds to a graph of gamma oscillation values at time t minus a lag ($t - \text{lag}$) on the y axis versus gamma values at time t on the x axis. Plots were drawn for each electrode, task and subject for lag time periods ranging from 1 to 20 ms. Then, linear regression models (Dwyer and Feinleib 1992), taking into account the clustering of measures within each subject, were built with gamma values as the dependent variable and group, task, electrode and gamma values at a given time lag ($\text{gamma}_{\text{lag}}$) as the independent variables. Geometrically, the regression coefficient associated with the $\text{gamma}_{\text{lag}}$ parameter corresponds to the slope of the local regression line of the ellipse in the phase diagrams. The present analysis of phase space representation was performed for each electrode site and is thus quite different from that of the degree of linear relatedness between two channels (i.e., the functional coupling of cerebral areas explored by the non-linear coherence function).

Fractal dilation was used to estimate the fractal dimension (a measure of complexity represented by a unique value) of the phase diagrams using the Fractal analysis software (Fractalyse, CNRS, Franche-Comté and Bourgogne University, Version: 2.4; downloadable from Web site: http://www.fractalyse.org). Then, fractal dimensions were compared between the two MCI groups for each task and electrode sites using unpaired Student's *t* test. In addition, univariate and multiple logistic regression models were built to assess the relationship between cognitive decline in MCI (binary dependent variable) and the fractal dimension of the gamma oscillation controlling for task and electrode site effects (independent variables). This method can also evaluate the amount of variability of the dependent variable (cognitive decline) that can be explained by the model and thus provide an estimate of the strength of their relationship. Statistical threshold was set at $p < 0.05$. Statistical analyses were performed using the Stata software package (Statcorp, College Station, TX, USA, 2007), release 10.1.

Results

Clinical data

One year after baseline assessment (range 12.0 ± 0.4 months), 16 (55%) of the original MCI cases demonstrated significant cognitive decline and constituted the progressive MCI group (PMCI). Among these cases, only three converted into AD. The remaining 13 cases (45%) showed no change in cognitive function, except an executive motor slowing indicated by the trail making test A (78.6 ± 32.0 vs. 96.1 ± 33.4 s; $p < 0.01$). This difference was not clinically significant with respect to normative thresholds and is consistent with the low test–retest

reliability of Part A in older adults (Mitrushina et al. 1991). These participants were therefore included in the stable MCI group (SMCI). PMCI cases showed a significant deterioration of their performances in the MMSE test (25.5 ± 1.8 vs. 23.3 ± 3.7; $p < 0.01$), verbal fluency (14.6 ± 4.8 vs. 11.1 ± 5.4; $p < 0.01$), Boston naming test (18.6 ± 1.5 vs. 17.4 ± 2.0; $p < 0.05$) and Buschke double memory test (3 blocks of 16 items) (total free recall: 16.9 ± 3.7 vs. 13.6 ± 3.4; $p < 0.01$).

Demographic and clinical characteristics at inclusion did not differ between SMCI and PMCI cases, for instance the mean age was 82.4 ± 9.6 and 83.1 ± 4.9 years ($p = 0.819$), respectively. Moreover, there was no significant difference in baseline scores for any of the neuropsychological tests between SMCI and PMCI. The HAD scale scores for anxiety and depression as well as gender distribution were comparable between groups.

Reaction times and performances in *n*-back tasks

All subjects performed well in the 2-back (SMCI $87.3\% \pm 3.9$ and PMCI $82.8\% \pm 6.0$) and detection tasks (SMCI $98.8\% \pm 2.2$ and PMCI $97.9\% \pm 2.2$). No significant differences were found in both performances and RT between SMCI and PMCI cases. In all groups, RTs significantly increased for the 2-back task ($F(1, 27) = 54.48$, $p < 0.001$).

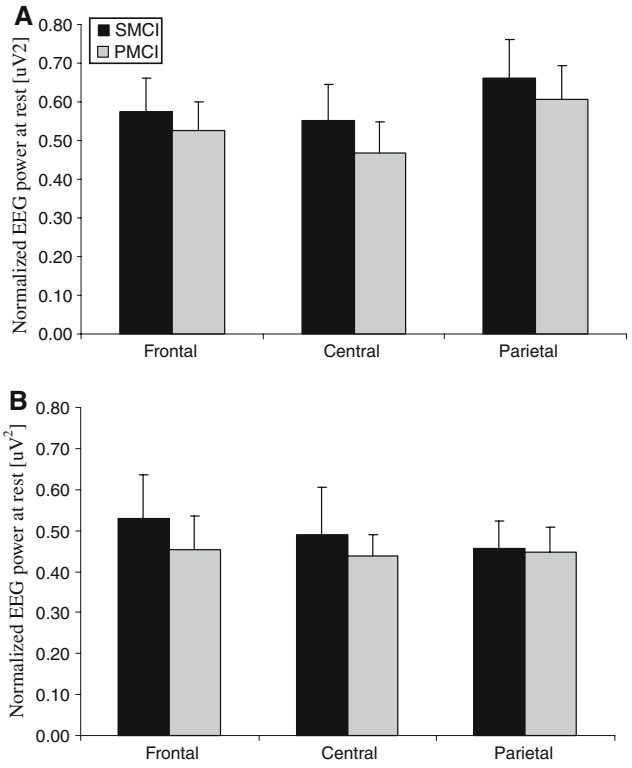

Fig. 1 Group effect on mean open eyes (**a**) and closed eyes (**b**) EEG power [μV^2] at rest in the 35–45 Hz frequency band at the frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrode sites. No differences were observed between the three diagnostic groups

Electrophysiological data

Spectral power analysis

The magnitude of gamma power open eyes at rest was independent of group ($F(1, 27) = 0.40$, $p = 0.53$), electrode ($F(2, 54) = 2.73$, $p = 0.08$) or interaction between group and electrode location ($F(2, 54) = 0.06$, $p = 0.94$) effects (Fig. 1a). Similarly, power gamma close eyes was independent of group-, electrode- or task-related effects (respectively, $F(1, 27) = 0.46$, $p = 0.57$; $F(2, 54) = 1.32$, $p = 0.28$; and ($F(2, 54) = 1.20$, $p = 0.31$) (Fig. 1b).

Repeated measure linear regression of event-related oscillations

The visual stimuli elicited a series of gamma oscillations in the time range 0–525 ms for the three electrode locations (Fig. 2). These oscillations did not depend on groups ($p = 0.877$), tasks ($p = 0.178$) or electrode location (central vs. frontal $p = 0.624$; parietal vs. frontal $p = 0.391$).

The assessment of regression coefficients showed that group differences in gamma dynamics concerned only two lag times (Table 1). When adjusted for gamma value at lag -2, and -3 ms in regression models, the gamma oscillations of PMCI were significantly different from SMCI ($t = -2.18$ and $t = -2.13$) during the interval 0–525 ms post-stimulus. The negative regression coefficients mean that the PMCI group (coded as 1) had lower average changes in gamma values (delta of gamma values between time and lag -2 or -3) than the SMCI group (coded as 0). As an example, Fig. 2 displays the phase diagram plots that correspond to the average frontal gamma oscillations at time t on the x axis and at lag time $t - 2$ on the y axis. It illustrates the elliptical shapes of the cyclic patterns and the lower variability of gamma dynamics in the PMCI compared to SMCI groups.

Fractal dimension comparisons between PMCI and SMCI

The distribution of fractal dimensions in PMCI and SMCI cases is illustrated in Fig. 3. For instance, in the 2-back task, the fractal dimension of PMCI cases (mean $\pm$ SD 0.88 ± 0.61) was significantly higher ($N = 29$; $t = -2.087$, degree of freedom 27, $p < 0.05$) compared to that of SMCI (mean $\pm$ SD 0.45 ± 0.49) cases. When considering the distinction between SMCI and PMCI as a binary

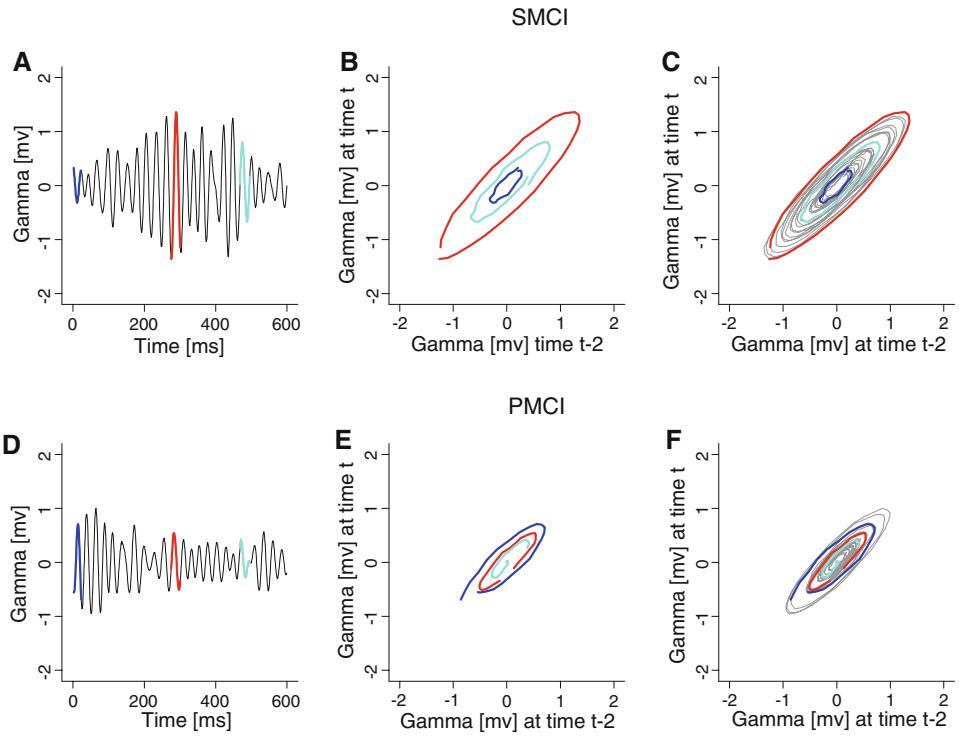

Fig. 2 **a** Average frontal gamma based on group during the 2-back task as a function of time (**a**, **d**), and as a function of average frontal gamma at lag time −2 (phase diagrams BC and EF). See text for details. The *colored* section represents the traces obtained during three limited time periods: *blue* (0 [ms] $< t <$ 24 [ms]), *red* (275 [ms] $< t <$ 301 [ms]) and *cyan* (468 [ms] $< t <$ 496 [ms]). They correspond to different loops of the ellipse in the SMCI and the PMCI group. For example, the *red* section corresponds to the envelope (external layer) of the ellipse in the SMCI group, but to an inner loop in the PMCI group

Table 1 Regression coefficients (μV) associated with group effects and their significance at different lag time from repeated measure linear regression models ($N = 29$ subjects; see text for details)

Lag (ms)	Adjusted for age, task, time and electrode sites		
	Coefficient	*t*	*P*
2	−0.00150	−2.16	**0.036**
3	−0.00210	−2.1	**0.041**
4	−0.00244	−1.96	0.056
5	−0.00250	−1.74	0.088
6	−0.00227	−1.48	0.146
7	−0.00185	−1.19	0.241
8	−0.00133	−0.89	0.377
9	−0.00084	−0.61	0.542
10	−0.00047	−0.4	0.690
11	−0.00030	−0.31	0.759
12	−0.00033	−0.43	0.671
13	−0.00053	−0.83	0.412
14	−0.00083	−1.25	0.219
15	−0.00112	−1.34	0.188
16	−0.00133	−1.23	0.227
17	−0.00141	−1.04	0.306
18	−0.00131	−0.82	0.416
19	−0.00107	−0.6	0.553
20	−0.00072	−0.38	0.707

The group coefficient corresponds to the average difference between SMCI and PMCI in the gamma amplitude adjusted for previous values of gamma at a given time lag, age, task, time and electrode sites

Bold values represent statistically significant results

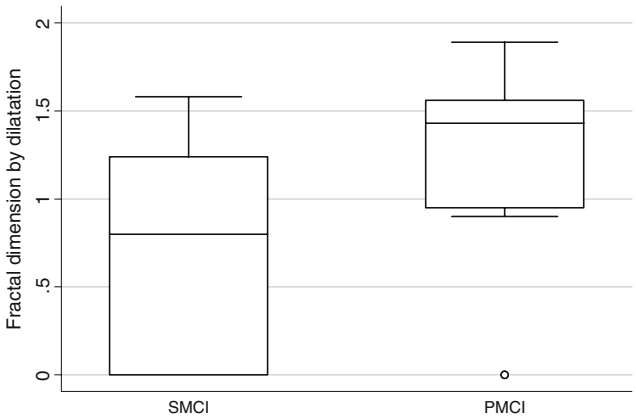

Fig. 3 *Dot plot* of the fractal dimension of phase space (frontal gamma power) for the 2-back at lag time −2 based on group (SMCI vs. PMCI). Each *dot* corresponds to one subject. The median of each group is represented by the *horizontal line*. See text for details

dependent variable, univariate logistic regression models showed that the fractal dimension of gamma oscillation was significantly related to the cognitive outcome and explained 11.8% of its variability (95% confidence interval 0.34–2.77, $p < 0.01$). This association persisted when controlling for task and electrode site (see Fig. 3).

In terms of MCI classification, the best combination of sensitivity and specificity (after controlling for task and electrode sites) was obtained for a threshold fractal dimension of gamma at 1.0 (sensitivity: 0.81, specificity: 0.85) with an area under the corresponding ROC curve

reaching 82%. This model correctly classified 79.3% of MCI cases.

Discussion

Earlier studies focusing on gamma band parameters in AD and MCI reported discrepant data due to sampling differences and variability in the assessment of gamma band oscillations (Driver et al. 2007; Koenig et al. 2005; Ribary et al. 1991; Stam et al. 2002; van Deursen et al. 2008; Wright et al. 2001). In agreement with the hypothesis of Singer (Singer 2009) who proposed to include internal timing mechanisms in the analysis of high brain oscillations, we observed significant differences in gamma band dynamics, but not in magnitude, between PMCI and SMCI. This observation cannot be due to motor processing or sensory deficits since our analysis was performed on correctly recognized non-target trials. The observed changes in gamma dynamics appear to be strictly related to the cognitive processes common to both detection and 2-back tasks, since they were absent in spectral power analysis at rest and also before stimulus onset. The *n*-back task used in our study involves not only a pure working memory component that becomes evident in the 2-back condition, but also a major attentional component engaged already in the detection task (Baddeley 1992; LaBar et al. 1999; Krause et al. 2000). Physiologically, previous magneto-encephalographic investigations indicated that the gamma band activity was specific to the retained stimulus during auditory short-term memory maintenance and postulated that stimulus-specific gamma band activity was related to neural activations preceding test stimuli rather than short-term memory load (Kaiser et al. 2003; Lutzenberger et al. 2002). Supporting further this hypothesis, a recent study based on delayed auditory matching-to-sample task revealed stimulus-specific gamma activity (>70 Hz) in anticipation of test stimuli that predicted short-term memory performance (Kaiser et al. 2009). In line with the involvement of gamma oscillations in attention processes, a cross-frequency coupling between theta (4–8 Hz) and gamma neuronal oscillations was recently reported (Demiralp et al. 2007; Jensen and Colgin 2007; Lisman and Buzsaki 2008). This coupling is necessary for the interaction between wide groups of neurons located within distant brain regions during cognitive processing. Recent studies demonstrated that attention processes need theta–gamma frequency coupling to facilitate the transient coordination of cortical areas required for this function (Canolty et al. 2006; Fan et al. 2007, 2005). Interestingly, our time–frequency analysis showed that the frontal-induced theta activity at baseline was significantly reduced in PMCI compared to SMCI in all *n*-back tasks that were similar in terms of directed attention requirements (Deiber et al. 2009). In conjunction with these observations, the present data suggest that theta–gamma frequency uncoupling during the activation of directed attention may be an early electrophysiological event that predicts worst cognitive evolution among MCI cases.

In our study, the lag time that makes it possible to distinguish SMCI from PMCI coincides strictly with the thalamo-cortical conduction time (Albe-Fessard et al. 1986; Allison et al. 1991; Pantev et al. 1991; Ribary et al. 1991). Cortical and deep brain thalamic implanted electrodes reported stimulus-evoked responses that point to the millisecond conduction time among thalamo-cortical axons in both humans and animals (Allison et al. 1991; Klostermann et al. 2002; Simons et al. 2007). Most importantly, previous contributions using magneto-encephalography and magnetic field tomography revealed waveform deterioration and intensity reduction of gamma oscillations at 2–3 ms lag times in AD (Ribary et al. 1991, 1990, 1989). These findings may be explained by the loss of long distance cortico-cortical connections that characterize AD (Koenig et al. 2005; Stam et al. 2006, 2003). In this context, our results are compatible with a disruption of long distance connections that would be already present in PMCI. One should note, however, that the increased gamma band power during task performance observed in normal aging persists even in certain AD patients (Fitzgibbon et al. 2004; van Deursen et al. 2008) suggesting that the local networks may be at least partly preserved in the course of neurodegeneration. Moreover, a significant increase of gamma band power was reported during cognitive activation in AD cases compared to healthy controls and MCI cases, implying the presence of compensatory mechanisms for a possible decrease in long distance connectivity (van Deursen et al. 2008). In line with our previous studies focusing on the research of EEG markers predictive of cognitive decline in MCI (Missonnier et al. 2007, 2006), the observed deficits in gamma band activation in PMCI were present despite the successful performance of the *n*-back task further supporting the presence of probable compensatory activation of additional cerebral areas. Accordingly, recent data suggest that high working memory performance can be maintained through the recruitment of alternative cortical networks even in presence of early brain activation deficits in MCI (Yetkin et al. 2006). The changes in the temporal evolution of gamma band value reported here were also identified at an individual level using the fractal dimension analysis that revealed only a limited overlap of individual scores between SMCI and PMCI cases. The average observed value of 0.88 for the PMCI group can be interpreted as being close to a straight line (dimension 1.0) and thus more complex, than the value of 0.45 for the SMCI group that

lies between a dot (dimension 0.0) and a straight line (dimension 1.0). This single EEG parameter predicts almost 12% of the cognitive variability in our MCI group. Although this percentage may appear modest, it is significantly higher than that reported for theta event-related synchronization in previous studies (Missonnier et al. 2007, 2006), suggesting that the investigation of early changes in high, rather than low, frequency brain oscillations may be useful to predict rapid cognitive decline in MCI. Importantly, our fractal dimension findings disagree with those reported recently by Gomez et al. (2009), who found a decrease of this parameter in AD cases. Several methodological differences may explain this discrepancy. First, magneto-electroencephalographic signal in this latter study was filtered between 0.5 and 40 Hz, and 72% of the MEG epochs that retained the majority of the signal energy were below 10.6 Hz. In contrast, EEG signal was band-pass filtered at 35–45 Hz in the present study. Second, our observations concern gamma reactivity during the successful performance of a working memory task, while Gomez et al. recorded background activity that was not influenced by functional compensation phenomena (van Deursen et al. 2008). Finally, fractal dilations were calculated in Pointcarré maps using the method of Minkowski and Bouligand in our study, whereas Gomez et al. used Higuchi's fractal dimension in EEG signals.

Several limitations should be considered when interpreting the present data. First, no distinction was made between different MCI subgroups (i.e., single versus multiple domain). Second, group differences for other lag times may be overlooked because of the small sample size. Most importantly, the analysis of gamma band oscillations in experimental paradigms exploring cognition showed that oscillations in the gamma band included three distinct components typically recorded within 500 ms after stimulus presentation: a gamma band-evoked response directly related to the stimulus, a 40-Hz steady-state response related to primary sensory processing and an induced component associated with meaningful information processing (Fell et al. 2003; Herrmann and Demiralp 2005; Klimesch 1999; Tallon-Baudry and Bertrand 1999). Given the limited number of MCI cases, no separate analysis of each of these components was made in this study. Although one can argue that p values may be significant by chance only with an alpha value set at 0.05 in our regression models, this is a highly unlikely scenario since the two significant p values are consecutive in a cyclic pattern, associated with the time lag instead of occurring randomly, and it holds after adjusting for age.

In conclusion, the present data reveal lower variability, but higher complexity, of the gamma signal over time in PMCI compared to SMCI cases that is already present before their rapid cognitive decline. Further longitudinal studies including larger cohorts of MCI subgroups including time–frequency analysis to differentiate induced from evoked functional processes, and use of additional paradigms addressing other cognitive modalities (i.e., directed attention) are needed to explore the possible relevance of gamma band abnormalities related to attentional and pre-attentional levels of cognitive processing in the prediction of dementia.

Conflict of interest statement This study has not been submitted elsewhere for publication, in whole or in part, and all the authors listed have approved the manuscript. The authors declare that there are no actual or potential conflicts of interest. All have read and have abided by the statement of ethical standards for manuscripts submitted to this journal.

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