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Analysis of neural dynamics in mild cognitive impairment and Alzheimer's disease using wavelet turbulence

Jesús Poza 1,2,3 , Carlos Gómez 1 , María García 1 , Rebeca Corralejo 1 , Alberto Fernández 4 and Roberto Hornero 1,2,3

¹ Biomedical Engineering Group, Department TSCIT, ETS. Ingenieros de Telecomunicación, University of Valladolid, Valladolid, Spain

² IMUVA, Instituto de Investigación en Matemáticas, University of Valladolid, Valladolid, Spain

³ INCYL, Instituto de Neurociencias de Castilla y León, Salamanca, Spain

⁴ Departamento de Psiquiatría y Psicología Médica, Facultad de Medicina, Complutense University of Madrid, Madrid, Spain

E-mail: jesus.poza@tel.uva.es

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Abstract

Objective. Current diagnostic guidelines encourage further research for the development of novel Alzheimer's disease (AD) biomarkers, especially in its prodromal form (i.e. mild cognitive impairment, MCI). Magnetoencephalography (MEG) can provide essential information about AD brain dynamics; however, only a few studies have addressed the characterization of MEG in incipient AD. *Approach.* We analyzed MEG rhythms from 36 AD patients, 18 MCI subjects and 27 controls, introducing a new wavelet-based parameter to quantify their dynamical properties: the wavelet turbulence. *Main results.* Our results suggest that AD progression elicits statistically significant regional-dependent patterns of abnormalities in the neural activity (p < 0.05), including a progressive loss of irregularity, variability, symmetry and Gaussianity. Furthermore, the highest accuracies to discriminate AD and MCI subjects from controls were 79.4% and 68.9%, whereas, in the three-class setting, the accuracy reached 67.9%. *Significance.* Our findings provide an original description of several dynamical properties of neural activity in early AD and offer preliminary evidence that the proposed methodology is a promising tool for assessing brain changes at different stages of dementia.

Keywords: Alzheimer's disease, mild cognitive impairment, magnetoencephalogram, continuous wavelet transform, wavelet turbulence

(Some figures may appear in colour only in the online journal)

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that progressively affects the brain function. Different brain regions, as well as their associated neural activity, become involved during the course of AD. In the last decades, growing efforts have been devoted to explore the underlying brain dynamics associated with AD. A key issue to explain such interest is the rising socio-economic impact of dementia in modern societies, partially because of the strong age-related incidence (Hampel *et al* 2011, Reitz *et al* 2011). AD is increasingly being recognized as a modern epidemic with an enormous impact on the health care systems (Hampel *et al* 2011, 2012). Nevertheless, despite the considerable progress made over the past two decades to understand AD mechanisms, further research is still required to gain deeper insights into the neural dynamics of AD. In this regard, a better and more comprehensive characterization of mild cognitive impairment (MCI) is essential for appropriate identification of incipient AD, since subjects with MCI are at a higher risk of developing AD (Mufson *et al* 2012). MCI is defined as the symptomatic predementia stage of AD in which subjects exhibit a memory impairment beyond what would be expected for their age, but do not fully accomplish the criteria for a diagnosis of dementia (Petersen 2010). As a consequence, MCI is considered a prodromal stage of dementia (Mufson *et al* 2012).

To address these tasks, several neuroimaging techniques are currently available: functional and structural magnetic resonance imaging (fMRI and sMRI), positron emission tomography (PET), fluorodeoxiglucose PET (FDG-PET), diffusion tensor imaging, magnetic resonance spectroscopy, electroencephalography (EEG) and magnetoencephalography (MEG), among others (Ewers *et al* 2011). Nowadays, none of the available neuroimaging measures is recommended for routine diagnostic purposes (McKhann *et al* 2011). However, scientific evidence points out that they can be potentially useful to delimit promising biomarkers for early AD detection (Ewers *et al* 2011, Hampel *et al* 2011).

Due to the still limited knowledge on the dynamical processes involved in the regulation of complex functional brain systems, non-invasive neurophysiological techniques, such as EEG and MEG, have been brought into focus (Hampel et al 2011, Reitz et al 2011). Mounting evidence suggests that they may provide essential information on the neural function (Georgopoulos et al 2007, Hampel et al 2011, Reitz et al 2011). Nevertheless, EEG and MEG provide slightly different views of neuronal dynamics (Rampp and Stefan 2007), partially because MEG is reference-free and is less affected by the volume conduction than EEG (Stam 2010). Evidence suggests that MEG can track downstream neuronal injury, taking into account the regional patterns of abnormalities. In fact, MCI and AD result in a wide range of structural and functional changes in the brain, which seem to reflect damage to neurons and synapses (Sperling et al 2011). There are also emerging data suggesting that early brain changes include a decline in the synaptic function and integrity of neurons, which may be present even before evidence of amyloid accumulation in the brain (Hampel et al 2012, Sperling et al 2011). However, the mechanisms of neural injury are still not fully understood (Hampel et al 2011, Mufson et al 2012).

In this context, MEG appears to provide evidence about the severity of dementia; however, there is a dearth of studies focused on analyzing resting-state MEG patterns in early phases of AD. Diverse findings support the notion that MCI can be associated with intermediate abnormalities between those observed in normal ageing and AD dementia. Specifically, MCI subjects show a slight decrease in low frequency power, an increase in irregularity and a decrease in disequilibrium when compared to AD patients (Bruña et al 2012, Fernández et al 2006a, 2006b, Osipova et al 2006). Different patterns of complexity have been found depending on the applied parameter. Studies using nonlinear measures have found an increase of complexity in MCI subjects in comparison to AD patients (Fernández et al 2010), whereas a decrease has been observed applying a statistical complexity definition (Bruña et al 2012). Functional connectivity analyses have also shown that AD increases the level of coherence in the delta band, while MCI tends to decrease the connectivity in the theta and alpha bands (Escudero *et al* 2011). Furthermore, it is noteworthy that subtle MCI-characteristic patterns have been reported when MCI subjects and cognitively elderly controls were analyzed (Bruña *et al* 2012, Escudero *et al* 2011, Fernández *et al* 2006a, 2006b, Gómez *et al* 2009). In summary, the neurophysiological substrate of neural dysfunction in MCI subjects is not yet well established. Further research is indeed required to establish a consistent description of neural dynamics associated with prodromal AD.

Recent studies suggested that the analysis of irregularity based on the spectral content from the short-time Fourier transform (STFT) can provide valuable information to understand brain dynamics in AD dementia (Poza et al 2008a). Likewise, AD-like patterns of brain changes were observed in a preliminary study at the stage of MCI (Poza et al 2012). Nevertheless, electromagnetic brain signals exhibit simultaneously high frequency and short time patterns, as well as low frequency and long time oscillations (Figliola and Serrano 1997). Accordingly, time-frequency representations with a variable time-frequency resolution are strongly required. The wavelet transform provides such an approach, varying window size across frequencies. Thus, wavelet analysis yields a good time resolution at high frequencies and a good frequency resolution at low frequencies (Figliola and Serrano 1997).

In this study, we applied a new wavelet-based parameter, named wavelet turbulence (WT), to characterize the timedependent content of MEG activity in MCI and AD. In the present research, we attempt to address the following questions: (i) Does the proposed methodology based on WT introduce an original description of neural dynamics to that provided by conventional spectral and nonlinear methods?; (ii) Do the changes in the MEG activity reflect the regional abnormalities of MCI and AD?; (iii) Can the proposed methodology be useful to account for the complexity of AD and provide further insights into the underlying brain dynamics associated with AD?

2. Materials

2.1. Selection of subjects

A total of 81 subjects were initially selected to participate in the study, according to the following inclusion and exclusion criteria.

- Inclusion criteria: (1) age > 60 years; (2) collaborative in the MEG recording procedure; (3) ability to complete medical, physical, neurological, psychiatric and neuropsychological evaluations; (4) free of any drug that could affect MEG recordings at the time of the study.
- Exclusion criteria: (1) history of any other significant medical, neurological or psychiatric disorder, excluding MCI or AD; (2) presence of a pacemaker or other implanted medical device that may interfere with the MEG equipment; (3) lack of written informed consent obtained from healthy volunteers or caregivers of patients.

Thirty-six patients with AD (12 men and 24 women, age = 74.1 ± 6.9 years, mean \pm standard deviation,

 $M \pm SD$) were recruited from the 'Asociación de Familiares de Enfermos de Alzheimer' and the Geriatric Unit of the 'Hospital Clínico Universitario San Carlos' (Madrid, Spain). Diagnoses were made on the basis of exhaustive medical, physical, neurological, psychiatric and neuropsychological examinations. All patients fulfilled the criteria for probable AD, according to the clinical guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (McKhann *et al* 1984). The cognitive and functional deficits were assessed by means of the mini-mental state examination (MMSE) and the functional assessment staging (FAST). AD patients obtained mean scores of 18.1 ± 3.4 and 4.2 ± 0.4 on the MMSE and FAST, respectively.

Eighteen MCI subjects from AFAL (8 men and 10 women, age = 74.9 \pm 5.6 years, M \pm SD) were also enrolled in the study. All patients were diagnosed with MCI following Petersen's criteria (Petersen *et al* 2001). Mean MMSE and FAST scores in this group were 25.7 \pm 1.8 and 3.0 \pm 0.0, respectively. It is noteworthy that neither MCI subjects nor AD patients were taking any medication that could affect MEG recordings at the time of study (like cholinesterase inhibitors, benzodiazepines or antidepressants).

Twenty-seven healthy volunteers (11 men and 16 women, age = 71.5 \pm 6.2 years, M \pm SD) were included in the study as a control group. Elderly controls were cognitively healthy subjects with no history of neurological or psychiatric disorders. Their mean MMSE and FAST scores were 29.0 \pm 1.2 and 1.6 \pm 0.5, respectively.

Nonsignificant differences were observed in the mean age and gender of AD patients, MCI subjects and controls (p > 0.05, Kruskal–Wallis test).

It is noteworthy that all participants and all patients' caregivers gave their informed consent prior to their participation in the study. Moreover, the study protocol was approved by the local Ethics Committee.

2.2. MEG recording

MEG signals were acquired using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging, San Diego, CA). MEG acquisition was carried out in a magnetically shielded room at the 'Centro de Magnetoencefalografía Dr Pérez-Modrego' (Complutense University of Madrid, Spain). In addition, subjects were asked to remain awake, relaxed and with their eyes closed, in order to minimize the presence of artifacts. MEG signals were continuously monitored to prevent drowsiness. Five minutes of spontaneous MEG activity were recorded from each subject with a sample frequency of 678.17 Hz. Initially, a 0.1-200 Hz hardware band-pass filter and a 50 Hz notch filter were applied. Then, each MEG recording was downsampled by a factor of 4 to reduce the data length. Artifact-free epochs of 10 s (26.6 \pm 5.7 artifactfree epochs per channel and subject, M \pm SD) were selected for further analysis. MEG signals were subsequently processed using a finite impulse response filter designed with a Hamming window and cut-off frequencies at 1 and 70 Hz. It should be noted that the frequency range was chosen to keep the relevant spectral content and minimize the presence of oculographic and myographic artifacts (Bruña *et al* 2012, Poza *et al* 2008b).

3. Methods

3.1. Continuous wavelet transform

Electromagnetic brain signals are non-stationary biomedical recordings (Blanco et al 1995). Non-stationary signal analysis techniques are then needed to appropriately characterize their time-varying properties. In this study, the time-scale maps were computed for each 10 s MEG epoch using the continuous wavelet transform (CWT). The CWT is a multiresolution signal decomposition method conceptually related to the STFT and useful for extracting local-frequency information from a signal. Wavelets are zero-mean functions localized in both time and frequency; thereby, different waveforms can be considered a wavelet. However, the waveform contained in the wavelet should also provide a biological plausible fit to the signal being modeled (Roach and Mathalon 2008). This is the case of the Morlet wavelet, which exhibits a Gaussian-windowed shape in both time and frequency, while maintaining a sinusoidal underlying structure. This function will be used in this study to generate a family of wavelets, including compressed and stretched versions of the 'mother wavelet' (Mallat 1998). In brief, several wavelets at different scales are generated. The CWT of each 10 s MEG epoch, x(t), is then defined as the convolution of x(t) with a scaled and translated version of the 'mother wavelet':

$$CWT(k,s) = \frac{1}{\sqrt{s}} \cdot \int_{-\infty}^{+\infty} x(t) \cdot \psi^* \left(\frac{t-k}{s}\right) dt, \qquad (1)$$

where $\psi(t, s)$ represents the 'mother wavelet', *s* is the scaling factor, *k* represents the time interval and * denotes the complex conjugate. The wavelet analysis was carried out for scales [1:128] to include the 1–70 Hz frequency range.

A simple way to represent the magnitude of the neuromagnetic oscillations at specific scales is the calculation of the wavelet power. Hence, the scalogram (WS) is a function that summarizes the distribution of wavelet power in the time-scale map (Percival 1995). The WS is calculated by squaring the magnitude of CWT coefficients:

$$WS(k, s) = |CWT(k, s)|^2.$$
 (2)

3.2. Wavelet turbulence

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From the time-scale map of WS, several parameters can be computed to summarize its dynamical properties. One of them is WT, which provides an estimate on how WS varies over time (Poza *et al* 2012). The calculation of WT is based on the comparison of WS values at consecutive time points by means of the correlation coefficient (Kelen *et al* 1991). Thereby, WT is able to summarize the regularity patterns of time-varying signals in terms of the strength of the relationship. Although WT can be computed over narrow-band ranges, in the present study this parameter was calculated considering the entire frequency range. Hence, the definition of WT can be read as

$$WT(k) = \tau[WS(k, s), WS(k+1, s)],$$
(3)

where $\tau[\cdot]$ denotes the Kendall correlation between WS(*k*, *s*) and WS(*k* + 1, *s*). WT could also be computed using the Pearson or the Spearman correlation. The Pearson correlation measures the degree of linear association between two variables, whereas the Spearman rank correlation is useful to detect nonlinear but monotonic associations, either increasing or decreasing (Jobson 1991). The Kendall correlation is an alternative measure of association based also on the property of monotonicity. However, it does not rely on any assumptions on the data distributions and provides a straightforward interpretation as a difference between the probability of concordance and the probability of discordance (Kendall and Gibbons 1990).

Due to the fact that we are analyzing finite-length time series, border distortion will be introduced at the beginning and end of WS. The WS region in which edge effects become important is named 'cone of influence' (Mallat 1998). Figure 1 illustrates the influence of border distortion on WT, introduced in the wavelet analysis. In order to avoid edge effects, the time intervals [0 1] s and [9 10] s were excluded from the computation of WT for each 10 s MEG epoch.

As illustrated in (4), WT is formed by the correlations between neighbor WS components at different time points. Several statistics were then computed from the time series formed by the Kendall correlation coefficients to characterize the data distribution, like those metrics intended to measure the location, spread and shape.

3.2.1. Measures of location. This kind of statistics is useful to summarize the central tendency of the distribution. The most commonly used statistic is the mean or sample average (Jobson 1991), which in the case of WT (\overline{WT}) summarizes the average degree of similarity between the WS components of adjacent time slices (Poza *et al* 2008b, 2012):

$$\overline{\mathrm{WT}} = \frac{1}{N-1} \cdot \sum_{k=1}^{N-1} \mathrm{WT}(k), \tag{4}$$

where N represents the number of time points.

Another measure of centrality is related to the maximum frequency in the histogram, named the mode (Jobson 1991). In the case of WT, its mode (WT_m) represents the most frequent value of correlation in the temporal series, namely the most likely value of WT. The WT_m definition is given by

$$WT_m = \underset{WT(k)}{\operatorname{arg\,max}} \{\operatorname{hist}[WT(k)]\},\tag{5}$$

where hist[WT(k)] denotes the histogram corresponding to the WT distribution.

3.2.2. Measures of spread. The most common measure of spread is the variance (Jobson 1991). Nevertheless, the standard deviation (σ_{WT}) was used instead of the variance in this study, since it provides a more intuitive description of the changes of variability in the correlation around the mean value (Poza *et al* 2008b, 2012). It is defined as

$$\sigma_{\rm WT} = \left\{ \frac{1}{N-2} \cdot \sum_{k=1}^{N-1} \left[WT(k) - \overline{WT} \right] \right\}^{1/2}.$$
 (6)



Figure 1. Grand-average of WT for each group, showing the border distortion at the edges of the 10 s time series. Shaded contours enclose regions where edge effects become important.

The interquartile range is an alternative to the standard deviation that provides a robust estimate of the spread of the data. In the case of WT (IQR_{WT}), it estimates the range of the central half of the correlation values (Jobson 1991):

$$IQR_{WT} = Q_3^{WT} - Q_1^{WT}, \qquad (7)$$

where Q_3^{WT} and Q_1^{WT} represent the third and first quartiles (i.e. the 25th and the 75th percentiles) of the WT distribution, respectively.

3.2.3. Measures of shape. Shape is usually concerned with the tails of the distribution. Hence, its characterization is based on the tail length and the symmetry of the left and right tails. The first measure of shape is the skewness (γ_{WT}), which is a quantifier of the asymmetry between the two tails of the distribution of correlation values (Jobson 1991):

$$\gamma_{\rm WT} = \frac{E\{[WT(k) - WT]^3\}}{\sigma_{\rm WT}^3},\tag{8}$$

where $E\{\cdot\}$ is the expectation function.

Another measure of shape is the kurtosis (δ_{WT}), which is related to the property of peakedness or to the length and the thickness of the tails of the WT distribution (Jobson 1991). Owing to the normalization of kurtosis with respect to the normal distribution (whose kurtosis is 3), δ_{WT} has been used as a quantifier of non-Gaussianity (Jobson 1991):

$$\delta_{\rm WT} = \frac{E\{[{\rm WT}(k) - {\rm WT}]^4\}}{\sigma_{\rm WT}^4} - 3.$$
(9)

Figure 2 illustrates the previous statistics (mean, mode, standard deviation, interquartile range, skewness and kurtosis), calculated from the WT distribution of a 10 s MEG epoch, for one subject from each group: (a) healthy control, (b) MCI subject and (c) AD patient.

3.3. Statistical analysis

It is noteworthy that the statistical and classification analyses were carried out in four steps: (i) exploratory analysis; (ii) global statistical analysis; (iii) sensor-level statistical analysis;



Figure 2. Histograms corresponding to WT, calculated for 10 s MEG epochs at sensor A107, for one subject from each group. (a) Control subject. (b) MCI subject. (c) AD patient. The corresponding WT statistics are also indicated (mean, \overline{WT} ; mode, WT_m ; standard deviation, σ_{WT} ; interquartile range, IQR_{WT}; skewness, γ_{WT} ; and kurtosis, δ_{WT}).

and (iv) three-class ROC (receiver operating characteristic) analysis.

Initially, an exploratory analysis was carried out to study the data distribution. After the descriptive analysis, variables did not meet parametric test assumptions.

Grand average WT statistics were then compared between AD patients, MCI subjects and controls by means of Kruskal–Wallis tests ($\alpha = 0.05$). Mann–Whitney U-tests adjusted for multiple comparisons by a Bonferroni correction were performed when previous analyses showed significant interactions ($\alpha = 0.05/3 = 0.0167$).

Due to the limitations of the previous tests to control type I error when a high number of comparisons should be made, the significance of the differences in WT statistics was analyzed at the sensor level using a multiple comparison nonparametric permutation test (Nichols and Holmes 2001). This test is useful to achieve a strong control over type I error in situations in which the multiplicity of testing must be taken into account (e.g. 148 sensors). The test computes the permutation distribution of the maximal sensor statistic, which is based on the *F* statistic obtained comparing each WT statistic between controls, MCI subjects and AD patients sensor by sensor. It is noteworthy that the goal of this step is to compute the permutation distribution for the maximal statistic F^{max} (i.e. the maximum of the sensor statistics for each permutation).

As a consequence, WT statistics should not necessarily be normally distributed. In this study, the maximal distribution was generated from 5000 permutations. Multiple comparisons were then corrected by selecting a critical threshold at the c + 1 largest member of the permutation distribution for F^{max} , where $c = \lfloor \alpha N \rfloor$, αN rounded down (α represents the significance level, typically 0.05, and N is the number of permutations, 5000). Sensors with F statistics exceeding this threshold exhibit evidence against the corresponding sensor hypothesis at level α . The corrected p-value for each sensor is estimated according to the proportion of the permutation distribution for F^{max} exceeding the observed sensor statistic (Nichols and Holmes 2001).

The classification performance of each WT statistic was finally evaluated using a three-class ROC analysis (Nakas and Yiannoutsos 2004). The three-dimensional generalization of the ROC curve, named ROC surface, extends the two-class classification task carried out in a conventional ROC analysis. Classification statistics were summarized in terms of true class (TC_{group}, group = {CON, MCI, AD}) and accuracy. TC_{group} represents the proportion of subjects of each group with a correct classification, whereas the accuracy is the total proportion of subjects with a correct classification. In the twoclass setting, statistics can be graphically represented by pairs, using ROC curves, whereas in the three-class setting a ROC

Table 1. Results of Mann–Whitney U-tests ($\alpha = 0.0167$, Bonferroni-corrected) and Kruskal–Wallis analysis ($\alpha = 0.05$) for the averaged WT statistics. Significant values have been highlighted.

		Kruskal–Wallis test		
Parameter	C versus AD	C versus MCI	MCI versus AD	C versus MCI versus AD
$ \frac{\overline{WT}}{WT_m} \sigma_{WT} IQR_{WT} \gamma_{WT} \delta_{WT} $	Z = -3.931, p = 0.0001 Z = -3.933, p = 0.0001 Z = -2.250, p = 0.0244 Z = -2.785, p = 0.0054 Z = -3.847, p = 0.0001 Z = -3.681, p = 0.0002	Z = -1.413, p > 0.05 Z = -1.332, p > 0.05 Z = -1.031, p > 0.05 Z = -1.089, p > 0.05 Z = -1.158, p > 0.05 Z = -1.251, p > 0.05	Z = -3.156, p = 0.0016 Z = -3.193, p = 0.0014 Z = -1.184, p > 0.05 Z = -1.688, p > 0.05 Z = -3.119, p = 0.0018 Z = -3.083, p = 0.0021	$\chi^{2} = 19.5, p = 0.0001$ $\chi^{2} = 20.0, p < 0.0001$ $\chi^{2} = 5.5, p = 0.0649$ $\chi^{2} = 8.6, p = 0.0136$ $\chi^{2} = 18.6, p = 0.0001$ $\chi^{2} = 17.5, p = 0.0002$

C: control group. MCI: mild cognitive impairment group. AD: Alzheimer's disease group.

surface is generated. The area under ROC curve (AUC) and the volume under ROC surface (VUS) were thereby used to quantify the probability that test values will allow a proper classification of two or three randomly selected subjects, one from each group (Nakas and Yiannoutsos 2004). It should be noted that the interpretation of AUC and VUS values must be carefully carried out. The volume under the ROC hypersurface in a *k*-class setting is in the range [1/k! 1], where the lower limit, 1/k!, is reached by a completely uninformative parameter and the upper limit, 1, is obtained when the *k* populations are perfectly separated (Nakas and Yiannoutsos 2004). Hence, a random classifier in the two-class setting would obtain an AUC value of 0.500, whereas in the threeclass setting it would yield a VUS value of 0.167.

Signal processing and statistical analyses were performed using the software packages Matlab (version 7.14 Mathworks, Natick, MA) and SPSS Statistics (version 20, IBM Corp, Armonk, NY).

4. Results

4.1. Statistical analysis

Initially, WT statistics were averaged over all sensors in order to obtain a single value per parameter and subject. Figure 3 depicts the boxplots corresponding to the averaged WT statistics for each group, whereas table 1 summarizes the results of the statistical analyses. WT statistics were subsequently analyzed at the sensor level in order to extract group-specific spatial patterns. Detailed results for WT statistics are shown in figure 4, where the differences in the spatial distributions for each pair of groups can be observed.

The spatial analyses of the measures of location (i.e. \overline{WT} and WT_m) showed a significant widespread increase for AD patients in comparison to controls, whereas this increment was more localized when compared to MCI subjects, including the left frontal, central and left parieto-occipital regions. On the other hand, MCI subjects exhibited an increase of \overline{WT} and WT_m in the right fronto-temporal region in comparison to controls.

Regarding the measures of spread (i.e. σ_{WT} and IQR_{WT}), AD patients obtained statistically significant lower values in the upper temporal and lower right temporal regions than controls. Spatial analyses showed that MCI subjects reached higher σ_{WT} and IQR_{WT} values than AD patients in the left frontal and left parieto-occipital regions. MCI subjects obtained lower σ_{WT} and IQR_{WT} values than controls in the temporal regions of both hemispheres.

Statistical analyses of the measures of shape (i.e. γ_{WT} and δ_{WT}) revealed that AD patients obtained a widespread pattern of significant increases compared to controls, including the temporal, central and right parieto-occipital regions, though the changes were more localized for δ_{WT} than for γ_{WT} . MCI subjects displayed a significant decrease of γ_{WT} and δ_{WT} in comparison to AD patients, which was mainly localized in the parietal region. MCI subjects exhibited simultaneously a slight increase of γ_{WT} and δ_{WT} in the right temporal region and a decrease in the upper left temporal region.

In summary, AD patients showed statistically significant different measures of location, spread and shape for WT when compared to MCI subjects and controls. Furthermore, MCI subjects exhibited intermediate WT statistics when compared to AD patients and controls. These results suggest that dementia progression can be associated with several changes in the spontaneous MEG activity like: (i) an increase of the average degree of similarity in WS and in the most frequent value of WT; (ii) a loss of variability in WT; and (iii) an increase in the asymmetry and peakedness of the data distribution calculated from WT. The correlation analyses with cognitive and functional tests support these ideas. WT statistics were correlated with MMSE and FAST scores (p < 0.05 using the Spearman correlation).

4.2. Classification analysis

In addition to the previous statistical results, the diagnostic ability of the proposed parameters was assessed following a two-step approach. Firstly, a two-class ROC analysis was carried out to analyze the classification performance of WT statistics to discriminate between pairs of groups. Secondly, a three-class ROC analysis was applied to study the global classification performance to simultaneously distinguish among the three groups. Table 2 summarizes the accuracies, AUC and VUS values for WT statistics averaged for the sensors that reached significant results in the two-group and three-group comparisons. $\sigma_{\rm WT}$ was not further analyzed, since no significant results were observed for any sensor (p > 0.05).

In a first step, the classification statistics for the twoclass ROC analysis indicated that the highest classification rates were achieved when discriminating between AD patients and controls. The highest AUC values were reached using



Figure 3. Boxplots for each group (C: healthy controls; MCI: MCI subjects; AD: AD patients) corresponding to the averaged WT statistics. (a) Mean, \overline{WT} . (b) Mode, WT_m . (c) Standard deviation, σ_{WT} . (d) Interquartile range, IQR_{WT}. (e) Skewness, γ_{WT} . (f) Kurtosis, δ_{WT} .

Table 2. Accuracies, A	AUC and	VUS	values f	for th	e sigr	nificant	WT	statistics
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Parameter		C versus AD	C versus MCI	MCI versus AD	C versus MCI versus AD
WT	AUC/VUS	0.794	0.626	0.765	0.546
	Accuracy (%)	79.4	68.9	75.9	66.7
WT_m	AUC/VUS	0.801	0.628	0.776	0.551
	Accuracy (%)	77.8	66.7	77.8	66.7
IQR _{WT}	AUC/VUS	0.761	0.667	0.662	0.492
	Accuracy (%)	77.8	66.7	74.1	64.2
γwt	AUC/VUS	0.801	0.605	0.769	0.546
	Accuracy (%)	77.8	66.7	79.6	67.9
$\delta_{\rm WT}$	AUC/VUS	0.794	0.634	0.759	0.542
	Accuracy (%)	76.2	66.7	77.8	66.7

AUC: area under ROC curve. VUS: volume under surface. C: control group. MCI: mild cognitive impairment group. AD: Alzheimer's disease group.

WT_m (AUC = 0.801, TC_{CON} = 66.7%, TC_{AD} = 86.1%, accuracy of 77.8%) and γ_{WT} (AUC = 0.801, TC_{CON} = 77.8%, TC_{AD} = 77.8%, accuracy of 77.8%). However, the highest accuracy was obtained with WT (AUC = 0.794, TC_{CON} = 63.0%, TC_{AD} = 91.7%, accuracy of 79.4%). The classification analysis for MCI and AD groups showed that the highest AUC value was reached using WT_m (AUC = 0.776, TC_{MCI} = 72.2%, TC_{AD} = 80.6%, accuracy of 77.8%). The highest accuracy was achieved with γ_{WT} (AUC = 0.769, TC_{MCI} = 72.2%, TC_{AD} = 83.3%, accuracy of 79.6%). The highest AUC value when discriminating between controls and MCI subjects was obtained with IQR_{WT} (AUC = 0.667, TC_{CON} = 51.9%, TC_{MCI} = 88.9%, accuracy of 66.7%), whereas the highest accuracy was obtained using \overline{WT} (AUC = 0.626, TC_{CON} = 63.0%, TC_{MCI} = 77.8%, accuracy of 68.9%).

In a second step, the three-class ROC analysis indicated that the highest VUS value was reached using WT_m (VUS = 0.551, TC_{CON} = 63.0%, TC_{MCI} = 44.4%, TC_{AD} = 80.6%,



Figure 4. Sensor level topographic maps of the statistics computed from WT (mean, \overline{WT} ; mode, WT_m ; standard deviation, σ_{WT} ; interquartile range, IQR_{WT}; skewness, γ_{WT} ; and kurtosis, δ_{WT}) between controls and MCI subjects (C versus MCI), MCI subjects and AD patients (MCI versus AD), and controls and AD patients (C versus AD). Dots indicate sensors showing statistically significant differences (p < 0.05 corrected for multiple comparisons).

accuracy of 66.7%), though the highest accuracy was achieved with γ_{WT} (VUS = 0.546, TC_{CON} = 55.6%, TC_{MCI} = 83.3%, TC_{AD} = 55.6%, accuracy of 67.9%).

Figure 5 depicts the ROC surface and the ROC curves corresponding to WT_m (figures 5(a) and (b)). ROC curves coincide with the projections of the ROC surface on the sides of the unit cube.

5. Discussion

In this study, we investigated the neural dynamics associated with AD, as well as with the prodromal phase of the disease (i.e. MCI). A new parameter, WT, was calculated using a CWT decomposition to quantify the changes of WS over time in spontaneous MEG activity. Our findings suggest that



Figure 5. Results of the ROC analysis corresponding to WT_m . (a) Three-dimensional ROC surface (TC_{CON}: true class for controls; TC_{MCI}: true class for MCI subjects; TC_{AD}: true class for AD patients). (b) ROC curves assessing the pairwise classification (C versus AD: controls versus AD patients; C versus MCI: controls versus MCI subjects; MCI versus AD: MCI subjects versus AD patients). *X*- and *Y*-axes for the ROC curves have been labeled using different colors depending on the pairwise comparison.

dementia progression is accompanied by several alterations in WT statistics, which reflect abnormal behavior of neural dynamics in MCI and AD.

5.1. Dynamical properties of neural activity

Regarding the first research question, our findings support the notion that WT statistics provide an original description of neural dynamics. Measures of location, spread and shape have proven their utility to extend the concepts of irregularity and variability, as well as to study new properties of symmetry and non-Gaussianity. Measures of location showed that AD patients obtained significantly higher \overline{WT} and WT_m values than MCI subjects and healthy controls. Likewise, MCI subjects displayed higher \overline{WT} and WT_m values than controls. These findings provide direct evidence that MCI and AD are associated with a loss of irregularity in comparison with normal ageing, which is in agreement with previous studies that reported a loss of irregularity in MCI (Bruña et al 2012, Poza et al 2012) and AD (Fernández et al 2006a, Poza et al 2007, 2008a, 2008b). Nevertheless, these results should be analyzed from two different points of view. First, WT reflects a progressive increase of the average degree of similarity in WS over the course of AD. Indeed, \overline{WT} provides an estimate of the average irregularity in MEG activity. At the same time, it introduces an alternative definition of irregularity that is neither based on the distance to the spectral uniform distribution (like spectral entropies or disequilibrium measures) nor on the variability of patterns (like nonlinear entropies). Secondly, WT_m indicates an increase in the most frequent value of WT as AD progresses. Certainly, WT_m and \overline{WT} are related, though they do not necessarily agree. Accordingly, WT_m extends the concept of similarity introduced by \overline{WT} . More specifically, WT_m quantifies the most probable degree of similarity in WS, i.e. it provides an estimation of the prevailing irregularity in the MEG activity.

Measures of spread indicated that AD patients reached lower σ_{WT} and IQR_{WT} values than MCI subjects and controls,

though only statistically significant differences between AD patients and controls were found for IQR_{WT}. MCI subjects exhibited intermediate σ_{WT} and IQR_{WT} values in comparison to AD patients and controls. These findings support the notion that MCI and AD elicit a variability decrease in the MEG activity when compared to normal ageing, though other neurodegenerative disorders might also exhibit similar variability patterns. Likewise, these results are in line with those reported by two previous studies, which found preliminary evidence of a loss of variability in the spectral content of patients with dementia (Poza et al 2008a, 2012). Our findings extend the results of these investigations, since IQR_{WT} introduces a robust estimate of data variability. Consequently, IQR_{WT} is less dependent on outliers than σ_{WT} . This is an essential issue to accurately detect subtle fluctuations in the WT distribution due to an inherent change of data variability.

Measures of shape showed that AD patients reached statistically higher γ_{WT} and δ_{WT} values than MCI subjects and healthy controls. As in the case of measures of location, MCI subjects obtained higher γ_{WT} and δ_{WT} values than controls, but the differences were not statistically significant. Our findings provide evidence that both MCI and AD elicit considerable changes in the shape of WT histograms. Abnormalities in $\gamma_{\rm WT}$ and $\delta_{\rm WT}$ suggest that dementia progression can be associated with an increase in the asymmetry and peakedness of WT distribution, respectively. Interestingly, the lack of symmetry might be related to a decrease of homogeneity. Certainly, γ_{WT} suggests that the WT distribution is biased toward low values for MCI subjects and AD patients, so that their WT values are less homogeneously distributed than in the case of healthy controls. As outlined earlier in the text, kurtosis can also be used as a quantifier of the property of non-Gaussianity. Thereby, our findings provide preliminary evidence that, as dementia progresses, the WT distribution of the neural activity moves away from a Gaussian distribution.

In summary, changes in irregularity, variability, symmetry and Gaussianity reflect an alteration in fluctuations of brain dynamics. Our results lead to suppose that changes in the previous properties could help to distinguish incipient AD and normal ageing. Nevertheless, future research should be carried out to delimit the role of the proposed methodology as a candidate to obtain a clinical differential diagnosis. Furthermore, abnormalities in the structure of the WT distribution involve changes of time-varying properties of neural activity and, therefore, of transient information flow dynamics. In fact, mounting evidence suggests that different psychiatric disorders can be characterized in terms of different kinds of cognitive information flow instabilities (Rabinovich et al 2012). Similar ideas have been raised in previous MEG studies, posing the hypotheses that changes in entropy and complexity due to AD might be related to a loss of information content (Bruña et al 2012) and a decrease in information processing within the brain cortex (Poza et al 2008b).

5.2. Regional abnormalities in MCI and AD

The second research question addressed the issue of whether the changes in the MEG activity could reflect the regional abnormalities of MCI and AD. In fact, our findings revealed marked regional differences in WT statistics. Frontal and temporal lobes, mainly in the right hemisphere, appear to be early affected in MCI, though no significant differences were found between MCI subjects and controls. Certainly, the temporal lobe is predominantly affected at early stages of AD, which results in typical clinical symptoms like impairment in cognition (Hampel et al 2011). In line with our results, previous studies did not find significant differences in synapse counts and the number of diffuse plaques between MCI and healthy elderly subjects (Mufson et al 2012). Similar spatial patterns of abnormalities have also been reported in previous studies based on FDG-PET, which observed the AD-like hypometabolic pattern in several brain regions of MCI subjects, including the precuneus and temporo-parietal cortex (Ewers et al 2011). Brain atrophy has been observed using sMRI in the medial temporal lobe, posterior cingulated and orbitofrontal cortex of MCI subjects (Ewers et al 2011). Interestingly, progressive brain atrophy of hippocampus was found to be correlated with decreased cortical alpha power in a previous study that combined sMRI and EEG (Babiloni et al 2009).

Our results indicate that AD progression is followed by several changes in frontal and parieto-occipital regions, mainly in the left hemisphere. These results are in agreement with previous research suggesting that the frontal and parietal association cortices are progressively affected along with disease progression (Hampel et al 2011). Spread of AD beyond the temporal lobe is accompanied by increasing deficits in spatial orientation, attention, executive functions, working memory and language (Hampel et al 2011). Functional and cognitive impairment can be partly explained by the significant loss of synapses observed in milder AD patients compared to both normal and MCI subjects (Mufson et al 2012). In this regard, accumulating evidence consistently showed that early AD patients exhibit a significant increase in the number of neuritic plaques and neurofibrillary tangles in several brain regions in comparison to MCI subjects (Mufson et al 2012).

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Furthermore, AD has been widely related to brain atrophy on sMRI in several regions (including the lateral temporal, parietal and prefrontal lobes), impaired connectivity patterns using fMRI in the 'default mode network' and decreased FDG uptake on PET in temporo-parietal cortex (Ewers et al 2011, McKhann et al 2011, Sperling et al 2011). Neurophysiological studies support the regional-dependent cerebral dysfunction observed in AD. Thus, intramodular losses in the parietal cortex, a reduction in synchronization in the left frontotemporal area and a decrease in functional connectivity in the posterior cingulated cortex have been reported (de Haan et al 2012, Franciotti et al 2013, Knyazeva et al 2013). The results of the pairwise comparisons in the present research suggest that distinct brain structures are differentially affected during the course of the disease. Extensive evidence is in line with this result (Hampel et al 2012). AD is a complex disease that elicits a heterogeneous spatial pattern of abnormalities. Our findings support this idea and suggest that temporal cortices play an important role in incipient AD. In fact, some studies highlighted a link between normal ageing and AD-related abnormalities, specifically regarding beta-amyloid $(A\beta)$ deposition and brain atrophy in the temporal cortex (Ferrer 2012, Sperling et al 2011). Nevertheless, MCI subjects showed an overlapped distribution of biochemical, cognitive, structural and functional abnormalities when compared to elderly controls. Hence, sharp distinctions between normal cognition and MCI are difficult (Sperling et al 2011).

5.3. Multifaceted nature of AD dementia

Regarding the last research question, we put forth the idea of whether the proposed methodology could be useful to account for the complexity of AD and to provide further insights into the underlying brain dynamics of this condition. Accumulating scientific evidence proposes that A β plaques deposition in the brain is a distinctive early lesion in the cascade of events leading to clinical impairment in AD. Abnormal changes in the A β metabolism result in altered cholinergic activity and subsequent neural degeneration (Hampel et al 2011). Nevertheless, there is lack of consensus about whether or not cholinergic deficits are an early or late feature of AD. Some studies suggest the hypothesis that these changes may be only detectable in specific brain regions (Mufson et al 2012). Certainly, AD etiology still remains unclear. The complex nature of prodromal AD suggests that disruption of $A\beta$ metabolism can be one among other important mechanisms underlying neuronal dysfunction (Hampel et al 2012). Emerging evidence points out that diverse factors, including synaptic, mitochondrial, metabolic, inflammatory, neuronal, cytoskeletal and other age-related changes, could be involved in the onset of neuronal degeneration (Mufson et al 2012, Sperling et al 2011). Neuroimaging techniques, such as MEG, provide further insights into the mechanisms of neural functions. Accordingly, they can be useful to understand dynamical processes involved in the regulation of complex functional brain systems. It should be stressed that neural injury, including damage in synaptic function and integrity of neurons, appears to be an early lesion in dementia (Hampel

et al 2012, Sperling *et al* 2011). Hence, MEG becomes a promising tool to understand the incipient changes of brain dynamics in AD.

An accurate characterization of MCI is crucial for early AD detection. Our results suggest that neural dynamics are significantly different in MCI and AD. Normal ageing and MCI exhibit an overlapped distribution of abnormalities, but some differences between controls and MCI subjects can be found. Hence, MCI displays intermediate changes in the MEG activity between those observed in normal ageing and AD. Our classification results support these ideas. The highest accuracy of 79.4% was reached when discriminating between AD patients and controls, whereas a maximum value of 68.9% was obtained when classifying MCI subjects and controls. Similar classification statistics were reported by previous MEG studies, which reached accuracies around 80% in the distinction between AD patients and controls (Bruña et al 2012, Escudero et al 2011, Fernández et al 2006a, Poza et al 2008b, Stam 2010), and around 65% when discriminating between MCI subjects and controls (Bruña et al 2012, Escudero et al 2011, Fernández et al 2006a, 2010, Gómez et al 2009). Furthermore, it is worth noting that the highest three-class accuracy was 67.9%. A plausible explanation for the relatively low classification statistics, as well as the similar WT statistics in MCI subjects and controls, could be the moderately low alteration in the neural dynamics associated with MCI. Our findings showed that regional patterns of abnormalities in WT statistics are generally in line with the results reported in other studies, which applied diverse techniques (de Haan et al 2012, Ewers et al 2011, Ferrer 2012, Franciotti et al 2013, Hampel et al 2011, Knyazeva et al 2013, Mufson et al 2012). They support the notion that MEG might be differentially sensitive to changes in brain dynamics at different stages of AD. Therefore, the proposed methodology based on WT provides valuable insights into the underlying brain dynamics associated with MCI and AD. Certainly, studies using other neuroimaging techniques, such as MRI and PET, obtained sensitivity and specificity values higher than 90% (Ewers et al 2011, Hampel et al 2011). They are considered as potential candidates to establish core biomarkers for the detection of AD; however, their inclusion for routine diagnostic purposes is still not recommended (McKhann et al 2011). In order to reach an accurate detection of AD, diverse studies acknowledge that a strategy for integrating different markers of AD pathophysiology is needed (Ewers et al 2011, Hampel et al 2012). The predictive value of multimodal neuroimaging is then brought in focus, due to the ability to detect structural and functional changes in the brain (e.g. sMRI, fMRI and FDG-PET) and provide a direct measure of the neural function (e.g. EEG and MEG) (Ewers et al 2011, Sperling *et al* 2011).

5.4. Limitations of the study and future research lines

Finally, further consideration should be devoted to several methodological and clinical issues. First, the time-scale analysis was based on the CWT using a real Morlet wavelet, though there are diverse 'mother wavelets' and time-scale representations that could also be considered. In a previous study, an analogous parameter to WT based on the STFT, named the spectral turbulence, was used to analyze global irregularity patterns in AD brain dynamics (Poza et al 2008a). The reported results are in agreement with the present findings, indicating a global decrease in irregularity of MEG activity due to dementia progression. Nevertheless, wavelet analysis is better suited than Fourier transform for non-stationary data. In this regard, the Morlet wavelet provides easily interpretable results in the time-scale domain, as well as qualitatively similar data to those obtained using a Fourier-based analysis. As a consequence, both real- and complex-valued Morlet wavelets (Ghuman et al 2011, Poza et al 2012) have been previously applied to describe brain dynamics. In this study, the realvalued Morlet was selected on the basis of previous research (Poza et al 2012). Nevertheless, further efforts should be carried out to analyze the role of real- and complex-valued wavelets in the characterization of MEG.

WT computation was based on the Kendall correlation. Nevertheless, other nonlinear association measures might also be considered, such as mutual information, statistical distances or divergences, among others. Further efforts should be devoted to analyzing the influence of the association measure on the description of time-varying WS properties. Furthermore, as previously indicated, WT was computed considering the entire frequency range from 1 to 70 Hz. Nevertheless, future studies should address the characterization of WT in different frequency bands to further analyze the frequency-dependent patterns associated with this parameter.

The diagnostic ability of WT statistics averaged over sensors was assessed by means of two- and three-class ROC analyses. Future studies should analyze whether the application of more sophisticated classification methodologies can be helpful to increase the classification performance. Likewise, it would be interesting to study whether different WT statistics and their spatial patterns could provide complementary information useful to improve classification statistics.

There is another important issue concerning the cohort of subjects enrolled in the study. Our research focused on analyzing brain activity at different stages of AD. However, other forms of dementia may also elicit similar abnormalities in neural dynamics. Further studies should be aimed at assessing whether the proposed methodology might be differentially sensitive to changes in the MEG activity due to diverse neurodegenerative dementias affecting the brain, such as Lewy body dementia, vascular dementia, fronto-temporal dementia or dementia associated with Parkinson's disease. In connection with the previous concern, it would be appropriate to increase the number of MCI subjects. The multifaceted nature of MCI involves that heterogeneous populations can be recruited across studies (Ward et al 2012). Consequently, longitudinal analyses should be carried out to account for the clinical MCI heterogeneity. They would be useful to characterize the brain patterns of subjects with stable MCI and those who later progress to AD, as well as to delimitate the differential utility of biomarkers given the diverse timing of progression to dementia (Sperling et al 2011).

6. Conclusions

WT statistics extend the concepts of irregularity and variability, and provide original insights into the characterization of time-varying signals, in terms of the properties of symmetry and non-Gaussianity. The proposed methodology has proven useful in addressing several dynamical aspects of neural activity, which may lead to a better understanding of incipient brain abnormalities in AD. Specifically, our findings support the notion that MCI and AD elicit several changes in MEG activity, including a progressive loss of irregularity, variability, symmetry and Gaussianity in the distribution of WT values. In this regard, our results suggest that WT changes in prodromal AD (i.e. MCI) could be early indicators of a subsequent neural dysfunction leading to AD.

Further studies will address the role of complex-valued wavelets to describe neural dynamics in MCI and AD. Moreover, future efforts will be devoted to analyzing whether WT statistics can be useful to differentially describe brain dynamics in other neurodegenerative disorders.

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