# Improving the specificity of EEG for diagnosing Alzheimer's disease

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## Abstract

**Objective**: EEG has great potential as a cost-effective screening tool for Alzheimer's disease (AD). However, the specificity of EEG is not yet sufficient to be used in clinical practice. In an earlier study, we presented preliminary results suggesting improved specificity of EEG to early stages of Alzheimer's disease. The key to this improvement is a new method for extracting sparse oscillatory events from EEG signals in the time-frequency domain. Here we provide a more detailed analysis, demonstrating improved EEG specificity for clinical screening of MCI (mild cognitive impairment) patients.

**Methods**: EEG data was recorded of MCI patients and age-matched control subjects, in rest condition with eyes closed. EEG frequency bands of interest were θ (3.5-7.5 Hz), $\alpha_1$ (7.5-9.5 Hz), $\alpha_2$ (9.5-12.5 Hz), and β (12.5-25 Hz). The EEG signals were transformed in

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the time-frequency domain using complex Morlet wavelets; the resulting time-frequency maps are represented by sparse bump models.

**Results:** Enhanced EEG power in the θ range is more easily detected through sparse bump modeling; this phenomenon explains the improved EEG specificity obtained in our previous studies.

**Conclusions:** Sparse bump modeling yields informative features in EEG signal. These features increase the specificity of EEG for diagnosing AD.

**Keywords**: Alzheimer's disease, EEG, screening, time-frequency, sparse bump modeling

# 1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder; one of its earliest signs is progressive memory loss. Since the number of individuals with AD is expected to increase considerably in the near future (Hebert et al. 2004; Wimo et al., 2003, see Figure 1), reliable treatment and diagnosis of AD are critical. Many approaches to treatment are currently being investigated (Roberson and Mucke, 2006; Goedert and Spillantini, 2006). A clinical diagnosis accuracy of approximately 85% of detection rate is commonly achieved, by a procedure of exclusion after structural or functional imaging tests – including quantitative electroencephalography (QEEG), laboratory and psychometric tests (Knott et al. 2001).

QEEG recordings of subjects in resting condition and with eyes closed are conventionally used in daily clinical routine as a diagnostic tool for AD (Besthorn et al. 1997; Leuchter et al. 1993; van der Hiele et al. 2007). The main advantage of QEEG is its low cost and its mobility. Several studies have demonstrated that QEEG is useful for investigating Alzheimer's disease (AD) (Babiloni et al. 2004; Brinkmeyer et al. 2004; Jelic et al. 1996, Kowalski et al. 2001, Kwak 2006; Leuchter et al., 1993; Nobili et al. 1999; Rodriguez et al. 1998). Topographical EEG power changes are believed to reflect early signs of cortical atrophy and/or compensatory cortical reorganization during the early stages of the disease (Hogan et al. 2003). More specifically, it is commonly believed that AD induces enhanced mean power of slow rhythms (0.5-8 Hz), and loss of fast (8-30 Hz) rhythms (Babiloni et al., 2004; Besthorn et al., 1997; Jelic et al. 1996, Jeong 2004; Dierks

et al., 1993). In the EEG of healthy subjects, recorded in resting condition with closed eyes, alpha rhythms are usually mostly distributed in the occipital area; in AD patients, the alpha rythms increasingly relocate towards anterior areas as the disease progresses (Babiloni et al., 2004, Claus et al.,1998; Ihl et al., 1996).

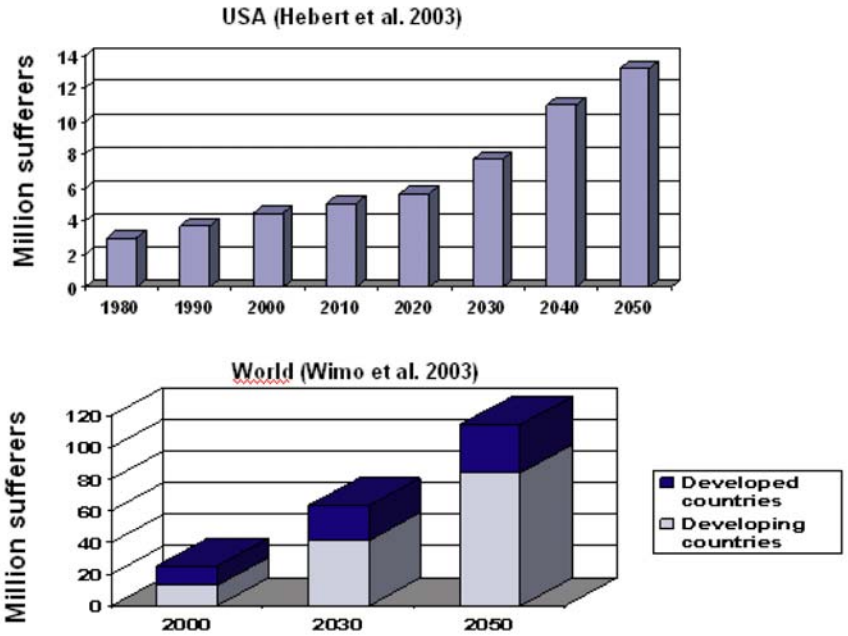


**Figure 1: Projection of the prevalence of AD and dementia in the near future. Illustration based on demographic estimates of Hebert et al. 2003 (projection of AD prevalence in USA) and Wimo et al. 2003 (projection of AD prevalence worldwide).**

More precisely, these effects have been shown to correlate with severity of AD expressed by mini mental state evaluation (MMSE, Rodriguez et al. 1998) and, more recently, with clinical dementia rating scale (CDR, Kwak, 2006).

Early stages of AD have been associated with an increase of theta activity and/or a decrease of alpha activity. In more severe stages of AD, an increase in both theta and delta activity has been observed, together with activity decrease in both alpha and beta frequency bands, in addition to a reduction in peak alpha frequency (Knott et al. 2001, Kwak, 2006).

Since EEG could be used as a cost-effective screening tool for early detection and diagnosis of the MCI stage (see Figure 2), it may change the objectives of treatment: if AD could be reliably diagnosed in an early stage, medical treatments would, instead of

being palliative, become curative: they may be used to delay or, hopefully, even bring the disease progress to a hault. However, EEG is not yet considered as a reliable diagnostic tool, because of its lack of specificity (Scinto, Daffner, 2000).

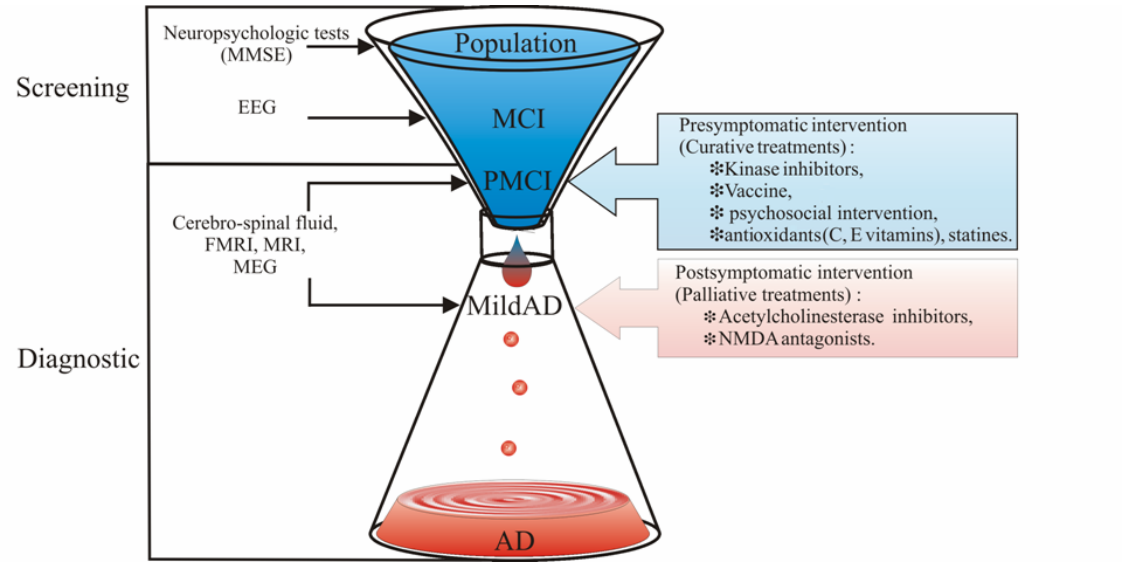


**Figure 2: EEG may be used as a screening tool for early-stage AD, since EEG recording technology is inexpensive and available in most hospitals. At an early stage of AD, presymptomatic interventions (curative treatments) may be investigated. However, EEG is not yet a reliable diagnostic tool: the specificity of EEG needs to be improved.**

Our long-term research objective is to develop signal processing methods that improve EEG specificity for diagnosing AD; we wish to discover EEG signal features that not only significantly differ in AD patients, but also allow us to reliably separate AD patients and control subjects. This approach is valuable for clinical purposes (as diagnostic tool for AD), and it also more fundamentally contributes to a better understanding of brain dynamics of AD patients. In this paper, we focus on time-frequency representations of EEG signals, which will enable us to extract EEG features that improve the specificity of EEG for diagnosing AD.

## 2. Methods

Most often clinical EEG of AD patients is analyzed either in time domain or in frequency domain (Fourier power analysis). However, those standard approaches entirely ignore the fact that EEG is mainly a non-stationary signal, i.e., the statistics of brain

rhythms evolve in time. Both signal domains, i.e., time domain and frequency domain, may be exploited simultaneously: instead of studying either time or frequency separately, we extract time-frequency information (Figure 3). This is possible through time-frequency representations, such as windowed Fourier transforms, or the more recently proposed wavelet time-frequency representations (WTFR). However, WTFR describe signals by means of thousands of coefficients. The information is distributed over those many coefficients and as a result, the coefficients cannot be used directly as signal features; therefore, additional processing is required before discriminative analysis can be carried out. In our previous work (Vialatte, et al., 2005), we extracted signal features from time-frequency maps by means of sparse bump models; those models consist of time-frequency patterns ("bumps") of high magnitude, lasting nearly 4 time periods centered at a specific frequency. Those patterns are likely to be representative of transient local synchronization of neuronal assemblies, conveying key information on higher order cognitive and sensory processing. The bump modeling approach allows us to capture oscillatory events in EEG on a trial-by-trial basis, which in turn me be considered as reliable characteristic signatures in LFP and EEG signals (Vialatte, et al., 2007; Vialatte, et al., 2009a). We hypothesize that those signatures contain significant EEG information about brain disorders such as AD.

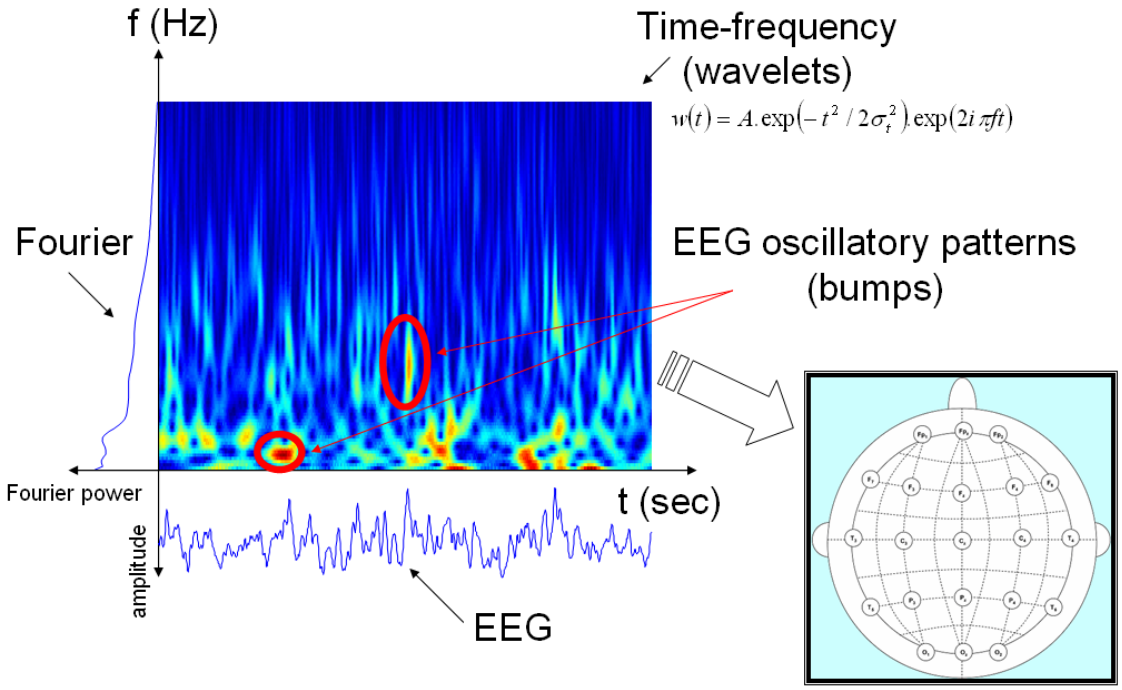


**Figure 3: Possible approaches to study EEG brain dynamics. From the time-domain EEG signals, spectral information, in frequency or time-frequency domain (including EEG time-frequency patterns), may be extracted. Afterwards, the spatial information is taken into account, through QEEG or synchrony measures.**

Computations were performed using Matlab 7.0 (The MathWorks, Inc.). Statistical analysis was performed using Sigmastat 3.5 (Systat software, Inc.). Wavelet analysis and time-frequency sparsification were performed using the ButIf Toolbox (Vialatte et al. 2007; Vialatte et al. 2008b; Vialatte et al. 2009c).

## *2.1. Subjects*

We used here a database with 22 patients in the early stage of Alzheimer's disease (mild cognitive impairment or MCI) and 38 control subjects. In the course of the clinical study, EEG was recorded in rest condition with closed eyes (under vigilance control), by 21 Ag/AgCl electrodes (disks of diameter 8mm), arranged according to the 10-20 international system. The EEG data was investigated by an EEG expert for artifacts, and sufficiently clean EEG segments of 20s were selected (on each of the 21 channels). Subject with less than 20 sec artifact-clean data were rejected, reducing their number to 22 and 38, respectively.

EEG was recorded with Biotop 6R12 (NEC San-ei, Tokyo, Japan) at a sampling rate of 200Hz with analog bandpass filtering in the frequency range 0.5-250Hz; the signals were then digitally bandpass filtered between 4 and 30Hz by a third-order Butterworth filter. The subjects comprised two study groups; the first group consists of 25 subjects who complained of memory problems. At the time of the EEG recordings, these subjects were diagnosed with mild cognitive impairment (MCI). Later on, they all developed mild AD. The average mini mental state exam (MMSE) score in the MCI group was 26 (SD of 1.8).

The other group consists of 56 age-matched healthy subjects who had no memory or other cognitive impairments. The average MMSE of this control group was 28.5 (SD of 1.6). The ages of the two groups were 71.9 ± 10.2 and 71.7 ± 8.3, respectively. The EEG data used here have been analyzed in previous studies (Musha, et al., 2002; Vialatte, et al., 2005; Cichocki, et al., 2005; Woon, et al., 2007; Dauwels, et al. 2009).

## 2.2. Time-frequency spectral analysis

Wavelet time-frequency maps are computed using complex Morlet wavelets. The (continuous) wavelet transform **W** of a time series **x** is obtained as:

$$\mathbf{W}(k,s) \stackrel{\Delta}{=} \sum_{l} \mathbf{x}(l)\psi^{*}\left(\frac{l-k}{s}\right),$$

where $\psi(k)$ is the (complex) "mother" wavelet, $s$ is a scaling factor, and * stands for complex conjugate. In this paper, we use the complex Morlet wavelet:

$$\psi(k) = A.\exp\left(\frac{-k^2}{2\sigma_t^2}\right).\exp(2i\pi f_0 k),$$

where $\sigma_t^2$ and $f_0$ jointly determine the number of oscillations in the wavelet. The complex Morlet wavelet results in the optimal resolution in time and frequency; it has also proven to be well-suited for EEG signals (Tallon-Baudry, et al., 1996; Ohara, et al., 2004; Herrmann, Grigutsch, and Busch, 2005; Chen, et al., 2007; Vialatte et al. 2008a; Vialatte et al. 2009b; see also Le Van Quyen, and Bragin, 2007 for review).

As a benchmark for the approach based on sparse time-frequency bump models (see below), we computed statistics directly from the WTFR. In particular, we computed WTFR relative power in four different frequency bands, i.e., θ (3.5-7.5 Hz), $\alpha_1$ (7.5-9.5 Hz), $\alpha_2$ (9.5-12.5 Hz), and β (12.5-25 Hz). We conducted linear discriminant analysis (LDA) with as features the relative power in those 4 frequency bands.

### 2.3. Sparsification

Next we extract oscillatory events ("bumps") from the time-frequency maps (Figure 4). Those oscillatory events are generally believed to be due to local synchrony of neural populations in the vicinity of the recording electrode (Le Van Quyen, and Bragin, 2007). We extract oscillatory bursts ("bumps") by sparse bump modeling (Vialatte, et al., 2007; Dauwels, et al., 2009; Vialatte, et al., 2008b; Vialatte, et al., 2009a; Vialatte, et al., 2009c). More specifically, we used the ButIf toolbox, developed in earlier work (Figure 4, Vialatte, et al., 2008b; Vialatte, et al., 2009c). We now describe this procedure in more detail.

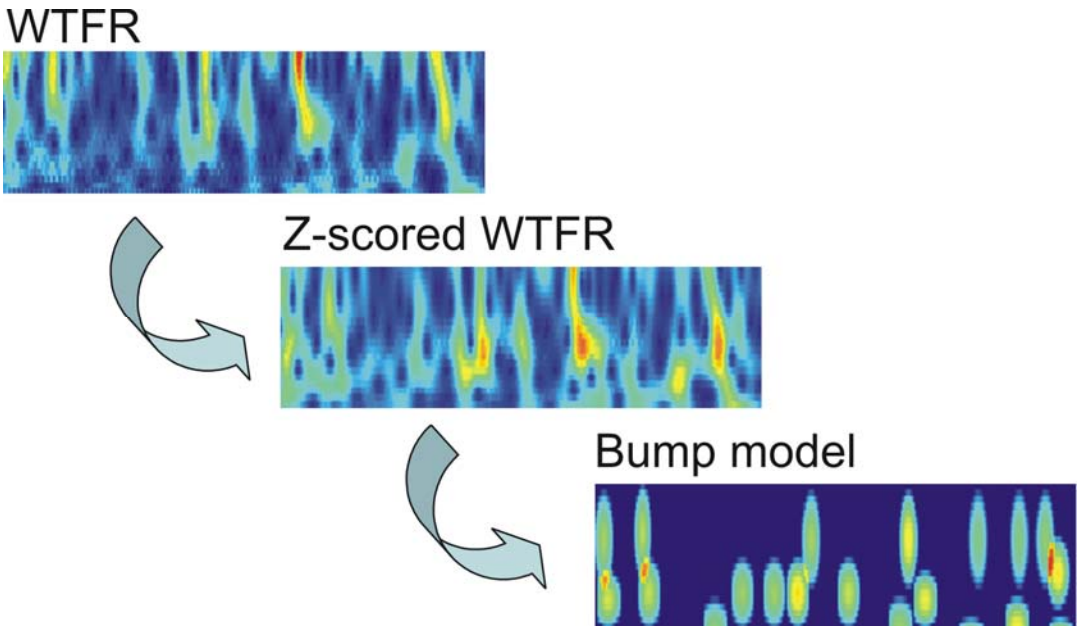


**Figure 4: from wavelet time-frequency representation (WTFR) to a sparse time-frequency bump model.**

Frequency dependent z-score normalization (Browne, and Cutmore, 2004; Vialatte et al., 2008c) was applied to each trial:

$$\mathbf{z}(f,t) = \frac{\mathbf{W}(f,t) - \mu_f}{\sigma_f},$$

where $\mu_f$ and $\sigma_f$ are the mean and standard deviation respectively of the wavelet map **W,** computed over the pre-stimulus period at frequency *f*. The resulting z-score maps $\mathbf{z}(f,t)$ are approximated by bump models $z_{bump}$ , which are sequences of basis functions *b* ( "bumps" ) with parameters $\theta_k$ (for more details about bump modeling, see Vialatte, et al., 2007):

$$\mathbf{z}(f,t) \approx \mathbf{z_{bump}}(\theta) = \sum_{k=1}^{N_b} b(\theta_k),$$

with $\theta = (\theta_1, \theta_2, \ldots, \theta_{N_b})$. This decomposition represents the most salient oscillatory events in the z-scored map $\mathbf{z}(f,t)$. As pointed out earlier, we hypothesize that those events are characteristic for EEG dynamics, and are therefore relevant for diagnosing AD. We used half ellipsoid basis functions *b*, and the parameters $\theta_k$ are vectors of five parameters: position in time and frequency, width in time and frequency, and amplitude. We computed the number of bumps in four different frequency bands, i.e., θ (3.5-7.5 Hz), $\alpha_1$ (7.5-9.5 Hz), $\alpha_2$ (9.5-12.5 Hz), and β (12.5-25 Hz). We conducted linear discriminant analysis (LDA) with as features the number of bumps in those 4 frequency bands.

## 3. Results and Discussion

In an earlier preliminary study, we observed that bump modeling leads to improved classification results (80-93% classification using leave-one-out classification, see Vialatte et al., 2005), compared to approaches based on WTFR directly, without bump modeling (70% classification).

We report here results of a more detailed study, which considers 4 separate frequency bands; so far, we had only considered the frequency band 4-30 Hz (Vialatte et al., 2005). We found significant differences in the theta and beta range (Mann-Whitney test, $p<0.01$). We compared the WTFR relative power in all four frequency ranges, before and after bump processing (Figure 5). The difference in theta range was enhanced by bump

modeling ($p=10^{-4}$ instead of 0.08), while the beta range difference was reduced but remained significant. The improvement of classification observed in Vialatte et al. 2005 is therefore mostly attributed to enhanced separation of EEG activity in the theta range.

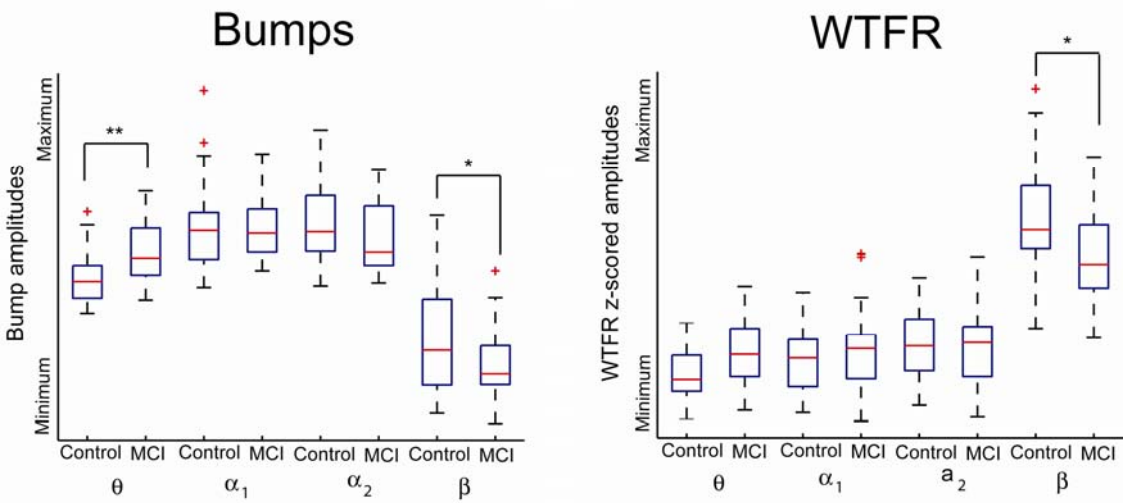


**Figure 5: Boxplot comparison of the time-frequency activity between the z-scored time-frequency representation, and its sparse bump representation. The center line is the median, the box represents the box represents the inter-quartile range, whiskers represent non-outlier observations, cross indicate outliers. * and ** indicates significant ($p < 0.01$) and very significant ($p<0.001$) differences.**

## 4. Conclusion

This paper investigates EEG features for diagnosing AD at an early stage. We observed that bump modeling enhances the statistical differences in EEG activity in the theta range between healthy subjects and MCI patients. This observation may explain the improved classification results by bump modeling, reported in Vialatte et al. 2005. This effect is also consistent with the existing literature on Alzheimer's disease: low frequency activity (0.5-8 Hz) is generally stronger for patients with AD, while the amplitude of higher frequencies (8-30 Hz) is generally decreased in AD patients (Babiloni et al., 2004; Besthorn et al., 1997; Jelic et al. 1996, Jeong 2004; Dierks et al., 1993). An increase of the theta range activity in the early stages of AD has often been demonstrated (Knott et al. 2001, Kwak, 2006), and this effect was indeed already visible using Fourier spectral analysis or WTFR, without bump modeling. However, bump modeling amplifies this effect, at least for the EEG data set at hand,

Oscillatory neuronal networks, as a model for brain dynamics, provide a unique interdisciplinary platform to study neurocognitive dynamics (Rojas-Líbano, Kay, 2008). The analysis of EEG data, though of high relevance in cognitive research, poses a number of technical challenges as EEG signals are clearly stochastic and highly non-stationary (Schinkel et al., 2007). The structural organization and associated functional role of EEG oscillations are still far from being completely understood.

In this paper we investigated the specificity of EEG oscillatory bursts as neural correlates of early-stage Alzheimer's disease. Whereas most studies focus on averaged EEG responses in time or frequency, this study considers oscillatory events in the time-frequency domain, without relying on EEG averages. We observed that these organized oscillatory events contain stronger discriminative signatures of the early stage of Alzheimer's disease than averaged spectral EEG statistics, which also explains our previously obtained classification results (Vialatte et al., 2005). Our results suggest that the effect of enhanced low-frequency activity in AD patients may be primarily due to more frequent time-frequency events.

We speculate that those slow-wave oscillatory events may be caused by sub-cortical damage, induced in the early stage of Alzheimer's disease (Helkala, et al., 1996; Fernández, et al., 2003). Background activity in EEG is mostly attributed to cortical neural events; on the other hand, the oscillatory bursts, generated by locally synchronous neural populations, could be related to inter-area connections, including sub-cortical areas. Indeed, low-frequency synchrony is probably representative of sub-cortical connectivity (Uhlhaas and Singer, 2006). Our results would then attribute the increase of slow wave activity as a probable correlate of sub-cortical damage induced in the early stage of Alzheimer's disease.

As we have shown recently (Vialatte, et al., 2009a), organized oscillatory bursts in EEG time-frequency activity seem to play a functional role in steady state visual evoked potentials, distinct from the more stationary ongoing EEG activity (activity not organized in bursts, representing 70-80% of the signal). We here provide additional evidence in favor of hypothesis that EEG background activity and EEG peak oscillatory activities, which can be retrieved by bump modeling (Vialatte et al., 2009c), play separate functional roles. This observation is consistent with the interpretation of time-frequency

oscillatory events as signatures of locally synchronous neural populations. As a consequence, both background EEG and oscillatory EEG bursts may be highly relevant for understanding and diagnosing brain disorders, including Alzheimer's disease.

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