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Original articles

Nonlinear analysis of brain magnetoencephalographic activity in Alzheimer disease patients

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Abstract

Objectives : Non-linear analysis was applied on MEG signals of Alzheimer Disease (AD) patients in order to investigate the underlying complexity of the brain dynamics.

Materials & methods : A Single channel SQUID was used to record the MEG signals in 9 AD patients and 5 normal individuals. The magnetic activity, for each patient, was recorded from a total of 64 points of the skull (32 points from each temporal lobe). Nonlinear analysis was applied in the abnormal MEG points of the brain.

Results : In AD patients some recorded points were found with high amplitudes and low frequencies in magnetic activity. By applying nonlinear analysis in these records low values in the correlation dimension D of the reconstructed phase space were found.

Conclusions : SQUID obtained MEG signaling from brains of AD patients showed a lower complexity compared to the brain of normal subjects.

Key words : Alzheimer Disease ; chaos ; MEG.

Introduction

Using Magnetoencephalographic (MEG) measurements we recorded the brain activity from patients who were suffering from Alzheimer disease (AD). In these recordings we used the biomagnetometer SQUID (Superconductive Quantum Interference Device) which can detect the magnetic fields emitted from the brain. The magnetic activity of the brain is produced by cellular microcurrents, which emerge from ionic movements, due to the dynamical variations of the neural membrane potentials. Such magnetic fields emitted from the brain are very weak (of the order of pT = 10^{-12} T) and only SQUID can detect and record these fields (SQUID has the ability to detect magnetic fields of the order of 10^{-15} T (= 1fT)).

Some clinical, as well as, theoretical studies, which have been published in the previous decade, have shown that the MEG method presents a number of very important and crucial advantages compared to the EEG (electroencephalogram) method (3, 4, 21, 30). More recent studies (8, 9, 10, 19, 20, 23, 28, 35), have proved the equivalent accuracy of the two techniques and that they are complementary.

Although the importance of MEG recordings in the investigation of normal and pathological conditions of the brain (and especially in the study of epileptic phenomena), has been noticed by several authors (1, 2, 3, 4, 12, 29), this methodology was also applied on Alzheimer's disease (AD) patients (5, 25-27). We detected abnormal brain magnetic activity, which exhibited high amplitudes and rhythmicity.

According to the theory of nonlinear dynamical systems and chaos (14, 15) the dynamics of any physical or biological system can be quantified and described by means of some new terms and concepts, such as the strange or chaotic attractor, the correlation dimension of the reconstructed phase space, the Lyapunov exponents and so on. These concepts reflect some geometrical properties of the reconstructed phase space of the dynamical system under consideration and it can be extracted. Of vital importance in the chaotic analysis of a dynamical system is the evidence for the existence of low dimension chaotic attractors and the estimation of the correlation dimension D of the attractor. In the present work the MEG time-series of the cortical magnetic activity of patients suffering from AD were recorded. In order to investigate for the existence of low dimensional strange attractors and to estimate the corresponding correlation dimension D the Grassberger-Procaccia algorithm (14, 15) was applied on the experimental time-series.

Material & methods

2.1. Patients and Recordings

AD patients were referred to the Laboratory of Medical Physics in Alexandroupolis, Greece, by practising neurologists. All patients had been diagnosed by the referral neurologists independently to suffer from Alzheimer disease. The age of patients ranged from 55 to 72 years (mean = 65.2, SD = 6.3). Furthermore, the clinical symptomatology of

AD patients included moderate memory disturbances, speaking and communication difficulties and orientation disorders (estimated abbreviated mental test score range 3-5). Whereas, all the control population are free of the above mention clinical symptomatology. The onset of symptomatology of AD patients ranged from 1 to 4 years before examination. In all cases informed consent for the methodology and the aim of the study was obtained from all patients prior to the procedure. The SQUID examination of patients has been approved by the local hospital authorities.

Biomagnetic measurements were performed using a second order gradiometer SQUID model 601 of the Biomagnetic Technologies Inc., which was located in an electrically shielded room. The noise level of the environment was of the order of 50 $fT/\sqrt{Hz}$. During the recording procedure the patients were relaxed lying on a wooden bed, with closed eyes, in order to avoid artefacts from eye flickering. The MEG recordings were performed after positioning the SQUID sensor 3 mm above the scalp of the patient, with the use of an optic positioning system.

The MEG measurements consisted of data recorded from the scalp of each patient at specified points as defined by a recording reference system. This reference system is based on the International 10-20 Electrode Placement System (17) which uses any one of the standard EEG recording positions as its origin (4). In this study we used the P3, P4, T3, T4, F3 and F4 recording positions. The reference system was devised to retrieve maximal information from a specified area of the skull given that the gradiometer coil is theoretically equally sensitive to all magnetic flux lines perpendicular to a circular area of the brain. In our case, this circle has an effective diameter of 2.36 cm, i.e., the diameter of the SQUID sensor coil. Around the origin (T3 or T4 for temporal lobes) a rectangular 32-point matrix was used (4 rows $\times$ 8 columns, equidistantly spaced in a 4.5 cm $\times$ 10.5 cm rectangle) for positioning of the SQUID (4) (Fig. 1).

The MEG was recorded from each cerebral hemisphere at each of the 32 matrix points on the scalp for 32 consecutive epochs. Each epoch was of 1 sec duration and was digitized with a sampling frequency of 256 Hz (frequency resolution of the power spectrum being 1 Hz). The MEG signal was band-pass filtered with cut-off frequencies of 0.1 and 60 Hz. The MEG recordings were digitized at 256 Hz using a 12 bit precision analog to digital converter and were stored in memory for off-line Fourier statistical analysis, and averaged amplitude spectra were calculated for each sampling position.

2.2. Data analysis

We applied nonlinear analysis to the MEG recorded from the AD patients. The nonlinear

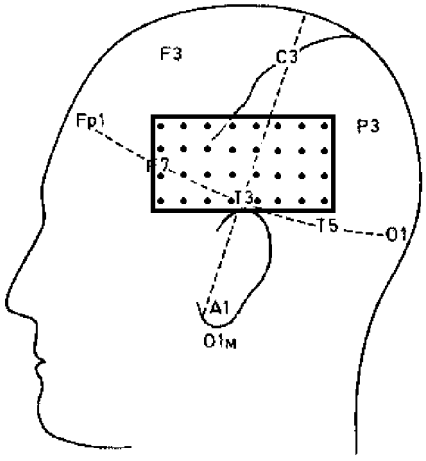

FIG. 1. — This figure is showing the 10-20 International Point System the points of which are served as origin in our rectangular reference system.

analysis is a powerful technique for the estimation of the dimension of the strange attractor which characterizes the MEG time series obtained from normal and AD patients. For the estimation of the dimension of the strange attractor we have considered the method proposed by Grassberger and Procaccia (15) which is based on the Theorem of the reconstruction of the phase space introduced by Takens (33).

Then, according to their method, the dynamics of the system under consideration can experimentally reconstructed from the observed time series of a single observable dynamic component, as it is in our case MEG. Thus, for the discrete time series $B_i = B(t_i)$ (i = 1,2...N) of the MEG, which is measured experimentally by the SQUID, the vector construction of V_i is given by the following equation :

$$V_i = \{B_i, B_{i+T}, ..., B_{i+(m-1)T}\} \quad (1)$$

This equation gives a smooth embedding of the dynamics in a m-dimensional phase space, and the resulting phase trajectory in the phase space, is topological equivalent to the original phase space. The reconstruction time T, is a suitable delay parameter, which may be chosen arbitrary, but it is usually taken to be equal to the decorrelation time of the MEG signal, i.e. the first zero crossing of the autocorrelation time of the signal. If the dynamics of the system under consideration is chaotic, the evolution of the system in the phase space, once transients die out, settles on a submanifold which is a fractal set, the strange attractor.

The concern of the strange attractors is of a great importance in chaotic dynamics, since its existence or absence is related to the behavior of the system as chaotic or deterministic.

If a strange attractor exists, it can be described by a geometrical parameter the correlation of fractal dimension D.

This parameter is related to the number of variables required to define the attractor within the phase space.

According to the method proposed by Grassberger and Procaccia (22), D can be estimated from an experimental time series by means of the correlation integrals C(r, m) defined as :

$$C(r, m) = \lim_{n\to\infty}(n(n-1)/2)^{-1}\sum_{\substack{i=1\\ i\neq j}}^{n-1}\sum_{j=1+i}^{n}\theta\,(r-|V_i-V_j|) \quad (2)$$

where (⊙(u) is the Heaviside function defined as (⊙(u) = 1 for u > 0 and ⊙(u) = 0 for u ≤ 0), m is the embedding dimension and n is the number of vectors constructed from a time series with N samples, given by the formula n = N-(m-1)τ (here τ is a delay parameter which is equal to the first zero crossing of the autocorrelation time of the MEG signal). The correlation integral C(r, m) measures the spatial correlation of the points on the attractor and it is calculated for different values of r in the range from 0 to r_{max} . The r_{max} is equal to $(m)^{1/2}$ (x_{max}-x_{min}), (assuming that x_{max} and x_{min} are the maximum and the minimum recorded values in the time series). For a chaotic system the correlation integrals should scale as $C(r, m) \sim r^{D(m)}$. Thus, the correlation dimension D of the attracting submanifold in the reconstruction phase space is given by :

$$D = \lim_{\substack{r\to 0\\ m\to\infty}} \partial(\ln C(r, m))/\partial(\ln(r)) \quad (3)$$

In the case of a chaotic signal exhibiting a strange attractor, there is a saturation value, (plateau) in the graph of the slopes ∂ (lnC(r, m)) / ∂ (ln(r)) vs ln(r). This value remains constant, although the signal is embedded in successively higher-dimensioned phase spaces and gives an estimation of the correlation dimension of the attractor.

Recording the MEG activity over the scalp in the case where the measurements are independent for each position (one-channel SQUID) requires that the MEG activity remains invariant in time. In order to ensure that the MEG activity was not influenced by long-term variations, we repeated the recordings at various positions at different times and found that there was very little difference in the measurements as such as 60 minutes apart during the experiments because there was a constancy in the D values. Thus the stability of MEG measurements in patients with CNS disorders justified in our view the use of a one-channel SQUID.

Using the above described method the correlation dimension D of the MEG time series for AD patients was estimated for the magnetic activity recorded from the AD patients and normal individuals using SQUID technology.

The purpose of this estimation was to investigate whether there is any biological differentiation in the dynamics in these two types of magnetic activities.

Table I

The correlation dimension of 9 patients with Alzheimer Disease

Subjects	Age	Correlation dimension
Women	69	9.7
	67	9
	72	9.9
	62	10.8
	55	11
	56	10
Men	66	10.1
	68	9.7
	72	10

Results

In 9 AD patients examined the mean value of D was 10.02 with standard deviation 0.59 (D-range 9 to 11 as it is indicated in Table I). In addition to our studies we have included five normal individuals where the dimension D of the strange attractor shifted to higher values (1, 2).

In Fig. 2 and 3 present examples of the MEG time series obtained from the brain of AD patients and the slopes of the correlation integrals (14, 15) which revealed the correlation dimension D (D = 9.7) of the strange attractor.

Fig. 4 and 5 give MEG time series and the correlation dimension for normal subjects and we can see that we are dealing with a chaotic system, which is characterized with infinite value of D, in opposite to the findings for non chaotic system as is in the case of AD patients.

Discussion

This study is the first MEG recordings analysis from AD patients using non linear analysis and chaos. In simple statistics in which we have applied Fourier data analysis we found differences in spectral power including amplitude and frequency for a group of AD patients relative to age-matched controls (5). The increases in low frequency magnetic power values and decreases in high frequency power values is in agreement with the results of previous EEG studies in AD patients (6, 7, 11, 13, 16, 18, 22, 24, 31, 32, 34).

Our nonlinear techniques referred to the reconstruction of the phase space from the MEG time-series of the system, the detection of the existence of strange attractor and the estimation of its correlation dimension. This task is performed by analyzing the MEG time-series, which were recorded

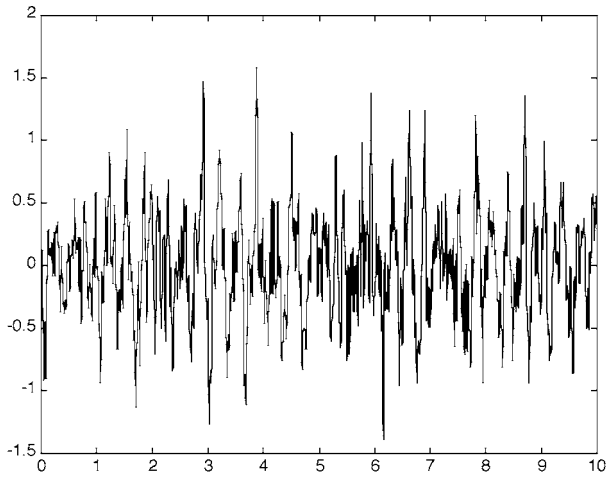

FIG. 2. — MEG time series for 10 sec duration obtained from a brain point of the AD patient.

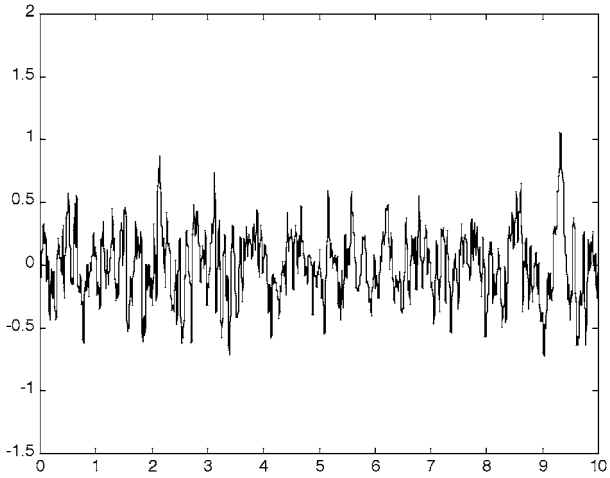

FIG. 4. — MEG time series for 10 sec duration obtained from a brain point of a normal subject for purpose of comparison.

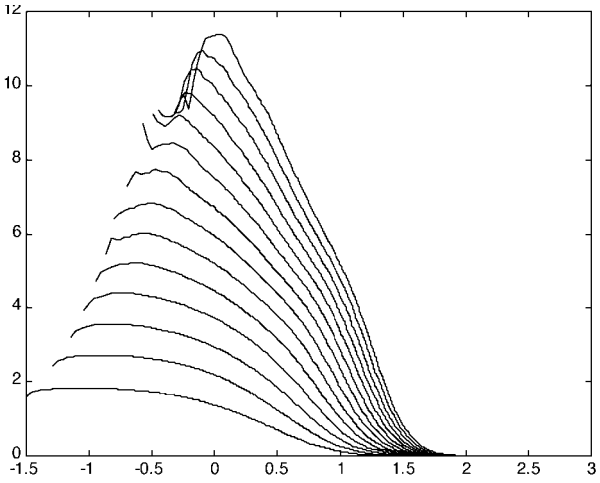

FIG. 3. — Plots of the slopes of the correlation integrals as a function of ln(r) for the MEG time series of Fig. 2.

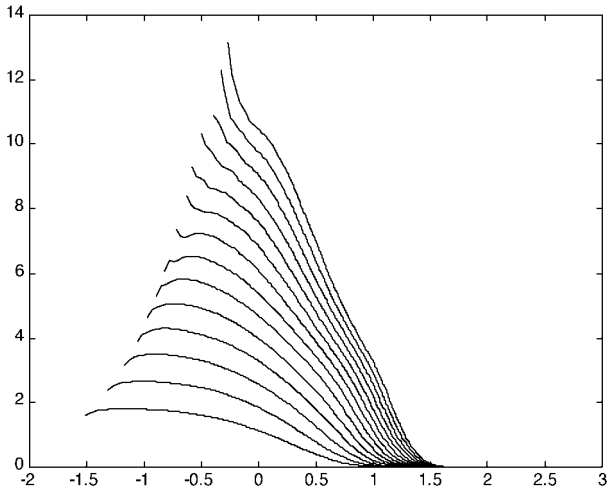

FIG. 5. — Plots of the slopes of the correlation integrals as a function of ln(r) for the MEG time series of Fig. 4.

from different points of the right and left temporal lobes, or from the frontal and occipital lobes of the brain of AD patients.

Dimensionality calculations (i.e. calculation of the correlation dimension of the strange attractor in the reconstructed phase space) can be utilized in the case of experimental biomedical signals, as is the case of MEG for the quantification of the complexity of the neuronal system under consideration. This is done using the embedding theorem (33) in order to reconstruct from a time-series of one dynamical component of the system, a topological equivalent phase space. Afterwards, the correlation integrals C(r,m) were calculated, for successively increasing values of the embedding dimension m, following the method of Grassberger and Procaccia (14, 15).

According to the dynamics of the system the observe MEG is a time series of $B_i = B(t_i)$ (i = 1,2...N). Therefore, the vector construction V_i which is given by equation 1 is representative of the pathology of the AD patients. On the other hand this pathology is the outcome of the degeneracy of all the neurons which are involved in the above pathology.

Another point which is very important to discuss here is the estimation of the largest Lyapunov exponents as a function of the evolution time since we are dealing with time series MEG records. Lyapunov exponents provide a quantitative measure of chaos by describing the mean rate of divergence of initially neighboring trajectories as we defined above in the data analysis.

In most applications are needs only to measure the largest Lyapunov exponent, by examining the evolution of an infinitesimally small displacement vector ξ_0 at a given point on the attractor.

For a chaotic system, the evolved vector ξ_t grows (on average) exponentially as $\xi_t = \xi_0 \cdot e^{\lambda \cdot t}$, $\lambda > 0$. The largest Lyapunov exponent λ is positive for a chaot-

ic system. An adaptation of this procedure for determiny the Lyapunov exponent from experimental data set was originally proposed by Wolf *et al.* (36).

REFERENCES

1. ANNINOS P. A., ADAMOPOULOS A., KOTINI A., TSAGAS N. Nonlinear analysis of brain activity in magnetic influenced Parkinson patients. *Brain Topogr.*, 2000, **13** (2) : 135-44.
2. ANNINOS P. A., KOTINI A., ADAMOPOULOS A., TSAGAS N. Magnetic stimulation can modulate seizures in epileptic patients. *Brain Topogr.*, 2003, **16** (1) : 57-64.
3. ANNINOS P. A., TSAGAS N., JACOBSON J. I., KOTINI A. The biological effects of magnetic stimulation in epileptic patients. *Panminerva Med.*, 1999, **41** : 207-15.
4. ANNINOS P. A., TSAGAS N., SANDYK R., DERPAPAS K. Magnetic stimulation in the treatment of partial seizures. *Int. J. Neurosc.*, 1991, **60** : 141-71.
5. BERENDSE H. W., VERBUNT J. P. A., SCHELTENS P., VAN DIJK B. W., JONKMAN E. J. Magnetoencephalographic analysis of cortical activity in Alzheimer's disease : a pilot study. *Clin. Neurophysiol.*, 2000, **111** : 604-12.
6. BRENNER R. P., ULRICH R. F., SPIKER D. G. *et al.* Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. *Electroenceph. Clin. Neurophysiol.*, 1986, **64** : 483-92.
7. CHIARAMONTI R., MUSCAS G. C., PAGANINI M. *et al.* Correlations of topographical EEG features with clinical severity in mild and moderate dementia of Alzheimer type. *Neuropsychobiology*, 1997, **36** : 153-8.
8. COHEN D., CUFFIN B. N. EEG versus MEG localization accuracy : theory and experiment. *Brain Topogr.*, 1991, **4** : 95-103.
9. CUFFIN B. N. EEG dipole source localization. *IEEE Eng. Med. Biol. Mag.*, 1998, **17** : 118-22.
10. CUFFIN B. N. Effects of local variations in skull and scalp thickness on EEG's and MEG's. *IEEE Trans. Biomed. Eng.*, 1993, **40** : 42-8.
11. DUFFY F. H., ALBERT M. S., MCANULTY G. Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. *Ann. Neurol.*, 1984, **16** : 439-48.
12. ELGER C. E., HOKE M., LEHNERTZ K. *et al.* Mapping of MEG amplitude spectra : Its significance for the diagnosis of focal epilepsy. In : *Topographic brain mapping of EEG and evoked potentials*. MAURER K. (ed). Berlin : Springer Verlag, 1989, 565-70.
13. ELMSTÅHL S., ROSÉN I., GULLBERG B. Quantitative EEG in elderly patients with Alzheimer's disease and healthy controls. *Dementia*, 1994, **5** : 119-24.
14. GRASSBERGER P., PROCACCIA I. Characterization of strange attractors. *Phys. Rev. Lett.*, 1983a, **50** : 346-9.
15. GRASSBERGER P., PROCACCIA I. Measuring the strangeness of strange attractors. *Physica D*, 1983b, **9** : 189-208.
16. GÜNTHER W., GIUNTA R., KLAGES U. *et al.* Findings of electroencephalographic brain mapping in mild to moderate dementia of the Alzheimer type during resting, motor and music-perception conditions. Psychiatry Res : *Neuroimaging*, 1993, **50** : 163-76.
17. JASPER H. H. The ten-twenty electrode system of the International Federation. *Electroencephalogr. Clin. Neurophysiol.*, 1958, **10** : 367-80.
18. JELIC V., SHIGETA M., JULIN P., ALMKVIST O., WINBLAD B., WAHLUND L.-O. Quantitative electroencephalographic power and coherence in Alzheimer's disease and mild cognitive impairment. *Dementia*, 1996, **7** : 314-23.
19. KRINGS T., CHIAPPA K. H., CUFFIN B. N., BUCHBINDER B. R., COSGROVE G. R. Accuracy of electroencephalographic dipole localization of epileptiform activities associated with focal brain lesions. *Ann. Neurol.*, 1998, **44** : 76-86.
20. LOPES DA SILVA F. H. Biophysical issues at the frontiers of the interpretation of EEG/MEG signals. *Electroencephalogr. Clin. Neurophysiol. Suppl.*, 1996, **45** : 1-7.
21. LOPES DA SILVA F., VAN ROTTERDAM A. Biophysical Aspects of EEG and Magnetoencephalogram Generation. In : *Electroencephalography*. NIEDERMEVER E., LOPES DA SILVA F. (eds.). Baltimore, Munich : Urban & Schwarzenberg, 1987.
22. MARTIN-LOECHES M., GIL P., JIMENEZ F., EXPOSITO F. J. *et al.* Topographic maps of brain electrical activity in primary degenerative dementia of the Alzheimer type and multi-infarct dementia. *Biol. Psychiatry*, 1991, **29** : 211-23.
23. OSSENBLOK P., WILTS G., NUMMINEN J., PETERS M. J., LOPES DA SILVA F. H. Locating the cortical sources of somatosensory evoked responses by integration of EEG and MEG. *Electroencephalogr. Clin. Neurophysiol. Suppl.*, 1996, **46** : 183-91.
24. PASSERO S., ROCCHI R., VATTI G., BURGALASSI N., BATTISTINI N. Quantitative EEG mapping, regional cerebral blood flow, and neuropsychological function in Alzheimer's disease. *Dementia*, 1995, **6** : 148-56.
25. PEKKONEN E., HIRVONEN J., JÄÄSKELÄINEN I. P., KAAKKOLA S., HUTTUNEN J. Auditory Sensory Memory and the Cholinergic System : Implications for Alzheimer's Disease. *NeuroImage*, 2001, **14** : 376-82.
26. PEKKONEN E., HUOTILAINEN M., VIRTANEN J., NÄÄTÄNEN R., ILMONIEMI R., ERKINJUNTTI T. Alzheimer's disease affects parallel processing between the auditory cortices. *NeuroReport*, 1996, **7** : 1365-8.
27. PEKKONEN E., JÄÄSKELÄINEN I. P., HIETANEN M. *et al.* Impaired preconscious auditory processing and cognitive functions in Alzheimer's disease. *Clin. Neurophysiology*, 1999, **110** : 1942-7.
28. PFURTSCHELLER G., LOPES DA SILVA F. H. Event-related EEG/MEG synchronization and desynchronization : basic principles. *Clin. Neurolphysiol.*, 1999, **110** : 1842-57.
29. RICCI G. B., LEONI R., ROMANI G. L., CAMPITELLI F., BUONOMO S., MODENA I. 3-D neuromagnetic localization of sources of interictal activity in cases. In : *Biomagnetism : applications and theory*. WEINBERG W., STROINK G., KATILA T. (eds.). New York : *Pergamon Press*, 1985, 304-10.
30. ROSE D. F., DUCLA-SOARES R. Comparison of electroencephalography and magnetoencephalography.

In : *Magnetoencephalography*. SATO S. (ed.). New York : Raven press, 1990, 33-7.
31. SCHREITER-GASSER U., GASSER T., ZIEGLER P. Quantitative EEG analysis in early onset Alzheimer's disease : a controlled study. *Electroenceph. Clin. Neurophysiol.*, 1993, **86** : 15-22.
32. SZELIES B., GROND M., HERHOLZ K., KESSLER J., WULLEN T., HEISS W.-D. Quantitative EEG mapping and PET in Alzheimer's disease. *J. Neurol. Sci.*, 1992, **110** : 46-56.
33. TAKENS F. Detecting strange attractors in the turbulence. *Lect. Notes Math.*, 1981, **898** : 366-81.
34. WADA Y., NANBU Y., JIANG Z.-Y., KOSHINO Y., YAMAGUCHI N., HASHIMOTO T. Electroencephalographic abnormalities in patients with presenile dementia of the Alzheimer type : quantitative analysis at rest and during photic stimulation. *Biol. Psychiatry*, 1997, **41** : 217-25.
35. WIERINGA H. J., PETERS M. J., LOPES DA SILVA F. H. The estimation of a realistic localization of dipole layers within the brain based on functional (EEG, MEG) and structural (MRI) data : a preliminary note. *Brain Topogr.*, 1993, **5** : 327-30.
36. WOLF A., SWIFT J. B., SWINNEY H. L., VASTANO J. A. Determing Lyapunov exponents from a time series. *Physica D.*, 1985, **16** : 285-317.

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