

# Strong Memory in Time Series of Human Magnetoencephalograms Can Identify Photosensitive Epilepsy<sup>1</sup>

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**Abstract**—To discuss the salient role of statistical memory effects in human brain functioning, we have analyzed a set of stochastic memory quantifiers that reflects the dynamical characteristics of neuromagnetic responses of magnetoencephalographic signals to a flickering stimulus of different color combinations from a group of control subjects, and compared them with those for a patient with photosensitive epilepsy. We have discovered that the emergence of strong memory and the accompanying transition to a regular and robust regime of chaotic behavior of signals in separate areas for a patient most likely identifies the regions where the protective mechanism against the occurrence of photosensitive epilepsy is located.

## 1. INTRODUCTION

Increasing attention has been paid recently to non-equilibrium statistical physics in the study of statistical memory effects in random processes that originate naturally. The role of memory has its roots in natural sciences since 1906, when the famous Russian mathematician Markov wrote his first paper on the theory of Markov random processes [1]. His theory is based on the notion of an instant loss of memory of the prehistory (memoryless property) of random processes. On the other hand, there is an abundance of physical phenomena and processes that can be characterized by statistical memory effects: kinetic and relaxation processes in gases [2] and plasma [3], condensed matter physics (liquids [4], solids [5], and superconductivity [6]), astrophysics [7], nuclear physics [8], and quantum [9] and classical [10] physics, to name but a few. At present, we can use a variety of statistical methods for the analysis of memory effects in diverse physical systems. Typical of such schemes are Zwanzig–Mori’s kinetic equations [11], generalized master equations and corresponding statistical quantifiers [12], Lee’s recurrence relation method [13], the generalized Langevin equation [14], etc.

In this paper, we demonstrate that the presence of statistical memory effects is of salient importance for the functioning of healthy physiological systems. This

can imply, in particular, that the presence of large memory time scales in the stochastic dynamics of discrete time series can characterize pathological (or catastrophic) violation of salutary dynamic states of the human brain. As an example, we demonstrate here that the emergence of strong memory time scales in the chaotic behavior of neuromagnetic responses of human brain as recorded by magnetoencephalograms (MEG) is accompanied by the likely initiation and the existence of photosensitive epilepsy (PSE).

We first consider a simplified version of the Markov processes. We introduce the conditional probability  $K_1(x_1, t_1|x_2, t_2)$  that  $x$  is found in the range  $(x_2, x_2 + dx_2)$  at  $x_2$  if  $x$  had the value  $x_1$  at  $t_1$ . For the Markov random process, the conditional probability that  $x$  lies in the range  $(x_n, x_n + dx_n)$  at  $t_n$  given that  $x$  had the values  $x_1, x_2, \dots, x_{n-1}$  – at times  $t_1, t_2, \dots, t_{n-1}$  depends only on  $x_{n-1}$ :

$$\begin{aligned} K_{n-1}(x_1, t_1; x_2, t_2; \dots, x_{n-1}, t_{n-1}|x_n, t_n) \\ = K_1(x_{n-1}, t_{n-1}|x_n, t_n). \end{aligned}$$

The equation states that, given the state of a Markov process at some time  $t_{n-1} < t_n$ , the forthcoming (future) state of the process at  $t_n$  is independent of all previous states at prior times. The equation is the standard definition of the Markov random process. Therefore, from the physical standpoint, the Markov process is a process without an aftereffect. This means that the “future” and the “past” of a process are independent of each other at the known “present.”

<sup>1</sup> The text was submitted by the authors in English.

## 2. MEASURES FOR MEMORY

One of the first measures of “memory” in physiological time series studied in electroencephalographic (EEG) and magnetoencephalographic signals, both of healthy subjects and of patients (including epilepsy patients) [15], was the detrended-fluctuation analysis [16].

The use of the Zwanzig–Mori kinetic equations provides an appropriate, and the most convenient, methodology for quantitative description of statistical memory effects of random processes in physiological data. In particular, using the reasoning put forward in [17], one can obtain a chain of coupled kinetic equations for the discrete time correlation function

$$a(t) \equiv M_0(t) = \frac{\langle \sigma x(t) \delta x(0) \rangle}{\langle \delta x^2(0) \rangle}$$

of the fluctuation

$$\delta x(t) = x(t) - \langle x(t) \rangle,$$

where

$$x(t) = (x_1; x_2; \dots; x_N)$$

is a random discrete-time process, i.e.,

$$x_j = x_j(t_j), \quad t_j = j\tau,$$

where  $\tau$  is a discretization time step,  $j = 1, 2, \dots, N$ . This zeroth-order function is then related iteratively to higher-order memory functions  $M_i(t)$ ,  $i = 1, 2, \dots$ . In this approach, the set of discrete memory functions  $M_i(t)$ ,  $i = 1, 2, \dots$ , of the  $i$ th order together with the corresponding relaxation parameters quantify the memory effects. The full set of memory functions includes all peculiarities of the memory effects for real complex systems. For discrete time series, the whole set of the  $M_i(t)$  functions and relaxation parameters can be calculated directly from the experimental data [17].

Following the argument in [17] provides adequate tools for studying the role of memory effects in discrete-time dynamics of complex systems. The characterization of memory is based on a set of dimensionless statistical quantifiers capable of measuring the strength of memory inherent in the complex dynamics. The first such measure is

$$\varepsilon_i(\omega) = \sqrt{\frac{\mu_i(\omega)}{\mu_{i+1}(\omega)}},$$

and the second follows as

$$\delta_i(\omega) = \left| \frac{\tilde{M}'_i(\omega)}{\tilde{M}'_{i+1}(\omega)} \right|,$$

where  $\mu_i(\omega) = |\tilde{M}_i(\omega)|^2$  denotes the power spectrum of the corresponding memory function,  $M_i(t)$ ,  $\tilde{M}'_i(\omega) = d\tilde{M}_i(\omega)/d\omega M_i(t)$ , and  $\tilde{M}_i(\omega)$  is the Fourier transform of  $M_i(t)$ . The measures  $\varepsilon_i(\omega)$  are suitable for quantify-

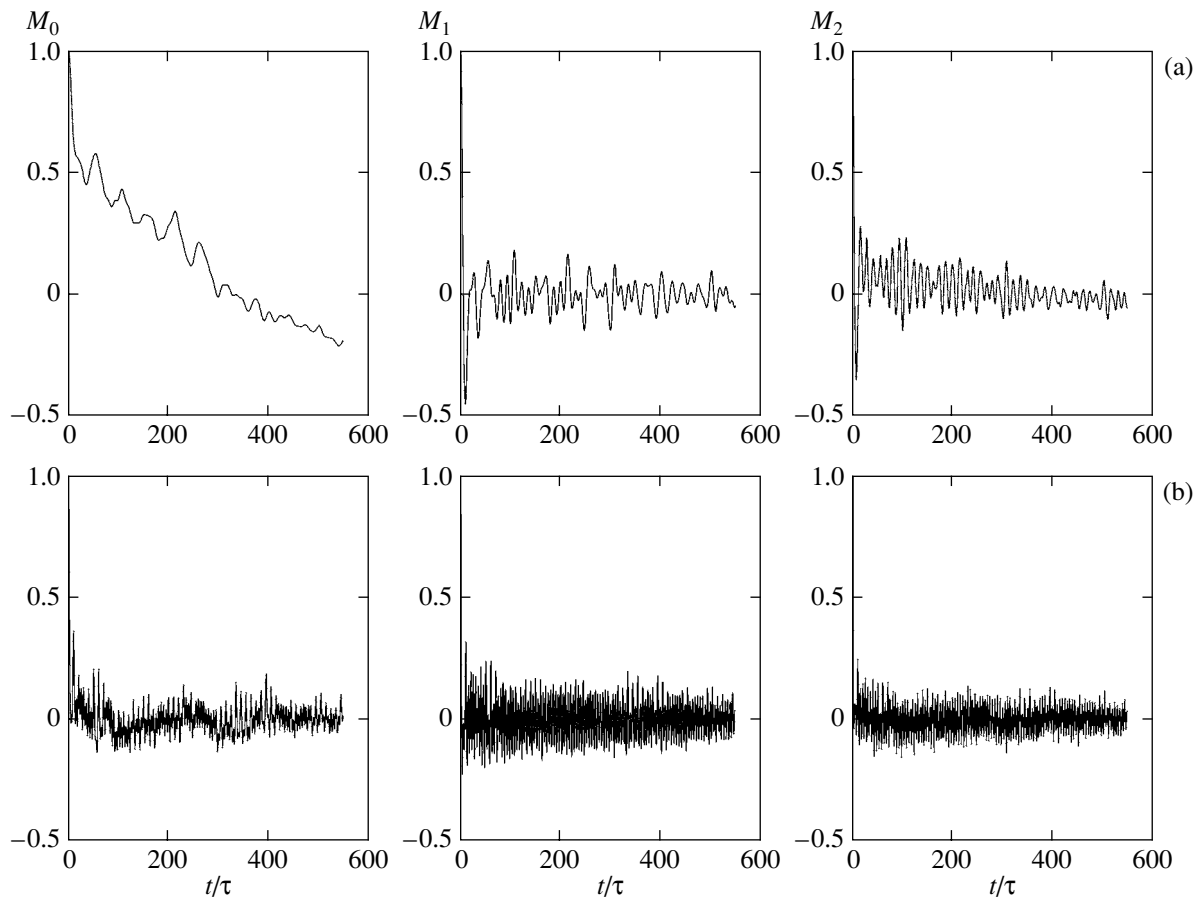
ing the memory on a relative scale, whereas the  $\delta_i(\omega)$  are useful for quantifying the amplification of relative memory effects occurring on different complexity levels. Both measures provide statistical criteria for the comparison of the relaxation time scales and memory time scales of the process under study. For values obeying  $\{\varepsilon, \delta\} \gg 1$ , one can observe a complex dynamics characterized by short-range temporal memory scales. In the limit, these processes assume a  $\delta$ -like memory with  $\varepsilon, \delta \rightarrow \infty$ . When  $\{\varepsilon, \delta\} > 1$ , one deals with a situation with moderate memory strength, and the case with both  $\varepsilon, \delta \sim 1$  typically constitutes a more regular and robust process with strong memory features.

## 3. EXPERIMENTAL DATA FOR PSE

Next, we proceed directly to the analysis of the experimental data: MEG signals recorded from a group of nine healthy human subjects and for a patient with PSE [18]. PSE is a common type of stimulus-induced epilepsy, defined as recurrent convulsions precipitated by visual stimuli, particularly by flickering light. The diagnosis of PSE involves finding paroxysmal spikes on an EEG in response to the intermittent light stimulation. To elucidate the color dependence of photosensitive in normal subjects, brain activities subjected to uniform chromatic flickers with whole-scalp MEG were measured in [18] (further details of the MEG experiment can be found in [18]).

Nine right-handed healthy adults (two females, seven males; age range 22–27) participated voluntarily. The subjects were screened for photosensitivity and personal or family history of epilepsy. The experimental procedures followed the Helsinki Declaration and were approved by the National Children’s Hospital in Japan. All subjects gave their informed consent after the aims and potential risks of the experiment were explained. During the recording, the subjects sat in a magnetically shielded room and were instructed to passively observe visual stimuli without moving their eyes.

Stimuli were generated by two video projectors and were delivered to the viewing window in the shielded room through an fiber-optic bundle. Each projector continuously produced a single color stimulus. Liquid-crystal shutters were located between the optical device and the projectors. By alternatively opening one of the shutters for 50 ms, a 10-Hz (square-wave) chromatic flicker was produced at a viewing distance of 30 cm. Three color combinations were used: red–green, blue–green, and red–blue. The CIE chromacity coordinates were  $x = 0.496$ ,  $y = 0.396$  for red;  $x = 0.308$ ,  $y = 0.522$  for green; and  $x = 0.153$ ,  $y = 0.122$  for blue. All color stimuli had a luminance of 1.6 cd/m<sup>2</sup> in otherwise total darkness. In a single trial, the stimulus was presented for 2 s and followed by an intertrial interval of 3 s, during which no visual stimulus was displayed. In a single session, a color combination was fixed.



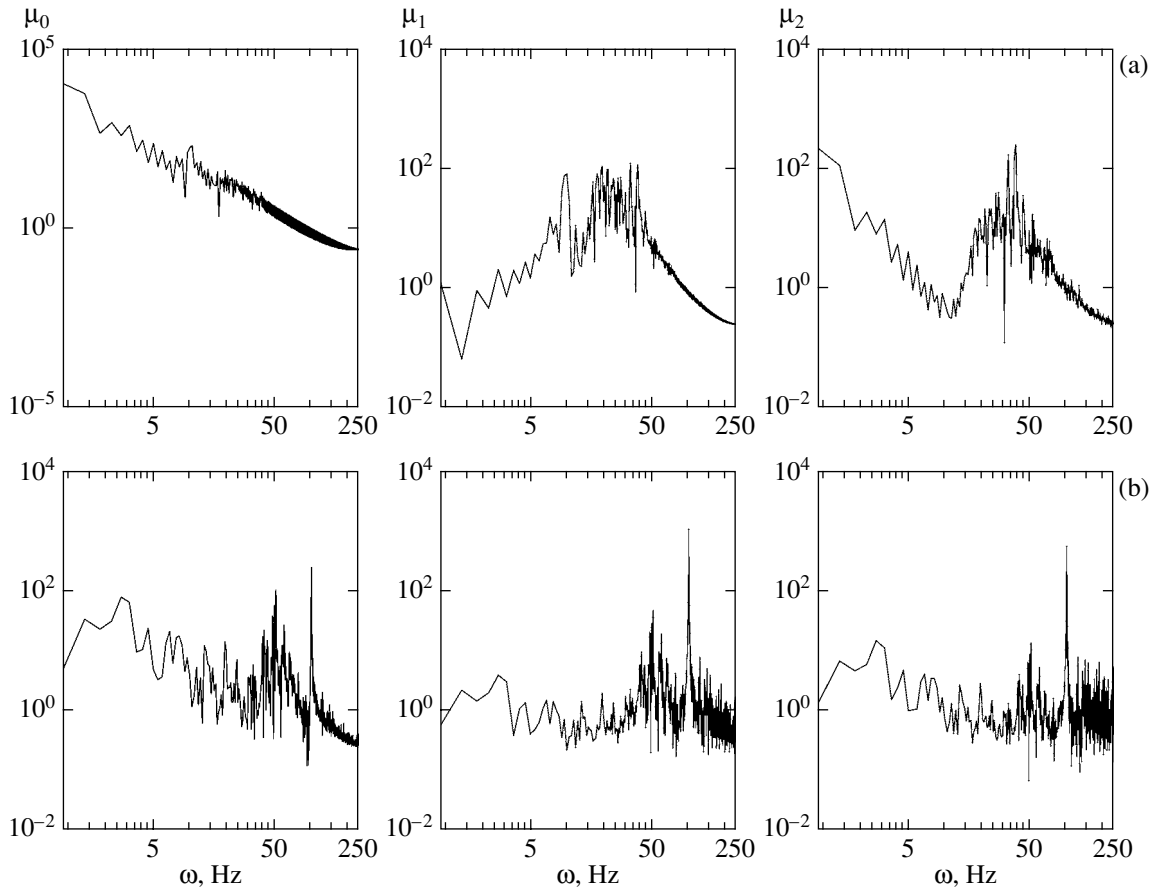
**Fig. 1.** Time dependences of time correlation function  $M_0(t)$  ( $i = 0$ ) and first two subordinate memory functions  $M_i(t)$ ,  $i = 1, 2$  for a healthy subject (no. 6) (a) and for a patient (b) with PSE for the SQUID number  $n = 10$ ,  $\tau = 0.2$  ms. The drastic distinctions of  $M_i(t)$  in a healthy person compared to a patient with PSE is clearly detectable. They consist in the appearance of significant long-range oscillations in the healthy subject and the suppression of high frequency noise in the patient with PSE.

Neuromagnetic responses were measured with a 122-channel whole-scale neuromagnetometer (Neuromag-122; Neuromag Ltd., Finland). The Neuromag-122 has 61 sensor locations, each containing two originally oriented planar gradiometers coupled to DC-SQUID (superconducting quantum interference device) sensors. The two sensors of each location measure two orthogonal tangential derivatives of the brain magnetic field component perpendicular to the surface of the sensor array. The planar gradiometers measure the strongest magnetic signals directly above local cortical currents. Starting at 200 ms, prior responses were analog-filtered (with a bandpass frequency of 0.03–100 Hz) and digitized at 0.5 kHz. Eye movements and blinks were monitored by measuring an electro-oculogram. Trials with MEG amplitudes  $>3000$  fT/cm and/or electrooculogram amplitudes  $>150$   $\mu$ V were automatically rejected from averaging. Trials were repeated until  $>80$  responses were averaged for each color combination. The averaged MEG signals were digitally low-pass filtered at 40 Hz, and then the DC offset during the baseline ( $-100$  to  $0$  ms) was removed. At each sensor loca-

tion, the magnetic waveform amplitude was calculated as the vector sum of the orthogonal components. Peak amplitudes were normalized for each subject with respect to the subject's maximum amplitude. The latency range of  $-100$  to  $-1100$  ms was divided into 100-ms bins. The peak amplitudes were then calculated by averaging all peak amplitudes within each bin.

#### 4. MEMORY ANALYSIS FOR THE PRESENCE OF PSE

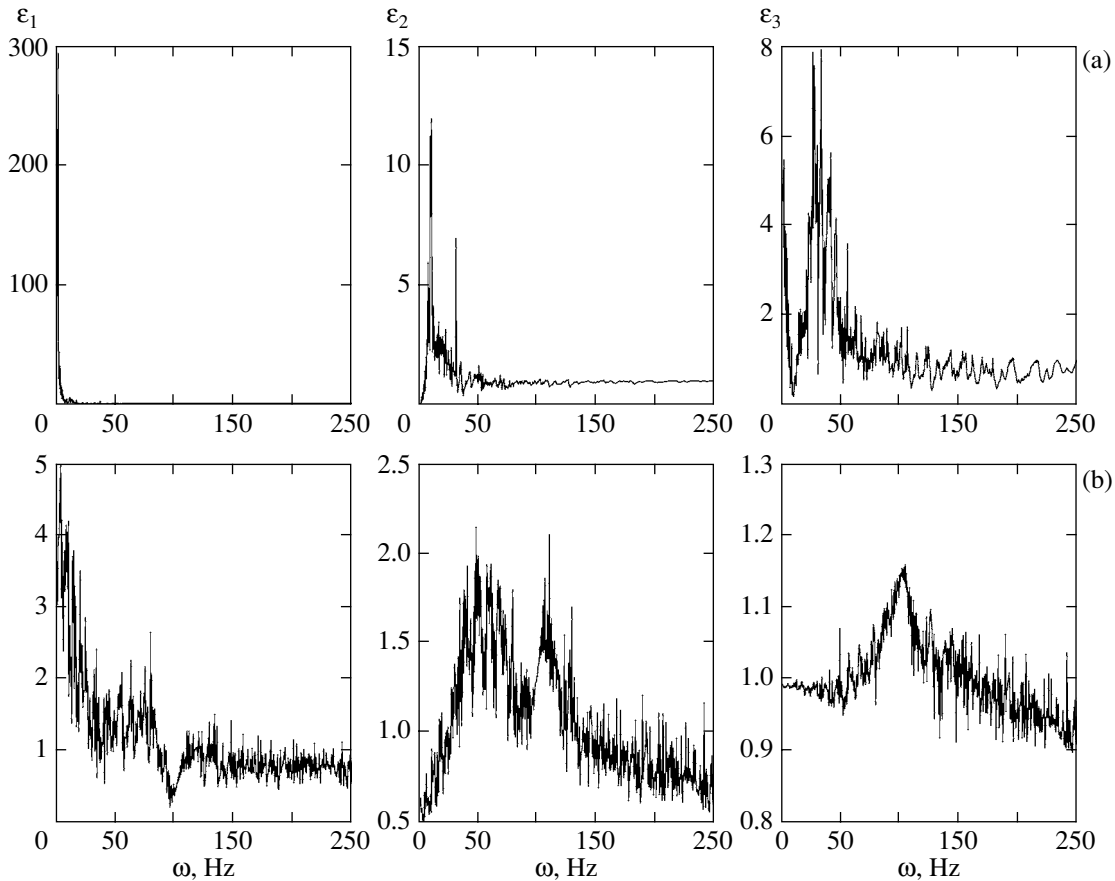
With our set in Figs. 1–5, we present the results of numerical calculations and the analysis of the experimental data in the framework of the nonequilibrium statistical approach to stochastic processes in discrete complex systems [17]. In Figs. 1–3, we depict the typical data for one healthy subject (no. 6) in comparison with a PSE patient in the case of a red–blue combination of the color stimuli. To make the conclusion about the role of the statistical memory effects, we also show the averaged data for the whole group of nine healthy subjects compared with the patient with PSE in Figs. 4



**Fig. 2.** Power spectra  $\mu_i(\omega)$ ,  $i = 0, 1, 2$ , for the memory functions in a healthy person (a) and in the patient with PSE (b) for the SQUID number  $n = 10$  in double-log scale. The spectra in the healthy person (no. 6) demonstrate the presence of electromagnetic waves at characteristic frequency scales  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , and  $\theta$  rhythms (in  $\mu_2(\omega)$ ). Noticeable peaks of electromagnetic excitations in a patient with PSE near 50 Hz and 100 Hz can be observed. Similar peaks are present in many other sensors of the human brain core with PSE. The fractal dependence  $\mu_0(\omega) \propto \omega^{-\alpha}$  that typifies a healthy person is absent in a patient with PSE. This transition plays a crucial role for the emergence of strong memory in a patient with PSE.

and 5. Figure 1 shows the time dependence of the time correlation function  $M_0(t)$  and the first two memory functions  $M_i(t)$ ,  $i = 1, 2$  for a healthy subject (no. 6) (Fig. 1a) compared with those for a patient with PSE (Fig. 1b). The time correlation function  $M_0(t)$  displays long-range oscillations in the healthy subject and a sharp decay for the patient with PSE. It can be seen from Fig. 2, where the power spectra of time correlation function and memory functions are represented, that the fractal dependence at order  $\alpha$ ; i.e.,  $\mu_0(\omega) \propto \omega^{-\alpha}$  with  $\alpha = 1.74$  in the time correlation function of the healthy person (Fig. 2a) transforms into a group of peaks corresponding to the  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , and  $\theta$  rhythms in the frequency behavior of the subordinate quantifiers  $\mu_i(\omega)$ , with  $i = 1, 2, 3$ . The typical picture in the patient with PSE (Fig. 2b) consists in (i) the characteristic absence of the fractal dependence for  $\mu_0(\omega)$ , (ii) the disappearance of the well-defined manifestation of physiological electromagnetic rhythms, and (iii) the appearance of a single spike peak at 10.15 Hz in all spectra and for all sensors  $n$ .

The most instructive singularities in the frequency dependence of the first three points of the measure of memory  $\varepsilon_i(\omega)$ ,  $i = 1, 2, 3$  (Fig. 3) are as follows. In a healthy person, we observe the fractal dependence in the low-frequency domain ( $\omega < 50$  Hz)  $\varepsilon_1(\omega) \propto \omega^{-\beta}$  with  $\beta = 1.67$ , the specific behavior  $\varepsilon_2(\omega) \rightarrow 0$ , and two single peaks in the domain of the brain-rhythm frequencies for the third point  $\varepsilon_3(\omega)$ . This behavior is characteristic only of healthy subjects. The role of increasing memory and the persistent transition from a more random (healthy) into a robust, more regular regime of the underlying chaotic process at all three subordinate measures  $\varepsilon_3(\omega)$ ,  $i = 1, 2, 3$ , is clearly detectable in the patient with PSE. The crucial role of the strong memory at the first level; i.e., for  $\varepsilon_1$ , is reflected by a decrease in the memory measure  $\varepsilon_1(\omega_0 = 0)$  by a factor of approximately 56. Moreover, a drastic change in the frequency spectra for  $\varepsilon_2(\omega)$  and  $\varepsilon_3(\omega)$  occurs.



**Fig. 3.** The frequency dependences of the first three subordinate statistical quantifiers measuring the strength of memory  $\varepsilon_i(\omega)$ ,  $i = 1, 2, 3$ , in a healthy person (no. 6) (a) and for the patient with PSE (b) for the SQUID number  $n = 10$ . A distinct reduction by the factor  $1/56.5$  in the zero-frequency value  $\varepsilon_1(\omega = 0)$  occurs from the healthy person to the patient with PSE. This feature quantifies the emergence of strong memory in the subject with PSE. It is further accompanied by a noticeable disappearance of sharp electromagnetic excitations at low frequencies and by the appearance of high-frequency noise.

The topographic dependence of  $\varepsilon_1(\omega = 0; n)$  depicted in Fig. 4 demonstrates the existence of a long-range time correlation accompanied by a pronounced increase in the role of the statistical memory effects in all MEG sensors with SQUID numbers  $n = 1, 2, \dots, 61$ , in the patient with PSE compared to healthy persons. The difference between a healthy subject and the subject with PSE is about an order of magnitude.

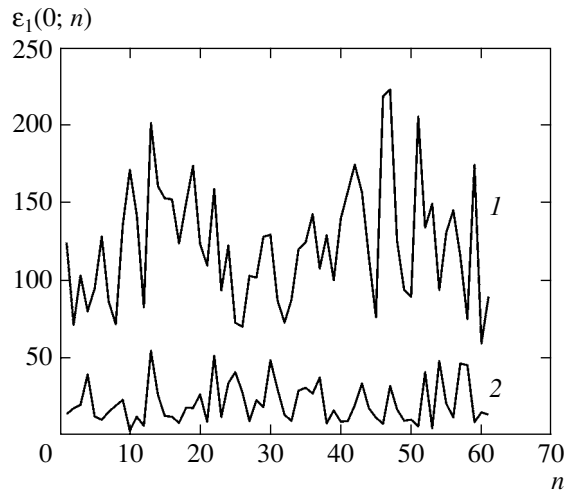
To specify the role of the strong memory, we further study the topographic dependence in terms of a novel information measure, the index of memory. It is defined by

$$v(n) = \frac{\delta_1^{\text{healthy}}(0; n)}{\delta_1^{\text{patient}}(0; n)}$$

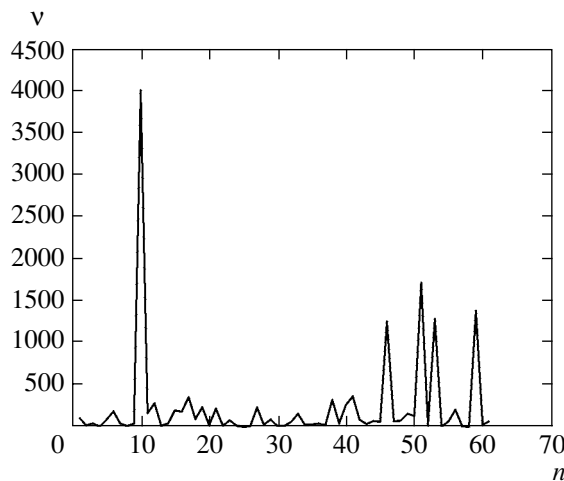
(see Fig. 5). This statistical quantifier measures the amplification of the memory effects for the magnetic signals of MEG in the patient with PSE compared with the healthy group. The sharp increase in the role of memory effects in the stochastic behavior of the magnetic signals is clearly visible for the SQUID numbers

$n = 10, 46, 51, 53$ , and  $59$ . The observed points of MEG sensors locate the regions of the protective mechanism against PSE in a human organism: frontal (sensor 10), occipital (sensors 46, 51, and 53) and right parietal (sensor 59) regions. The early activity in these sensors may reflect the protective mechanism that suppresses cortical hyperactivity due to chromatic flickering.

One might remark that some earlier steps towards the understanding of the normal and diseased human brain have already been set in other fields of science such as neurology, clinical neurophysiology, neuroscience and so on. The numerous studies applying the linear and nonlinear time series analysis to EEG and MEG in epileptic patients are discussed in detail in [18, 19] with the neurophysiological basis of epilepsy, in particular photosensitive epilepsy, taken into account. Specifically, the results in [18] suggested that a significant nonlinear structure was evident in the MEG signals for control subjects, whereas nonlinearity was not detected for the patient. In addition, the couplings between distant cortical regions were found to be greater for control subjects. The important role of com-



**Fig. 4.** The topographic dependence of the information measure for memory  $\varepsilon_1(\omega = 0; n)$  in a healthy person—*1* (at a fixed  $n$ , the mean value for the whole group of the 9 control subjects) is compared with the patient with PSE—*2*,  $n = 1, 2, 3, \dots, 61$  is the SQUID number on the human brain core. The crucial role of the strong memory for  $n = 10, 46, 51, 53,$  and  $59$  is clearly detectable. All sensors depicting  $\varepsilon_1(\omega = 0; n)$  clearly demonstrate the emergence of statistical memory effects in the chaotic behavior of magnetic signals. Nevertheless, the role of strong memory effects, i.e., the minimum values for  $\varepsilon_1(\omega = 0; n)$ , appreciable increases in the patient in SQUID sensors with the numbers  $n = 10, 46, 51, 53,$  and  $59$ .



**Fig. 5.** Topographic dependence of the index  $v(n)$  versus sensor  $n$ , being the SQUID number on the human brain core. This indicator measures the amplification of the role of memory effects. The sharp increase of  $v(n)$  for  $n = 10, 46, 51, 53,$  and  $59$  characterizes a noticeable increase of memory effects in the chaotic behavior of magnetic signals in the patient with PSE and thus emphasizes the crucial role of the location and the pathological mechanism of PSE.

binational chromatic sensitivity in sustained cortical excitation was also confirmed. These previous findings lead to the hypothesis that a healthy human brain is most likely equipped with an essentially nonlinear neu-

ronal process reflecting an inherent mechanism that protects against hyperexcitation to chromatic flickering stimulus, and such a nonlinear mechanism is likely to be impaired for a patient with PSE.

## 5. CONCLUSIONS

This study of the chaotic behavior of the neuromagnetic signals of human MEGs with PSE and in a group of healthy subjects elucidates the role of statistical memory as an important criterion that measures the functioning of the human brain. Even an insignificant amplification of the memory effects tests the pathological changes in the brain of a patient with PSE. The pronounced sharp increases in memory effects in our set of statistical quantifiers in the neuromagnetic signals indicates a pathological state of a patient with PSE within separate areas of the brain. Our statistical approach, being conveniently constructed from the set of subordinate memory functions that yield the rate of change of the autocorrelation function of the measured complexity dynamics, allows one to characterize the neuromagnetic signals in the human brain in terms of statistical indicators. These statistical quantifiers in turn measure both the role and the strength of statistical memory that the underlying time series accommodates. Many natural phenomena are described by distributions with time-scale-invariant behavior [20]. The suggested approach makes it possible to treat the stochastic dynamics of neuromagnetic signals in the human brain in a probabilistic manner and search for its statistical singularities.

From the physical standpoint, the results can be used as a test to identify the presence or absence of brain anomalies as they occur in a patient with PSE. The set of our quantifiers is uniquely associated with the emergence of memory effects in the chaotic behavior of the human brain core. The detection of the behavior of those indicators as discussed here is then of beneficial use for detecting the pathological state of separate areas (sensors 10, 46, 51, 53, and 59) in the brain of a patient with PSE. There also exist other quantifiers of different nature, such as the Lyapunov exponent, Kolmogorov–Sinai entropy, and correlation dimension, which are widely used in nonlinear dynamics and related applications (see [21]). In the present context, we find that the employed memory measures are not only convenient for analysis but also ideally suited to identify anomalous brain behavior. The search for yet other quantifiers, and foremost, the optimization of such measures when applied to complex, discrete-time dynamics presents a true challenge. This objective holds particularly true when attempts are made to identify and quantify anomalous functioning in living systems. The present work presents an initial step towards understanding the fundamentals of physiological processes in the human brain.

PSE is a type of reflexive epilepsy that originates mostly in visual cortex (both striate and extrastriate) but with a high possibility of propagating to other cortical

regions [22]. Healthy brain may possess an inherent control (or defense) mechanism against this propagation of cortical excitations, the breakdown of which makes the brain vulnerable to trigger epileptic seizures in patients [23]. However, the exact origin and dynamical nature of this putative defense mechanism is not yet fully known. Earlier, we showed in [18] that brain responses to chromatic flickering in healthy subjects represent strong nonlinear structures, whereas nonlinearity is dramatically reduced to a minimum in patients. Here, we report that a patient's brain show significantly stronger statistical memory effects than healthy brains. A complex network composed of an interacting nonlinear system with a memory component is inherently stable and critically robust to external perturbations. A rapid inhibitory effect, which is essential for the prevention of PSE, is made possible by the faster signal processing between distant regions. Further, such a network is capable of facilitating flexible and spontaneous transitions between many possible configurations as opposed to being entrained or locked with the external perturbations [24]. In short, our findings are in line with the growing body of evidence that physiological systems generate activity fluctuations on many temporal and spatial scales and that pathological states are associated with an impairment of this spatiotemporally complex structure.

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