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Entropy maps characterize drug effects on brain dynamics in Alzheimer's disease

Laurent Pezard[a,b,*], Jacques Martinerie[a], Francisco J. Varela[a], Florence Bouchet[a], David Guez[c], Christian Derouesné[d], Bernard Renault[a]

[a]*Unité de Neurosciences Cognitives and Imagerie Cérébrale, LENA (CNRS UPR 640) 47 Bvd de l'Hôpital, 75651 Paris Cedex 13, France*
[b]*Laboratoire de Neurosciences Comportementales, Université René Descartes (Paris 5), 45 Rue des Saints Pères, 75270 Paris Cedex 06, France*
[c]*IRI Servier, 6 place des pléïades, 92415 Courbevoie Cedex, France*
[d]*Service de Neurologie, Hôpital de la Salpêtrière, 75651 Paris Cedex 13, France*

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Abstract

Non-linear quantifiers of brain electrical dynamics (entropy maps computed from the degradation of temporal forecasting of EEG signals) were studied in relation to drug treatment of Alzheimer's disease. A placebo condition was compared to three drug doses (50, 100 and 200 mg). A significant general effect of the drug was found when compared to placebo and specific contrasts between placebo and each of the three drug doses only reveal a significant entropy increase for the highest dose. These effects were localized bilaterally in fronto-temporal areas and support changes in the dynamics of the cerebral structures involved in memory processes.

Keywords: Alzheimer's disease; Dynamical systems; Multi-channel electroencephalogram; Non-linear forecasting; Chaos; Entropy; Pharmacological treatment

The quantification of non-linear dynamical indicators has been used in order to differentiate between control and pathological groups [3,6,11]. In the case of Alzheimer's disease (AD), it has been shown that pathological brain dynamics have a lower correlation dimension than controls [17,18,20]. In the present study, we quantify drug activity on EEG dynamics as a function of doses in the case of patients suffering from AD. Since AD is characterized by a decrease in brain dynamics' complexity [17,18,20], we assumed that the drug, if efficient, should induce an increase in EEG complexity [9,14].

Non-linear tools are subject to important methodological drawbacks. The spatial extension of the brain leads to compute either complexity indices on the basis of single-channel recordings or global complexity indices on the basis of multi-channel recordings [2]. The first approach has been demonstrated to be inadequate in the characterization of brain dynamics [8,15]; the second one does not deal with the spatial heterogeneity of the brain [1,15]. Furthermore, signals generated by linear stochastic processes can exhibit similar characteristics as non-linear deterministic systems especially for EEG-like data [19]. Thus, in order to ensure the adequacy of our non-linear quantification, local characteristics of EEG data were computed on the basis of multi-channel recordings and surrogate data tests were performed.

We used a method combining multi-channel recordings and non-linear forecasting [12,13]. The complexity of the dynamics was characterized by the degradation pattern of the EEG-segments predictability, which we refer to as entropy (K). In turn, an increase of entropy corresponds to less predictable signals and thus, to a more complex dynamic. The quantifiers were computed from electrode-related prediction curves for local entropy and from mean prediction curves (averaged across electrodes) for global entropy.

* Corresponding author. Tel.: +33 1 42161169; fax: +33 1 44243954.

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Table 1

For the five experimental conditions, mean local entropy values obtained on the electrodes where significant effects between placebo and the 200 mg drug dosage were found (KF7: mean local entropy for F7 in s^{-1})

	Day 0	Placebo	50 mg	100 mg	200 mg
K_{F7}	23.5 (3.3)	19.6 (3.8)	25.2 (3.4)	20.8 (2.4)	28.9 (3.3)
K_{T3}	36.3 (5.5)	28.4 (4.6)	35.9 (6.5)	35.9 (5.2)	39.0 (4.4)
K_{T5}	42.3 (4.1)	43.8 (3.8)	49.8 (4.3)	48.4 (5.4)	52.7 (4.2)
K_{P3}	46.2 (3.6)	43.0 (5.6)	50 4 (3.8)	47.7 (4 3)	55.8 (4.7)
K_{O2}	45.8 (4.4)	51.6 (4.0)	57.9 (3.9)	52.1 (4.3)	60.1 (4.3)
K_{F8}	24.2 (2.2)	18.8 (3.4)	25.3 (3.8)	26.0 (3.3)	31.7 (3.8)
K_{T4}	39.4 (4.6)	30.0 (4.0)	39.3 (5.2)	35.2 (3 8)	49.6 (3.8)
K_{T6}	41.9 (2.9)	43.0 (3.7)	52.6 (4.0)	49.6 (4.8)	54.2 (4.5)

The standard errors are given in parenthesis.

A group of 12 patients was selected (nine females and three males; aged from 50 to 81 years, mean age 64) with a diagnosis of AD according to NINCDS/ADRDA criteria [10]. The other criteria were: a Mini-Mental Status (MMS) ranging from 18 to 24, a score to the geriatric depression scale (highest possible score: 30) lower than 18, an Hachinski score lower than four and a recent scanner or MRI compatible with the diagnosis of AD. The patients did not present other neurological or psychiatric disease. Cautions about biological drug tolerance were taken. Ethic recommendations were followed according to the French legislation (patients' consent and committee agreement).

An experimental molecule (S 12024–2) which has been proved to increase memory capacity in animals was used for a 'Phase II' experimental protocol. This molecule facilitates noradrenergic transmission and is characterized by a half-life time of about 20 h in man. Phase I tests have shown an increase of speed in memory tasks and no significant undesirable effects in elderly adults.

Subjects were recorded in one passive and two active conditions. Two tones of identical duration (150 ms) but of different frequencies (800 and 1200 Hz) were randomly presented via earphones in both ears (random inter-stimulus interval from 500 to 800 ms). Low tones were frequent (80%) and high tones were rare (20%, target stimuli). The difference between the active conditions was the side the subject had to pay attention to in order to respond to target stimuli. The data from three subjects had to be discarded because of too many artefacts. In the remaining subjects (six females and three males, mean age: 65 years), EEG-recordings were free of artefacts in the passive condition only.

EEG was recorded from 19 derivations set on the scalp according to the 10–20 international electrode placement system [7] and referred to the ears. Horizontal and vertical electro-oculograms were simultaneously recorded in order to correct eye movements [5]. The lower band-pass limit was 0.16 Hz and the upper one was 30 Hz for EEG and EOG. The data were digitized on-line on 12 bits using a 250 Hz sampling rate.

The patients were free of drugs for the first recording session (day 0) which took place 2 weeks after a session of familiarization (day 15). Patients' brain activity was then recorded four times with a 3-week delay between each recording session. This 3-week period consisted in 2 weeks of placebo administration (wash-out period) and 1 week of drug (or placebo) administration. The four doses (0, i.e. placebo, 50, 100, 200 mg daily dose) were randomly administered to the patients.

For each subject, in each recording session, two contiguous epochs of 32.8 s (8192 samples) were analyzed. For each channel, the signal was shifted to zero mean and rescaled to unit variance. The trajectory of the system was then reconstructed separately for each epoch (90 in total) in a 19-dimensional space using the multi-channel method [2,12]. For each EEG-segment, global and local entropies were computed [13]. Each subject in each of the five recording conditions (day 0, placebo, 50, 100 and 200 mg) was characterized using a set of 19 local entropies averaged over the two EEG-segments.

The global entropy (K) obtained for each EEG-segment was used to test the null hypothesis, i.e. the measures are obtained from a linear stochastic process. This is done by comparing (K) obtained from the raw data to the mean value of (K) computed from a set of 39 multivariate surrogate data [16]; 3600 segments were thus analyzed (90 raw data and $39 \times 90 = 3510$ surrogate data). Only when the entropy of the surrogate data was significantly higher than that of the

Table 2

Values of the statistical tests between placebo and 200 mg drug dosage on local entropy for the electrodes where significant effects ($P < 0.05$) of the drug were found

	$F(1,8)$	P
F7	8.52	0.02
T3	5.31	0.05
T5	6.31	0.04
P3	5.00	0.05
O2	6.28	0.04
F8	6.15	0.04
T4	11.26	0.01
T6	5.29	0.05

raw data did we accept the time series as truly non-linear. The null hypothesis was formally rejected by the two tailed test at the 95% significance level in 37 of the 90 windows (41%) and similar percentages of rejections are observed for each recording condition (44% for day 0, 50% for placebo, 33% for 50 mg, 44% for 100 mg and 33% for 200 mg). The overall number of rejections is considerably higher than expected if the null hypothesis was true for all the data sets (4.5 windows for 5%); this establishes the presence of a strong non-linear EEG component and thus justifies the use of non-linear methods.

Characteristics of brain dynamics modifications have been investigated using entropy maps. The specific effects of the drug conditions on entropy maps have been tested using a MANOVA with two factors: the experimental conditions (4 levels: 0, i.e. placebo, 50, 100 and 200 mg) and the electrodes (19 levels). A global significant effect of the electrode factor was found ($F(18,144) = 16.2$; $P < .001$). The effect of the experimental condition and the interaction between the factors were not significant. A significant difference was observed between placebo and the three drug doses taken together (contrast analysis, $F(1,8) = 6.11$; $P = 0.04$). No significant effect was observed between placebo and 'day 0', placebo and 50 mg and between placebo and 100 mg. Only the highest dose (200 mg) significantly differed from the placebo condition ($F(1,8) = 6.5$; $P = 0.03$). In this case, local differences were therefore tested: a significant increase in local entropies was observed on 8 electrodes (F7, F8, T3, T5, T4, T6, P3 and O2; $P < 05$); the detailed results are given in Tables 1 and 2 and depicted on Fig. 1.

In this study, the local measurements are obtained with a method which takes into account the dependence between EEG-signals and estimates the contribution of each signal to the whole brain's complexity. The local entropy maps show that the drug effects are not similar in all drug conditions. Only the highest dose (200 mg) confirms our assumption: it induces a bilateral fronto-temporal increase in entropy. The locations of these effects correspond to the cortical areas (prefrontal and medial temporal lobes) where atrophy and

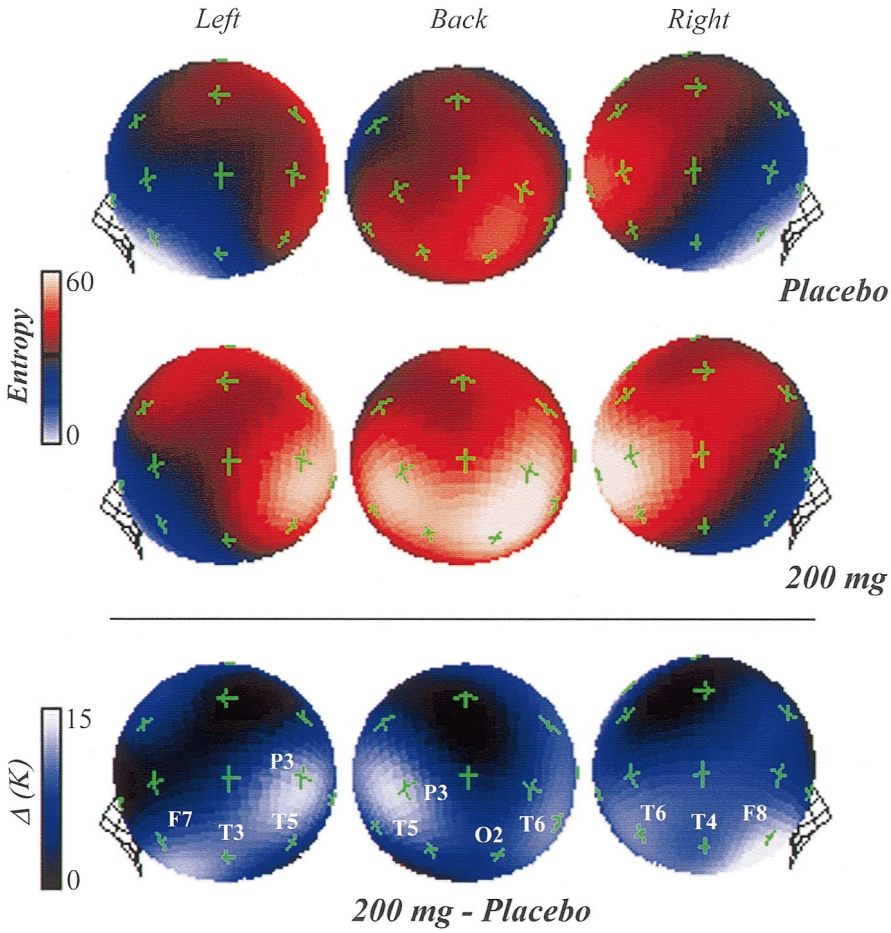

Fig. 1. Averaged maps for the placebo condition and the active drug dosage (200 mg). The first two rows depict averaged maps of local entropy (in s^{-1}) and the third row represents the averaged maps of entropy differences between these two conditions (Δ(K) = K(200 mg) – K(Placebo). The electrodes where significant differences were observed are indicated in white characters on the figures of the last row. Three views of the head are shown for each row: left side, back side and right side of the head. The green crosses represent the electrodes. The interpolation between electrodes has been computed using spline interpolation on a spherical model.

hypometabolism are preferentially observed in AD. Our results thus strongly suggest that the drug-induced increase in the noradrenergic transmission causes a pharmacological reactivation of the fronto-temporal structures involved in memory processes.

The indices computed in this study quantify 'macroscopic' dynamical characteristics of brain activity instead of 'microscopic' neuronal processes. Their exact physiological significance is thus not straightforward and they should be related to dynamical reorganizations of brain activity, such as changes in the interactions between areas [4], rather than to precise neuronal mechanisms. However, our results emphasize the potential use of non-linear methods as useful tools for diagnosis and pharmacological treatments evaluations.

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