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Nonlinear EEG Changes Associated with Clinical Improvement in Depressed Patients

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Assuming that the depressive syndrome could be related to a cerebral "dynamical disease," we attempted to describe in a longitudinal and quantitative manner the modifications of brain electrical activity during depressive episodes treatment. This study tested whether mood improvement during therapy (pharmacological treatment or electroconvulsive therapy) is related to concomitant modifications of brain dynamics. The evolution of brain activity and mood were measured, every two days during treatment for three depressed patients and over three weeks for a control subject. Complexity of brain electrical activity was computed for each site of recording (EEG with 31 electrodes), leading to maps of complexity; depressive mood modulations were quantified using a self-assessment scale. The results show a specific organization of depressed patients' brain dynamics compared to the control's dynamics. Moreover, covariations between nonlinear changes in brain dynamics and mood improvement are observed during the remission of depressive episodes.

KEY WORDS: depression; dynamical disease; EEG; nonlinear dynamics; depressive mood.

INTRODUCTION

The development of nonlinear dynamics analysis has provided useful tools in the study of physiological systems' activity. Within this framework, it has been proposed that transition between a healthy behavior towards

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a pathological state could be related to a bifurcation, e.g. the transition between a chaotic behavior to a periodic one, or vice versa. This phenomena called ''dynamical diseases'' (Bélair, Glass, an der Heiden, & Milton, 1995; Mackey & Glass, 1977; Mackey & Milton, 1987) is related to modifications in physiological systems' control parameters leading to abnormal dynamics.

In the case of depression, altered biological rhythms such as circadian rhythm (Wehr, Goodwin, Wirz-Justice, Craig, & Breitmeier, 1982) cortisol secretion (Hollister, Davis, & Davis, 1980; Lemelin, Baruch, Vincent, Everett, & Vincent, 1997; Lemelin & Baruch, 1998) or melatonine secretion (Rubin, Heist, McGeoy, Hanada, & Lesser, 1992) have been observed. Moreover, depressed speech rhythms are altered due to an increase in pause time (Georgieff, Dominey, Michel, Marie-Cardine, & Dalery 1998; Szabadi, Bradshaw, & Besson, 1976) and overall behavior is slowed down as revealed by actometric studies (Dantchev & Widlöcher, 1998; Widlöcher, 1983). Furthermore, electroencephalogram (EEG) studies have also shown alterations in brain dynamics during depressive episodes (Nandrino *et al.,* 1994; Pezard *et al.,* 1996). All these rhythm modifications observed in depression have been considered as landmarks of a ''dynamical disease'' expressed both at physiological and behavioral levels (Bélair *et al.,* 1995).

In such dynamical framework, depression could be related to a bifurcation from an healthy brain dynamics to a pathological one (Mackey & Glass, 1977; Mackey & Milton, 1987). Since this process can not be experimentally observed, we considered the reverse transition: the clinical improvement in depressed patients during their treatment. We hypothesized that changes in brain dynamics from a pathological towards an healthy state could occur in accordance with clinical improvement. These changes can either be related to an abrupt change in the brain dynamics' characteristics (i.e. bifurcation) or to progressive modifications related to nonstationarity. In order to test this hypothesis, our study quantifies one of the main characteristics of depression (i.e. painful mood) and nonlinear changes in brain dynamics every two days during therapy. We then investigated the relation between brain dynamics' modifications and clinical improvement.

Depressive mood was evaluated with a self-assessment scale (von Zerssen, Koeller & Rey, 1970) which takes into account various subjective dimensions corresponding to a depressive ''state of mind'' (Horowitz, 1987). Brain dynamics' complexity was quantified using a nonlinear method based on multi-channel recordings and nonlinear forecasting (Pezard, Martinerie, Breton, Bourzeix, & Renault, 1994; Pezard, Martinerie, Müller, Varela, & Renault, 1996). The complexity of the dynamics was characterized by the degradation pattern of the EEG time series predictability, which we refer to as entropy. This method characterizes the spatio-temporal brain dynamics using either global entropy or maps of local entropy. Multivariate surro-

gate data (Prichard & Theiler, 1994) were used to test the presence of nonlinear processes in our EEG data.

Furthermore, modifications of brain dynamics have been studied using decomposition of local entropy measurements into principal components. This analysis permits one to define the main spatial patterns involved in the brain dynamics evolution along therapy and the complexity associated with each pattern. Drastic changes in these patterns were considered as signs of bifurcations.

The ''dynamical disease'' principle implies that, whatever the therapy used, the clinical improvement should be associated with similar brain dynamics reorganization. In order to test the generality of this principle, depressed patients with different histories of depression and therapies were recorded. Two depressed patients with pharmacological treatment presenting either a recurrent or a first depressive episode, and a patient with electroconvulsive therapy (ECT), suffering from severe depression were recorded every two days during hospitalization. Finally, since no previous study has dealt with such a longitudinal study of nonlinear brain dynamics modifications, a control subject free of any treatment was also recorded.

MATERIALS AND METHODS

Subjects

After being given complete information about the goal of the investigation, three depressed patients (Mrs. G., Mss. H. and Mrs. R.) and a control subject (Mrs. I.) gave their written consent to participate to this research. The depressed patients stayed in La Salpêtrière Hospital (Paris) and received either pharmacological treatment or ECT with regards to depression intensity and resistance. They were selected according to the DSM-IV (American Psychiatric Association, 1987) criteria for a major depressive episode. Their scores to depression rating scales assessed their depressive state at the arrival (Table 1).

Mrs. G. (53 years old) had already suffered at least three major depressive episodes and was treated by pharmacotherapy. Her pharmacological treatment started after a one week wash-out of previous medication. Mss. S. (30 years old) entered hospital for a first depressive episode, was medication-free and received a pharmacological treatment. Mrs. R. (39 years old) suffered from resistant depression for several years and asked for ECT. The time-course of treatments and experimental sessions are described in Fig. 5.

The control subject, Mrs. I. (47 years old) suffered neither any psychia-

Table 1. Scores to Global Rating Scales of Depression (HAMD-21 & MADRS), to Psychomotor Retardation (ERD), and Anxiety (COVI) Scales Performed Upon Arrival and Discharge of Each Patient

		MADRS	HAMD-21	ERD	COVI
	Mrs G.	27	25	8	22
Arrival	Mss S.	20	21	12	4
	Mrs R.	24	20	25	4
	Mrs G.	12	11	3	18
Discharge	Mss S.	10	10	5	2
	Mrs R.	8	9	15	2

tric episode nor any neurological trouble. In her case, depression scales proved the absence of depressive symptoms.

Experimental Protocol

Subjects have been examined every two days during their hospitalization (between two and three weeks). The EEG-recordings and mood self-assessment were performed between 9H. and 11H. AM in order to minimize mood nyctemeral variations. Mrs. G. was thus submitted to 10 experimental sessions (EEG and self-assessment), Mrs. R. and Mss. S. to 7, and Mrs. I. (control subject) to 9.

Two kinds of clinical evaluations were chosen to evaluate the depression intensity and the subjects' mood evolution: (a) Clinical interviews using global rating scales of depression (HAMD-21: Hamilton, 1960; MADRS: Montgomery & Asberg, 1979) and scales pointing out specific dimensions of depression (psychomotor retardation: Widlöcher, 1983; anxiety: Lipman & Covi, 1976) were realized at the patients' arrival and discharge. (b) Before each EEG-recording, the subjects filled the BfS' scale questionnaire (von Zerssen, Koeller, & Rey, 1970; French translation: Bobon & Bobon-Shrod, 1974). This scale permits a scalar evaluation (between 0 and 56) of depressive mood intensity from ''relaxed'' (low scores) to ''extremely depressed'' (high scores).

EEGs were recorded, in a resting eyes closed condition, on 31 derivations referred to the ears and set on the scalp in an equidistributed manner (Fisch, 1991). Vertical electro-oculograms (EOG) were recorded in order to perform off-line correction of eye movements (Gratton, Coles, & Donchin, 1983). The lower band-pass limit was 0.08 Hz for EEG and 0.02 for EOG. Both upper band-pass limits were 100 Hz. The data were digitized on-line on 12 bits using a 1 kHz sampling rate. The signal was stored on the hard

disk of a PC and then transferred onto the disk of a HP-K200 server for further processing.

Methods

Nonlinear Quantification

Brain electrical activity was analyzed using a numerical method based on multi-channel recordings and non-linear forecasting (Pezard *et al.,* 1994; Pezard, Martinerie *et al.,* 1996). It permits one to obtain local and global entropies (respectively noted K and ⟨K⟩) which quantify the loss of predictability for each of the 31 recording sites (K) and for the global EEG recording (⟨K⟩). In turn, an increase of entropy corresponds to less predictable signals and in consequence to a more complex dynamics. For each day of recording, each subject was characterized by indices (either local or global) averaged over the selected EEG-segments.

Moreover, since signals generated by linear stochastic processes can exhibit similar characteristics as nonlinear deterministic systems (Rapp, Albano, Schmah, & Farwell, 1993), the presence of nonlinear structure in EEG-segments was ensured by testing the significance of the difference between ⟨K⟩ obtained for raw data and ⟨K⟩ obtained for a set of 39 multi-channel surrogate data (Prichard & Theiler, 1994). We describe below the procedure (summed up in Fig. 1) repeated for each subject and each recording session.

For each recording session, ten 8-second multi-channel EEG-segments free of EEG and eyes movements artifacts were selected (except in the case of Mss. S. recording session n°4 for which only 5 EEG-segments were obtained). A total of 325 EEG-segments were thus used in this study (10×10 for Mrs. G., $6 \times 10 + 5$ for Mss. S., 7×10 for Mrs. R. and 9×10 for Mrs. I.). For each channel, the signal was shifted to zero mean and rescaled to unit variance. Each EEG-segment was used to build an observation matrix corresponding to the multi-channel embedding of a trajectory defined by 8192 measurement-vectors in a 31-dimensional space.

Nonlinear forecasting of the system time evolution was computed using a simple local linear model (Sugihara & May, 1990). The linear correlation coefficient $\rho j(p)$ between the jth component of the observed measurement-vectors (value on the jth channel) and the jth component of the predicted vectors was computed for each prediction time p ($p = 1, \ldots, 10$). This procedure leads to a prediction curve for each channel, which we will enter in the computation of the localized entropy (K). The average value:

$$\langle \rho(p) \rangle = (1/k) \sum_{j=1}^{k} \rho_j(p) (\mathrm{p} = 1, \ldots, 10)$$

constitutes the average prediction curve which will enter in the computation of the global entropy ($\langle K \rangle$).

We then defined the entropy (either local or global), equivalent to Kolmogorov entropy, as the rate of predictability loss in our signals from the relation (Tsonis & Elsner, 1992; Wales, 1991):

$$\ln(1 - \rho) = 2 \ln(S_0/(2\sigma)) + 2KP\tau$$

where S_0 is an index of representativity of the learning set, σ the variance of the observed values, $p\tau$ the first few prediction steps (τ is the sampling period). In our case, we used the first three points of each prediction curve (either localized or average) to estimate K.

Surrogate Data Construction and Linearity Test

Surrogate data were constructed from raw data by randomizing their phases in the Fourier domain (Theiler, Eubank, Longtin, Galdrikian, & Farmer, 1992). To analyze the presence of non-linearities in multichannel EEG recordings, we used multivariate surrogate data that preserve the cross-correlation between channels (Prichard & Theiler, 1994). For each EEG segment, $\langle K \rangle$ was obtained from the raw data and an ensemble of surrogate data. Sets of 39 surrogate data were used to ensure a confidence level of .025 for the one-tailed test of the null hypothesis. In order to ensure reliable null hypothesis test we used, as a robust empirical measure of significance (Rapp, Albano, Schmah, & Farwell, 1993), the Monte-Carlo probability (Barnard, 1963; Hope, 1968):

$$P_m = [\surd(\langle K_{raw} \rangle \leq \langle K_{sur} \rangle)]/(39 + 1)$$

(where $\surd$ denotes the number of cases fulfilling the condition). We accepted the dynamics to be nonlinear when entropy ($\langle K \rangle$) for the surrogate data was significantly higher than that for the raw data. 13,000 multi-channel segments were thus characterized in this study (325 raw data + 39 $\times$ 325 surrogate data).

Principal Component Analysis (PCA)

PCA was used to better characterize the neuronal changes involved in the remission of depressive episode. It was computed on the data sets

composed of 31 entropy measurements obtained for all the EEG-segments (between 65 to 100) and for each subject. Such a representation serves to disentangle independent predominant components of the dynamics (Eckart & Young, 1939). These components are characterized by their loadings (contribution of each electrode to spatial organization of the component) and by their scores (projections of the measurements on the principal component). We obtained spatial pattern of the dynamics by projecting each score onto the electrode space (Fig. 5).

Statistical Tests

For each subject, the correlation coefficient (ρ) between the mood evaluation and the physiological indices (either global entropy or spatial mode scores) along the n experimental sessions were computed. Since the data were recorded from the same subject, we assessed the statistical significance of ρ using a non-parametric test based on a Monte-Carlo simulation (Lebart, Morineau, & Fénelon, 1982). Namely, we built $n!$ permutations of the physiological indices series and computed ρ between those surrogate series and mood assessment scores. The null hypothesis of independence was rejected when the probability to obtain $\rho_{\text{surrogate}} > \rho_{\text{observed}}$ was lower than 0.05.

RESULTS

In the case of the patients, the decrease between arrival and discharge scores to global depression, psychomotor retardation and anxiety rating scales, shows an improvement of at least 50% (Table 1) and fulfils criteria of clinical remission. Furthermore, scores to mood-assessment scales indicate an attenuation of the depressive mood (Fig. 5).

For each subject, surrogate data test ensures the presence of nonlinear processes in EEG-signals: the null hypothesis of linearly correlated noise was formally rejected for 26% of the segments studied (18% for Mrs. G., 27% for Mss. S., 24% for Mrs. R. and 36% for the control subject). These results are higher than the 2.5% of rejection which should be observed if the linear hypothesis was true, and they thus justify the use of nonlinear methods for EEG-quantification.

For the patients, averaged global entropy slightly decreases along treatment (negative slopes of the regression line: Mrs. G.: -1.0; Mss. S.: -1.2; Mrs. R.: -6.1) and depicts an important significant correlation with the mood modulation (Table 2 and Fig. 2). For the control subject (Mrs. I.),

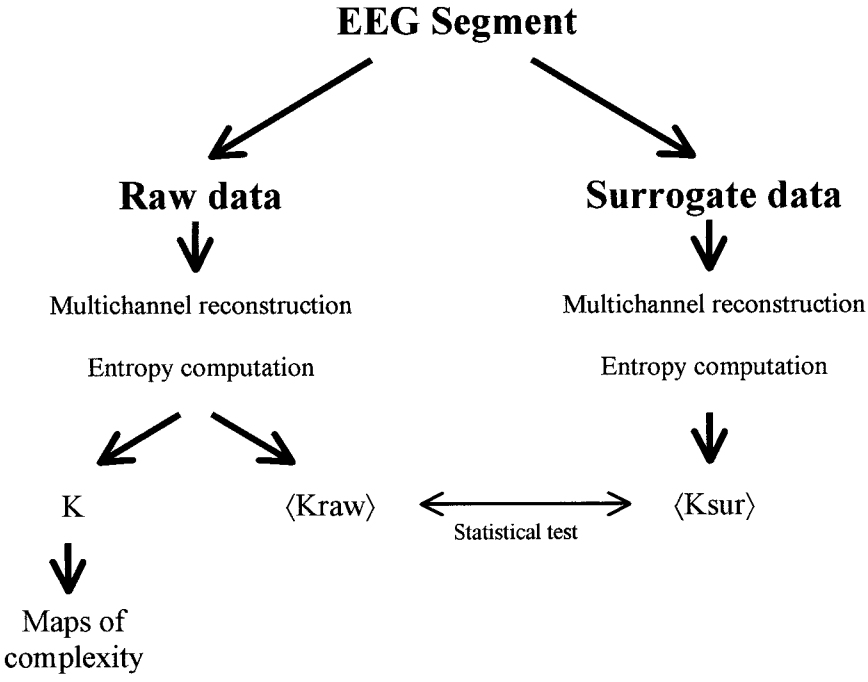

Fig. 1. Summary of the numerical procedure. See text for details.

this index slightly increases along the recording sessions (positive slope of the regression line: +0.9) and does not co-vary with her mood (Table 2 and Fig. 2).

In order to approach the neuronal changes involved in the clinical improvement, we proceed to PCA decomposition on the entropy maps

Table 2. Co-Evolution Between Mood Assessment Scores and Physiological Indices (Either Global Entropy and First Principal Component Scores) for the Depressed Subjects (Mrs G. Mss S. and Mrs R.) and the Control Subject (Mrs I). ρ: Correlation Coefficient; P: Probability of the Independence Hypothesis Rejection. Non-Significant Covariations Between Mood and Physiological Indices are Shown in Italics

	Global Entropy		First Component Scores	
	ρ	P	ρ	P
Mrs G.	0.65	0.036	0.64	0.028
Mss S.	0.91	0.004	0.83	0.016
Mrs R.	0.92	0.002	0.90	0.007
Control	−0.45	0.890	−0.50	0.900

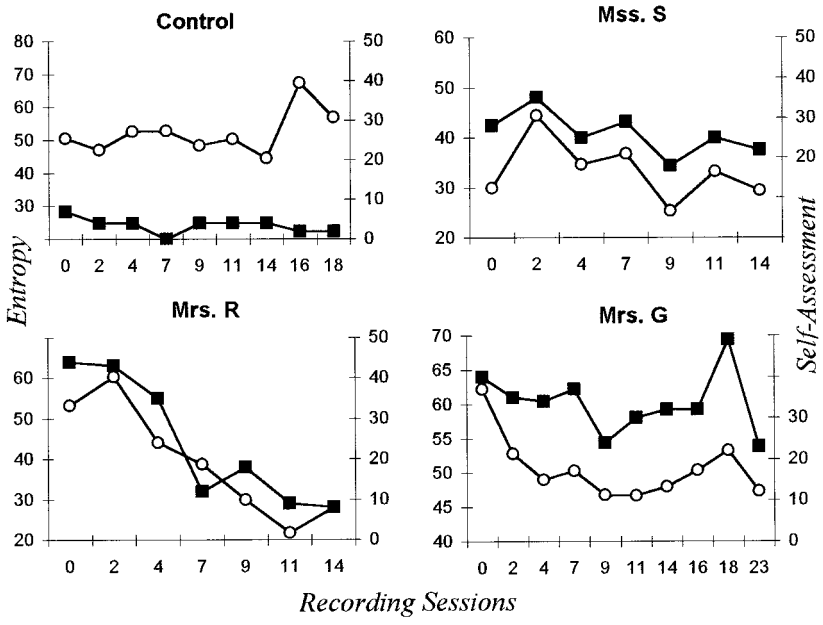

Fig. 2. Longitudinal variation of global entropy ($\langle K \rangle$) and scores to mood assessment scale for each subject. Entropy evolution is represented with open circles, and corresponds to the left ordinate axis scale. Depressive mood modulation is depicted with black squares and corresponds to the right ordinate axis scale. Days of recording are given in abscissa. Depressed patients: Mrs. G., Mss. S. and Mrs. R.; Control: Mrs. I.

data sets. The percentages of variance explained by the first ten components are depicted on Fig. 3. For each subject, the first two principal components were selected since each explains at least 10% of variance (cumulated percentages of variance: 38.6% for Mrs. G.; 48.2% for Mss. S.; 62.0% for Mrs. R. and 40.0% for the control). Their loadings are depicted on Fig. 4 and present two different patterns: (1) the first principal component corresponds, for all the subjects, to an overall level of complexity equidistributed over the scalp and (2) the second principal component depicts different patterns between the control subject and the depressed patients; the frontal electrodes have important loadings in the control subject whereas they have low ones in the depressed patients.

On the basis of the strong and significant correlation observed between the global entropy and mood scores for the patients only, we used the principal components to study, in their case, the correspondence between the spatio-temporal brain dynamics complexity and depressive mood along the recording sessions.

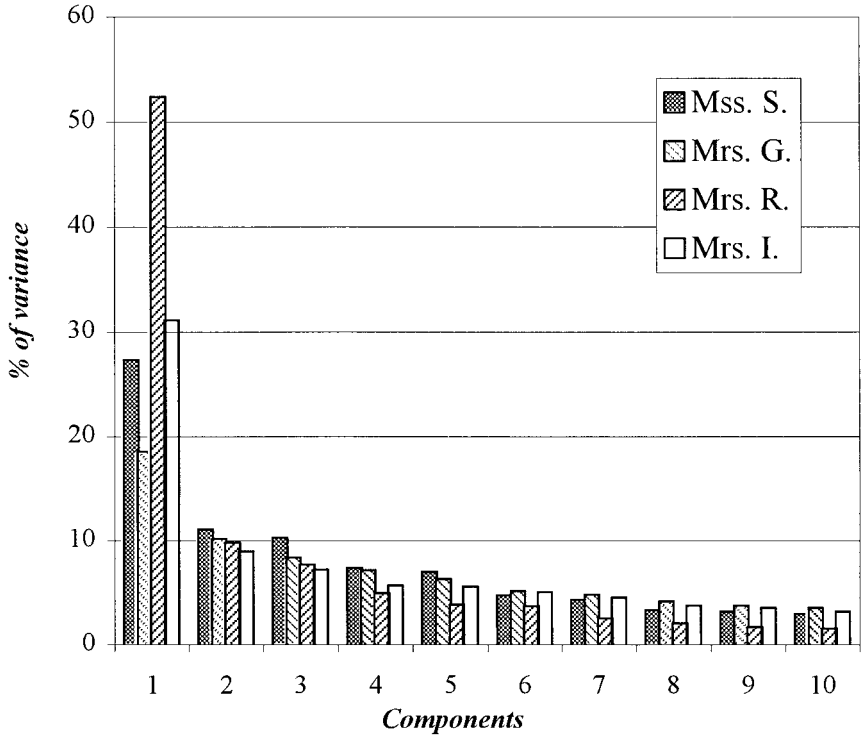

Fig. 3. Percentage of variance explained by the 10 first components of the principal component analysis of entropy maps in the four subjects (Depressed patients: Mrs. G., Mss. S. and Mrs. R.; Control: Mrs. I.).

For the patients, the evolution of the two main principal components scores along the recordings session is different: the first component scores co-vary with mood whereas the second component ones do not. The evolution of the first component reveals the daily modulation of brain dynamics (Fig. 5): It represents the *global level of the dynamics' complexity* and can thus be compared to $\langle K \rangle$. For all the patients, its scores values decrease with treatment and clinical improvement. Significant positive correlations between the first component scores and self-assessment scores were observed in all patients (Table 2). Moreover, in the case of Mrs. R., a drastic change in the global level of brain dynamics' complexity between day 4 and day 7 is associated with a clear drop of the mood assessment score. This phenomenon could be interpreted as a bifurcation (see Fig. 5c). For the other patients, the changes are less abrupt and could be related to nonstationarity of the brain dynamics. The evolution of the second compo-

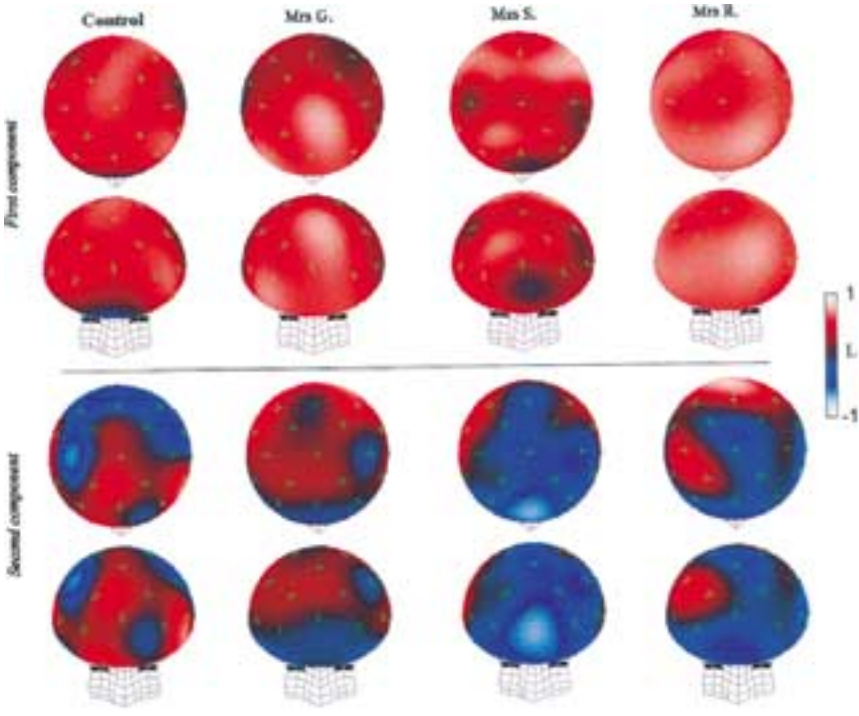

Fig. 4. Representation of the loadings (L, normalized for each subject to vary between −1 and 1) for the first two principal components and for each subject. Top and bottom of the figure represent the spatial organization of respectively the first and the second principal component. For each mode, top and frontal views of the head are respectively represented on the first and on the second line. Depressed patients: Mrs G., Mss. S. and Mrs. R.; Control: Mrs. I.

nent scores does not depict any significant correlation with mood assessment scores. This component is thus not directly associated with mood improvement.

DISCUSSION

On the basis of a covariation between depressive mood and global brain dynamics' entropy, we attempted to characterize the nonlinear changes of spatio-temporal brain activity that occur during the treatment of depressed patients. The entropy patterns decomposition has provided us with two major components. The first one is similar for all the subjects and depicts

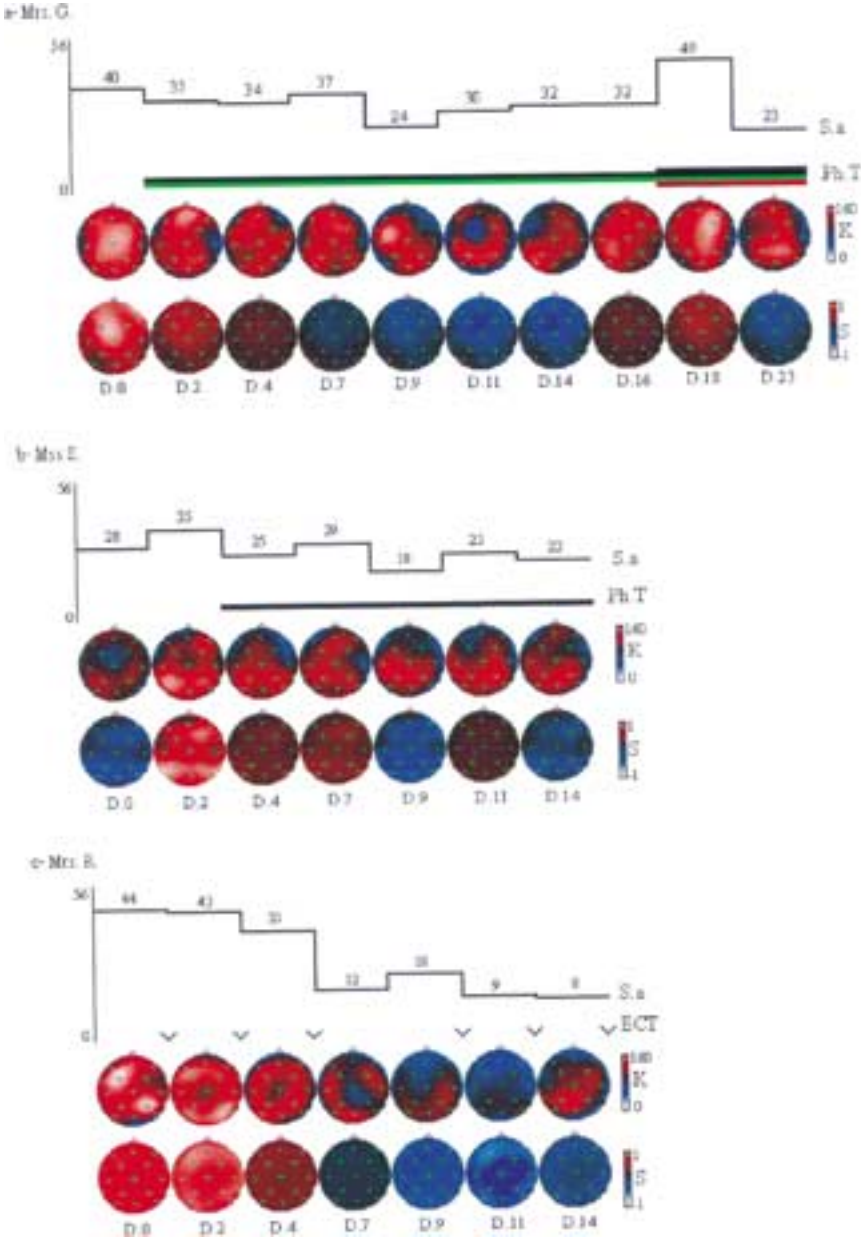

Fig. 5. Evolution of self-assessment scores (S. a.), treatments (Ph. T.: pharmacological; ECT: electroconvulsive therapy), maps of local entropies (K in sec^{-1}) and first principal component scores (S) along therapy for each patient. (a): Mrs. G. was treated with an anti-depressant (black line: citalopram, 20 mg/day from day 1 to day 16 and 40 mg/day after), anxiolytic (middle line: alprazolam, 20 mg/day) and a hypnotic (bottom line: cyamemazine 25 mg/day). (b): Mss S. was treated with an anti-depressant (black line: clomipramine 150 mg/day). (c): Mrs. R.'s ECT sessions are represented by V signs.

a pattern of equidistributed loadings which can be related to the global level of entropy. On the contrary, the second one depicts a specific organization characterized by lower loadings in the frontal areas of the depressed patients as compared to the control subject. This organization could be related to the alteration in the functioning of the frontal and prefrontal cortex (George, Ketter, & Post, 1994) in depression and may be a possible electrophysiological basis for the observed deficiency of cognitive processes.

The major observation of our study concerns the co-evolution of the global entropy and of the first component scores with mood variations along patients' treatment. Moreover, raw entropy maps depict comparable patterns for similar self-assessment scores in each patient (see for example Mrs. G.: day 0 and 18 are related to high scores whereas day 9 and 16 are related to low scores). These nonlinear changes of brain dynamics, in accordance with clinical improvement, attest of a correspondence between a mental state (depressive mood) and a cerebral state (brain dynamics characteristics). They thus appear as a common expression of behavioral and psychological recovery, independently from the treatment used. Such results strongly suggest that mood can be considered as a phenomenon emerging from the *global* interactions in brain activity as revealed by dynamical methods.

The changes in the first component scores, along treatment, can be related, in the case of Mrs. R., to the existence of a bifurcation in brain dynamics concomitant with mood modulation. This is particularly illustrated during her ECT treatment where a clear drop in her mood level is associated with a drastic change in the entropy level (Krystal, Zaidman, Greenside, Weiner, & Coffey, 1997). Nevertheless, in pharmacological treatments, such nonlinear changes are less abrupt and seem to lead to less stable states than in the case of ECT. It appears that the two treatments do not act in the same manner on the brain dynamics: ECT would lead to a critical change i.e. bifurcation and pharmacotherapy induce a progressive modification. Moreover, these results show that the first component is associated with mood improvement inducing the clinical recovery. In this way, this component could be compared to a principal spatial mode implied, as a driving mode, in the bifurcation process (Haken, 1987).

Concerning the second component, specific frontal reorganization in depressed brain dynamics has been reported, but it has not been directly implicated in mood improvement. These observations suggest that this second component could be compared to a second spatial mode depending upon the first one in the bifurcation process. In other words, cognitive processes recovery in the depressive syndrome, represented by the second component, could be driven by painful mood improvement represented by the first component.

The existence of nonlinear changes in brain dynamics associated with the changes in the patients' clinical state leads to reconsider the debate between state and traits in depression. We have shown that brain dynamics is not a constant trait of the pathology but rather the sign of a particular state. The passage between state, i.e. the clinical improvement, would thus be a modification of the depressed brain dynamics towards a new state.

CONCLUSION

This longitudinal and quantitative study of three depressed patients' brain dynamics demonstrated their specific spatial organization in regards to one control subject: The first two spatial modes have been respectively associated to global depressive mood and to cognitive processes. However, the main topic was the demonstration of a longitudinal covariation between brain dynamics complexity and mood, during different treatments of depressed patients. It demonstrates for these subjects a clear association between state of mind and brain dynamics organization. Moreover, whatever the therapeutic strategy used, the brain dynamics' evolution is similar for all patients and reveals a common way of recovery.

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