Nonlinear Dynamics, Psychology, and Life Sciences, Vol. 6, No. 3, July 2002 (© 2002)

Nonlinear EEG Changes in a 48-Hour Cyclic Manic-Depressive Patient

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This research report presents the case study of a 48-hour cyclic manic-depressive patient which further demonstrates the association between nonlinear EEG characteristics and mood variations as previously reported by Thomasson et al. (2000). The evolution of brain dynamics and mood were daily measured during a week. Global complexity of brain electrical activity was estimated by a nonlinear index (entropy) and mood modulations were evaluated by a clinical self-assessment scale (BfS'). Illustrating the concept of "dynamical disease," a significant co-variation between the nonlinear EEG index and mood evolution (Spearman correlation coefficient $\rho = 0.92$, $p = .008$) was observed. This result strengthens the previous ones and demonstrates a clear association between nonlinear brain dynamics and state of mind in psychopathology.

KEY WORDS: nonlinear analysis; EEG; manic-depressive II illness; bipolar disorder.

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1090-0578/02/0700-0259/0

INTRODUCTION

A *dynamical disease* (Mackey & Glass, 1977) is a pathological state associated with dynamical modifications in a physiological system's functioning (Glass & Mackey, 1979; Mackey & Milton, 1987; Bélair, Glass, an der Heiden & Milton, 1995a, 1995b). In particular for major depression, brain dynamics recover towards healthy characteristics after clinical remission of a first depressive episode (Nandrino et al., 1994; Pezard, Nandrino, et al., 1996). In a longitudinal study, Thomasson, Pezard, Allilaire, Renault and Martinerie (2000) showed that depressive mood improvement during treatment was associated with concomitant modifications of brain dynamics. These studies used nonlinear EEG quantifications to reveal brain dynamics changes. Other studies have also shown the usefulness of nonlinear tools for the characterization of EEG (e.g., Abraham, 1997; Basar, 1990; Lehnertz, Arnold & Grassberger, 2000; Watters, 1999). To further investigate the relationship between mood and brain dynamics, the present note reports the study of mood and brain dynamics in the case of a 48-hour cyclic manic-depressive patient.

Manic-depressive illness is a bipolar mood disorder characterized by the alternation between manic and depressive phases. It also depicts several modifications in physiological rhythms such as circadian rhythm (Bunney & Hartmann, 1965; Jenner et al., 1967; Paschalis, Pavlou & Papadimitriou, 1980), thyroidic secretion (Cho, Bone, Dunner, Colt & Fieve, 1979; Cowdy, Wehr, Zis & Goodwin, 1983; Bauer, Whybrow & Winokur, 1990), and sleep and temperature rhythms (Wehr & Goodwin, 1979; Wehr, Goodwin, Wirz-Justice, Craig & Breitmeier, 1982; Wehr, Muscettola & Goodwin, 1980). Consequently, the concept of "dynamical disease" is appropriate to consider this affliction. According to our previous results, we made the hypothesis of a concomitant variation between mood and brain dynamics.

Among bipolar disorders, 48-hour cycle manic-depressive trouble is an unusual case presenting a phase alternation each day, whereas usual time-course of the illness ranges from months to years (Sénon, Sechter & Richard, 1995). This exceptionally short time oscillation makes this trouble a promising model for experimental study of alternation of mood and EEG dynamics.

MATERIAL AND METHODS

Subject

M. O. is a 46 year-old man suffering with a chronic bipolar II disorder with rapid cycles (DSM-IV, 1994). He has presented an alternation of hypomanic periods and depressed periods (with psychomotor retardation) for eight years. A complete 48-hour cycle counts one 24-hour hyperactive

episode and one 24-hour hypothymic episode with retardation. However, hypomanic or depressed episodes may be more or less intense; when M. O. was recorded, depressed episodes were more salient than hypo-manic ones.

The hypomanic episode happens as following : M. O. wakes up between 4 and 5 am, his vigilance is normal and his appetite important. His work begins at 6 am. His mood is excellent and does not vary during the day. M. O. works late and can not fall asleep easily (more than one hour to be asleep). His circle describes him as a very active person "being too much on form." After a broken up sleep, M. O. can hardly get up and lays in bed till 10 am. He gets to work with difficulty and cannot concentrate; he feels excessively tired and his gesture are slowed down. Daytime is characterized by phases of drowsiness, morbid thought and a total loss of appetite. He comes back home early, goes to bed early, and falls asleep quickly. He sleeps without stopping once and wakes up next morning at 4 am. Then, a hypomanic period follows.

At the time of recordings M. O. did not receive any pharmacological treatment and was not hospitalized.

Experimental Sessions

In a case of daily evaluation of patients' mental state, only clinical self-assessment scales are valid. An analogical scale of depression feeling was used. It consisted in a straight line of 10 centimeters on which the subject had to draw a mark indicating his mood at 10 am and 10 pm every day. Mood was also assessed using the BfS' questionnaire (von Zerssen, Koeller & Rey, 1970; French translation: Bobon and Bobon-Schrod, 1974). To fill it out, the patient had to choose between two opposite adjectives (or none of them) the one which best corresponded to his state of mind. This scale contains 28 pairs of adjectives, which permit a scalar evaluation of the mood. Its scores vary between 0 ("relaxed" clinical state) and 56 ("extremely depressed" state). The latter scale was used to study the correlation that may exist between mood and brain dynamics.

EEG recordings were performed, as clinical assessment, every day during one week, with 31 leads referred to the ears and set on the scalp in an equi-distributed manner (Fisch, 1991). Vertical electro-oculograms (EOG) were recorded in order to perform off-line correction of eye movements (Gratton, Coles & Donchin, 1983). The upper band-pass limit was 0.08 Hz for EEG and 0.02 for EOG. Both lower 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 during the experiment on a hard disk of a Pentium 90 MHz, and then transferred onto the disk of a HP-K200 server for further processing.

EEG activity was recorded during an attentional listening task involving a motor response (Ragot, 1990). Two tones of identical duration (150 ms) but

of different frequencies (550 Hz and 1500 Hz) were randomly presented via earphones to the left or the right ear. On average, low and high tones were equi-probably distributed in each ear. The subject had to respond, as fast and as accurate as possible, by pressing a key with his right index finger for the low tones (80%) and with his left index finger for the high tones (20%), whatever the ear stimulated. The stimulus/response compatibility was thus implicitly manipulated (Ragot, 1990): the subject was not told about the stimulated ear, and consequently, about compatibility (ipsilateral response to the stimulated ear) or incompatibility (controlateral response to the stimulated ear) between the auditive stimulation and the motor response. Four categories of reaction time (RT) have thus been distinguished: a "compatible RT" and an "incompatible RT" for rare stimuli (high tones) and a "compatible RT" and an "incompatible RT" for frequent stimuli (low tones).

Nonlinear EEG analysis was performed on ten 8000-point (i.e. 8 sec.) EEG segments free of artifacts. The trajectory of brain dynamics was reconstructed for each segment in a 31-dimensional space by using multi-channel method (Dvorák, 1990; Pezard, Lachaux, Thomasson & Martinerie, 1999; Witney, 1936). Then, a nonlinear forecasting method (Pezard, Martinerie, Breton, Bourzeix & Renault, 1994; Sugihara & May, 1990) was applied. This procedure provides prediction curves depicting the decrease of the correlation coefficient between observed and predicted EEG as the prediction time increases. The initial decrease of predictability is used to compute an index called entropy ($\langle K \rangle$), which quantifies the loss of predictability during times (Pezard, Martinerie, Müller-Gerking, Varela & Renault, 1996; Wales, 1991). The higher the entropy, the more complex the EEG dynamics.

Since signals generated by linear stochastic processes can exhibit similar characteristics as nonlinear deterministic systems (Rapp, Albano, Schmah & Farwell, 1993), the presence of nonlinear processes in brain dynamics was ensured using multivariate surrogate data test (Prichard & Theiler, 1994). Surrogate data are constructed from the raw data by randomizing their phase in the Fourier domain (Theiler, Galdrikian, Longtin, Eubank & Farmer, 1992). The validity of nonlinear indices was tested by comparing K measures obtained on raw data to K measures calculated from 39 multivariate phase-randomized surrogates data (Pritchard & Theiler, 1994). EEG segments were considered as nonlinear when K computed on the surrogate data was significantly higher to K obtained on raw data (Rapp, Albano, Zimmerman & Jiménez-Montaño, 1994).

Finally, in order to evaluate the strength of the relationship between clinical and electrophysiological indices, a Spearman correlation coefficient was computed between the scores to the Bfs' scale and the entropy values averaged for each day.

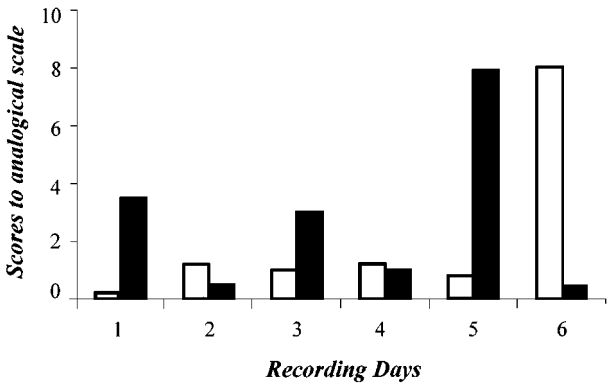

Fig. 1. Evolution of scores to analogical mood scale along the six consecutive recording days. Results were collected at 10 am (white bin) and at 10 pm (black bin). In the morning of odd days and evening of even days M. O. is not depressed, his scores are near 0.

RESULTS AND DISCUSSION

Analogical scales allow one to approximate when the change of clinical phase takes place. Indeed, in the morning of odd days and in the evening of even days, M. O. does not report depressed mood; otherwise, he reports depressive mood in the morning of even days and the evening of odd days (Fig. 1). These evaluations demonstrate that the clinical phase transition takes place during the evening, before 10 pm. Scores to BfS' depict the evolution of M. O.'s clinical states. An alternation between two levels of scores appears (Fig. 3): on even days, scores between 0 and 10 are obtained and on odd days, scores between 41 and 50 are obtained. These scores confirm the oscillation between relaxed and extremely depressed states along a 48-hour period.

Reaction times revealed a sensorimotor organization which differs according to the clinical phase (Fig. 2). During hypomanic phases: frequent sounds are treated faster than rare sounds, whatever the stimulus/response "compatibility" or "incompatibility" (respectively: $F_{1,16} = 17.14$, $p < .01$ and: $F_{1,16} = 14.81$, $p < .01$) and "compatible sounds" are treated faster than "incompatible sounds" (rare sounds: $F_{1,16} = 12.57$, $p < .05$; frequent sounds: $F_{1,16} = 17.42$, $p < 0.01$). During depressed phase, frequent stimulus are treated faster than rare ones as in hypo-manic phase ("compatibility": $F_{1,16} = 12$, $p < .05$ and "incompatibility": $F_{1,16} = 13$, $p < .05$). Otherwise, "compatible" or "incompatible" situations are treated with the same speed, be it associated with frequent or rare sounds (respectively $F_{1,16} = 4.57$, $p < .05$ and $F_{1,16} = 5.42$, $p < .05$).

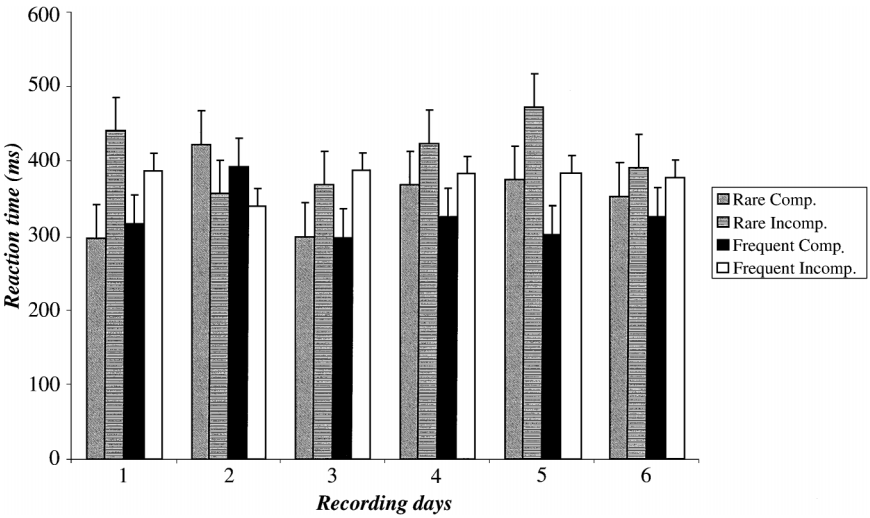

Fig. 2. Daily reaction times obtained in each experimental situation (see captions). During the depressed phase (even days), the stimulus/response compatibility or incompatibility does not affect the speed processing. Mean and standard deviation in each situation are: for rare compatible sound, 348.39 ± 45.13; for rare incompatible sounds, 415.33 ± 44.58; for frequent compatible sounds, 314.08 ± 38.63; for frequent incompatible sounds, 367.19 ± 23.20.

These results reveal a correspondence between behavioral strategies and clinical phases. Indeed, during the hypomanic phase, M. O.'s response strategies are equivalent to those observed in control subjects (Ragot, 1990); whereas during the depressed phase, the compatibility and incompatibility situations do not influence the processing speed unlike in controls. The sensorimotor organization is thus perturbed during depressive phase. However, this reorganization remains transitory and it is changed the following day.

Nonlinear techniques have been applied to EEG signals to obtain entropy index which have been statistically tested using surrogate data. In the present study, the hypothesis according which EEG segments are linearly correlated noise was rejected in 36% of the analyzed segments. This result justifies the use of nonlinear quantifiers.

Fig. 3 shows the daily alternation of clinical phases (mental states) and nonlinear EEG quantifiers (brain states). A correspondence between mood and brain dynamics is evidenced: high values of K are related to important scores to mood (i.e. depressed day), otherwise low values of K are associated with low scores to the mood scale (i.e. hypo-manic day). The Spearman correlation coefficient ($\rho = 0.92$) quantifies a significant ($p < .01$) correspondence between nonlinear EEG characteristics and mood alternation in this 48-hour cycle manic-depressive patient.

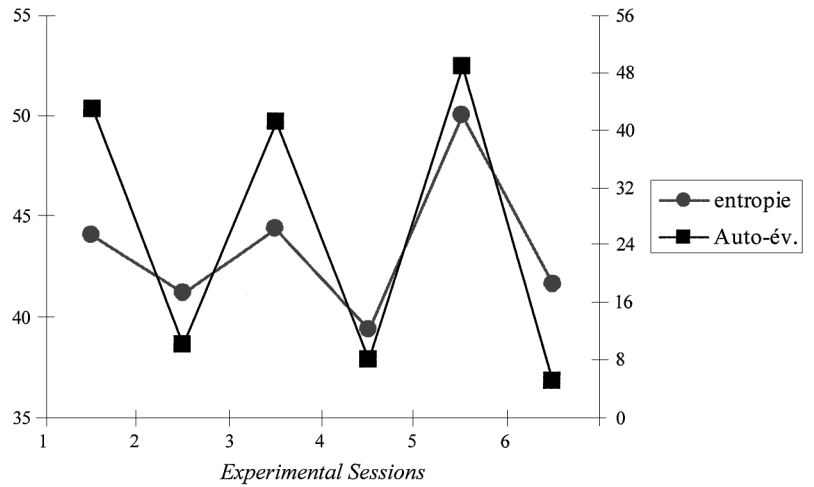

Fig. 3. Daily evolution along the six consecutive recording days (experimental sessions, *X*-axis) of the scalar mood scale (Bfs') and electrophysiological indices. Oscillations in clinical phase are given by the variations of scores to self-assessment scale (black squares), notified by the right *Y*-axis. Changes in brain dynamics are rendered by the evolution of nonlinear EEG index (entropy, in gray circles), notified by the left *Y* axis (Spearman correlation coefficient = 0.92; $p < .01$).

These results show the existence of two cerebral functioning depending on mood during rapid oscillations in a case of bipolar II disorder. This strengthens previous observations where an attenuation of depressive mood during hospitalization was associated with a decrease of entropy in brain dynamics (Thomasson et al., 2000).

This longitudinal study of a manic-depressive illness with a 48-hour cycle characterizes clinical states using behavioral and nonlinear EEG indices. It demonstrates that brain dynamics and sensorimotor strategies alternate, following mood, between two organizations. Indeed, a low level of entropy of the brain dynamics (hypomanic phase) is associated to sensorimotor characteristics similar to those previously found in control subjects (Ragot, 1990), whereas a higher level (depressive phase) corresponds to an altered sensorimotor organization. Mood alternation is thus associated with simultaneous modifications of nonlinear EEG characteristics and behavioral organization. These changes demonstrate a narrow relationship between specific pathological mental states and cerebral/behavioral functioning.

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