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Discovery of recurrent multiple brain states in non-convulsive status epilepticus

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Abstract

Objective: We study burst-like patterns of epileptiform discharges in non-convulsive status epilepticus (SE).
Methods: Epileptiform burst-like transients were identified by estimating the amplitude envelope of the EEG signal, and recurrence and similarities were identified by pairwise matching in the time-domain.
Results: We identified similarities in the onset of a significant fraction of the epileptiform bursts, and a bimodal distribution of the burst durations.
Conclusions: Bursts of epileptiform discharges during a non-convulsive SE are manifestations of multiple patterns of recurring brain states.
Significance: Quantitative description of ictal phenomena in epilepsy and status epilepticus adds to the knowledge of abnormal brain behavior and may assist in improved patient care.

Keywords: Seizures; Non-convulsive status epilepticus; Bursts; Nonlinear; Self-similarity

1. Introduction

In various neurological conditions, the EEG shows abrupt transitions between periods of relatively low-voltage activity and large-amplitude burst-like events in the form of spikes, poly spikes or sharp and slow waves. These burst-suppression (BS) patterns may occur in states of severe cerebral damage in postanoxic encephalopathy, anesthesia, or prematuritas. Remarkably, burst-like transients are also observed in neuronal cell cultures (van Pelt et al., 2004a,b).

Similar EEG phenomena can sometimes be observed in patients suffering from a generalized status epilepticus. Treiman (Treiman et al., 1990) describes five identifiable EEG patterns in a predictable sequence during the course of a generalized convulsive status epilepticus in humans. Treiman stage I, for instance, is characterized by discrete seizures, with interictal slowing, and Treiman stage IV by ictal discharges with relatively quiescent periods of generalized low-voltage activity with a duration of 0.5–8 s. The phenomena observed during the ictal discharges in these patients are periodic or almost periodic, while this may be less prominent in a BS EEG pattern.

However, one of the pronounced similarities between a BS-pattern and the states as described by Treiman is the presence of relatively abrupt large-amplitude events punctuated by low-amplitude events. The common clinical feature is that in all these burst-like conditions, consciousness is severely reduced or absent. It is indicative of

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abnormal or – in the case of prematuritas – immature, brain function.

Various attempts have been made to explain the cause and dynamics of the brain derangement that is present in burst-like brain conditions. Some theories suggest a reduction of thalamic afferent input (Andersen et al., 1967) or, alternatively, a loss of the insulating properties of white matter (van Leeuwen, 1964). To explain burst-like conditions, these theories need to take into account a marked variation in both the burst-like and suppression durations. Rae-Grant (Rae-Grant and Kim, 1994) proposes that a burst-suppression pattern is consistent with type III intermittency (Pomeau and Maneville, 1980) behavior. This behavior is reminiscent of that of nonlinear dynamical systems operating at a transition to chaos. Their study included eight patients, suffering from head injury or anoxic encephalopathy. Type III intermittency is presumably also present in some cases of human partial epilepsy. By quantitative analysis of the duration of the burst-like regular or almost periodic phases during the ictal events, Perez Velazquez et al. (Velazquez et al., 1999) suggest the presence of transient stabilizations of otherwise unstable states. Quite generally, however, the phenomenology of a change of stability in a nonlinear system (with a fixed number of degrees of freedom) is difficult to distinguish from a neural network with intermittent levels of interconnectivity.

In this paper, we study the phenomenology of the onset of burst-like transients in two patients suffering from a non-convulsive SE. In this pathology, the burst-phenomena show distinct patterns of repeating behavior, even when the bursts themselves appear randomly in time. In Section 2, we discuss the patients' history and our method of EEG analysis. The results are described in Section 3, and we summarize our findings in Section 4.

2. Patients and methods

Patient G, a 55-year-old female, was admitted to our hospital for analysis of potential renal failure. In the morning of the second day in the hospital she was found unconscious. Computed tomography showed no abnormalities; laboratory investigation showed high urea and creatinine, without additional abnormalities. Suspicion of a non-convulsive status epilepticus was raised. Subsequent EEG recording showed more or less periodic epochs with epileptiform discharges and periods with low-voltage slow waves. The epileptiform discharges were mainly limited to the right hemisphere. She was transferred to the intensive care unit and treated with propofol, until the EEG showed disappearance of the epileptiform discharges. She recovered well from the status epilepticus, but unfortunately died 3 days later from a non-neurological condition.

Patient W, a 60-year-old female, was admitted to our hospital on June 8, 2005. She suffered from a single tonic–clonic seizure, but did not recover consciousness after 1–2 h. Computed tomography of the brain showed no abnormalities. Subsequent EEG monitoring (16 h) showed periods with epileptiform discharges, punctuated with low-voltage activity and slowing. This continued for several hours, while she was treated with phenytoin intravenously. In the course of 1–2 days, she slowly recovered, and the EEG normalized. Interestingly, the severe depression she was known with had completely disappeared.

EEG fragments of both patients are presented in Fig. 1. A detail of the EEG recording of patient G is displayed in Fig. 2. The burst-like appearance of the epileptiform discharges is evident. In this paper, we will denote these events with epileptiform discharges by burst-like transients or sometimes by bursts only.

2.1. EEG recordings

EEGs were recorded with a Brainlab digital EEG system (OSG, Belgium) using a 250 Hz sampling frequency (16 bit). Filter settings were 0.16–70 Hz. The EEGs were recorded with Ag/AgCl electrodes placed at the Fp2, Fp1, F8, F7, F4, F3, A2, A1, T4, T3, C4, C3, T7, T5, P4, P3, P2, O1, Fz, Cz, and Pz loci of the international 10–20 system. Impedance was kept below 5 KΩ. Total recording time in patient G was approximately 100 min, in patient W approximately 17 h.

2.2. Detecting bursts

We observe bursts with mean amplitudes of 80 μV or more, while the low-amplitude inter-burst EEG shows amplitudes of the order of 20 μV. Typically, therefore, the ratio between the bursts and the low-amplitude events is approximately 4:1 or higher. We now proceed as follows.

Data were analyzed in epochs of 1000 s. In this epoch the amplitude of the EEG was normalized by dividing the signal by the maximum of the RMS, realizing a normalized signal with values in the range [0–1]. A total recording time of 83 min was available in patient G, and of more than 600 min in patient W.

Subsequently, the mean amplitude of the normalized signal, S^*, was estimated for subsequent epoch lengths (step size 1/250) with duration of 250 samples (1 s). This provides an envelope of the signal, with values between 0 and 1. By setting an appropriate threshold, typically between 0.2 and 0.4, the beginnings of the burst-like transients were identified. The threshold was determined by visual inspection of the initial phases of the bursts.

Since the epileptiform discharges were present synchronously in various bipolar derivations on one of the hemispheres, analysis was performed on a single bipolar derivation, T6-O2, in both patients. We note that this was not critical, and other bipolar derivations would yield similar results.

The correlation between the initial phases of all possible burst-like transients was determined using an automatic routine written in Fortan90. Bursts were considered initially identical for the period of 600 ms if the correlation in this interval was $\geqslant 0.925$. To ensure optimal alignment,

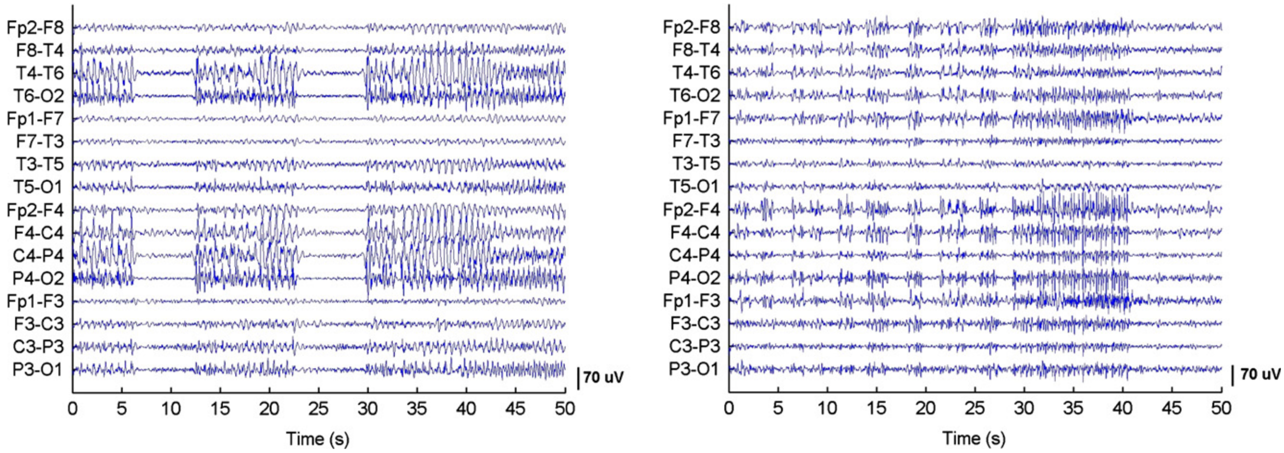

Fig. 1. Part of the two EEG recordings from our patients. Both EEGs show epileptiform discharges punctuated by low-voltage'flat periods'. Left: from patient G, Right: from patient W. A detail is shown in Fig. 2.

after the initial detection of the initial phases of the bursts, one of the bursts was shifted over a distance of −50 to 50 samples, starting at the detected burst threshold, and the correlation coefficient was calculated for each time lag. Optimal alignment was defined by the maximum value of the correlation coefficient.

From this procedure the following parameters were obtained: burst frequency (BF), inter-burst intervals (IBI), and burst durations (BD). In addition, we estimated the fraction of bursts that repeat (RF), defined as the number of bursts that repeat at least once (BR), normalized by the total number of bursts (B), i.e.

$$\mathrm{RF} = \frac{\mathrm{BR}}{B}. \tag{1}$$

All other routines were implemented in Matlab (The Mathworks, Inc.).

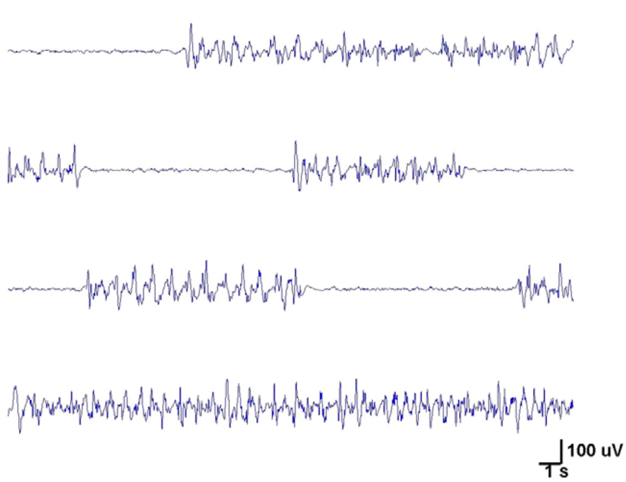

Fig. 2. Example of 80 s of EEG (bipolar derivation P_4–O_2 from patient G). Each trace is 20 s in duration; 4 consecutive epochs are shown. Note the flat periods with durations of the order of seconds.

3. Results

An illustration of the time series, with the corresponding 'envelope', is presented in Fig. 3. By setting the appropriate threshold, the beginning and end of all epileptiform discharges was identified.

To obtain a first impression of the time course of the various events, we estimated the spectrum of the envelope. Results of this analysis are presented in Fig. 4. At least two significant peak frequencies are observed. Patient G shows dominant frequencies at approximately 0.01 and 0.1 Hz, where patient W shows dominant frequencies at approximately 0.1 and 0.2 Hz.

In Fig. 5, the distribution of the duration of the ictal discharges (BD) and the interictal periods (IBI) is presented for both patients. In addition, we investigated if (parts

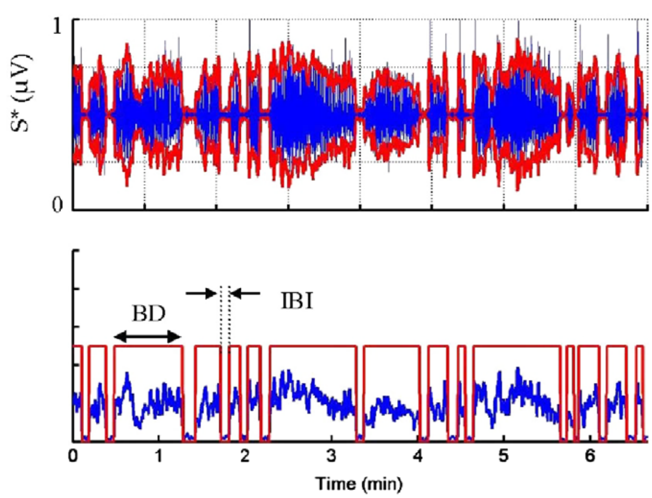

Fig. 3. Top: Part of the envelope of a particular EEG channel in patient G (red curve). Setting the appropriate threshold (in this case 0.20) allows estimation of the duration of the phases with and without epileptiform discharges, as indicated in the bottom curve. IBI, inter burst interval; BD, burst duration.

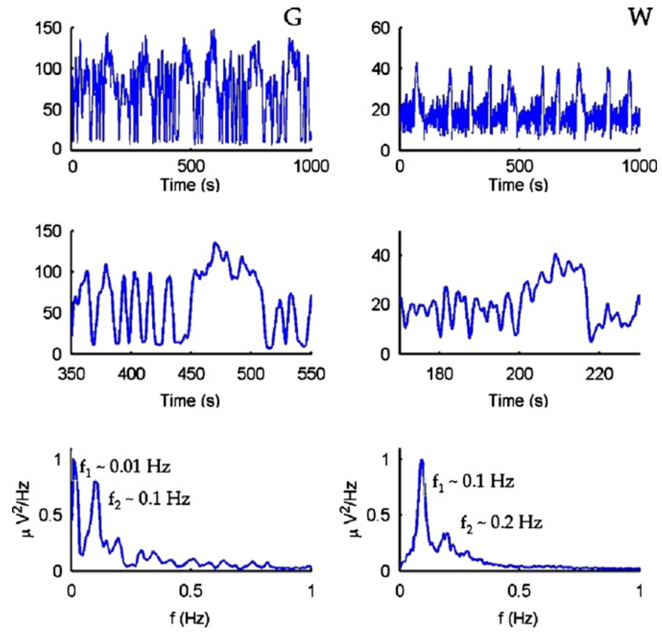

Fig. 4. Upper two graphs show part of the time series obtained after estimation of the mean power from 1 s duration epochs, for subsequent epochs shifted in time by 0.2 s. Middle row shows detail from both patients. Note the multiple 'high-frequency' oscillations that precede the period characterized by a longer duration of the epileptiform discharges. At the bottom, the spectra are shown. There are two major peaks visible, indicating the presence of (at least) two oscillators. Left: patient G, Right: patient W.

of) the distribution showed a power law distribution. The inserts show the various distributions on a log-log scale, where the data are binned into exponentially wider bins, letting them appear evenly spaced. The lines are fitted to the first mode of the bimodal distribution, i.e., the short bursts, with slopes between $\sim\!-0.9$ and -3, as indicated.

Detailed examination of the beginnings of the various burst-like transients reveals the presence of various similar waveforms during the first 600 ms (or longer), followed by divergence of the waves. This is exemplified in Fig. 6. The initial part of the tracings is almost similar, but divergence of the two waveforms occurs after about 0.4–1 s, indicating sensitivity to initial conditions. Approximately 37% of the bursts in patient G and 59% of the bursts in patient W were at least 'repeated' once. The time intervals between recurrent bursts varied from 10 to more than 1000 s. An overview of the burst features is presented in Table 1.

4. Discussion

The electroencephalographic discharges that can be observed during status epilepticus show a rich phenomenology, which includes continuous and discontinuous patterns, as well as periodic and non-periodic features. In patients suffering from generalized convulsive status epilepticus, Treiman et al. described five different EEG patterns, which occur in a predictable sequence (Treiman et al., 1990). Similar phenomena can be observed in experimental epilepsy models in rats as well (Treiman et al., 1990;Koplovitz and Skvorak, 1998).

In this paper, we noted similar phenomena in two patients suffering from a *non-convulsive status epilepticus*. In fact, the EEG patterns observed in our patients bear a strong similarity to the Treiman stage IV, that is characterized by continuous ictal discharges, punctuated by brief (0.5–8 s) episodes of generalized flattening on the EEG. According to the original description by Treiman, this EEG pattern is associated with overt or subtle focal clonic movements or no motor symptoms at all. In our patients, no motor symptoms were noted, and they were clinically classified as suffering from a non-convulsive SE. Of course, we cannot exclude that patient G did experience Treiman stages I–III clinically unnoticed, for instance due to a short duration and the intermittent nature of our clinical evaluations.

Spectral analysis was primarily intended to obtain a first impression of the frequency characteristics of the various events. In both patients, spectral analysis of the envelope of the time series disclosed two significant frequencies. The oscillators responsible for their occurrence are not strictly periodic, as can be observed from visual inspection of the time series and the width of the spectral peaks.

Another common feature in our two patients was the bimodal distribution of the duration of the epileptiform discharges. Although this seems less clear in the distribution of patient G (due to the smaller amount of data available), it is present in this patient as well. In fact, this information is also contained in the time series presented in Fig. 4, showing many 'short-duration' events and less often events with a longer duration. Additional analysis suggests a power law for the short-duration bursts.

Power laws are observed in a wide variety of natural phenomena and mathematical models. Examples include Gutenberg–Richter's law of earthquakes, Zipf's law in linguistics and size distributions of avalanches in models of self-organized criticality (bak, 1996a). If a power law behavior is observed, it implies that the system is scale free, i.e., its behavior is similar for different observational scales. As an example, the phenomena that are relevant in a devastating earthquake are similar to the phenomena during a minor earthquake. Distributions that potentially obey power law behavior are characterized by a long-tail, in contrast to exponential distributions. Observations that are limited to a few orders of magnitude, therefore, are sometimes insufficient to discriminate between these two alternatives. Some propose to claim power law behavior only, if a linear relationship exists only if a straight line is present on a log-log graph over 3 or more orders of magnitude. Therefore, the results presented in Fig. 5 need to be interpreted with caution, since the linear relationship between the burst duration of burst interval and the number of bursts extends only over 1–2 decades. Nevertheless, we can conclude, however, that both the transitions and the burst durations have a distribution with a long tail, suggesting that the transitions occur randomly in time.

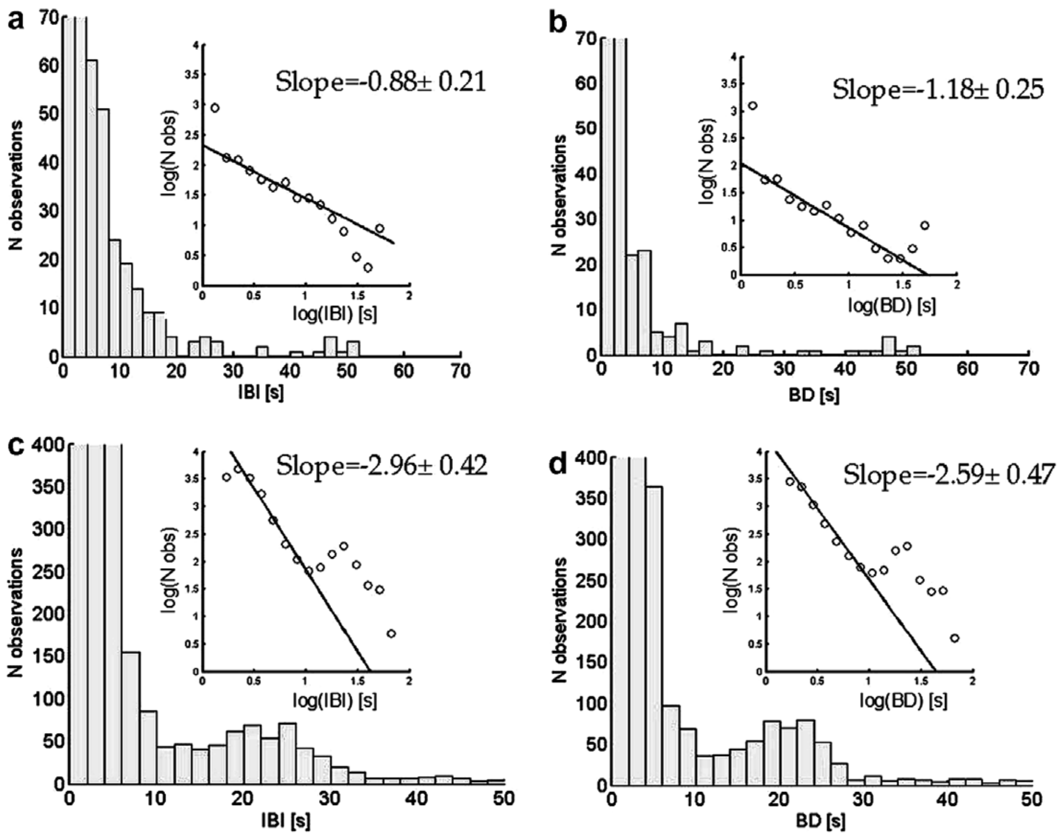

Fig. 5. Distribution of the inter-burst durations (IBI) and the burst durations (BD). Distributions are truncated on the *y*-axis to allow a view of the distribution of the less common events. Upper two graphs, (a and b) are from patient G; lower two graphs (c and d) are from patient W. The inserts show the distribution on a log-log scale. Lines are fitted to the linear part of the distribution of the first mode of the bimodal distribution; slopes obtained are indicated.

A random temporal structure in transitions has been observed previously in models of bi-stable neural networks (Suffczynski et al., 2004). Intermittent transitions have also been studied recently by Suffczynski et al. using both data from animal models of absence epilepsy, human epilepsies and in vitro models (Suffczynski et al., 2006). Distributions of ictal and interictal events were fitted with a gamma distribution. This study showed, amongst others, that the transitions between the ictal and interictal states can be modeled by a Poisson process operating in a bi-stable network.

The type III intermittency reported in a previous study (Velazquez et al., 1999) is not evident in our two patients, given the values of the slopes found (values between ~ -0.9 and -3) and the bimodal distributions. Bimodal distributions are observed in various other conditions, e.g., in the evolution of ocean waves (Wang and Hwang, 2000), where it indicates the presence of nonlinear wave–wave interactions.

The most striking feature in our patients was the observation of a large fraction (∼40–60%) of recurrent bursts, characterized by a strong initial similarity in waveform

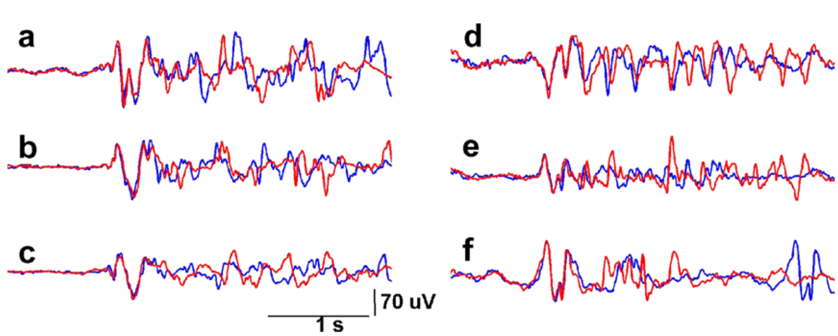

Fig. 6. Morphology of the epileptiform discharges. Left (a–c): data from patient G and Right (d–f): from patient W. The initial portions of the pairs of traces shown are similar, with divergence of later waveforms (red and blue, respectively).

Table 1
Overview of mean burst characteristics of the two patients analyzed

Patient	BF (Hz)	BD (s)	IBI (s)	RF (%)
G	0.11	4.0	5	37
W	0.22	2.9	1.5	59

BF, burst frequency; BD, burst duration; IBI, inter burst interval; RF, repeat fraction.

during the first 600 ms (or longer) of the burst. Although previous authors have discussed stereotypy in burst-suppression EEGs (Hughes, 1986), this was related to the recurrence of similar bursts. The ictal discharges observed in our patients, however, show *initial similarity* of waveforms and *subsequent divergence* of waveforms. These results are also different from those reported in the paper by Rae-Grant (Rae-Grant and Kim, 1994), discussing burst-suppression patterns. They do not observe divergence of waveforms, but rather manifestations of different burst morphologies, that are seemingly randomly followed by a variety of different bursts. We note, however, that the additional evidence for type III intermittency in this paper is convincing through thorough analysis of their EEG patterns.

The initial overlap between bursts of the same type in our analysis extends over a period of about 400 ms. For this reason, the identification of burst-type was by matching in the time-domain over a window of 600 ms. Changing the correlation threshold to a value slightly different from 0.925 does not change the number of types of bursts found.

The recurrent self-similar burst patterns observed in our patients strongly suggest the presence of several unstable equillibria. We attribute this to a change of stability in an underlying nonlinear process, as when approaching a saddle point in a nonlinear system or in the formation thereof due to a change in system parameters. This is supported by the accurate reproduceability of the observed self-similarity over extended periods of burst-patterns. The nonlinear process may represent coherent and synchronous behavior in a neural network with a commensurate reduction to a low number of degrees of freedom. The divergence of initially similar bursts can be caused by a strong dependence on the initial conditions, as in a nonlinear system in transition to chaos. However, the same behavior may represent a gradual restoring of normal behavior in a neural network by stochastic decay of aforementioned coherence. The EEG data do not have sufficient resolution to distinguish between such alternatives, e.g., by discriminating between exponential behavior, described by a Lyapunov exponent, and power-law behavior, described by a time-scale of intermittency associated with aforementioned restoring towards normal behavior.

It should be mentioned that the phenomenology observed in two patients of the present study has also been observed in 6 other patients. The overall behavior is very similar to the presented results, so that these clinical results do not add to particular EEG dynamics reported here in non-convulsive SE. Such larger group of patients is needed, however, to derive clinically relevant parameters, for instance for prognostication or evaluation of treatment effects. It is noted, however, that recordings of this kind are not easy to obtain, given the (presumed) low incidence. For this reason, the present analysis is applied on an incremental basis in our hospital for future research.

In summary, we report on the discovery of recurrent bursts with initial self-similarity in patients suffering from a non-convulsive status epilepticus. We attribute the observed self-similarity to the presence or spontaneous emergence of saddle points in a nonlinear large-amplitude dynamical process. This is an important result, as it appears in a significant fraction of the bursts which has not hitherto been identified in the phenomenology of epileptic seizures. This lends considerable support that these pathological states are well described by nonlinear dynamics, probably associated with a spontaneous formation of coherent behavior in a neural network with anomalous reduction of the number of degrees of freedom. This is consistent with the strong reduction in consciousness as observed in these two patients.

Acknowledgements

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