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Exposure induced changes in EEG phase synchrony and entropy: A snake phobia case report[1]

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ABSTRACT. In this case study the electroencephalographic (EEG) activity of a 23 years old snake phobic patient was recorded one week before treatment, one week after successful one-session exposure therapy, and one year later. EEG recordings were obtained at rest and during exposure to pictures of snakes, pictures of equivalent arousing power, and emotionally neutral images, all of them taken from the International Affective Pictures System. Measures of brain dynamics were sample entropy (SampEn) for each EEG signal/channel and phase synchronization between pairs of EEG channels. Results showed dramatic changes in both measures one week after treatment: SampEn increased and phase synchrony decreased at all sites and pairs of channels respectively. At follow-up, however, we found patterns of entropy and synchrony change across conditions that were similar to the pre-treatment ones, while the patient did not report any fear at all. Despite the limitations of single case studies, these results suggest that the exposure-induced changes in EEG entropy and synchronization are large but

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transient. The transient increase of the brain's flexibility could be one of the working neurophysiological mechanisms of exposure therapy.

KEY WORDS. Exposure therapy. EEG. Entropy. Synchronization. Single case experiment.

RESUMEN. En este estudio de caso único se registró la actividad electroencefalográfica (EEG) de una paciente fóbica a las serpientes una semana antes del tratamiento, una semana después de una exitosa terapia de exposición en una sesión y un año después. El EEG se obtuvo en situación de reposo y durante la presentación de imágenes de serpientes, imágenes con un valor de activación equivalente e imágenes emocionalmente neutras, todas ellas pertenecientes al Sistema Internacional de Imágenes Afectivas. Se midió la entropía (SampEn) de cada señal/canal y la sincronización de fase entre pares de canales EEG. Los resultados mostraron cambios pronunciados una semana después de la intervención: la entropía aumentó en todas las localizaciones y la sincronía de fase decreció en todos los pares de canales analizados. En el seguimiento, la paciente no presentaba ningún miedo pero los patrones de cambio en EEG eran similares a los observados antes de la intervención. A pesar de las limitaciones metodológicas, estos resultados sugieren que los cambios inducidos por la exposición en la entropía y sincronización del EEG son importantes pero pasajeros. El aumento de la flexibilidad cerebral podría ser uno de los mecanismos neuropsicológicos de la terapia de exposición.

PALABRAS CLAVE. Terapia de exposición. EEG. Entropía. Sincronización. Experimento de caso único.

Despite the extensive use of many behavior therapy techniques, such as desensitization or exposure, there are however little empirical evidence about the involved neurophysiological mechanisms in behavioral changes elicited by those techniques. According to a recent review by Choy, Fyer, and Lipsitz (2007) physiological outcome measures are less used than self-reported measures in specific phobia treatment studies. For example, only six of the 31 follow-up studies examined by the authors included physiological measures (heart rate and blood pressure). Furthermore, none of the 31 studies included measures of the central nervous system activity. To search for those «working mechanisms» clinical research should explore changes in the patient's biological (*e.g.*, neurophysiological or psychophysiological) variables. In a broader sense, Bornas and Noguera (2002) pointed out that cognitive behavior therapy should use contemporary science concepts (chaos, fractals, complexity, self-organization, and so on) to find out renewed and more complete scientific foundations for its techniques.

The electroencephalography is a classical technique to examine brain activity changes related to behavioral processes. There is now an extensive literature providing different EEG parameters, which could be very useful in clinical contexts. There are, however, only a few studies devoted to the analysis of EEG changes as consequence of behavior therapy. As an example of the gap between basic (neurophysiological) and applied research in cognitive-behavioral psychology, despite the growing number of studies on

the role of entropy (irregularity) and EEG phase synchrony in cognitive functioning (see below), little is known about either entropy or synchronization among EEG channels in clinical settings. Regarding specific phobias, while the clinical efficacy and effectiveness of one-session exposure procedures (Öst, 1989) has been widely demonstrated (see for example the recent study by Bermúdez-Ornelas and Hernández-Guzmán, 2008), the effects of such procedures on the EEG are almost unknown. Technical difficulties related to obtaining EEG recordings from several participants at the same time might account for the small number of exposure treatment group studies reporting EEG data (the Davidson, Marshall, Tomarken, and Henriques [2000] study on social phobia is a good exception to this rule, as it is the one carried out by Merckelbach, Muris, Pool, and De Jong [1998] with spider phobics).

Single case treatment studies, on the other hand, allow for a detailed description of the neurophysiological data collected before and after exposure therapy. As pointed out by Virués-Ortega and Moreno-Rodríguez (2008), one of the aims of single-case studies is to report some new procedure or technique. In this study, we used EEG phase synchronization as a measure of nonlinear brain functioning that has not been used in any previous treatment study. Furthermore, single-case reports can be very useful to better understand emotions. The study of the bioelectrical macroscopic brain activity during anxiety/fear has been largely based on the induction of this emotional state in healthy volunteers by means of stimuli presentation (*e.g.*, pictures or videoclips) or actualization in memory of experienced emotionally significant events (*e.g.*, Aftanas, Reva, Savotina, and Makhnev, 2006; Costa, Rognoni, and Galati, 2006). Despite the valuable knowledge achieved with this method, a crucial question remains unsolved: how can we be sure of what specific emotion are they feeling? The same picture (*e.g.*, a mutilated human body or a snake) can evoke fear in one person, disgust in another one, and sadness in a third one. Nevertheless, if we can look at the EEG of a phobic person while he or she is experiencing fear then we would be able to describe the "true" fear-induced changes in the bioelectrical activity of the patient's brain.

Phase synchronization

It is now widely accepted that behavior arises from communication between neurons within and between complex networks. In this context, the EEG can record electrical brain activity from simultaneous dendritic activity in a large population of neurons, and it seems possible to investigate the network properties on a macro-level, such as, for example, phase synchronization and entropy. Long range synchrony, or the synchronous firing of neural ensembles located in different brain regions, has been proposed as a major candidate mechanism for integrating information in the brain (*i.e.*, a mechanism of "binding" the activity in parallel networks). The role of long range synchronization has been investigated in relation to processes as different as working memory (Stam, van Cappellen van Walsum, and Micheloyannis, 2002), listening to music (Bhattacharya, Petsche, and Pereda, 2001), visual perception (Rodríguez *et al*., 1999; see also Makeig *et al*., 2002), consciousness (Thompson and Varela, 2001), seizure and mania (Bhattacharya, 2001), and schizophrenia (Breakspear, 2006; Lee, Williams, Breakspear, and Gordon, 2003) among others. It seems reasonable to expect that long range synchrony could also play

a relevant role during the emotional experience of fear. From a psychopathological point of view it is interesting the idea that while synchrony "may facilitate integrative functions requiring co-operative processing in different networks across the brain [...] desynchronization may allow the brain to switch flexibly between one coherent state and another" (Breakspear, 2002, p. 176). Phobic fear can be seen as the inability to switch between states: the feared stimuli can capture the whole attention of the patient who feels unable to look at any other place, or, on the contrary, may evoke a strong avoidance response and the patient will not look at all at the stimuli. In both cases, however, there is a common inability to switch. Therefore one of our hypotheses is that fear would evoke a clear increase in long range synchronization. In addition to theoretical reasons, the recent study by Costa *et al*. (2006) reported EEG synchronization increase in several frequency bands when participants were presented emotional clips (happiness, sadness, neutral). Although it is not a treatment study and subjects were healthy volunteers, results point out the same relationship between emotional state and changes in EEG synchronization described in our hypothesis.

Entropy

A further feature of the EEG is its irregularity and non-dynamical properties. Approximate entropy (ApEn) was introduced by Pincus (1991) as a measure of irregularity and complexity (Pincus, 1995) in relatively short and noisy time series like the ones that usually are found in the output from living systems. ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on the next incremental comparison (Pincus, 2000). Richman and Moorman (2000) introduced the sample entropy (SampEn) as a new and related complexity measure which "is largely independent of record length and displays relative consistency under circumstances where ApEn does not" (p. H2039). SampEn (m, r, N) is the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point. Nowadays ApEn is a nonlinear measure used by researchers from very different areas such as anaesthesiology (Bruhn, Ropcke, and Hoeft, 2000; Sleigh, Olofsen, Dahan, Goede, and Steyn-Ross, 1991), hormone secretion (Pincus, Veldhuis, and Rogol, 2000; Svensson, Veldhuis, Iranmanesh, Bengtsson, and Johannsson, 2002), aging (Lipsitz, 2002; Pikkujämsä *et al*., 1999), gender differences (Kuo and Yang, 2002), neuroscience (Bhattacharya, 2000), and cardiology (Pincus, 2000; Vigo *et al*., 2004; Wagner and Persson, 1998; Wessel *et al*., 2000). Generally speaking, the results of these studies are in accordance with the above mentioned general principle. For example, lower values of ApEn have been found in the frontal (Fp1, Fp2) EEG of anaesthetized patients (Bruhn *et al*., 2000). Indeed, in this study, the ApEn values changed proportionally to the concentration of desflurane (the sole anesthetic agent after the traquea was intubated). Recently, Bornas, Mühlberger, Llabrés, Wiedemann, and Pauli (2009) reported differences in entropy between flight- and spider phobics at rest. Differences were found at several sites and both under eyes open and eyes closed conditions, and entropy of spider phobics was always lower than entropy in flight phobics. If irregularity is a sign of health and, on the other hand, the inability to switch between emotional states characterizes phobic fear, then entropy

should be low under fear conditions (before treatment and during exposure to fearful stimuli) and high in safety non-fear conditions (*e.g.*, after successful treatment).

The aim of this single-case report (Montero and León, 2007) is to explore (a) how entropy and synchronization between EEG channels changes as a result of exposure to feared stimuli, and (b) if an effective exposure therapy induces any entropy and/or synchronization change both in the short (one week) as well as in the long term (one year).

Method

Participants

The patient P was a 24 years-old female undergraduate student. She asked for psychological help to one of the authors (J.Ll.). During the clinical interview (ADIS-IV) (Brown, DiNardo, and Barlow, 1994) a specific snake phobia diagnose was made according to the DSM-IV-TR (American Psychiatric Association, 2002) criteria. She reported she had fear of snakes since she was 18 years-old, but she did not remember the exact onset of her fear nor any specific traumatic or conditioning event. Fear grew up in the last two years, to the extent that she was unable to eat spaghetti or fish because the shape and the fish skin surface respectively reminded her a snake. She rated as 8 (in a scale from 0 to 8) her level of fear and avoidance, and 6 the current interference, although she was very worried about what she could do in the future when she would be a teacher and she had to play with young children who probably would have snake-shaped toys. A one-session exposure treatment was proposed to her as part of a more complex single case experiment which included electrophysiological recording. Written informed consent to participate was obtained from P.

Instruments

EEG data recording and processing. The EEG signals were recorded from 8 sites (F7, F8, P3, P4, T3, T4, T5, and T6) placed in accordance with the International 10-20 System, refered to linked earlobes, and filtered online with a bandpass filter (0-40 Hz). The EOG was measured with electrodes located 2 cm above and below the right eye. A ground electrode was placed anteriorly to the location of the Fpz (midprefrontal) electrode. Signals were amplified by a BIOPAC MP150 data acquisition system. The sampling rate was 500Hz, and the electrode impedance was kept below 10k©. EEG recordings were first visually inspected to find ocular and movement artifacts. Signals from sites F7 and F8 were very contaminated by muscle movements elicited when the patient started crying when she saw the pictures of snakes. Therefore, these signals were excluded from further analysis. Only one minute (30000 data points) of continuous artifact-free EEG recording the other six sites was taken from the middle part of each condition's EEG and further analyzed.

Procedure

To test what changes in entropy and EEG synchrony were induced by feared stimuli we designed the following assessment protocol, which was used in each one of

three assessment sessions (one week before treatment, one week after and at one-year follow-up). While P was comfortably seated the experimenter placed a standard EEG recording cap (BIOPAC Systems, Inc.). EEG recording started with a 3- to 5-minutes accommodation phase. Eleven experimental conditions were presented in the following sequence: resting baseline (BL1), .2Hz paced breathing (PB1), resting baseline (BL2), anticipation (ANT), exposure to 10 pictures of snakes (EXPSNK), recovery from phobic pictures (RECSNK), exposure to 10 pictures with the same arousal ratings than phobic pictures (EXPSARO), recovery from arousal pictures (RECSARO), exposure to 10 neutral pictures (EXPNEUT), paced breathing at a rhythm of .2 Hz (PB2), and resting baseline (BL3). Each condition lasted 3 mins. All pictures were selected from the IAPS[3] (Lang, Bradley, and Cuthbert, 1995), and presented for 18 seconds on a 19'' computer screen located one meter in front of the patient. During anticipation a countdown clock was presented on the screen showing the time remaining for the presentation of the phobic stimuli. During baseline and recovery conditions, a red cross was displayed on the screen for eye fixation.

One week after the first assessment session, the patient attended the exposure therapy session, which was conducted by one of the authors (MTF) at the clinical practice laboratory of the university. A behavior avoidance test was prepared using a terrarium containing a snake (1 m. Phyton regius). The box was on a table at the end of a room adjacent to the lab. The door of this room was closed and from the door to the glass box the distance was about 4 meters. P was encouraged to open the door and to walk as far as she could towards the glass box with the snake. However she was not able to open the door, so that she avoided totally the phobic stimuli.

One-session exposure treatment for specific phobias based on the description given by Öst (Öst, 1989; Öst, Brandberg, and Alm, 1997) was carried out. The first suitability criterion is that the phobia should be monosymptomatic and only concern one specific situation or object. Further, patient should be motivated enough to get rid of his/her phobia. The treatment consisted of prolonged therapist-directed graded exposure with guided modeling to snakes and snake related stimuli. Graded exposure included confrontation with a) rubber, wood, and cloth snake toys, b) snake pictures, c) real death snakes formol-preserved (Macroprotodon Mauritanicus, Rinechis Scalaris), d) snake skin from anaconda (Eunectes Murinus), and e) an alive snake (Phyton regius) into a terrarium. Pre-treatment instructions to the patient were given as usual in the one-session treatment for animal specific phobias. Treatment was conducted entirely in the same room of the laboratory and was videorecorded. It lasted 4 hours and a half, ending when the patient was holding the alive snake with her hands without gloves and reporting no anxiety. A copy of the video was delivered to the patient. She was instructed to look at the video at home in the next days. The snake pictures and toys used during the exposure session were also given to the patient suggesting her to be located in some place at home where could be visible.

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[3] IAPS pictures of snakes: 1030, 1040, 1050, 1070, 1080, 1090, 110, 1111, 1113, 1120; equivalent arousal: 1200, 1201, 1220, 1230, 1240, 1270, 1274, 1275, 1300, 1930; neutral: 5531, 7006, 7009, 7010, 7035, 7080, 7217, 7233, 7235, 7500.

One week later, the patient came to the lab for a second EEG session following the same protocol used during the pre-treatment session. In addition a brief interview revealed the complete absence of self-reported fear in front of snakes (see Results section below). A third EEG session was carried out one year later. The same sequence of experimental conditions was followed again this time, and P did not report any fear at all.

Data analysis

Phase synchrony estimation. The first step in this data analysis is to estimate the phases from scalar signals. In our study the signal is an EEG, then the phase of each channel of the EEG signal can be obtained by means of the analytic signal concept based on the Hilbert Transform (Pikovsky, Rosenblum, and Kurths, 2000) explained below.

Taking any oscillatory observable s(t) of a chaotic system, one can construct the called analytic signal:

$$\sigma(t) = s(t) + is_H(t) = A(t)e^{i\phi(t)}$$

Where $S_H^{(t)}$ is the Hilbert transform (HT) of *s(t)* and unambiguously obtain the instantaneous phase $\phi^{(t)}$.

The next step in the data processing is to analyze the behavior of the estimated phase difference $\psi(t) = \phi_1(t) - \phi_2(t)$ between two channels or, in a more general case $\psi_{n,m}(t) = n\phi_1(t) - m\phi_2(t)$.

We calculate integer values m and n for each difference by least square fitting over

$$\phi_1(t) = \alpha + \frac{m}{n}\phi_2(t)$$

Finally, synchronization can be detected in a straightforward way: by plotting $\psi_{n,m}(t)$ versus time and looking for horizontal plateaus in this presentation. To illustrate this, we plot a line for each difference.

Results

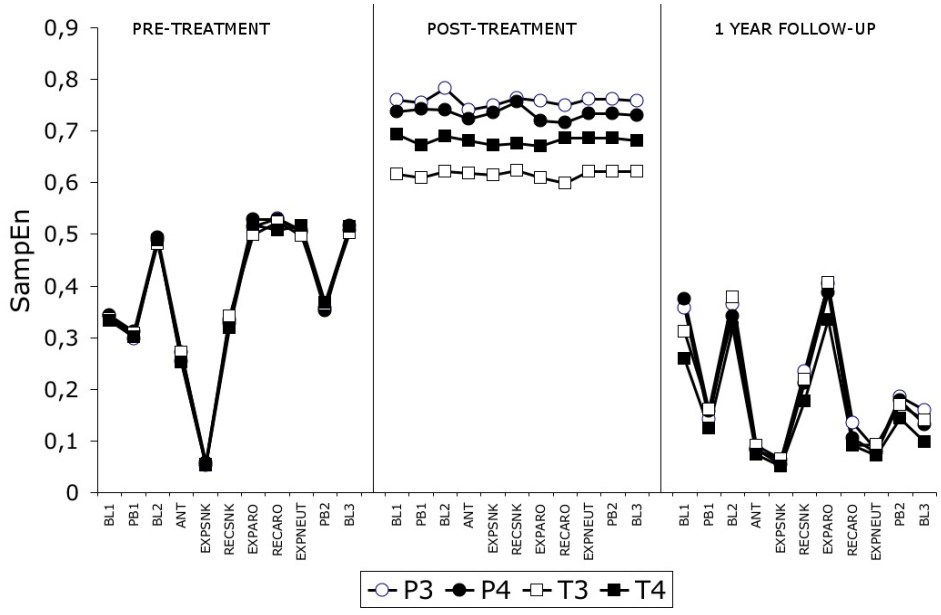
Self-reported fear and behavioral avoidance

At post-treatment and at one-year follow up both fear and interference were rated as zero, in a 0-8 scale. During the first week after treatment all of the most relevant avoidance behaviors had completely disappeared: she ate fish and spaghetti, she was able to walk alone in gardens near bushes, she looked every day at the snake pictures (located in the front wall of her desk at home) and at the snake toys (hanging in her car). She also went to the zoo and remained for a long time in front of the snake terrarium.

Sample entropy

As can be seen in the left panel of Figure 1, exposure to snake pictures lowered dramatically the Sample Entropy in all six EEG channels (as T5 and T6 showed the same pattern we do not include these data in the figure for the sake of clarity) while exposure to same arousal pictures or neutral images had no effect on the entropy measure. Entropy during these conditions was similar to the levels found at BL2 and BL3, which can be taken as the normal levels (the lower level of entropy seen at BL1 can be due some anticipatory anxiety related with the participation in the experiment). Entropy decreased markedly from BL2 to anticipation to exposure to snakes pictures, then raised during recovery and reached the baseline level while arousing pictures were presented. Paced breathing (PB2) also decreased entropy in all the recorded sites. The global picture at pre-treatment, on the other hand, shows a flexible system (*i.e.,* a system that is sensitive to environmental changes). When we look at post-treatment, when snake phobia was completely cured, two main features come up. First, entropy levels are higher than before treatment at all sites in all experimental conditions. Second, the system seems to be less sensitive to environmental changes than it was before treatment, as the high level of entropy remains high disregarding what kind of stimuli is being presented or what is the breathing pattern. At follow-up P reported no snakes fear at all and the EEG entropy seemed to be back to pre-treatment level. Entropy changed across consecutive experimental conditions but the low entropy found under exposure to snakes pictures was almost the same when P was looking at neutral pictures.

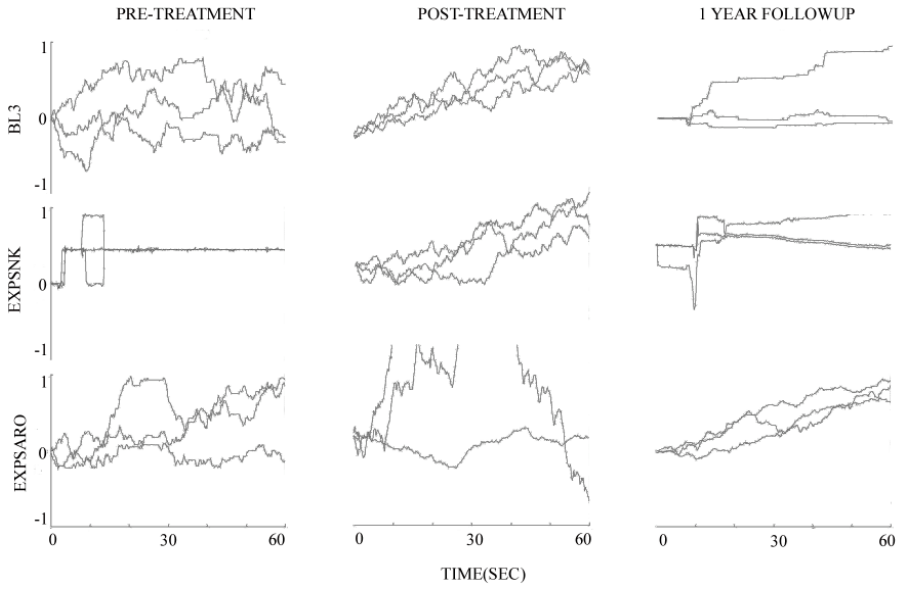
FIGURE 1. Entropy along the 11 experimental conditions at pre-treatment, post-treatment, and follow-up.



Phase synchronization

If we look at the left column of Figure 2, between channels phase synchrony is clearly higher when the feared stimuli were presented to the patient. All three pairs of channels show long horizontal lines (*i.e.,* long periods of time during which the phase difference between each pair remained constant). Short periods of synchronization can be seen, nevertheless, under the presentation of the pictures of equivalent arousal (*e.g.*, during sec 20 and 30). No synchrony can be seen in the pre-treatment baseline figure (first row of left column). One week after treatment, no synchronization was found in the snakes' exposure condition (middle column, middle row). It cannot be seen during baseline either. A pattern similar to the pre-treatment one can be seen at follow-up (right column, middle row) during snakes pictures viewing, although lines are not as horizontal as before treatment (*i.e.*, phase difference between channels was increasing slowly). Surprisingly, during baseline (top row of right column) long synchronization periods can be easily seen. On the contrary, during equivalent arousal pictures presentation no synchrony can be found.

FIGURE 2. Phase synchronization between channels P3-P4, T3-T4, and T5-T6 during baseline (upper row), exposure to snake pictures (middle row), and exposure to equivalent arousal pictures (lower row) at pre-treatment (left column), post-treatment (middle column) and one-year follow-up (right column).



Discussion

One obvious limitation of any single-case study is that other cases, even with the same clinical disorder (snake phobia), could show quite different characteristics. Therefore results should be discussed very cautiously. We will focus our discussion on the «big picture» only and we will avoid comments on too specific results (*e.g.*, the meaning of changes at each EEG site or channel). The experiment provided a big picture about what happens with EEG entropy when a one-session exposure was used to successfully treat the patient's snake phobia. First, a global entropy increase took place in the patient's recorded brain sites. High entropy has been usually found in healthy biological systems (Guastello, 2004), and therefore this entropy increase can be viewed as a positive general effect of exposure therapy. Raising the system's entropy would be a way to prepare it to cope with fear and to learn strategies to manage emotional distress. Unfortunately we have no data until one year later, so that we cannot know how long the entropy increase lasted. The fact that one year later the recorded entropy was back at pre-treatment levels but P reported no fear at all can be seen as a return to P's usual entropy level. Nevertheless, the cross-conditions pattern at follow-up is different from the one seen at pre-treatment. Further research is needed to understand the meaning of such differences (*e.g.*, EEG entropy in front of snakes' pictures is the same than in front of neutral pictures but both are much lower than in front of arousing images).

Synchronization results point at the same direction than the entropy related ones. The only pre-treatment condition where across-channels synchronization was clearly visible was the exposure-to-snakes condition. Shorter but visible epochs of synchronized activity were also found during anticipation (not shown in Figure 2). One week after treatment this long-range synchronization was gone and the graph looked similar to the graphs from any other condition. However, the pre-treatment pattern was back again at one year follow-up. Therefore the loss of phase synchronization would be considered as a short term treatment effect which, like entropy increase, could prepare the system to better cope with feared stimuli. Again, however, some questions raised that need further research, for example the presence of clearly visible periods of long-range synchronization during baseline conditions at follow-up. It should be underlined that the lack of data from other sessions before follow-up (*e.g.*, one month after treatment) prevents knowing to what extent the patterns seen at follow-up have any relationship to the exposure therapy. Treatment group studies with phobic and non-phobic patients should be conducted in order to answer such questions.

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