

Chaotic EEG Patterns During Recall of Stressful Memory Related to Panic Attack

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Summary

Chaotic transitions likely emerge in a wide variety of cognitive phenomena and may be linked to specific changes during the development of mental disorders. They represent relatively short periods in the behavior of a system, which are extremely sensitive to very small changes. This increased sensitivity has been suggested to occur also during retrieval of stressful emotional experiences because of their fragmentary, temporally and spatially disorganized character. To test this hypothesis we recorded EEG during retrieval of fearful memories related to panic attack in 7 patients and retrieval of anxiety-related memories in 11 healthy controls. Nonlinear data analysis of EEG records showed a statistically significant increase in degree of chaotic dynamics after retrieval of stressful memories in majority of patients as well as in control subjects. This change correlated with subjective intensity of anxiety induced during the memory retrieval. The data suggest a role of nonlinear changes of neural dynamics in the processing of stressful anxiety-related memories, which may play an important role in the pathophysiology of panic disorder.

Key words

Memory • Panic disorder • Phobia • Stress • EEG • Lyapunov exponent • Chaos

Introduction

Recent neurodevelopmental findings suggest that stressful experiences are associated with increased risks of later panic attack and that specific phobic states are important etiological factors for the development of panic disorder (Jacobs and Nadel 1999, Goodwin *et al.* 2005). According to several findings characteristic etiological differences between panic attack and specific

phobia are closely related to the developmental stage of critical negative emotional experience (Nadel 1994, Schacter and Tulving 1994, Jacobs and Nadel 1999). Stressful experiences occurring early in development lead later to panic disorder, while stressful memories occurring later in development probably lead to specific phobias (Jacobs and Nadel 1985, 1999). Panic disorder evolves from unexplained panic attacks and involves retrieval of disaggregated memory fragments probably

originating in early stressful experiences. Recovery of these early memories occurs most frequently in the conditions of excessive stress and stress-related hormonal disruptions of hippocampal functions (Jacobs and Nadel 1985, 1999).

Psychological fragmentation of memory contents corresponds to recent evidence of the neural dissociability of the memory processes (Phillips and LeDoux 1992, LeDoux 1992, 1993, 1994). The evidence supports the view that memory systems concerned with encoding emotion and context are dissociable at psychological, physiological, and anatomical levels (Bechara *et al.* 1995). There is evidence that stress disrupts normal activity and memory consolidation in the hippocampus and prefrontal cortex (Diamond and Rose 1994, Ruel and de Kloet 1985, Bureš and Lánský 2004, Payne *et al.* 2006). This process leads to memories that are stored without a contextual or spatiotemporal frame. Neurophysiological processes that lead to consolidation of stressful emotional experiences therefore produce memories, which are often fragmentary, temporally and spatially disorganized, mainly because they originate from entirely unrelated events. Recent findings suggest that the memories stored without a common spatiotemporal frame display specific spatio-temporal dynamics during recall (Davis *et al.* 1994, Fanselow 1994, Vermetten and Bremner 2004). According to Putnam (1997) retrieval of fragmentary, disaggregated memories may lead to rapid changes of mental state. A specific characteristic of this neural dynamic may be chaotic shifts with extreme sensitivity to very small changes (Bob 2003, Putnam 1997). Although the term chaos has its historical roots in the work of Poincaré at the end of 19th century, the application of the methods of nonlinear mathematics to the field of neuroscience is relatively new. The purpose of this approach is understanding of relatively short periods in the behavior of a neural system, which are extremely sensitive to very small changes. The increased sensitivity during these critical times characterizes initiation of new trends in the system's evolution, which later emerge as very different macroscopic patterns of neural activity. Recent evidence also indicates that various measures used in clinical neurophysiology, such as EEG, display chaotic behavior and enables to study chaotic transitions (Stam 2005, Velazquez *et al.* 2003). Such chaotic transitions probably emerge in a wide variety of cognitive phenomena and may be linked to specific changes during development of mental disorders such as depression, schizophrenia or

dissociative disorders (Korn and Faure 2003, Melancon and Joannette 2000, Huber *et al.* 1999, Paulus and Braff 2003, Putnam 1997, Bob 2003). The above reported findings suggest that symptoms of panic disorder could reflect fragmentary, temporally and spatially disorganized memories with resulting chaotic transitions. If this hypothesis was true, evaluation of these transitions by suitable nonlinear dynamic measures could be useful for assessment of disease evolution and therapeutic progress.

Methods

Subjects

Seven patients with diagnosis of panic disorder (according to DSM IV criteria) and 11 healthy controls participated in the study. Exclusion criteria were any form of epilepsy or confirmed epileptiform abnormalities, organic illnesses involving the central nervous system and mental retardation. The patients were 2 males and 5 females in average age 26.2 ± 8.8 . Healthy control group consisted of healthy volunteers (5 males and 6 females) recruited among medical students and hospital staff (average age 28.2 ± 7.7). The study was approved by local ethical commission. Informed consent was obtained from all subjects.

EEG measurement and procedure

EEG was recorded using the BrainScope EEG recording system from 8 Ag/AgCl electrodes imbedded in 32 channels EEG cap, which were placed according to the International 10-20 system (F3, F4, C3, C4, T3, T4, P3, P4). The signal was analog bandpass filtered (0.5-30 Hz) and sampled at 2000 Hz. A therapeutic interview preceded the measurements in patients. The data were recorded under 2 conditions. The first was a resting state (5 min). This was followed by a state of active retrieval of anxiety-related memories associated with panic attack (lasting 1.5 min), which was induced by appropriate instructions of the experimenter (e.g. "Now imagine the situation related to intense anxiety during panic as you know it from your previous experience"... After the instruction, physician performing the experiment described in detail such event from the patient's anamnesis). The same procedure was repeated after reassurance and 5 minutes of rest in all the patients. During the recordings patients were sitting quietly, with no significant movements and with closed eyes in order to facilitate memory retrieval (Wagstaff *et al.* 2004). Similar procedure was performed also in the healthy

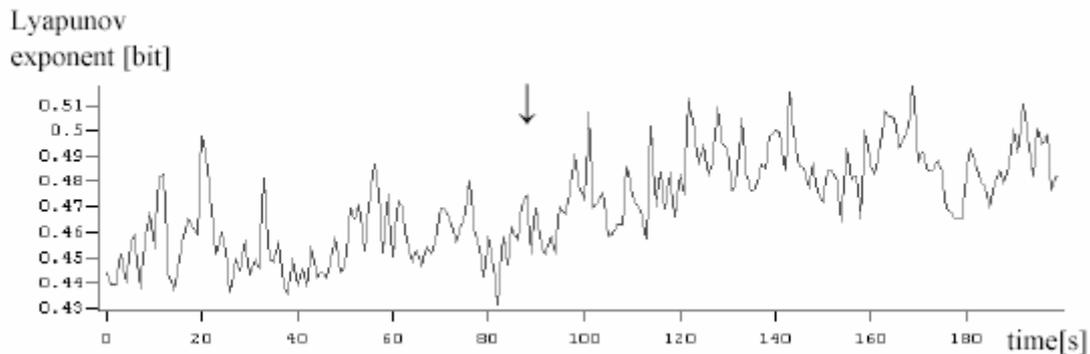


Fig. 1. Example of largest Lyapunov exponents calculated from EEG data before and after the retrieval of stressful memory in patient 1 (channel F4) during the first recall task which show increased values after retrieval. The onset of retrieval is marked by arrow.

control group. After the resting period the control subjects were instructed to imagine a stressful situation of intense anxiety from their previous experience. This was induced by appropriate instruction (“Now imagine the situation related to intense anxiety as you know it from your previous experience!”). After the period of memory retrieval all subjects were asked to estimate the intensity of the memory-induced anxiety on a self-rating scale, which ranged from 0 (no anxiety) to 5 (very strong).

Data Analysis

200 s long artifact-free EEG time series (100 s before and 100 s after the retrieval of stressful memory) were selected and processed by nonlinear data analysis using software package Dataplore. In the analysis mutual information, False Nearest Neighbours, embedding dimension and largest Lyapunov exponents were calculated (Kantz and Schreiber 1997). False Nearest Neighbours technique utilizes geometric principles for the finding of embedding dimension which determines reconstruction of underlying chaotic dynamics by means of Lyapunov exponents (Kantz and Schreiber 1997). Largest Lyapunov exponents were calculated using the method of 5 s long sliding window (10 000 data points) which enables to approach to algorithmic criteria for signal stationarity (Fig. 1). A difference between degree of chaos measured by positive Lyapunov exponents in resting state before retrieval and state after re-living of the stressful memory was assessed in a statistical evaluation that included means, Pearson product moment correlation and t-test for independent samples. Evaluation of results in nonlinear data analysis was performed in blind study without any information about the patient’s clinical state and the patient’s experiences during clinical experiment.

Results

Results of the nonlinear analysis of EEG records from all EEG channels and subjects are presented in Table 1. Displayed are values of the t-statistics of the difference between the largest Lyapunov exponents in the condition of fearful memory retrieval and resting condition. In 2 patients the difference was significant in all 8 channels (cases 1 and 2). In both of these patients repeated retrieval did not lead to increase in Lyapunov exponents, although they reported similar emotional response as during the first retrieval trial. Two other patients (case 3 and 4) who responded less intensely in the first retrieval trial, responded similarly also in the second retrieval trial. Two patients (case 5 and 6) did not manifest increased largest Lyapunov exponents at first retrieval trial and also did not report induced anxiety. On the second retrieval one of the patients (case 5) displayed a significant increase in Lyapunov exponents and a prolonged emotional response, which lasted only shortly in the first retrieval. Reversed pattern of activation characterized by decreased Lyapunov exponent during retrieval was observed in a patient, who reported well developed coping strategies to panic state-related anxiety (case 7). Decreased Lyapunov exponent was also seen in patient 1 during the second recall. Such reversed activation pattern was observed also in 3 control subjects (cases 9, 10, 18). This suggests that decreased Lyapunov exponents in response to anxiety retrieval is a consequence of inhibitory control over the response-related brain regions, which leads to inhibition of emotional response. Other subjects from the control group display increased Lyapunov exponents during retrieval task (cases 11-17). From these two subjects displayed significantly increased largest Lyapunov exponents in all 8 EEG channels.

Table 1. Statistical differences between largest Lyapunov exponents before and during retrieval task of stressful memory calculated by t-test.

		Values of t-tests in 8 EEG channels									Subjective intensity	
Subject no.	Recall	C3	C4	F3	F4	P3	P4	T3	T4			
Patients	1	1 st	-9.956	-10.215	-7.079	-10.873	-10.415	-11.328	-3.719	-9.462	3	
		2 nd	-1.532	-0.852	1.747	2.186	0.165	-1.386	1.747	2.396	2	
2		1 st	-3.617	-2.563	-2.702	-3.556	-4.592	-4.022	-1.982	-2.664	2	
		2 nd	-0.957	-0.549	-0.203	-0.699	-1.042	-0.811	0.285	-0.056	3	
3		1 st	0.337	-5.981	0.251	-0.973	-4.209	-2.250	-3.086	-1.316	1	
		2 nd	-0.917	-3.219	-0.188	-2.044	-0.480	0.537	-0.503	-4.745	2	
4		1 st	-1.827	1.128	1.038	-1.071	-2.849	-2.364	-1.996	-0.522	2	
		2 nd	0.445	0.490	-1.074	0.013	-1.463	-2.134	-0.455	-1.528	1	
5		1 st	-0.295	-0.392	-1.342	-1.652	-1.280	0.440	0.122	-0.587	shortly	1
		2 nd	-0.617	-1.031	-2.978	-3.340	-1.975	-3.673	-0.091	-0.775	1	
6		1 st	0.074	-0.081	-1.300	-0.500	0.690	-0.761	0.172	-0.623	0	
		2 nd	0.660	-0.238	1.025	0.710	-0.664	0.575	0.701	1.554	0	
7		1 st	0.579	-1.135	0.589	-0.511	2.708	0.583	1.217	0.986	2	
		2 nd	2.955	-0.700	-1.073	-0.060	1.187	-1.301	0.199	-0.097	2	
Controls	8	1 st	0.330	1.289	0.611	-5.926	-2.283	-0.969	-2.633	-3.001	2	
9		1 st	1.673	8.912	1.943	-0.558	-1.791	-0.064	-0.935	1.029	0	
10		1 st	6.637	0.725	7.565	4.783	8.214	11.244	12.730	12.572	1	
11		1 st	-9.826	-2.886	3.392	-1.728	-0.987	-1.365	-2.944	0.247	2	
12		1 st	-19.508	-16.213	-18.376	-16.398	-17.023	-19.734	-19.875	-16.812	2	
13		1 st	-4.768	-1.726	-6.495	-7.179	-1.572	-4.793	-6.767	-4.928	1	
14		1 st	-6.683	-16.225	-4.883	-1.221	-4.735	-10.208	-0.540	-7.139	2	
15		1 st	-3.099	-1.191	-1.714	-1.022	-2.035	-1.550	0.212	-4.744	1	
16		1 st	-6.330	-7.766	-5.677	-3.645	-8.400	-5.333	-8.142	-3.541	2	
17		1 st	-3.025	-4.506	-3.300	-2.856	-6.750	-5.230	-5.532	-1.079	2	
18		1 st	1.760	3.650	0.511	5.591	0.810	1.568	-0.855	2.598	shortly	1

Note. Embedding dimension is 4 for all measured intervals, df =198 degree of freedom for all calculated Lyapunov exponents, All calculated largest Lyapunov exponents were positive (higher than zero), t-test – between resting state and state after the retrieval, -t = Lyapunov exponents increases after retrieval task, for absolute value t=1.982 and higher the t-values are **statistically significant** (p<0.05), Scale evaluating subjective anxiety is from 0 (absence) to 5 (strong anxiety).

As shown in Table 2 differences in Lyapunov exponents calculated for EEG recordings (as indexed by value of t-statistics) significantly correlated with subjective ratings of intensity of the memory-induced anxiety mainly in the central and parietal channels. These empirical data indicate significant correlations between differences in Lyapunov exponents calculated for EEG channels characterized by t-value and subjective experience of anxiety reported on the scale from 0 to 5 mainly in the central and parietal channels (Table 2).

A between-group comparison revealed that the mean largest Lyapunov exponent was significantly lower

in the patients than in the controls in both the resting state and during the memory recall (Table 3).

Discussion

Results of this study revealed significant increase in largest Lyapunov exponents during the state of stressful memory retrieval in majority of patients and controls who reported a lasting negative emotional state. Our findings thus support the hypothesis that anxiety states are characterized by chaotic transitions of disaggregated memory fragments.

Table 2. Correlations of statistical differences between largest Lyapunov exponents before and during retrieval of stressful memory calculated by t-test and intensity of subjective experience.

	Values of t-tests in 8 EEG channels							
	C3	C4	F3	F4	P3	P4	T3	T4
1 Subj. int. 1 st retrieval	-0.55*	-0.59**	-0.35	-0.49*	-0.50*	-0.50*	-0.33	-0.43
2 Subj. int. 1 st +2 nd retrieval	-0.43*	-0.48*	-0.26	-0.36	-0.36	-0.38	-0.24	-0.35

Note. 1st line of table: correlation of subjective intensity and t-value in EEG channel during 1st retrieval in patients and controls (n=18). 2nd line of table: correlation of subjective intensity and t-value in EEG channel during 1st and 2nd retrieval in patients and 1st retrieval in controls (N=25), Scale evaluating subjective anxiety is from 0 (absence) to 5 (strong anxiety), *p<0.05, **p<0.01.

Table 3. Descriptive statistics of differences between largest Lyapunov exponents before and after retrieval of stressful memory in patients and healthy controls.

	Mean Lyap-patients	Mean Lyap-Controls	t-test	df	p
pre-retrieval	0.378968	0.497633	-9.78148	198	0.000000
during retrieval	0.385490	0.512962	-9.66584	198	0.000000

The Lyapunov exponent characterizes degree of sensitivity of a dynamic system. This in extreme cases corresponds to a metaphor whether or not a butterfly flaps its wing in one part of the world may cause a tornado in some other part of the world (the so-called exponential divergence). In the brain, this sensitivity is linked to a large number of complex and interrelated neural states, which lead to extreme instability with respect to competition of many possible behavioral patterns (Freeman 2000, Korn and Faure 2003). Positive Lyapunov exponent ($\lambda > 0$) indicates a chaotic neural state and the degree of chaos elevates with increasing Lyapunov exponent. In case of negative Lyapunov exponent ($\lambda < 0$) the neural state is stable and deterministic. For zero Lyapunov exponent ($\lambda = 0$) the neural state may tend to a periodic repetitive process.

The reversed activation pattern characterized by decreased Lyapunov exponent during retrieval was observed in 2 patients (case 7 during the first recall task and the case 1 during the second recall) and 3 control subjects. The data also indicate that the patients have significantly lower values of the largest Lyapunov exponents than the control group. These findings suggest that decrease in Lyapunov exponents as a response to anxiety retrieval is a consequence of inhibitory control over the response related brain regions, which leads to inhibition of emotional response. This inhibitory over-control may cause the lower values of Lyapunov exponents in the patients with panic disorder. This could lead to dysregulation of inhibitory control during attacks

and to impairment of executive functions as seen in other disorders such as ADHD, schizophrenia or dissociative disorders (Stevens *et al.* 2002, Yücel *et al.* 2002, Yates and Nasby 1993). This is consistent with findings that increased chaos may reflect the competition and interference associated with cognitive conflict (Korn and Faure 2003, Bob 2003). From this point of view the inhibitory control that suppresses cognitive conflict may likely lead to decrease in Lyapunov exponents.

The result indicates that the neural state related to retrieval of stressful memory is significantly more chaotic than the resting state before the event. The data thus hypothetically suggest an underlying chaotic process, which is related to spatiotemporal fragmentation of memory contents consolidated under stressful conditions. Future perspective of these findings may be a possible explanation of relatively frequent occurrence of epileptiform discharges in patients with panic disorder (Bystritsky *et al.* 1999, McNamara and Fogel 1990), because epileptiform discharges display significantly higher chaotic behavior than normal EEG activity (Velazquez *et al.* 2003, Stam, 2005). A possible role of stressful events on epileptiform activity likely caused by kindling mechanisms documented in several studies (Teicher *et al.* 2003, Post *et al.* 1995, Putnam 1997, Velišek and Mareš 2004) thus might be mediated by characteristic nonlinear changes of neural dynamics mainly in temporal lobe and limbic structures that probably play a major role in the pathophysiology of panic disorder.

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Reprint requests

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