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Sharp-wave EEG abnormalities and neural complexity in depressive patients: preliminary report

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Abstract

Background: According to recent findings cognitive and emotional dysregulation in depression and psychiatric disorders may be related to deficits in inhibitory functions and temporo-limbic seizure-like activity due to specific changes in neural dynamics and complexity of neural networks.

Methods: In order to evaluate the clinical utility of nonlinear analysis of EEG complexity (measured by Lyapunov exponents) and to assess underlying epileptiform changes, we studied a sample of 19 depressive patients including nine depressive patients with episodic sharp-wave EEG abnormalities and ten depressive patients without any abnormalities, and compared also subgroups of these patients who used benzodiazepine medication to assess its influence on EEG complexity.

Results and findings: The results show that the depressive patients with episodic sharp-wave EEG abnormalities had significantly lower EEG complexity than the control groups of patients. The data also indicate that benzodiazepines significantly influence neural complexity and increase it in the subgroup of patients with sharp wave abnormalities, and on the other hand decrease the level of complexity in the control subgroup of depressive patients.

Conclusions: In agreement with other findings results of this study suggest that sharp waves or other underlying epileptiform EEG abnormalities related to abnormal neural excitability and disturbances in brain inhibitory systems may be reflected in specific changes of EEG complexity. These specific changes in EEG complexity may be related to treatment resistance to usual medications in several depressive patients and might represent clinical indicators for anticonvulsant treatment.

Keywords: Anticonvulsants, Complexity, Depression, EEG, Epilepsy, Epileptiform activity

Introduction

Cognitive and emotional dysregulation related to depression in many cases may be linked to abnormal neural excitability and deficits in inhibitory functions that may also lead to temporo-limbic seizure-like activity which in certain neural mechanisms is similar to epilepsy (Post et al. 1988; Roberts et al. 1992). These findings are in agreement with evidence of positive clinical response to anticonvulsant treatment in many psychiatric patients (Silberman et al. 1985; Varney et al. 1993; Johannessen 2008; Vigo & Baldessarini 2009; Kaufman 2011). In addition this increased vulnerability related to kindling and sensitization may cause that the brain becomes more sensitized and the

onset of future relapses is more sensitive to stressful life events than at the beginning of the disease (Post et al. 1988; Bob et al. 2011a; Bob et al. 2011b).

Interesting new findings that could explain underlying dynamics of sensitization and kindling processes provide data about spatio-temporal structure of epileptiform neural dynamics that may be more regular with excessive order and lower neural complexity than normal, or more irregular, as uncorrelated randomness with higher complexity (Dawson 2004; Varela et al. 2001; Stam 2005). Together these data suggest that this process of increased or decreased neural complexity calculated from the EEG and other psychophysiological measures may reflect processes during activity of independent areas with increased complexity, which enable desynchronized parallel information processing or may reflect increased synchrony and coordinated neural activities with decreased brain complexity (Tirsch et al. 2004; Weng et al. 1999). Decreased levels of complexity are related to synchronization phenomena in the brain that are closely linked to the integration of different neural events into a coherent whole which typically occurs during epileptic seizures (Varela et al. 2001; Stam 2005). In order to evaluate the clinical utility of nonlinear analysis of EEG complexity in assessing underlying epileptiform changes, we compared EEG records of 19 depressive patients including nine depressive patients with episodic sharp-wave EEG abnormalities and ten depressive patients without any abnormalities.

Method

Participants

The sample of patients included 19 patients with unipolar depression diagnosed according to DSM-IV criteria (mean age 44.15; SD = 18.35; nine females, ten males), right-handed, with high school education, who used mainly antidepressant medication (both SSRI and non-SSRI) and some patients used also other types of medication that included anticonvulsants, atypical antipsychotics, psychostimulants, benzodiazepines and other types of medication (Table 1). Patients gave written informed consent for therapeutic and research purposes of this study. The research was performed in collaboration with the project of Center for neuropsychiatric Research of Traumatic Stress and Charles University (PRVOUK) that was approved by Charles University ethical

Table 1 Types of medication in the subgroups of depressive patients

	Sharp-wave p.	Control p.
Anticonvulsant	1	1
SSRI	2	6
Non-SSRI anti-depressant	2	3
Atypical antipsychotic	3	1
Benzodiazepines	2	3
Pain medication	1	1
Psychostimulants	1	2
Sleep aid	1	0
Stimulant	1	2
Alpha 2A adrenergic agonist	1	0
Thyroid medication	2	1

committee. The patients were divided into two groups. The first included nine patients who had episodic sharp-wave EEG abnormalities (mean age 44.20; SD = 15.62; four females, five males) and the second included ten depressive patients, who were without any abnormalities (mean age 44.10; SD = 18.44; five females, five males). These two groups were matched for age, gender and medication and these patients had not any other psychiatric or neurological diagnoses.

EEG measurement

EEG records from each participant were measured using 20 channels placed in EEG cap (based on the International 10/20 System) and Silver silver-chloride electrodes were used. The acquisition-sampling rate was at 500 Hz and the filter settings were at 0.015 and 70. Because the aim of this study was to find relatively subtle changes that may be significantly disrupted by outside stimuli, all EEG measurements were performed in a quiet room in resting state with eyes closed. During the EEG recording, the participant was seated in a comfortable chair and the EEG measurements were performed in a room with temperature of about 23 °C. For further processing were used 200 s EEG time series in order to calculate EEG complexity.

Data analysis

In the majority of previously reported studies, EEG complexity was calculated using an algorithm for correlation dimension (D2), from a single-channel or from a multichannel EEG as the global complexity, or using calculation of Largest Lyapunov exponents that characterize brain complexity and sensitivity (Stam 2005; Elbert et al. 1994; Kantz & Schreiber 1997; Palus 1998). More effective application to non-stationary data that was used in this study provide momentary largest Lyapunov exponent series (MLLE) of "point" values for short time intervals (Stam 2005; Kantz & Schreiber 1997). The Largest Lyapunov exponents were calculated using the method of 5 s long sliding window using software package Dataplore. In the analysis mutual information, False Nearest Neighbours, embedding dimension and largest Lyapunov exponents for each channel were calculated. False Nearest Neighbours technique utilizes geometric principles for the finding of embedding dimension which determines reconstruction of underlying dynamics of EEG complexity by means of Lyapunov exponents (Stam 2005; Kantz & Schreiber 1997).

In the study we have analyzed 180 EEG channels from nine patients who had episodic sharp-wave EEG abnormalities and 200 EEG channels from ten depressive patients without any abnormalities. These individual channels as dynamical characteristics then were used to compare the data of these two groups, following the hypothesis that underlying dynamics of patients with episodic sharp waves and the control of depressive patients without EEG abnormalities might have different EEG complexity. All MLLE calculations were performed on the raw data and separately for each EEG channel. Statistical evaluation of MLLE values was performed using the software package Statistica version 8.0 (StatSoft Inc., Tulsa, OK, USA) and included descriptive statistics and Kruskal-Wallis ANOVA. Because of non-parametric data distribution the Kruskal-Wallis ANOVA represents most appropriate method that provides valid information; even it does not provide standardized method to assess effect sizes.

Results and findings

The results indicate that MLLEs values specifically characterize these groups of patients and show that the depressive patients with episodic sharp-wave EEG abnormalities (Mean = 0.5369; SD = 0.0026; N = 180; confidence interval +95 %, −95 %; 0.5317; 0.5419) have lower MLLEs than the control group of depressive patients who were without any abnormalities (Mean = 0.5429; SD = 0.0024; N = 200; confidence interval 0.5381; 0.5477). In the analysis with a purpose to assess influences of benzodiazepine medication were compared also sub-groups of patients (within both groups) who used benzodiazepines (Fig. 1). The data suggest that benzodiazepines significantly influence neural complexity and increase it in the patients with sharp wave abnormalities, and on the other hand decrease the level of complexity in the control group of depressive patients. The analysis indicates that differences assessed by Kruskal-Wallis ANOVA were statistically significant ($Z > 2.8$; $H = 20.2$; $p < 0.01$).

Discussion

In agreement with other findings results of this study indicate that sharp waves or other epileptiform or epileptic EEG abnormalities related to abnormal neural excitability and disturbances in brain inhibitory systems may be reflected in specific changes of EEG complexity (Dawson 2004; Stam 2005). In this context, results of this study are in agreement with findings about spatio-temporal structure of epileptiform neural dynamics that may be more regular with excessive order and lower neural complexity than normal, or more irregular, as uncorrelated randomness with higher complexity (Dawson 2004; Varela et al. 2001; Stam 2005). Decreased levels of complexity are frequently related to synchronization phenomena in the brain that are closely linked to the integration of different neural events into a coherent whole which typically occurs during epileptic seizures, nevertheless there is evidence that strongly as well as weakly coupled networks may

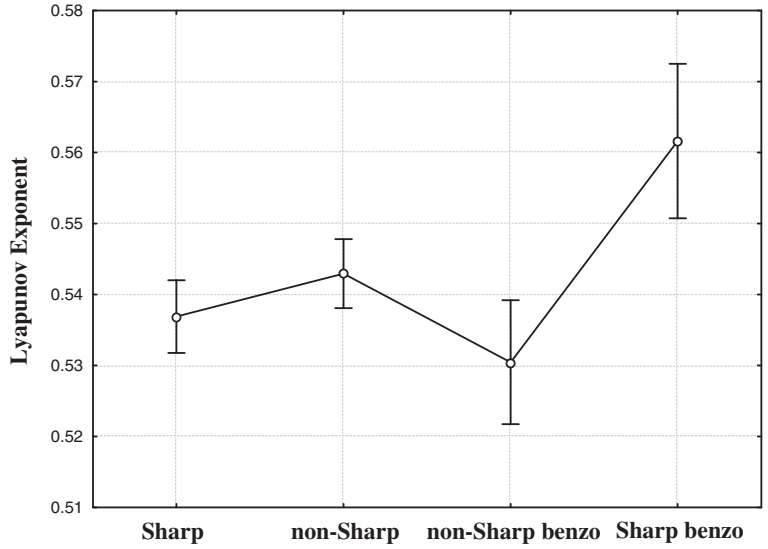

Fig. 1 Differences in EEG complexity described by Momentary Largest Lypunov exponents (MLLE means and standard deviations) for the groups of 9 depressive patients with sharp wave abnormalities (2 patients used benzodiazepines- Sharp benzo) and the control group of 10 depressive patients without EEG abnormalities (3 patients used benzodiazepines- non-Sharp benzo)

generate seizure activity (Varela et al. 2001; Stam 2005). On the other hand increased EEG complexity may reflect processes during activity of independent areas and desynchronized parallel information processing (Tirsch et al. 2004; Weng et al. 1999).

These recent findings show that strongly coupled networks and neural bursting are prerequisites for the generation of synchronized neural activity and also epileptic activity, but likely also weakly coupled cortical networks and a reduction in synaptic transmission can create the same process (van Drongelen et al. 2005). In this context there is evidence that GABAergic neurons provide both inhibitory and disinhibitory modulation of cortical and hippocampal circuits and contribute to the generation of oscillatory rhythms and participate in discriminative information processing (Jacob et al. 2008). Critical role in these processes likely play cortical inhibitory systems that enable modulation of neural plasticity and organize cortical processes to an intended action and also prevent aberrant activations (Jones 1993). In this context, results of this study indicate that depressive patients with "sharp" epileptiform abnormalities have different values of complexity than the control group of depressive patients, which suggests specific differences in inhibitory modulation among these subgroups of depressive patients that might represent compensatory mechanism as a response to epileptiform activity. On the other hand the data suggest that benzodiazepines that specifically modulate GABA system (Vigo & Baldessarini 2009; Kaufman 2011) may have significant effect on the values of complexity. This finding suggests that increased or decreased complexity measured by MLLEs in various specific conditions could represent an indicator of underlying epileptiform dynamics.

In context of recent findings this study provides results that potentially may explain specific changes in EEG complexity underlying treatment resistance to usual medications in several depressive patients (Post et al. 1988; Roberts et al. 1992; Silberman et al. 1985; Varney et al. 1993; Johannessen 2008) and also a possible clinical indicator for appropriate anticonvulsant treatment. These findings also support recent data that likely there is a link between disturbances in the GABA system and changes of EEG complexity that may explain some processes in pathogenesis of depression and other mental disorders, and their resistance to usual psychotropic medication that may be compensated using anticonvulsant treatment (Stam 2005; Tirsch et al. 2004; Weng et al. 1999; Jacob et al. 2008).

The preliminary results of this short communication are limited and further research including large samples is necessary to confirm these results and also large clinical study is needed to find whether these specific indicators of subclinical epileptiform activity could provide clinically meaningful information. Major limitation of these data is low number of patients and also combined medication. In addition this study was cross-sectional and without detailed information about development of the disease in each patient and possible co-morbidities in the past that might play a role in patient's current status. Relationships of the EEG complexity with respect to age and gender were not found but further analysis is necessary to make any conclusions because of limited number of patients included in the study.

On the other hand these two groups were defined by distinct parameters based on EEG descriptive analysis providing information about presence or absence of sharp waves in the records that as individual channels were used in the non-linear analysis. Even these "sharp" waves distinguished from the background of other EEG activities

were present as episodic abnormalities in distinct channels, the results of complexity analysis suggest that sharp waves represent just an episodic visible sign of widespread and large scale brain abnormalities. Although the results without replication on large samples are far from any conclusions, the data suggest useful methodological approach to measure underlying dynamic EEG abnormalities that might be very useful for clinical practice as possible indicators of anticonvulsant treatment.

Competing interests
The author declare that he has no competing interests.

Authors' contributions
PB data analysis and writing manuscript.

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