Physiol. Res. 55 (Suppl. 1): S107-S112, 2006

Limbic Irritability and Chaotic Neural Response During Conflicting Stroop Task in the Patients with Unipolar Depression

P. BOB, M. ŠUSTA, A. PROCHÁZKOVÁ-VEČEŘOVÁ, M. KUKLETA[1], J. PAVLÁT, F. JAGLA[2], J. RABOCH

Center for Neuropsychiatric Research of Traumatic Stress & Department of Psychiatry, First Faculty of Medicine, Charles University, Prague, [1]Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic and [2]Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Slovak Republic

Received October 27, 2006
Accepted November 17, 2006
On-line available December 22, 2006

Summary

According to recent findings activation of anterior cingulate cortex (ACC) is related to detecting cognitive conflict. This conflict related activation elicits autonomic responses which can be assessed by psychophysiological measures such as heart rate variability calculated as beat to beat R-R intervals (RRI). Recent findings in neuroscience also suggest that cognitive conflict is related to specific nonlinear chaotic changes of the signal generated by neural systems. The present study used Stroop word-color test as an experimental approach to psychophysiological study of cognitive conflict in connection with RRI measurement, psychometric measurement of limbic irritability (LSCL-33), depression (BDI-II) and calculation of largest Lyapunov exponents in nonlinear data analysis of RRI time series. Significant correlation 0.61 between largest Lyapunov exponents and LSCL-33 found in this study indicate that a defect of neural inhibition during conflicting Stroop task is closely related to limbic irritability. Because limbic irritability is probably closely related to epileptiform abnormalities in the temporolimbic structures, this result might represent useful instrument for indication of anticonvulsant treatment in depressive patients who are resistant to antidepressant medication.

Key words
Depression • Stress • Limbic irritability • HRV • Lyapunov exponent • Chaos • Anticonvulsants

Introduction

Recent information processing models consider attention as a filter, as a resource, and as a mechanism for selection of action (Eccleston and Crombez 1999). Attention can be defined as selection among potential conscious contents and is characterized by global distribution of information (Baars 1999, 2002). Function of attentional mechanism is to select the stimulus and bring different cognitive events into the consciousness. The higher cortical functions participating in attentional mechanisms may constitute a way of resolving cognitive

Fax +420 241 062 164
E-mail: physres@biomed.cas.cz http://www.biomed.cas.cz/physiolres

and behavioral conflict by allowing certain competing task relevant stimuli to dominate over the other. This enables to discriminate among mental events in accordance with dominant criteria for interpretation of perceptual information. The higher cortical structures of ventrolateral prefrontal cortex probably play a key role in filtering out irrelevant information and selecting among competing stimuli, responses and associations (Hazeltine *et al.* 2000, Leung *et al.* 2000, Bunge *et al.* 2001). On the other hand higher activation of anterior cingulate cortex (ACC) is related to detecting cognitive conflict and signaling the need for greater allocation of attention for the purpose of resolving conflict (MacDonald *et al.* 2000, Bunge *et al.* 2001, Oschner *et al.* 2001, Raz *et al.* 2005, Egner *et al.* 2005). Well-known experimental approach to neurophysiological study of cognitive conflict is Stroop word-color test (Stroop 1935). For example, in a typical Stroop experiment subject is required to name the ink color which may be non-conflicting (e.g. red is printed in red ink) or conflicting (e.g. red is printed in green ink). To perform the conflicting task it is necessary to ignore the meaning of the printed word which is related to response inhibition. The neural interference related to cognitive conflict predominantly occurs in the ACC structures and elicits autonomic responses in sympathetic as well as in parasympathetic nervous system which are related to psychophysiological measures such as changes in heart rate variability measured as beat to beat R-R intervals (RRI) or electrodermal activity (Critchley *et al.* 2003, Matthews *et al.* 2004, Bušek *et al.* 2005). Recent findings in mathematical neuroscience also suggest that cognitive conflict is related to specific nonlinear chaotic changes of the signal generated by neural systems participating in response to cognitive conflict (Freeman 2000, Korn and Faure 2003, Bob 2003). These chaotic changes are likely related to specific changes during development of mental disorders such as depression, schizophrenia or dissociative disorders (Korn and Faure 2003, Huber *et al.* 1999, Paulus and Braff 2003, Bob 2003). Because these chaotic nonlinear changes probably may reflect dynamical patterns of neural organization related to conflict response, it is possible to suggest the hypothesis that specific dynamical changes may reflect also cognitive conflict during Stroop task and that symptoms of depression or symptoms of limbic irritability reflecting the symptoms of defective inhibition might be related to non-linear measures calculated from psychophysiological signals by more appropriate way than commonly used autonomic measures.

Patients and Methods

Patients

For empirical examination of suggested hypothesis the methods of ECG recording, nonlinear data analysis and psychometric measures were used in 30 patients (20 outpatients and 10 inpatients) with diagnosis of unipolar depressive disorder confirmed according to DSM IV criteria (American Psychiatric Association 1994). Exclusion criteria were organic illnesses involving the central nervous system, any form of epilepsy and mental retardation. The patients were 7 males and 23 females in average age of 39.0±9.6 years predominantly with high-school education. The study was approved by local ethical committee.

ECG measurement

After obtaining informed consent from the participants, the ECG was recorded using SAM unit and Psylab software (Contact Precision Instruments) connected to computer in the room temperature 21°C. Three standard ECG electrodes with electrolyte were attached to the right flank, to the left collar-bone and reference electrode to the left arm. ECG measurement was performed with sampling frequency 1000Hz. During ECG measurement three states have occurred. The first was resting state (100 second); the second state was during procedure of non-conflicting Stroop task (four tables with words: green by green ink, red by red ink, blue by blue ink, yellow by yellow ink); and third state was during conflicting Stroop task (four tables with words: green by red ink, red by green ink, blue by yellow ink, yellow by blue ink); both with regularly changing questions: “name the color”, “name the word”, with 20 s pause between the non-conflicting and conflicting Stroop task.

Psychometric measures

For the screening of depression was used Beck depression inventory BDI- II (Beck *et al.* 1996) that represents 21-items questionnaire for assessing depression. Subjects indicate degree of their experience on 4-point likert scale.

Limbic irritability was assessed by Limbic System Checklist (LSCL-33) (Teicher *et al* 1993). LSCL-33 is designed to measure temporo-limbic activity in the form of somatic, sensory, behavioral and memory symptoms associated with phenomena of ictal temporal lobe epilepsy. These symptoms may be generally

Table 1. Correlations of largest Lyapunov exponents and t-test values characterizing statistical differences between the exponents with measures of limbic irritability (LSCL-33) and depression (BDI-II).

	Lyap-rest	Lyap-Strnon	Lyap-Strcon	t-restnon	t-restcon	t-noncon	LSCL-33	BDI-II
LSCL-33	0.21	0.38*	0.61***	-0.12	-0.39*	-0.14	1.00	0.38*
BDI-II	-0.08	-0.10	0.44**	0.12	-0.50**	-0.39*	0.38*	1.00

Note. Lyap-rest: largest Lyapunov exponents during rest; Lyap-Strnon: largest Lyapunov exponents during non-conflicting Stroop task; Lyap-Strcon: largest Lyapunov exponents during conflicting Stroop task; t-restnon: t-test value between largest Lyapunov exponents during rest and non-conflicting Stroop task; t-restcon: t-test value between largest Lyapunov exponents during rest and conflicting Stroop task; t-noncon: t-test value between largest Lyapunov exponents during non-conflicting and conflicting Stroop task; *p<0.05, **p<0.01, ***p<0.001.

described as brief hallucinations, paroxysmal somatic disturbances, automatisms and dissociative disturbances. The present study has used the LSCL-33 as an index of limbic irritability with respect to failure of neural inhibition during conflicting Stroop task. Subjects indicate degree of their experience on 4-point likert scale (never, rarely, sometimes, often).

Psychometric measures were administered in small groups (from 3 to 5) and situated in the quiet room with the help of one physician or psychologist.

Data Analysis

R-R intervals (RRI) time series calculated from ECG without artifacts were divided to three periods. Then 100 seconds long period before Stroop task and two approximately 20-30 seconds long periods during non-conflicting and conflicting Stroop task were 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 7 s long sliding window (7 000 data points, embedding dimension 3 for all calculated time series) which enables to approach to algorithmic criteria for signal stationarity. A difference between degree of chaos, measured by positive largest Lyapunov exponents in resting state before the Stroop task and states during non-conflicting and conflicting Stroop tasks, was assessed in a statistical evaluation using t-test for independent samples. Statistical evaluation for largest Lyapunov exponents, t-test values and results of psychometric measures included Pearson product moment correlation.

Results

Data obtained by nonlinear analysis of RRI time series in Table 1 display significant correlation between largest Lyapunov exponent during conflicting Stroop task and psychometric measures (Table 1, Fig. 1). Most important seems to be the correlation 0.61 ($p<0.001$) with symptoms of limbic irritability assessed by questionnaire LSCL-33 and correlation 0.44 ($p<0.01$) with depressive symptoms assessed by Beck depression inventory (BDI-II). Similar meaning has also finding of significant change in neural dynamics during conflicting Stroop task which indicates also correlation between t-test value characterizing statistical differences between largest Lyapunov exponents during rest and Stroop task periods. Correlation –0.50 ($p<0.01$) indicates that increasing depression is significantly related to increasing Lyapunov exponents during conflicting Stroop task with respect to resting state. Similar result represents also correlation –0.39 ($p<0.05$) between LSCL-33 and t-test value characterizing statistically significant changes in neural dynamics measured by largest Lyapunov exponents during rest and Stroop task periods. Significant correlation also has been found between largest Lyapunov exponents during non-conflicting Stroop task and LSCL-33 (0.38; $p<0.05$), and also for BDI-II and t-test value between largest Lyapunov exponents during non-conflicting and conflicting Stroop task.

Significant correlation 0.38 ($p<0.05$) between LSCL-33 and BDI-II which indicate certain relationship between growing depression and symptoms of limbic irritability is also worth of attention.

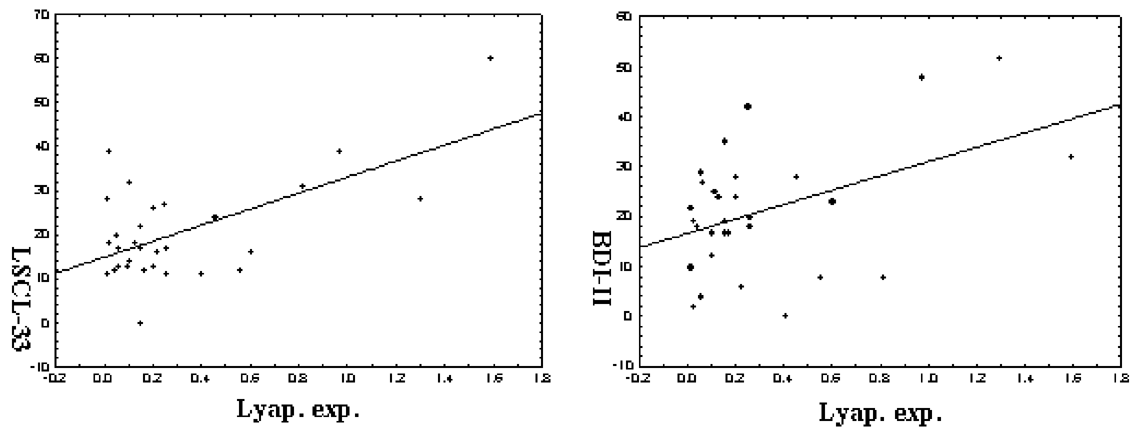

Fig. 1. Dependency graph of largest Lyapunov exponents during conflicting Stroop task with LSCL-33 (left), and with BDI-II (right).

Discussion

Results of this study are in accordance with several recent findings which indicate that ACC activity is closely related to heart rate variability (HRV). According to fMRI studies the ACC activity is highly correlated with HRV and these findings also provide evidence that autonomic nervous system modulation by the ACC is closely related to the cognitive processing of this structure (Matthews *et al.* 2004, Hazeltine *et al.* 2000, Critchley *et al.* 2003). ACC is a part of the central autonomic network which includes also insula and medial temporal lobe structures such as the amygdala, and hippocampus that integrate emotional and cognitive information and exert a modulatory role on lower brain centers that control autonomic nervous system (Matthews *et al.* 2004, Benarroch 1993). These findings also indicate that increased ACC activation is also needed for response inhibition that enables cognitive and emotional integration. During conflicting Stroop task it is necessary to ignore the meaning of the printed word which is related to response inhibition and failure of this inhibition leads to error information processing (Stroop 1935, Matthews *et al.* 2004). Recent findings show that complex functions of cognitive-emotional integration are particularly vulnerable to stressful events in early childhood which may be a cause of serious traumatization also in the later periods of life (Post *et al.* 1995, Putnam 1997, Teicher *et al.* 2003, 2006). There is also evidence that different brain regions have unique periods when they are maximally sensitive to the effects of early stress (Teicher *et al.* 2006). Cognitive and emotional discoordination related to traumatic stress is closely linked to defective inhibitory functions and often leads to temporo-limbic epileptiform abnormalities which may emerge as symptoms of ictal temporal lobe epilepsy such as somatic, sensory, behavioral and memory symptoms assessed by questionnaire LSCL-33. These symptoms have been found to play a significant role also in etiology of depressive disorder (Silberman *et al*. 1985, Bob *et al*. 2005).

Significant correlation 0.61 between largest Lyapunov exponents and LSCL-33 found in this study indicate that conflict related defect of neural inhibition during conflicting Stroop task is closely related to limbic irritability. Results of this study indicate that this limbic irritability, probably related to epileptiform discharges, displays significantly higher positive largest Lyapunov exponents, which represent a criterion for higher degree of chaoticity of neural dynamics. This is in accordance with evidence that epileptiform neural activity displays higher chaotic behavior than normal brain electrophysiological 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, Velíšek and Mareš 2004) thus might be mediated by characteristic nonlinear changes of neural dynamics which probably play a significant role in the pathophysiology of depression (Huber *et al.* 1999) and other psychiatric diseases (Paulus and Braff 2003, Bob 2003). Close relationship between nonlinear measures and symptoms of limbic irritability associated with epileptiform discharges found in this study might represent very useful instrument for indication of anticonvulsant treatment in a great subgroup of depressive patients who are resistant to antidepressant medication.

Acknowledgements

Authors thank for support by research project of Centre for Neuropsychiatric Research of Traumatic Stress 1M06039, research project MSM0021622404, and by VEGA Grant No. 2/5049/26.

References

AMERICAN PSYCHIATRIC ASSOCIATION: *DSM IV*, *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. American Psychiatric Association, Washington DC, 1994.

BAARS BJ: Attention versus consciousness in the visual brain: differences in conception, phenomenology, behavior, neuroanatomy, and physiology. *J Gen Psychol* **126**: 224-233, 1999.

BAARS BJ: The conscious access hypothesis: origins and recent evidence. *Trends Cogn Sci* **6**: 47-52, 2002.

BECK AT, STEER RA, BROWN GK: *Manual for Beck Depression Inventory-II. Psychological Corporation*. San Antonio, TX, 1996.

BENARROCH EE: The central autonomic network: functional organization, dysfunction and perspective. *Mayo Clin Proc* **68**: 988-1001, 1993.

BOB P: Dissociation and neuroscience: history and new perspectives. *Int J Neurosci* **113**: 903-914, 2003.

BOB P, ŠUSTA M, PAVLÁT J, HYNEK K, RABOCH J: Depression, traumatic dissociation and epileptic-like phenomena. *Neuroendocrinol Lett* **26**: 321-325, 2005.

BUNGE SA, OCHSNER KN, RESKOND JE, GLOVER GH, GABRIELI JDE: Prefrontal regions involved in keeping information in and out of mind. *Brain* **124**: 2074-2086, 2001.

BUŠEK P, VAŇKOVÁ J, OPAVSKÝ J, SALINGER J, NEVŠÍMALOVÁ S: Spectral analysis of heart rate variability in sleep. *Physiol Res* **54**: 369-376, 2005.

CRITCHLEY HD, MATHIAS CJ, JOSEPHS O, O'DOHERTY J, ZANINI S, DEWAR BK, CIPOLOTTI L, SHALLICE T, DOLAN RJ: Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* **126**: 2139-2152, 2003.

ECCLESTON C, CROMBEZ G: Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull* **125**: 356-366, 1999.

EGNER T, JAMIESON G, GRUZELIER J: Hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe. *Neuroimage* **27**: 969-978, 2005.

FREEMAN WJ: Mesoscopics neurodynamics: from neuron to brain. *J Physiol Paris* **94**: 303-322, 2000.

HAZELTINE E, POLDRACK R, GABRIELI JDE: Neural activation during response competition. *J Cogn Neurosci* **12**: (Suppl 2) 118-129, 2000.

HUBER MT, BRAUN HA, KRIEG JC: Consequences of deterministic and random dynamics for the course of affective disorders. *Biol Psychiatry* **46**: 256-262, 1999.

KANTZ H, SCHREIBER T: *Nonlinear Time Series Analysis*. Cambridge University Press, Cambridge, 1997.

KORN H, FAURE P: Is there chaos in the brain? II. Experimental evidence and related models. *C R Biol* **326**: 787-840, 2003.

LEUNG HC, SKUDLARSKI P, GATENBY JC, PETERSON BS, GORE JC: An event-related functional MRI study of the Stroop color word interference task. *Cereb Cortex* **10**: 552-560, 2000.

MACDONALD AW, COHEN JD, STENGER VA, CARTER CS: Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* **288**: 1835-1838, 2000.

MATTHEWS SC, PAULUS MP, SIMMONS AN, NELESEN RA, DIMSDALE JE: Functional subdivision within anterior cingulate cortex and their relationship to autonomic nervous system function. *Neuroimage* **22**: 1151-1156, 2004.

OCHSNER KN, KOSSLYN SM, COSGROVE GR, CASSEM EH, PRICE BH, NIERENBERG AA, RAUCH SL: Deficits in visual cognition and attention following bilateral anterior cingulotomy. *Neuropsychologia* **39**: 219-230, 2001.

PAULUS MP, BRAFF DL: Chaos and schizophrenia: does the method fit the madness? *Biol Psychiatry* **53**: 3-11, 2003.

POST RM, WEIS, SR, SMITH, MA: Sensitization and kindling. In: *Neurobiological and Clinical Consequences of*

Stress: from Normal Adaptation to Posttraumatic Stress Disorder. M J FRIEDMAN, DS CHARNEY, AY DEUTCH (eds), Lipincott-Raven, Philadelphia, 1995, pp 203-224.

PUTNAM F: *Dissociation in Children and Adolescents*. *A Developmental Perspective*, London, The Guilford Press, New York, 1997.

RAZ A, FAN J, POSNER MI: Hypnotic suggestion reduces conflict in the human brain. *Proc Natl Acad Sci USA* **102**: 9978-9983, 2005.

SILBERMAN E, POST R, NURENBERGER J, THEODORE W, BOULENGER J: Transient sensory, cognitive, and affective phenomena in affective illness: A comparison with complex partial epilepsy. *Br J Psychiatry* **146**: 81-89, 1985.

STAM CJ: Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. *Clin Neurophysiol* **116**: 2266-2301, 2005.

STROOP JR: Studies of interference in serial verbal reactions. *J Exp Psychol* **18**: 643-662, 1935.

TEICHER MH, GLOD, CA, SURREY J, SWETT C JR: Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *J Neuropsychiatry Clin Neurosci* **5**: 301-306, 1993.

TEICHER M, ANDERSEN SL, POLCARI A, ANDERSON CM, NAVALTA CP, KIM DM: The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* **27**: 3-44, 2003.

TEICHER M, TOMODA A, ANDERSEN SL: Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Ann NY Acad Sci* **1071**: 313-323, 2006.

VELÍŠEK L, MAREŠ P: Hippocampal afterdischarges in rats. I. Effects of antiepileptics. *Physiol Res* **53**: 453-461, 2004.

VELAZQUEZ JLP, CORTEZ MA, SNEAD III OC, WENNBERG R: Dynamical regimes underlying epileptiform events: role of instabilities and bifurcations in brain activity. *Physica D* **186**: 205-220, 2003.

Reprint requests

P. Bob, Center for Neuropsychiatric Research of Traumatic Stress & Department of Psychiatry, First Faculty of Medicine, Charles University, Ke Karlovu 11, 128 00 Prague 2, Czech Republic. E-mail: Petr.Bob@lf1.cuni.cz