Dissociation, cognitive conflict and nonlinear patterns of heart rate dynamics in patients with unipolar depression

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A B S T R A C T

Recent findings in cognitive neuroscience indicate that activation of anterior cingulate cortex (ACC) is related to detecting cognitive conflict. Conflict related ACC activation elicits responses in central autonomic network which can be assessed by psychophysiological measures such as heart rate variability (i.e. 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 the neural systems. The present study used Stroop word-colour test as an experimental approach to the study of cognitive conflict in connection with RRI measurement, psychometric measurement of dissociation (DES) and calculation of largest Lyapunov exponents in nonlinear data analysis of RRI time series in 40 patients with unipolar depression and 35 healthy controls. Significant correlation 0.58 (p < 0.01) between largest Lyapunov exponents and DES found in depressive patients indicate that cognitive conflict related neural interference during conflicting Stroop task is closely related to dissociative processes. These results present first supportive evidence that degree of chaos could be related to dissociation.

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1. Introduction

According to recent findings the higher cortical functions participating in attentional mechanisms may constitute a way of resolving cognitive and behavioral conflict by discrimination among mental events in accordance with dominant criteria for interpretation of perceptual information (Baars, 1999, 2002). The higher cortical structures of ventrolateral prefrontal cortex probably play a key role in selection among competing stimuli (Hazeltine et al., 2000; Leung et al., 2000; Bunge et al., 2001) whereas higher activation of anterior cingulate cortex (ACC) is related to detecting cognitive conflict (MacDonald et al., 2000; Bunge et al., 2001; Ochsner et al., 2001; Raz et al., 2005; Egner et al., 2005; Yeung and Cohen, 2006). The aim of the selection among competing stimuli is to find whether these stimuli may fit into existing cognitive schemes. When the selection and attentional filtering is not momentarily possible, the competition leads to the cognitive conflict that needs great allocation of attention and may produce new adaptive response or a defense resolution and behavioral response leading to dissociated state (Bob, 2008).

Well-known experimental approach to neurophysiological study of cognitive conflict is Stroop word-colour test (Stroop, 1935). In a typical Stroop experiment subject is required to name the ink colour 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 Stroop task it is necessary to ignore the meaning of the printed word. This process is related to response inhibition, sensory rejection and the Stroop task has been used as a model of the stress defense reaction in humans (Hoshikawa and Yamamoto, 1997; Freyschuss et al., 1988).

Conflicting streams of information lead to cognitive and neural interference that predominantly occurs in the ACC structures and elicits autonomic responses in sympathetic as well as in parasympathetic nervous system that can be measured as heart rate variability calculated as beat to beat R–R intervals (RRI) or other psychophysiological measures (Critchley et al., 2003; Matthews et al., 2004). Recent neuroscience findings suggest the hypothesis that specific nonlinear chaotic changes of the signal generated by neural systems participating in response to stress are related to cognitive conflict and inhibitory deficits (Freeman, 2000; Korn and Faure, 2003; Bob, 2003, 2007; Bob et al., 2006). 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). However, chaotic neural process in principle must not be related only to pathological processing but may represent the potential existence of a new adaptive level in neurophysiological process that enable resolution of the cognitive conflict (Bob, 2007).

Similarly as in the case of cognitive conflict which reflects the competition and interference of many possible behavioral patterns and mental representations during “chaos in the mind”, a characteristic feature of neural chaotic states is that they lead to transient periods of...
high brain complexity during activity of independent areas and enable fast parallel information processing which runs in a distributed mode (Bob, 2003, 2007). It means that numerous processes from sensory and cognitive channels are executed simultaneously and this desynchronized neural state may be related to active information processing in the cortex (Tirsch et al., 2004). This enhanced parallel distributed mode of neural activity is probably typical for trauma related dissociative processes (Bob, 2003; Li and Spiegel, 1992). There is also relevant assumption that chaotic neural mechanism is related to concomitant chaotic psychological process (Peditidatikis, 1992; Sel, 1997; Putnam, 1997; Bob, 2003). According to Putnam (1997) retrieval of fragmentary, dissociated memories may lead to rapid changes of mental state. Specific characteristic of this neural dynamic might be chaotic shifts with extreme sensitivity to very small changes which lead to significantly different mental states and behavioral patterns (Bob, 2003, 2007; Putnam, 1997).

Dissociation as partial or total disconnection of certain competitive mental images, affects and memories which does not fit into current cognitive scheme is on the psychological level closely related to confusion and cognitive conflict, when a possible solution in a stressful situation is not found. This process manifests as a competition among very high number of prototype mental images representing a possible solution. These mental representations of possible solutions constitute different behavioral patterns and strategies. On neural level these processes are probably linked to a large number of complex and interlinked neural states which lead to extreme instability with respect to competition of many patterns of neural activity (Freeman, 1991, 2000; Korn and Faure, 2003; Bob, 2003, 2007).

In this study we have examined whether nonlinear chaotic changes as related to mental disorder in the case of depression, reflect cognitive conflict during Stroop test and whether this conflict related activity displays a significant relationship to dissociation.

2. Methods

2.1. Subjects

For empirical examination of suggested hypothesis the methods of ECG recording, nonlinear data analysis, Stroop test and psychometric measures of dissociation and depression were used in 40 outpatients of university hospital (mean of age 34.98, age range 20–55, SD=10.22) and 35 healthy controls (mean of age 34.09, age range 20–48, SD=7.06). Consecutively selected patients had diagnosis of unipolar depressive disorder (21 patients with depressive episode and 19 patients with recurrent depression with mean period of depression 2.8 years), confirmed by clinical interview according to DSM IV criteria (American Psychiatric Association, 1994) and were also assessed by structured psychiatric interview M.I.N.I. version 5.0.0 (Sheehan et al., 1998). In remission were 6 patients, 18 in partial remission and 16 were in relapse, with lasting depression less than 8 years and not more than 4 hospitalizations (average number of hospitalizations 1.8). Patients’ treatment at the time of recruitment was based only on serotonergic antidepressant medication in usual recommended doses (paroxetine 10–40 mg; fluoxetine 20–40 mg; fluvoxamine 100–200 mg; sertraline 100–200 mg; citalopram 20–40 mg; escitalopram 10–20 mg). Exclusion criteria for both groups were organic illnesses involving the central nervous system, heart disease, any form of epilepsy and mental retardation [IQ Raven higher than 90], psychotic disorders, electroconvulsive therapy, bipolar disorder, alcohol and drug abuse. The reason for including unipolar depression among other types of depression was the aim to exclude patients with reactive depression that may be significantly influenced by momentarily psychosocial factors and on the other hand to exclude bipolar patients, who may have different pathogenic mechanisms caused by alterations between depressive and manic states in comparison to unipolar depressive states. Because high numbers of outpatients are treated by serotonergic antidepressants we used this criterion for sample homogeneity. At this point the sample homogeneity was also criterion why we did not include unmedicated patients.

The healthy controls were selected from general population that included hospital and university stuff members (N=17), university students (N=14) and other persons who responded to advertising (N=4). All the controls were psychiatrically healthy according to M.I. N.I. The patients were 16 men and 24 women and the control group involved 14 men and 21 women both predominantly with high-school education. All the patients and controls gave written informed consent and the clinical study was approved by the university ethical committee.

2.2. Stroop test and ECG measurement

Autonomic responses related to cognitive conflict and neural interference have been assessed during conflicting Stroop task (Stroop, 1935). In a typical Stroop experiment subject is required to name the ink colour 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 Stroop task it is necessary to ignore the meaning of the printed word. This process is related to response inhibition, sensory rejection and the Stroop task has been used as a model of the stress defense reaction in humans (Hoshikawa and Yamamoto, 1997; Freyschus et al., 1988). The neural interference related to cognitive conflict predominantly occurs in the ACC and elicits autonomic responses in sympathetic as well as in parasympathetic nervous system that can be measured as heart rate variability calculated as beat to beat R–R intervals (RRI) or other psychophysiological measures (Hoshikawa and Yamamoto, 1997; Freyschus et al., 1988).

ECG measurement was performed using SAM unit and Pylab software (Contact Precision Instruments) connected to computer in the room temperature 23 °C. Three standard ECG electrodes with electrolyte were attached to the right flank (right hypogastrium), under the left collar-bone and reference electrode to the left arm (upper margin of left cubital fossa). ECG measurement was performed with sampling frequency 1000 Hz. After 5 min rest ECG measurement during three states was performed. The first was resting state (100 s); the second state was during non-conflicting Stroop task (four tables with words: green by green ink, red by red ink, blue by blue ink, yellow by yellow ink); the third state was during conflicting Stroop task (four tables with words: green by green ink, red by green ink, blue by yellow ink, yellow by blue ink); with regularly changing questions: “name the colour”, “name the word”. Tables (A4, with types size 72 mm) with conflicting and non-conflicting stimuli were presented at distance about 50 cm. Subjects were required to complete 4 words with 5 s pause after each response with 20 s pause between non-conflicting and conflicting Stroop task.

2.3. Psychometric measures

For the screening of psychic dissociative symptoms the validated Czech version of the questionnaire Dissociative Experiences Scale (DES) was used (Bernstein and Putnam, 1986). DES represents 28 items self-reported questionnaire examining main dissociative phenomena such as absorption, amnesia, depersonalization, derealization, reality distortion, and others. Subjects indicate a degree of their experience on 4-point Likert scale.
Psychometric measures in the patients and healthy controls were administered individually with the help of physician and situated in a quiet room.

2.4. Data analysis

R-R intervals (RRI) time series calculated from ECG without artifacts as intervals between successive peaks of a signal are useful to detect rhythms and deviations from periodicity in a signal showing peaks or iterated patterns (American Heart Association, 1996). The analysis of unfiltered and artifact-free time series was performed using software package Dataplore according to common algorithm for peak to peak intervals that converts R-R intervals to a time series by interpolating data points at a fixed sampling rate 1000 Hz. Then 100 s time series during rest and approximately 25–50 s long RRI time series 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 LLEs 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 largest Lyapunov exponents (LLEs) (Kantz and Schreiber, 1997). LLEs were calculated using the method of 7 s long sliding window (7000 datapoints, embedding dimension 3 for all calculated time series) which enables to approach algorithmic criteria for signal stationarity. For a positive LLE (larger than zero) the state of the system is chaotic and degree of chaos elevates with increase in LLEs. For a negative LLE (lower than zero) the state is stable and deterministic. For zero LLE the state may tend to periodic repetitive behavior (Kantz and Schreiber, 1997).

In addition, the same analysis using the surrogate data was performed. The basic idea of the surrogate-data testing is to first perform the nonlinear analysis on the actual experimental time series. The resulting values of the nonlinear measure are then compared with the same calculations performed on suitably constructed control surrogate signals that are linearly filtered Gaussian white noises, which have the same mean, the same variance, the same autocorrelation function and the same power spectrum as the original sequence but nonlinear phase relations are destroyed. The null hypothesis that the original data represent linearly filtered Gaussian white noises can be rejected if the results of the nonlinear data analysis obtained from actual and surrogate values are statistically significantly different. In this case the results cannot be understood as a consequence of the linear data properties. Surrogate data techniques thus permit the statistical testing of nonlinearities in neural dynamics (Kantz and Schreiber, 1997).

Statistical evaluation for LLEs and results of the psychometric measures included descriptive statistics, Pearson product-moment correlations, t-test for independent samples and nonparametric Mann–Whitney test for independent samples.

3. Results

Results indicate that in depressive patients LLEs during conflicting Stroop task display significant correlation with symptoms of dissociation measured by DES ($r=0.58$, $p=0.000001$) and depression measured by BDI-II ($r=0.35$, $p=0.013$) (Fig. 1). Significant correlation has been also found between BDI-II and DES ($r=0.40$, $p=0.005$).

The relationship between DES and LLEs during Stroop conflict was also confirmed between group comparison for depressive patients with higher ($N=9$, DES$>20$) and lower ($N=31$, DES$<20$) dissociation. In the group of highly dissociated patients were 6 women and 3 men. This comparison of depressive patients with higher and lower dissociation shows that the subgroups have also statistically significantly different LLEs ($r=3.5$, $p=0.001$) (Table 1). Between group comparison with higher and lower dissociation using nonparametric Mann–Whitney test (Table 1) shows that the subgroups have also statistically significantly different LLEs during Stroop conflict ($Z=-2.2$, $p=0.029$) and during nonconflicting Stroop task ($Z=2.0$, $p=0.043$).

Significant correlation in healthy controls has been found only between BDI-II and DES ($r=0.34$, $p=0.023$). Other statistically significant correlations in the healthy control group were not found [correlation between LLEs during conflicting Stroop task and DES is $r=0.02$ ($p>0.05$) and between LLEs and BDI-II is $r=0.04$ ($p>0.05$)].

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Between group comparison for depressive patients with higher and lower dissociation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean low DES ± S.D.</td>
</tr>
<tr>
<td>Age</td>
<td>34.97 ± 10.17</td>
</tr>
<tr>
<td>DES</td>
<td>8.07 ± 4.56</td>
</tr>
<tr>
<td>BDI-II</td>
<td>18.40 ± 10.94</td>
</tr>
<tr>
<td>LLEs con.</td>
<td>0.19 ± 0.21</td>
</tr>
<tr>
<td>LLEs rest</td>
<td>0.22 ± 0.13</td>
</tr>
<tr>
<td>LLEs non.</td>
<td>0.29 ± 0.27</td>
</tr>
<tr>
<td>S LLEs con.</td>
<td>0.16 ± 0.26</td>
</tr>
<tr>
<td>S LLEs rest</td>
<td>0.16 ± 0.27</td>
</tr>
<tr>
<td>S LLEs non.</td>
<td>0.18 ± 0.30</td>
</tr>
</tbody>
</table>

Note. DES — Dissociative Experiences Scale; higher DES ($N=9$, DES$>20$); lower DES ($N=31$, DES$<20$); LLEs — largest Lyapunov exponents; BDI-II—Beck Depression Inventory; df=38; con. — conflicting Stroop task; non — nonconflicting Stroop; rest — resting condition; S — surrogate values.

Fig. 1. Dependency graph of largest Lyapunov exponents [in bit/s] during conflicting Stroop task with DES ($r=0.58$, $p=0.000001$) and BDI-II ($r=0.35$, $p=0.013$).
However, no significant correlations \( (p = 0.05) \) during non-conflict-
ing Stroop task between LLEs and DES in the patients \( (r = -0.14) \) and controls \( (r = 0.09) \) or between LLEs and BDI-II in the patients \( (r = -0.30) \) and controls \( (r = -0.03) \) were found. Similarly, no significant correlations during rest between LLEs and DES in the patients \( (r = 0.01) \) and controls \( (r = 0.13) \) or between LLEs and BDI-II in the patients \( (r = 0.03) \) and controls \( (r = 0.14) \) were found.

Results of descriptive statistics for psychometric measures show means: BDI-II for the patients 20.73 (SD=11.99) and for the controls 6.83 (SD=5.95). Differences between the patients and controls were not statistically significant. Differences of LLEs between the groups for the states during the experiment assessed by t-test for independent samples were statistically significant \( (t = 2.97, p = 0.004; \text{for} \text{BDI-II} \ t = 7.02, p < 0.0000001) \). Differences of LLEs between the groups for the states during the experiment assessed by t-test for independent samples were not statistically significant \( (t = 1.11, p = 0.05) \).

Statistical comparison between men and women in both groups did not show significant differences in psychometric measures or LLEs.

Comparison between LLEs calculated from original and surrogate time series was performed by nonparametric Mann–Whitney test for independent samples. The results confirmed with high statistical significance in depressive patients \( (Z \text{of Mann–Whitney test from} 3.37 \text{to} 3.53, p < 0.001) \) and also in healthy controls \( (Z \text{from} 6.98 \text{to} 7.19, \text{p < 0.0000001}) \) that LLEs calculated from the original data are significantly different from LLEs calculated from the surrogate data and did not represent linearly filtered Gaussian white noises. In addition, correlation between LLE during conflicting Stroop task calculated from surrogate time series and DES \( (r = 0.09, p > 0.05) \), and BDI-II \( (r = -0.19, p > 0.05) \) is not statistically significant which strongly suggest that the results cannot be explained from the linear data properties. These results provide evidence for nonlinear dynamics in autonomic nervous system as measured by ECG. Because all the LLEs were positive, these data indicate the presence of chaotic dynamics.

4. Discussion

Results of this study indicate that nonlinear chaotic changes calculated from RRI in the patients with depression, reflect cognitive conflict during conflicting Stroop task and that this conflict related chaotic neural activity displays a significant relationship to dissociation. This relationship is in accordance with recent findings which indicate that ACC activity is closely related to heart rate variability (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 \( (\text{Matthews et al., 2004; Hazeltine et al., 2000; Critchley et al., 2003}) \). 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 \( (\text{Matthews et al., 2004; Benarroch, 1993}) \). During increased ACC activation related to 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 \( (\text{Stroop, 1935; Matthews et al., 2004}) \). Recent findings show that complex functions of cognitive–emotional integration are particularly vulnerable to stressful events mainly in early childhood, which may be a cause of serious traumatization and dissociation also in the later periods of life \( (\text{Post et al., 1995; Putnam, 1997; Teicher et al., 2003}) \). These findings also show that stressful life events frequently cause abnormal brain development and that ACC is a particularly important brain region for the attention and intentional control mediating stress response particularly vulnerable to stress \( (\text{Cohen et al., 1999, 2006; Teicher et al., 2003}) \). For example, in studies of association between early life stress and brain morphometry decreased ACC volumes in traumatized patients and in patients with PTSD have been found \( (\text{Cohen et al., 2006; Araki et al., 2005}) \). Recent findings also indicate that depression in adulthood may be significantly influenced by experienced traumatic stress and dissociation \( (\text{Wilkeson et al., 2000; Bob et al., 2005; Sar and Ross, 2006}) \). In this context, significant correlation between BDI and DES, and significantly increased level of depression in highly dissociated patients found in this study is in agreement with the findings that dissociation as frequent consequence of traumatic stress may present a significant factor in etiology of depression. These findings suggest that ACC alterations found in depression \( (\text{Drevets and Savitz, 2008}) \) must not be related to depression per se but may present a consequence of certain stress related changes, which may cause the patients to respond to experimental stressor differently than the healthy controls. Because SSRI antidepressants may influence attentional bias \( (\text{Merens et al., 2007}) \) and may cause decrease in dissociative symptoms \( (\text{Marshall et al., 2007}) \) it is possible that they may facilitate the Stroop task. This facilitation may attenuate inner psychological conflict and partially improve inhibitory deficits related to dissociation. The improvement in inhibitory functions due to medication consequently may cause that the relationship of dissociation, depression and chaos in physiological response could be stronger in unmedicated patients. These observed deficits of neural inhibition in cognitive functions related to dissociation are also in accordance with theoretical concepts of neural processing such as connectionist model of memory, known as parallel distributed processing (PDP) \( (\text{Yates and Nasby, 1993; Bob, 2003}) \). From this point of view dissociation can be described as a kind of divided or parallel neural process where several systems may have some independence. It refers also to a compartmentalization of mental experience which as a defense mechanism may be conceptualized as a failure of neural inhibition resulting from disturbed balance of fundamental excitatory or inhibitory synaptic processes. Similarly also recent findings in both animals and humans indicate that characteristic response to traumatic stress may not be only emotional arousal but also active defensive or antiralus intrapsychic mechanisms. These intrapsychic mechanisms relate to excitatory and inhibitory influences that are experienced as engagement that represent active emotional response and disengagement (e.g. avoidance, withdrawal or denial) related to response inhibition \( (\text{Mason et al., 2001}) \). Failure of this inhibition caused by abnormal intensive affect manifests itself as a continuum of pathological dissociation from mild forms as repression, to serious forms such as splitting, amnesia, fugues, dissociative identity disorder and other dissociative states. The PDP concept is also in accordance with reported interaction between attentional context and dissociation for Stroop interference \( (\text{DePrince and Freyd, 1999}) \), which suggests that dissociation may enable to control the information flow and may have certain adaptive functions as a compensatory mechanism of defective neural inhibition. Mild levels of dissociation similarly as mild levels of depressed mood so may have adaptive functions that enable new forms of adaptive cognitive and behavioral patterns. In this context, already Morton Prıncipe proposed that dissociation is a general principle governing the normal psycho–nervous mechanism and therefore in a highly marked form only is pathological \( (\text{Bernstein and Putnam, 1986}) \).

Several recent findings indicate a possible role of neural chaos in the processing of the dissociated traumatic memory that may represent an underlying neural process related to psychopathology \( (\text{Bob, 2007}) \). These data are in accordance with findings that characteristic nonlinear changes of neural dynamics probably play a certain role in the pathophysiology of depression \( (\text{Huber et al., 1999; Gortzchalk et al., 1995}) \); schizophrenia and other psychiatric diseases \( (\text{Paulus and Braff, 2003; Bob, 2003; Putnam, 1997}) \). Chaotic neural processes as a consequence of competition among cognitive and behavioral patterns may produce extremely different outcomes with respect to previous state because of their sensitivity to initial conditions (the so-called butterfly effect). This suggests interesting perspectives for further research because these extremely different outcomes as a consequence of neural chaos might illuminate the neural basis of abrupt shifts in
mood and behavior which are typical for traumatic stress related memories manifesting as dissociative states.

5. Conclusions

The results of the present study provide first supportive evidence that degree of chaos in heart rate dynamics during Stroop conflict assessed by LLEs is related to dissociation in unipolar depressed people. These data strongly suggest that a level of sensitivity related to a degree of neural chaos during experimental conflict reflects a level of chronic conflicting conditions linked to cognitive disintegration and disrupted information flow in dissociative states.

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