Dissociation, epileptic-like activity and laterized electrodermal dysfunction in patients with schizophrenia and depression

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Summary

OBJECTIVES: Recent evidence indicates frequent EEG abnormalities in dissociated patients. This evidence is in agreement with findings that in certain psychiatric patients, psychosensory symptoms of epileptogenic nature, the so-called complex partial seizure-like symptoms occur. With respect to these findings, a hypothesis examined in this study states that increased level of experienced traumatic stress and dissociation in pathological conditions such as schizophrenia or depression relates to increased score of complex partial seizure-like symptoms. Also is suggested that the complex partial seizure-like symptoms might be related to unilateral hemispheric electrophysiological dysfunction, stress and dissociation.

PARTICIPANTS AND METHODS: Psychometric assessment of dissociation, stress and measurement of right-left asymmetry of bilateral EDA in patients with schizophrenia (N=34) and depression (N=41) in comparison to healthy controls (N=36).

RESULTS: Results indicate that increased traumatic stress and dissociation in both groups of patients significantly relate to increased level of complex partial seizure-like symptoms, and may cause the right-left EDA asymmetry.

CONCLUSIONS: The data suggest relationship between left-hemispheric asymmetry and sympathetic over-activation in schizophrenia, and between right-hemispheric asymmetry with sympathetic under-activation in depression.

INTRODUCTION

Dissociation was for the first time systematically described at the end of the nineteenth century by Pierre Janet (van der Kolk and van der Hart, 1989). Janet defined dissociation as a mental event, caused by traumatic or stressful experience splitted off from consciousness because it does not fit into existing cognitive schemes (van der Kolk and van der Hart, 1989; Bob, 2003). Mental event that induces dissociation most often represents exposition of a trauma in childhood because of physical or emotional abuse or other traumatic events such as accidents, nature calamities, humanitarian catastrophes, losing a close person etc. (Spiegel and Cardena, 1991). Characteristic reactions on these events are psychic
dissociative symptoms such as memory losses, fragmentation of knowledge of the self and experience, splitting of emotional and/or cognitive aspects of experiences, numbing of affect, psychological escape from unpleasant stimuli, trance-like states, increased suggestibility and greater hypnotizability (Putnam, 1997; van der Kolk and van der Hart, 1989). For example, identity changes that may appear as depersonalization or in extreme case as multiple personality disorder (MPD), characterized by distinguished personalities in one person. Frequently experienced symptoms are also changes in notion of external world such as derealization, hallucinations, or pathological changes of memory, for example psychogenic amnesia or MPD (Putnam, 1997; Spiegel and Cardena, 1991). On the other hand also somatic components of dissociation have a profound role in the long-term adaptation to traumatic experience and lead to a lack of integration of somatoform components of experience, reactions, and functions (the so-called somatoform dissociation) (Nijenhuis et al., 1996).

Dissociation typically affects memory systems that may lead to memory loss restricted to a circumscribed period of time or category of events within the individual's life that causes exclusion of the experience from consciousness and the inaccessibility of voluntary recall of mental events associated with the trauma (Nemiah, 1991; Bob et al., 2005, 2006; Bob, 2007). Typical physiological reactions to traumatic stress and dissociation are disturbances of self-regulatory systems such as HPA axis resulting in hyperarousal, tachycardia or other symptoms of autonomic nervous system instability (Newport and Nemeroff, 2000; Teicher et al., 2003; Read et al., 2001). HPA axis is functionally closely related to neuroendocrinological balance, control hormonal levels, energetic metabolism, neuroimmunomodulation and disturbances of memory during stress reaction (Newport and Nemeroff, 2000; Mason et al., 2001; Payne et al., 2006; Plotsky et al., 1998; Teicher et al., 2003; Gavrilovic and Dronjak, 2005; Nakayama et al. 2005; Takahashi et al. 2005; Umegaki et al., 2006). According to neurodevelopmental research are most serious disturbances of HPA axis caused by traumatic events such as childhood abuse or neglect in the first years of life and often have long-term impact on emotional, behavioral, cognitive, social and physiological functions and vice versa love and social care also may influence these functions and improve dissociative disturbances (Teicher et al. 2003; Read et al. 2001; Esch and Stefano, 2005; Stefano and Esch, 2005).

A form of neurophysiological dysregulation related to traumatic stress and dissociation are also epileptic-like dysfunctions (Spiegel, 1991; Putnam, 1997; Teicher et al., 2003; Bob, 2003). Already at the second half of the nineteenth century, French neurologist Jean-Martin Charcot thought that dissociative symptoms characteristic for MPD might relate to epileptic process (Putnam, 1997). This relationship support further historical and recent studies that document frequent EEG abnormalities in the patients with MPD and epileptic activity during personality alterations in MPD or identity shift in temporal lobe epilepsy (Spiegel, 1991; Putnam, 1997; Teicher et al., 2003; Bob, 2003). Further reported evidence also confirms the relationship of temporal lobe abnormalities and pathological dissociation (Putnam, 1997; Teicher et al., 2003; Bob, 2003). A number of studies also indicate a role of epileptic activity in dissociative states during depersonalization (Sierra and Berrios, 1998), dissociative disorders not otherwise specified, dissociative seizures (the so-called pseudo-epilepsy) (Bowman and Coons, 2000) and dissociative states of consciousness such as possession, out of body experiences, near death experiences or religious experiences (Putnam, 1997; Bob, 2003). On the other hand, dissociation-like symptoms such as depersonalization, fugues, amnesias, and autoscopy (seeing an externalized image of oneself) are sometimes reported ictally and perictically, by seizure patients (Putnam, 1997). In this context, recent data support the evidence that temporal-limbic seizure activity can produce dissociative symptoms even without neurological focal lesion (Spiegel, 1991). This evidence linking dissociative symptoms and the temporal-limbic epileptic activity in non-epileptic conditions is consistent with data that the dissociative symptoms in temporal lobe epilepsies occur during interictal periods and not during the ictal state (Spiegel, 1991). The relationship between dissociation and epileptic activity likely may explain influence of repeated stressful events that lead to an increase in responsiveness to a stress stimuli resulting from repeated stressors with kindling-like progression (Post et al., 1995; Putnam, 1997; Teicher et al., 2003). The kindling-model of stress-related sensitization seems to be in agreement with suggestive evidence that stress may influence significantly increased occurrence of EEG abnormalities. The abnormalities reported in significantly traumatized patients mainly in the frontotemporal region consisted of spikes, sharp waves, or paroxysmal slowing, predominantly in the left hemisphere (Putnam, 1997; Teicher et al., 2003).

These findings are in agreement with evidence that in certain psychiatric patients, often without apparent EEG abnormalities, psychosensory symptoms of epileptogenic nature occur (the so-called complex partial seizure-like symptoms) (Roberts et al., 1992; Hines et al., 1995). These symptoms normally belong to characteristic manifestations of temporal lobe epilepsy but may also emerge without apparent seizures in the so-called Epilepsy Spectrum Disorders (Roberts et al., 1992; Hines et al., 1995; Jampala et al., 1992). Characteristic symptoms are memory gaps, confusion spells, staring spells, episodic irritability, episodic rhinitis, episodic aphasia, jamais-vu, olfactory hallucinations, gustatory hallucinations, visual illusions (e.g., scintillations), paresthesia, anesthesia, auditory illusions (e.g., phone ringing). In addition, patients suffer from headache with nausea and/or photophobia, abrupt mood shifts, deja-vu, abdominal sensations, intrusive thoughts and parasomnias (Roberts 1992; Hines et al.,
A great many of these symptoms are characteristic for the Epilepsy Spectrum Disorder (ESD). Although the phenomenology of ESD and the positive clinical response to anticonvulsant seen in most ESD patients suggest the presence of subclinical electrophysiological dysfunction, the lack of clear non-behavioral evidence of CNS dysfunction (i.e., EEG) may obscure the underlying neurophysiological nature of ESD (Roberts, 1992; Hines et al., 1995).

These findings regarding traumatic stress, dissociation and epileptiform abnormalities seem to be important in context of reported data that document lateralized temporal-limbic dysfunction in patients with schizophrenia and depression (Hugdahl, 2001). According to reported findings different schizophrenia syndromes may be related to asymmetry of limbic functioning and overactivation most probably in the left hemisphere (Gruzelier and Venables, 1974; Gruzelier, 1983). Flor-Henry (1969) reported asymmetries of bilateral electrodermal activity (EDA) in schizophrenia and described an association between dysfunction in the left (dominant) temporal lobe and schizophrenia also confirmed by recent neuroimaging data (Hugdahl, 2001). Flor-Henry also found that epileptic patients with predominantly schizophrenic symptoms had a high incidence of epileptic foci in the left temporal lobe while the epileptic patients with depression had a high incidence of foci in the right temporal lobe (Flor-Henry, 2003; Hugdahl, 2001).

The association between temporal-limbic epileptic abnormality and EDA asymmetry is in agreement with evidence that EDA is governed mainly by limbic modulation influences. The EDA is mainly modulated by amygdala activity, although also other structures such as ventromedial and dorsolateral prefrontal cortices, anterior cingulate gyrus, parietal lobe, insula and hippocampus in EDA modulation are involved (Mangina and Beuzeron-Mangina, 1996; Critchley, 2002; Phelps et al., 2001). For example, intracranial study by Mangina and Beuzeron-Mangina (1996) indicate that activity in the limbic structures (mainly the amygdala) influenced by electrical stimulation relates to increased ipsilateral EDA. Typical for EDA is that it reflects activity within the sympathetic axis of the autonomic nervous system. Sympathetic activity is closely linked to emotion, and EDA is widely used as a sensitive index of emotion-related sympathetic activity (Dawson et al., 2000; Critchley, 2002). Research of the relationship between EDA and dissociation has a long historical tradition beginning at the break of 19th and 20th century. In 1908 M. Prince and F. Peterson reported EDA measurement (the so-called galvanic skin response- GSR) in a patient with MPD and found distinct emotional reactions on personally meaningful stimuli indicating amnestic barrier among different personalities (Prince and Peterson, 1908). At the same time C.G. Jung published his famous work “On psychophysical reactions of the associative experiments” that has documented direct relationship between EDA and dissociated fragments (related to traumatic memories) called “complexes” (Jung, 1907). Later EDA studies found also changes in laterality during different alter-personality states in MPD and indicate that certain alter-personalities relate to opposite hemispheric preference (Brende, 1984; Ahern et al., 1993; Putnam, 1997). Contemporary evidence reports further specific changes of EDA in dissociation related disturbances such as depersonalization (Sierra and Berrios, 1998), MPD (Putnam, 1984, 1997) or posttraumatic stress disorder (PTSD) (Orr and Roth, 2000).

Taken together, these findings indicate a relationship among traumatic stress, dissociation, complex partial seizure-like symptoms and kindling-like mechanism that could be linked to unilateral electrophysiological dysfunction and EDA asymmetry. The relationship suggest a hypothesis that increased level of experienced traumatic stress and dissociation in pathological conditions such as schizophrenia or depression is related to increased score of complex partial seizure-like symptoms and that these conditions also influence right-left asymmetry of bilateral EDA.

PARTICIPANTS AND METHODS

Participants

The participants consisted of 34 adult schizophrenic outpatients, 41 depressive inpatients from the university hospital and 36 healthy controls from general population. The 18 males and 16 females from schizophrenia group, 13 males and 28 females from depressive group and the 13 males and 23 females from healthy controls group took part in the study. Schizophrenic patients had diagnosis of paranoid schizophrenia and depressed patients had diagnosis of bipolar (N=4) or unipolar (N=37) depression. All the schizophrenia patients were in partial remission. Their treatment at the time of the recruitment was based on antipsychotic medication. Treatment status of the depressive patients was in partial remission without psychotic symptoms. Exclusion criteria were organic illnesses involving the central nervous system, substance, and/or alcohol abuse, mental retardation and significant extra-pyramidal symptomatology. Two of the authors of this article independently reexamined the patient’s diagnoses according to DSM IV criteria (American Psychiatric Association, 1994). All the participants were strongly right handed according to Waterloo Handedness Questionnaire (Elias et al., 1998).

Design

In the clinical assessment, four psychometric measures for symptoms of dissociation, traumatic stress and complex partial seizure-like symptoms and measurement of bilateral electrodermal activity in the patients and healthy controls were used. Investigations took place in a quiet room and all the psychometric measures were performed individually with informed consent of all the participants.
**Psychometric measures**

Psychic dissociative symptoms were assessed by Dissociative Experiences Scale (DES) (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 the continuum from 0% to 100%.

Somatoform dissociative symptoms were assessed using 20-item self-reported somatoform dissociation questionnaire SDQ-20 (Nijenhuis et al., 1996). Somatoform dissociative symptoms represent alterations in sensations of pain (analgesia, kinesthetic anesthesia), alterations of perception, motor inhibition or loss of motor control, gastrointestinal symptoms, etc. Subjects indicate the degree of their experience on 5-point Likert scale.

For investigation of childhood traumas, TSC-40 (Trauma Symptom Checklist) (Briere, 1996) was used. TSC-40 is a self-reported 40-item questionnaire on a 4-point Likert scale. Total scores of TSC-40 higher than 70 are associated with symptoms of significant childhood traumas.

For assessment of complex partial seizure-like symptoms that reflect temporal lobe epileptic-like activity the 35-item Structured Clinical Interview (the so-called Iowa interview) was used (Roberts, 1992). Symptoms experienced by patients are indicated on 6-point Likert scale.

**Electrodermal measurement**

After obtaining informed consent from the participant, the EDA was recorded bilaterally using two channels SAM unit and Psylab software (Contact Precision Instruments) connected to personal computer. Measurement was performed in a quiet room, with room temperature of about 21°C (69.8 F). The participant was instructed to sit down into comfortable chair. Then two pairs of Ag/AgCl electrodes (8 mm diameter active area) filled with electro-conductive-paste (KY jelly) were attached to medial phalanges of the index and middle finger of each hand. After two minutes relaxation with closed eyes experimental EDA recording began and takes time of two minutes.

**Statistical methods**

Descriptive statistics in a statistical evaluation included medians, means, Pearson product-moment correlation coefficients, standard deviations and t-test for independent samples. For the statistical evaluation the software package Statistica version 6 was used.

**RESULTS**

Examined correlations among psychometric measures for the schizophrenic patients (N=34), depressive patients (N=41) and for the healthy controls (N=36) (Table 1) indicate significant relationship among measures of traumatic stress, dissociation and complex partial seizure-like symptoms. Results of psychometric measures (Table 2) also indicate statistically significant differences between the patients and controls for all the psychometric measures using t-test (p<0.01). Descriptive statistics of EDA indicate significant hyperarousal in the patients with paranoid schizophrenia and significant hypoarousal in the patients with depression in comparison to healthy controls using t-test (p<0.01) (Table 2). EDA results also indicate significant bilateral asymmetry in the patients in comparison to healthy controls. In the patients with schizophrenia EDA is significantly higher on the left side than on the right, which is confirmed by t-test between left and right side (t=3.92 (p=0.0002). In the patients with depression EDA is significantly higher on the right side than on the left (t=2.33, p=0.022). In the control group significant bilateral asymmetry in the t-test between left and right side has not been found (t=0.37 for p=0.71).

**DISCUSSION**

Results of psychometric measures support the hypothesis that epileptic-like phenomena assessed in the form of complex partial seizure-like symptoms relate to traumatic stress and dissociation in schizophrenia and depression. EDA asymmetry in the patients confirm previous findings that unilateral electrophysiological

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**Table 1. Correlations among psychometric measures for the schizophrenic patients (N=34), depressive patients (N=41) and for the healthy controls (N=36).**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DES</th>
<th>SDQ-20</th>
<th>TSC-40</th>
<th>IOWA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCH.</td>
<td>DEP.</td>
<td>CONT.</td>
<td>SCH.</td>
</tr>
<tr>
<td>DES</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.45**</td>
</tr>
<tr>
<td>SDQ-20</td>
<td>0.45**</td>
<td>0.59***</td>
<td>0.27</td>
<td>1</td>
</tr>
<tr>
<td>TSC-40</td>
<td>0.5**</td>
<td>0.39**</td>
<td>0.32</td>
<td>0.63***</td>
</tr>
<tr>
<td>IOWA</td>
<td>0.37</td>
<td>0.57***</td>
<td>0.79***</td>
<td>0.58***</td>
</tr>
</tbody>
</table>

Note: DES= Dissociative Experiences Scale; SDQ-20= Somatoform Dissociation Questionnaire; TSC-40= Trauma Symptom Checklist; Iowa= Structured Clinical Interview for Complex Partial Seizure-like Symptoms; Sch.= schizophrenia; Dep.= depression; Cont.= controls; marked correlations are significant at: * p < 0.05, ** p < 0.01, *** p < 0.001, +p=0.055
Table 2. Descriptive statistics for the schizophrenic patients, depressive patients and for the healthy controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenic patients N=34</th>
<th>Depressive patients N=41</th>
<th>Healthy controls N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>26.91±19.84</td>
<td>26.08±13.24</td>
<td>26.53±8.79</td>
</tr>
<tr>
<td>DES</td>
<td>13.91±12.43</td>
<td>14.17±13.24</td>
<td>8.86±8.02</td>
</tr>
<tr>
<td>SDQ-20</td>
<td>20.0±7.71</td>
<td>29.68±10.94</td>
<td>23.94±3.38</td>
</tr>
<tr>
<td>TSC-40</td>
<td>30.51±20.99</td>
<td>43.34±19.81</td>
<td>18.67±11.84</td>
</tr>
<tr>
<td>Iowa</td>
<td>21.03±18.32</td>
<td>30.51±20.99</td>
<td>9.5±11.21</td>
</tr>
<tr>
<td>EDA-left</td>
<td>7.08±5.9</td>
<td>1.61±1.31</td>
<td>2.91±1.51</td>
</tr>
<tr>
<td>EDA-right</td>
<td>2.87±2.10</td>
<td>2.56±2.28</td>
<td>2.79±1.26</td>
</tr>
</tbody>
</table>

Note. DES= Dissociative Experiences Scale; SDQ-20= Somatoform Dissociation Questionnaire; TSC-40= Trauma Symptom Checklist; Iowa= Structured Clinical Interview for Complex Partial Seizure-like Symptoms; EDA= electrodermal activity [micro-Siemens]

dysfunction predominantly occurs on the left in schizophrenia and on the right in depression (Dawson et al., 2000; Hugdahl, 2001). With respect to similar findings in epileptic patients with left or right temporal foci related to schizophrenia and depression, reported EDA dysfunction, predominantly on the left in schizophrenia and on the right in depression, may relate to epilepti-

like activity and kindling (Flor-Henry, 1969, 2003). Because of the great sensitivity of EDA on emotional stress, it is reasonable to suppose that traumatic stress in schizophrenia and depression is related to electrod-
ermal dysfunction and asymmetry that was not observed in the healthy control group. These findings support possible relationship between temporal-limbic dysfunction measured by EDA and traumatic stress related to sensi-
tization and kindling mechanism. Results of the present study are also in accordance with recent findings that schizophrenia and depression have a close relationship to a loss of physiological balance between excitation and inhibition, which leads to autonomic hyperarousal in paranoid schizophrenia and hypoarousal in depression. The significant loss of physiological equilibrium is observed also in epilepsy as over-excitation. Conversely, schizophrenia or depression are likely connected to over-inhibition in the structures of the limbic system. In epilepsy, the normal equilibrium between excitation and inhibition permanently alters by repeated focal excita-

tion or kindling, resulting in a permanent state of excessive focal excitability and spontaneous seizures (Stevens, 1999). Recent findings indicate that similar “kindling” or sensitization may originate in inhibitory systems in response to focal physiological pulsed discharges of limbic and hypothalamic neurons and this excess of inhibitory factors may then manifest as a psychosis (Stevens, 1999). Similar situation is also in depression, because decreased activity of serotonin, norepinephrine, dopamine, and GABA may facilitate the kindling process (Kanner and Balabanov, 2002). These findings are also in agreement with reported cases of forced normalization or alternative psychosis in which decreasing of epileptic symptomatology is linked to increased psychopath-

ogy in a form of psychosis or depression and vice versa (Krishnamoorthy et al., 2002).

The results discussed above in the context of kindling, traumatic stress and dissociation might explain lateralized right hemispheric sympathetic under-activation in depression or left hemispheric sympathetic over-activa-
tion in schizophrenia because of asymmetric autonomic control within the brain. The left hemisphere affects predominantly parasymptathetic functions, while the right hemisphere predominantly governs the sympathetic functions (Hilz et al., 2001; Avnon et al., 2004). This is in accordance with several findings in schizophrenia, which suggest that psychotic states affect the autonomic nervous system and suppress the parasympathetic function without affecting sympathetic function (Toichi et al., 1999; Takashi et al., 2003). These data are consistent with the above hypothesis of the kindling in inhibitory systems because of repeated emotional disturbances. Lateralized activation of left-sided inhibition in schizophrenia due to kindling may lead to suppression of parasympathetic function without affecting sympathetic function and vice versa in depression in which right-sided inhibition may lead to suppression of sympathetic function without affecting parasympathetic function as is evident from electrodthermal measures indicating lowering of sympathetic activity in depression. This interpretation of results is also consistent with several findings that emo-
tional stress may lead to two predominant forms of stress response. The first form of stress response leads to pre-
dominantly sympathetic influences and the second form of stress response relates to predominant parasympathetic functions (Ul’yaninskii, 1995; Mason et al., 2001). This corresponds to known experience that mainly chronic stress often leads to a passive defense and predominant parasympathetic influences on metabolic activity. From this point of view it is probable that increased traumatic stress and dissociation might cause the electrodthermal dysfunction that relates to sympathetic over-activation in schizophrenia and sympathetic under-activation in depression.
The probable influence of psychosocial stressors on bilateral EDA asymmetry reported in this study might also indicate relationship between traumatic dissociation on the psychological level and related “functional dissociation” of the hemispheres in the form of significant bilateral asymmetry that may be a consequence of reversible influence on information transfer across the corpus callosum (Spitzer et al., 2004). This can potentially explain why certain dissociative symptoms are similar to symptoms in the patients with split brain, because of anatomical “dissociation” between hemispheres (Galin, 1974; Brende, 1984). The functional dissociation might be a defense mechanism that enables to health hemisphere to inhibit the negative impulses from the dysfunctional hemisphere, similarly as in psychological dissociation that inhibits a certain negative psychological impulses, which does not fit into current cognitive scheme. Potentially, the relationship among dissociation, functional EDA dissociation and indirectly measured epileptic-like activity by complex partial seizure-like symptoms could have a practical implication for the purpose to find diagnostically useful criteria for therapeutic indication of anticonvulsant drugs also in the absence of apparent EEG abnormalities on the scalp EEG.

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