Lateralized brain and neuroendocrine dysregulation as response to traumatic stress

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Abstract

Stressful life events cause a variety of conditions affecting cerebral and neuroendocrine functions. Repeated stressful events also may determine sensitization leading to an increase in responsiveness to stress stimuli. Recent findings suggest that cognitive and emotional dysregulation related to traumatic stress likely is linked to defective inhibitory functions that may also lead to temporolimbic seizure-like activity, increased vulnerability to stressors, and dysregulated asymmetry in neural activity patterns that may influence interhemispheric dissociation. Together recent data show that dysregulation in the brain asymmetry and mental functioning may be caused by stress-related activation that can influence also the peripheral endocrine glands through the HPA axis and other pathways connecting the CNS and the target endocrine glands.

INTRODUCTION

Traumatic or stressful events are related to extremely negative afect that is not congruent with current cognitive scheme and is split off from consciousness with resulting inner conflict, contradictory tendencies and traumatic memory (van der Kolk and van der Hart, 1989; Putnam, 1997; Bob, 2003a,b). Stressful life events cause a variety of conditions affecting cerebral and neuroendocrine functions and one of the typical reactions are disturbances of self-regulatory systems such as hypothalamus-pituitary-adrenal axis (HPA) resulting in hyperarousal, tachycardia, autonomic nervous system instability, neuroendocrinological balance and control hormonal levels, energetic metabolism, and neuroimunnomudolation during stress reaction (Payne *et al*., 2006; Umegaki *et a*l., 2006; Newport and Nemeroff, 2000; Teicher *et al*. 2003; Bob *et al*., 2007a,b; Fisar and Raboch, 2008).

Repeated stress also determines functional defects in the hippocampus that lead to decreasing inhibitory control of the hippocampus on the HPA axis and cause a positive feedforward cascade of glucocorticoide levels (Bao *et al*., 2007). Recent data indicate that most serious disturbances of HPA axis caused by traumatic events such as childhood abuse or neglect in the first years of life 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 (Ito *et al*., 1998; Teicher *et al*. 2003; Read *et al*., 2001; Esch and Stefano 2007; Stefano and Esch, 2007). These neuroendocrinological and neurophysiological dysfunctions related to trauma cause memory disturbances, dissociation and also a vari-

ety of somatic symptoms that 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 (Nijenhuis *et al*., 1996, 2004; Bowman and Coons, 2000).

Repeated stressors and reexperiencing of the traumatic event in childhood often cause the delayed effects of severe psychological trauma that lead to enhancement of the self-preservative catecholamine states related to anger, fear, meaninglessness and a blunting of the emotional responses of the attachment behavior associated with dysfunction of the locus coeruleus, amygdala and hippocampal systems (Henry, 1992, 1997).

Repeated stressful events also may determine sensitization leading to an increase in responsiveness to stress stimuli resulting to significantly increased vulnerability to stressors that have more lasting consequences with kindling-like progression (Post *et al*., 1995; Post and Weiss, 1998; Kraus, 2000). The kindling-model of stress-related sensitization (Post et al., 1995) seems to be in agreement with suggestive evidence that stress may influence significantly increased occurrence of EEG abnormalities that have been reported in significantly traumatized patients mainly in the frontotemporal region, which consisted of spikes, sharp waves, or paroxysmal slowing, predominantly in the left hemisphere (Teicher et al., 1993, 2003, 2006; Putnam, 1997; Ito *et al*., 1993). Stress-related sensitization has been proposed to cause changes in GABA postsynaptic receptors that may lead to overstimulation of neurons mainly in the limbic system, resulting in limbic system irritability manifesting as markedly increased prevalence of symptoms suggestive of temporal lobe epilepsy (Teicher *et al*., 2003, 2006; Post *et al*., 1995; Bob, 2007). Recent data strongly suggest that traumatic stress may determine limbic irritability and temporal-limbic seizure-like activity (Teicher *et al*., 2003, 2006; Spigelman *et al*., 2002; Bob *et al*., 2005, 2007e) and close link between limbic irritability and defects in cerebellar vermis has been reported (Teicher *et al*., 2003, 2006; Anderson *et al*., 2002).

These findings suggest that cognitive and emotional dysregulation related to traumatic stress likely is linked to defective inhibitory functions that may also lead to temporo-limbic seizure-like activity. This epileptic-like process may emerge in the form of symptoms similar to ictal temporal lobe epilepsy such as somatic, sensory, behavioral and memory symptoms that may occur also in nonepileptic conditions (Teicher *et al*., 2003, 2006; Silberman *et al*., 1985; Roberts *et al*., 1992; Hines *et al*., 1993).

TRAUMATIC STRESS, KINDLING AND TEMPORO-LIMBIC ASYMMETRY

Reported evidence that confirms the relationship of temporal lobe abnormalities and pathological dissociation (Ahern *et al*., 1993; Putnam, 1997; Sierra and Berrios, 1998; Teicher *et al*., 2003; Bob, 2003) in non-epileptic conditions is consistent with data that the dissociative symptoms in temporal lobe epileptics 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 also seems to be in agreement with suggestive evidence that stress may influence significantly increased occurrence of EEG abnormalities (Teicher *et al*., 2003).

There are good reasons for using limbic kindling as a model of epileptogenesis in focal human limbic epilepsy or complex partial seizures with secondary generalization (Adamec, 1990, 1997; Albright and Burnham, 1980; Loscher *et al*., 1986). This concept is supported by findings of repeated electrical stimulation in human hippocampus that caused an epileptic disorder, which was not present before the experiment and similar data of kindling in thalamus were reported (Adamec, 1990, 1997; Sramka *et al*., 1977; Monroe 1982). Another reason is the evidence that time-dependent spread of epileptic excitability occurs independently on tissue pathology as a consequence of organic damages (Adamec, 1990, 1997). According to some findings damage creates kindling stimulus that leads to a seizure disorder and the delay between trauma and onset of seizures in humans is consistent with the hypothesis (Adamec, 1990). These findings are also supported by reported cases of successful prophylactic anticonvulsant therapy following head trauma with neurological signs of brain damage that reduce the incidence of an epileptic disorder development (Adamec, 1990, 1997; Servit and Musil 1981).

Kindling may be also used as a concept for explanation of psychopathological processes as a mirror of altered limbic functions. In manic depressive psychosis the role of kindling was hypothesized in the study of influence of carbamazepin on mood and its anticonvulsant and antikindling effect that is in agreement with the anticonvulsant effect of carbamazepin in complex partial seizures and also its influence on mood of these patients (Adamec, 1990, 1997). Likely the effectiveness of carbamazepin in the treatment of manic depressive disorder in nonepileptics is due to its limbic anticonvulsant properties that suggest limbic neural mechanism underlying manic depressive disorder (Adamec, 1990, 1997; Dalby, 1975). Dopaminergic hypothesis of schizophrenia provides similar results that show schizophrenic symptoms as consequences of hyperdopaminergic kindling in mesolimbic dopaminergic system (Adamec, 1990, 1997). Some findings also suggest the effect of limbic seizures on dopaminergic functions (Adamec, 1990, 1997) and a relationship of reciprocity between that kindling in mesolimbic dopaminergic and

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similar EEG activity in temporal neocortex in patients with temporal lobe epilepsy (Pakalnis et al., 1988).

The concept of kindling as a model for psychopathology is also in accordance with recent findings that schizophrenia as well as depression are related to a loss of physiological balance between excitation and inhibition (Stevens, 1999). The significant loss of physiological equilibrium is observed also in epilepsy that is linked to over-excitation whereas 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 excitation or kindling, resulting in a permanent state of excessive focal excitability and spontaneous seizures (Stevens 1999; Goddard et al., 1969). 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, 1992, 1999). Similar situation is also in depression because of decreased activity of serotonin, norepinephrine, dopamine, and GABA that may facilitate the kindling process (Kanner and Balabanov, 2002).

These findings are in accordance with reported cases of forced normalization or alternative psychosis in which decreasing epileptic symptomatology is linked to increased psychopathology in the form of psychosis or depression and vice versa (Jobe et al., 1999; Krishnamoortthy *et al*., 2002). The kindling in inhibitory systems might also explain occurrence of complex partial seizure-like symptoms in psychiatric patients because of close relationship among traumatic stress, dissociation and complex partial seizure-like symptoms (Bob, 2007; Bob et al., 2005, 2006). These data suggest the relevance of the kindling model of dissociative states as a consequence of repeated traumatic stress (Post et al., 1995; Putnam, 1997) in various psychiatric conditions such as depression or schizophrenia.

Above findings support the kindling hypothesis for explanation of several neurobiological mechanisms of repeated traumatic stress in etiopathogenesis of psychiatric disorders and are also in accordance with published data that document lateralized temporal-limbic dysfunction in patients with schizophrenia and depression, likely caused by subclinical electrophysiological dysfunction (Hugdahl, 2001). According to findings by Gruzelier and Venables different schizophrenic 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 in the form of observable differences between the left- and right-hand recordings and described an association between dysfunction in the left temporal lobe and schizophrenia which has been supported also by recent brain imaging studies (Hugdahl, 2001). Flor-Henry also found that psychotic patients with predominantly schizophrenic symptoms had a high incidence of epileptic foci in the left temporal lobe while depressive patients had a high incidence of foci in the right temporal lobe (Flor-Henry, 2003; Hugdahl, 2001). This association between unilateral hemispheric dysfunction, ipsilateral temporal-limbic epileptic focus (Flor-Henry, 2003; Shulman, 2003; Hugdahl, 2001) and EDA asymmetry is in accordance with recent evidence that EDA is governed mainly by limbic modulation influences and correlates with amygdala activity (Mangina and Beuzeron-Mangina, 1996; Critchley, 2002; Phelps et al., 2001). Additionally, recent data reported in intracranial study by Mangina and Beuzeron-Mangina (1996) indicate that increased activity in the limbic structures caused by electrical stimulation relates to increased ipsilateral EDA.

EDA asymmetry in the patients with temporal epilepsy is in agreement with findings of unilateral electrophysiological dysfunction that predominantly occurs on the left (dominant hemisphere) in schizophrenia and on the right (non-dominant) 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 epileptic-like activity and kindling (Flor-Henry, 1969, 2003). Because of the great sensitivity of EDA on emotional stress, it is possible to suppose that traumatic stress in schizophrenia and depression is related to electrodermal dysfunction because of the asymmetry that was not observed in the healthy control group (Bob *et al*., 2007c,d). These findings support possible relationship between temporal-limbic dysfunction measured by EDA and traumatic stress related to sensitization and kindling mechanism. Results of these studies 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 findings 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-activation in schizophrenia because of asymmetric autonomic control within the brain. The left hemisphere affects predominantly parasympathetic 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; Takahashi *et al*., 2003, 2005). 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 electrodermal measures indicating lowering of sympathetic activity in depression. This interpretation is consistent with several findings that emotional stress may lead to two predominant forms of stress response. The first form of stress response leads to predominant 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 neuroendocrine metabolic activity.

TRAUMATIC STRESS AND INTER-HEMISPHERIC DYSFUNCTION

Above reviewed findings strongly suggest that traumatic stress may influence patterns of brain asymmetry and interhemispheric dysregulation. It is in agreement with recent findings the right hemisphere is more vulnerable to traumatic influences than the left (Henry, 1993, 1997). Reason for that is likely increased right hemispheric connection with the limbic system in comparison with the left hemisphere. The right (more often non-dominant) hemisphere is also more connected with autonomic nervous system and has predominant role in the physiological and cognitive aspects of emotional processing and is more than the left specialized for neuroendocrine and autonomic activation, for the secretion of the stress hormones, corticotrophin releasing factors and cortisol (Spence *et al*., 1996; Sullivan and Gratton, 1999a,b; Wittling and Pfluger, 1990; Schore, 2001, 2002, 2005). Evidence for this lateralization provide studies dealing with the relationship between conditioned fear response and amygdala function, which show that this activation is right hemisphere dominant (LaBar et al., 1998). Also has been reported that partial kindling of the right and not the left amygdala induces a long-lasting increasing in anxiety-like behavior (Adamec, 1997, 1999), and that the kindling in the right amygdala induces increased production of the corticotrophin releasing factors (Adamec and McKay, 1993). Recent evidence also suggests that the right amygdala is more involved in the storage of fearful faces and in the expression of emotionally influenced memory of aversive experiences with respect to the left (Morris *et al*., 1999; Isenberg *et al*., 1999; Coleman-Mensches and McGaugh, 1995; Schore, 2002). Certain neuropsychological studies of alexithymia also suggest a right-hemispheric dysfunction linked to a defect of information transfer across the corpus callosum that leads to a physiological disconnection of the two hemispheres and resulting inability to coordinate the affective expression of the right hemisphere with the verbal expression of the left hemisphere (Dewaraja and Sasaki, 1990; Schore, 2001). This dysfunction typically leads to a difficulty in verbal expression of emotions "no words for feelings" that is typical for alexithymia. Alexithymia is closely related to dissociation (Kooiman *et al*., 2004; Sayar *et al*., 2005; Frewen *et al*., 2006) and similar defects of information transfer across the corpus callosum in alexithymia (Tabibnia and Zaidel, 2005; Romei *et al*., 2008) and dissociation has been observed (Spitzer *et al*., 2004). This hemispheric dysfunction might indicate a relationship between traumatic dissociation on the psychological level and related "functional dissociation" of the hemispheres. This functional dissociation according to literature may be a form of reversible blocking of information transfer across corpus callosum (Bogen and Bogen, 1969). This might explain why certain dissociative symptoms are similar to symptoms in the patients with split brain as a consequence of anatomical "dissociation" between hemispheres which occur after surgical cut of corpus callosum (Ahern et al., 1993; Galin, 1974; Brende, 1984; Bob, 2003; Bogen and Bogen, 1969; Spitzer et al., 2004). 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. In this context Nasrallah (1985) suggested that one of the vital components of interhemispheric integration is the inhibition of any awareness by the verbally expressive hemispheric consciousness (predominantly the left) that it actually receives and sends thoughts, intentions, and feelings from and to another (right hemispheric) consciousness. This inhibition guarantees the unity of the right and left hemispheres into one "self" in the normal person and is disturbed in schizophrenia, because of defective interhemispheric integration that may lead to disinhibition of the awareness by the left hemisphere that it is being "influenced" by an unknown "external force", which is in fact the right hemisphere. Schneiderian delusions such as thought insertion and withdrawal and passivity feelings may be a direct outcome of such a deficit (Nasrallah, 1985). In this context, also Miller (1992) suggested that borderline splitting and borderline pathology may have a neural basis because of split between emotional and cognitive constitution and its lateralization in the brain. Because interhemispheric communication is necessary for mental unity, childhood emotional trauma may cause the two separate, unintegrated and alternating mental systems that are related to congenital abnormality in brain structure or function and may be a primary factor in borderline pathology (Miller, 1992).

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CONCLUSION

Together recent data show that dysregulation in the brain asymmetry and mental functioning may be caused by stress-related activation that can also influence the peripheral endocrine glands through the pituitary gland and also via direct neural pathways between the CNS structures and the target endocrine glands. Recent data suggest that adequate control of the target neuroendocrine structures requires asymmetry of neural regulation and that the patterns of cerebral asymmetry can be retroactively modified by the endocrine glands (Gerendai and Halasz, 2001). Recent data from animal models indicate that there is a functional asymmetry in the medial prefrontal cortex concerning neuroendocrine and autonomic stress responses and that both prestress and acute restraint stress-induced plasma corticosterone levels are lower in animals with right or bilateral lesion of the medial prefrontal cortex (Gerendai and Halasz, 2001; Edwards et al., 2000). In the context of kindling and lateralized epileptiform discharges there are also clinical data suggesting the asymmetry of the temporal lobe in the control of peripheral glands related to reproductive functions. For example, among women with partial seizures of temporal lobe origin, reproductive disorders are unusually common and was found that polycystic ovarian syndrome is predominantly associated with left-sided epileptiform discharges, whereas hypothalamic amenorrhea is related predominantly to right-sided discharges (Herzog, 1993; Gerendai and Halasz, 2001). These data suggest that also relationship between stress and kindling may potentially explain various dysfunctions and diseases related to disturbed asymmetry in neuroendocrine regulation.

An important aspect of the present findings is lateralized regulation of stress responses at the level of the mPFC that indicates close relationship between stress or emotionality-related processes and right brain mechanisms (Sullivan and Gratton, 1999a,b, 2002). Prelimbic and infralimbic regions of mPFC have an influence to visceral motor regions and autonomic function and emotional expression, and present an important region for the integration of neuroendocrine and autonomic activity with the behavioral states and cognitive processes (Sullivan and Gratton, 1999a,b, 2002). These studies suggest that although the right mPFC is necessary for a normal stress response and adaptation, excessive activity of this region is predominantly maladaptive. Further research regarding relationship between stress exposure and the level of neuropsychological, autonomic and neuroendocrine asymmetry may perspectively show other possible connections of these processes to excessive epileptic-like neural activity that may present common neural mechanism of various levels of the stress response because of increased neural excitabilty and dysregulated asymmetry in neural activity patterns.

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REFERENCES

1 Adamec RE (1990). Does kindling model anything clinically relevant? *Biol Psychiatr* **27**: 249–79.
2 Adamec R (1997). Transmitter systems involved in neural plasticity underlying increased anxiety and defense-implications for understanding anxiety following traumatic stress. *Neurosci Biobehav Rev* **21**: 755–65.
3 Adamec RE (1999). Evidence that limbic neural plasticity in the right hemisphere mediates partial kindling induced lasting increases in anxiety-like behavior: effects of low frequency stimulation (Quenching?) on long-term potentiation of amygdala efferents and behavior following kindling. *Brain Res* **839**: 133–152.
4 Adamec RE and McKay D (1993). Amygdala kindling, anxiety, and corticotopin releasing factor (CRF). *Physiol Behav* **54**: 423–431.
5 Ahern GL, Herring AM, Tackenberg J, Seeger JF (1993). The association of multiple personality and temporolimbic epilepsy: Intracarotid amobarbital test observations. *Arch Neurol* **50**: 1020–1025.
6 Albright PS and Burnham BM (1980). Development of a new pharmacological seizure model: Effects of anticonvulsants on cortical and amygdala-kindled seizures in the rats. *Epilepsia* **21**: 681–689.
7 Anderson CM, Teicher MH, Polcari A, Renshaw PF (2002). Abnormal T2 relaxation time in the cerebellar vermis of adults sexually abused in childhood: potential role of the vermis in stress-enhanced risk for drug abuse. *Psychoneuroendocrinology* **27**: 231–44.
8 Avnon Y, Nitzan M, Sprecher E, Rogowski Z, Yarnitsky D (2004). Autonomic asymmetry in migraine: augmented parasympathetic activation in left unilateral migraineurs. *Brain* **127**: 2099–2108.
9 Bao AM, Meynen G, Swaab DF (2008). The stress system in depression and neurodegeneration: Focus on the human hypothalamus. *Brain Res Rev* **57**: 531–53.
10 Bob P (2003a). Dissociation and Neuroscience: History and New Perspectives. *Int J Neurosci* **113**: 903–914.
11 Bob P (2003b). Subliminal Processes, Dissociation and the "I". *J Anal Psychol* **48**: 307–316.
12 Bob P (2007). Dissociation, forced normalization and dynamic multistability of the brain. *Neuro Endocrinol Lett.* **28**: 231–246.
13 Bob P, Susta M, Pavlat J, Hynek K, Raboch J (2005). Depression, traumatic dissociation and epileptic-like phenomena. *Neuro Endocrinol Lett.* **26**: 321–325.
14 Bob P, Susta M, Chladek J, Glaslova K, Fedor-Freybergh P (2007a). Neural complexity, dissociation and schizophrenia. *Med Sci Monit* **13**: 1–5.
15 Bob P, Fedor-Freybergh P, Susta M, Pavlat J, Jasova D, Zima T, Benakova H, Hynek K, Raboch J (2007b). Depression, prolactin and dissociated mind. *Neuro Endocrinol Lett* **28**: 639–642.
16 Bob P, Susta M, Glaslova K, Fedor-Freybergh P, Pavlat J, Miklosko J, Raboch J (2007c). Dissociation, epileptic-like activity and lateralized electrodermal dysfunction in patients with schizophrenia and depression. *Neuro Endocrinol Lett.* **28**: 868–74.
17 Bob P, Susta M, Glaslova K, Pavlat J, Raboch J. (2007d) Lateralized electrodermal dysfunction and complexity in patients with schizophrenia and depression. *Neuro Endocrinol Lett.* **28**: 11–5.
18 Bob P, Glaslova K, Susta M, Jasova, D, Raboch J (2007e). Traumatic dissociation, epileptic-like phenomena, and schizophrenia. *Activitas Nervosa Superior*. **49**: 81–86.
19 Bogen JE and Bogen GM (1969). The other side of the brain: III. The corpus callosum and creativity. *Bull Los Angeles Neurol Soc* **34**: 191–220.

20 Bowman ES and Coons PM (2000). The differential diagnosis of epilepsy, pseudoseizures, dissociative identity disorder, and dissociative disorder not otherwise specified. *Bull Menninger Clin* **64**: 164–80.
21 Brende JO (1984). The psychophysiologic manifestations of dissociation. *Psychiatr Clin North Am* **7**: 41–50.
22 Coleman-Mensches K and McGaugh JL (1995). Differential involvement of the right and left amygdalae in expression of memory for aversively motivated training. *Brain Res* **670**: 75–81.
23 Critchley HD (2002). Electrodermal Responses: What Happens in the Brain. *Neuroscientist* **8**: 132–142.
24 Dawson ME, Shell AM, Filion DL (2000). The electrodermal system. In: Cacioppo JT, Tassinary LG, Bernston GC, editors. *Handbook of Psychophysiology* (pp 200–23). Cambridge, MA: Cambridge University Press.
25 Dewaraja R and Sasaki Y (1990). A left to right callosal transfer deficit of nonlinguistic information in alexithymia. *Psychother Psychosom* **54**: 201–207.
26 Edwards HE, MacLusky NJ, Burnham WM (2000). The effect of seizures and kindling on reproductive hormones in the rat. *Neurosci Biobehav Rev* **24**: 753–62.
27 Esch T and Stefano GB (2005). The neurobiology of love. *Activitas Nervosa Superior* **49**: 1–18.
28 Fisar Z and Raboch J (2008). Depression, antidepressants and peripheral blood components. *Neuro Endocrinol Lett.* **29**: 17–28.
29 Flor-Henry P (1969). Psychosis and temporal lobe epilepsy: A controled investigation. *Epilepsia* **10**: 363–395.
30 Frewen PA, Pain C, Dozois DJ, Lanius RA (2006). Alexithymia in PTSD: psychometric and FMRI studies. *Ann N Y Acad Sci* **1071**: 397–400.
31 Flor-Henry P (2003). Lateralized temporal-limbic dysfunction and psychopatology. *Epilepsy Behav* **4**: 578–590.
32 Galin D (1974). Implications for psychiatry of left and right cerebral specialization. *Arch Gen Psychiatry* **31**: 572–583.
33 Gerendai I and Halász B (2001). Asymmetry of the neuroendocrine system. *News Physiol Sci* **16**: 92–5.
34 Goddard GV, McIntyre GC, Leech CK (1969). A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol* **25:** 295–330.
35 Gruzelier JH (1983). Disparate syndromes in psychosis delineated by direction of electrodermal response lateral asymmetry. In: Flor-Henry P and Gruzelier J, editors. *Laterality and Psychopathology* (pp. 525–538). Amsterodam: Elsevier.
36 Gruzelier JH and Venables PH (1974). Bimodality and lateral asymmetry of skin conductance orienting activity in schizophrenics: Replication and evidence of lateral asymmetry in patients with depression and disorders of personality. *Biol Psychiatry* **2**: 131–139.
37 Henry JP (1993). Psychological and physiological responses to stress: the right hemisphere and the hypothalamo-pituitary-adrenal axis, an inquiry into problems of human bonding. *Integr Physiol Behav Sci* **28**: 369–87
38 Henry JP (1997). Psychological and physiological responses to stress: the right hemisphere and the hypothalamo-pituitary-adrenal axis, an inquiry into problems of human bonding. *Acta Physiol Scand* **161**: 10–25 (Suppl).
39 Herzog AG (1993). A relationship between particular reproductive endocrine disorders and the laterality of epileptiform discharges in women with epilepsy. *Neurology* **43**: 1907–1910.
40 Hines M, Swan C, Roberts RJ, Varney NR (1995). Characteristics and mechanisms of epilepsy spectrum disorder: An explanatory model. *Appl Neuropsychol* **2**: 1–6.
41 Hilz MJ, Dutsch M, Perrine K, Nelson PK, Rauhut U, Devinski O (2001). Hemispheric influence on autonomic modulation and baroreflex sensitivity. *Ann Neurol* **49**: 575–84.
42 Hugdahl K (2001). *Psychophysiology, The Mind-Body Perspective*. Cambridge: Harvard University Press.
43 Isenberg N, Silbersweig D, Engelien A, Emmerich S, Malavade K, Beattie B, Leon, A.C. (1999). Linguistic threat activates the human amygdala. *Proc Natl Acad Sci USA* **96**: 10456–10459.
44 Ito Y, Teicher MH, Glod CA, Harper D, Magnus E, Gelbard HA (1993). Increased prevalence of electrophysiological abnormalities in children with psychological, physical, and sexual abuse. *J Neuropsychiatry Clin Neurosci* **5**: 401–8.
45 Kanner AM and Balabanov A (2002). Depression and Epilepsy. How closely related are they? *Neurology* **58**: 827–839.
46 Kooiman CG, van Rees Vellinga S, Spinhoven P, Draijer N, Trijsburg RW, Rooijmans HG (2004). Childhood adversities as risk factors for alexithymia and other aspects of affect dysregulation in adulthood. *Psychother Psychosom* **73**: 107–16.
47 Kraus JE (2000). Sensitization phenomena in psychiatric illness: Lessons from the kindling model. *J Neuropsychiatry Clin Neurosci* **12**:328–342.
48 Krishnamoortthy ES, Trimble MR, Sander JW, Kanner AS, Andres M (2002). Forced normalization at the interface between epilepsy and psychiatry. *Epilepsy Behav* **3**: 303–308.
49 La Bar KS, Gatenby JC, Gore JC, Le Doux JE, Phelps EA (1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron* **20**: 937–945.
50 Loscher W, Jackel R, Czucvar J (1986). Is amygdala kindling in rats a model for drug-resistant partial epilepsy? *Exp Neurol* **93**: 211–226.
51 Mangina CA and Beuzeron-Mangina JH (1996). Direct electrical stimulation of specific human brain structures and bilateral electrodermal activity. *Int J Psychophysiol* **22**: 1–8.
52 Mason JW, Wang S, Yehuda R, Riney S, Charney DS, Southwick SM (2001). Psychogenic lowering of urinary cortisol levels linked to increased emotional numbing and a shame-depressive syndrome in combat-related posttraumatic stress disorder. Psychosom Med **63**: 387–401.
53 Miller RJ (1992). Is there a neural basis for borderline splitting? *Compr Psychiatry* **33**: 92–104.
54 Monroe RR (1982). Limbic Ictus and Atypical Psychoses. *J Nerv Ment Dis* **170**: 711–716.
55 Morris JS, Ohman A, Dolan RJ (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci USA* **96**: 1680–1685.
56 Nasrallah HA (1985). The unintegrated right cerebral hemispheric consciousness as alien intruder: A possible mechanism for schneiderian delusions in schizophrenia . *Compr Psychiatry* **26**: 273–282.
57 Newport DJ and Nemeroff CJ (2000). Neurobiology of posttraumatic stress disorder. *Curr Opin Neurobiol* **10**: 211–218.
58 Nijenhuis ER, van der Hart O, Kruger K, Steele K (2004). Somatoform dissociation, reported abuse and animal defence-like reactions. *Aust N Z J Psychiatry* **8**: 678–86.
59 Pakalnis A, Drake ME, Kuruvilla J, Blake JK (1988). Forced normalization. *Arch Neurol* **45**: 139.
60 Payne JD, Jackson ED, Ryan L, Hoscheidt S, Jacobs JW, Nadel L (2006). The impact of stress on neutral and emotional aspects of episodic memory. *Memory* **14**: 1–16.
61 Phelps EA, O'Connor KJ, Gatenby JC, Gore JC, Grillon C, Davis M (2001). Activation of the left amygdala to a cognitive representation of fear. *Nat Neurosci* **4**: 437–441.
62 Post RM, Weis SR, Smith MA (1995). Sensitization and kindling. In: Friedman MJ, Charney DS, Deutch AY, editors. *Neurobiological and clinical consequences of stress: From normal adaptation to posttraumatic stress disorder.* Philadelphia: Lipincott-Raven.
63 Post RM and Weiss RB (1998). Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: The role of serotonergic mechanisms in illness progression. *Biol Psychiatry* 44:193–206.
64 Putnam F (1997). *Dissociation in Children and adolescents. A developmental Perspective*. London, New York: The Guilford Press.
65 Read J, Perry BD, Moskowitz A, Connolly J (2001). The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. *Psychiatry* **64**: 319–45.
66 Roberts RJ, Gorman LL, Lee GP, Hines ME, Richardson ED, Riggle TA, Varney NR (1992). The phenomenology of multiple partial seizure like symptoms without stereotyped spells: An epilepsy spectrum disorder? *Epilepsy Res* **13**: 167–177.
67 Romei V, De Gennaro L, Fratello F, Curcio G, Ferrara M, Pascual-Leone A, Bertini M. (2008). Interhemispheric transfer deficit in alexithymia: a transcranial magnetic stimulation study. *Psychother Psychosom* **77**: 175–81.

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68 Sayar K, Kose S, Grabe HJ, Topbas M (2005). Alexithymia and dissociative tendencies in an adolescent sample from Eastern Turkey. *Psychiatry Clin Neurosci* **59**: 127–34.

69 Schore AN (2001). The effects of early relational trauma on right brain development, affect regulation and infant mental health. *Infant Ment Health J* **22**: 201–269.

70 Schore AN (2002). Dysregulation of the right brain: a fundamental mechanism of traumatic attachment and the psychopathogenesis of posttraumatic stress disorder. *Aust N Z J Psychiatry* **36**: 9–30.

71 Servit Z and Musil F (1981). Prophylactic treatment of posttraumatic epilepsy: results of a long-term follow-up in Czechoslovakia. *Epilepsia* **22**: 315–320.

72 Shulman MB (2003). Laterality and psychopathology circa 1976. *Epilepsy Behav* **4**: 576–7.

73 Sierra M and Berrios GE (1998). Depersonalization: Neurobiological Perspectives. *Biol Psychiatry* **44**: 898–908.

74 Spence S, Shapiro D, Zaidel E (1996). The role of the right hemisphere in the physiological and cognitive components of emotional processing. *Psychophysiology* **33**: 112–122.

75 Spiegel D (1991). Neurophysiological correlates of hypnosis and dissociation. *J Neuropsychiatry Clin Neurosci* **3**: 440–5.

76 Spigelman I, Li Z, Banerjee PK, Mihalek RM, Homanics GE, Olsen RW (2002). Behavior and physiology of mice lacking the GABAA-receptor delta subunit. *Epilepsia* **43**: 3–8.

77 Spitzer C, Willert C, Grabe HJ, Rizos T, Moller B, Freyberger HJ (2004). Dissociation, hemispheric asymmetry, and dysfunction of hemispheric interaction: A transcranial magnetic stimulation approach. *J Neuropsychiatry Clin Neurosci* **16**: 163–169.

78 Sramka M, Sedlak P, Nadvornik P (1977). Observation of kindling phenomenon in treatment of pain by stimulation in thalamus. In: Sweet W, editor *Neurosurgical treatment in psychiatry* (pp 651–654). Baltimore: University Park Press.

79 Stefano GB and Esch T (2005). Love and stress. *Activitas Nervosa Superior* **26**:173–4.

80 Stevens JR (1992). Abnormal reinnervation as a basis for schizophrenia: a hypothesis. *Arch Gen Psychiatry* **49**: 238–243.

81 Stevens JR (1999). Epilepsy, schizophrenia and the extended amygdala. *Ann NY Acad Sci* **156**: 548–561.

82 Sullivan RM and Gratton A (1999a). Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. *J Neurosci* **19**: 2834–2840.

83 Sullivan RM and Gratton A (1999b). Medial prefrontal cortex, laterality, and stress. *J Neurosci* **19**: 2834–2840.

84 Sullivan RM and Gratton A (2002). Prefrontal cortical regulation of hypothalamic–pituitary–adrenal function in the rat and implications for psychopathology: side matters. *Psychoneuroendocrinology* **27**: 99–114.

85 Tabibnia G and Zaidel E (2005). Alexithymia, interhemispheric transfer, and right hemispheric specialization: a critical review. *Psychother Psychosom* **74**: 81–92.

86 Takahashi O, Motomi T, Morimitsu S (2003). Influences of an anticholinergic antiparkinsonian drug, parkinsonism, and psychotic symptoms on cardiac autonomic functions in schizophrenia. *J Clin Psychopharmacol* **23**: 441–447.

87 Teicher MH, Glod CA, Surrey J, Swett C Jr (1993). Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *J Neuropsychiatry Clin Neurosci* **5**:301–306.

88 Teicher M, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* **27**:3–44.

89 Teicher M, Tomoda A, Andersen SL (2006). Neurobiological consequences of early stress and childhood maltreatment: Are results from human and animal studies comparable? *Ann N Y Acad Sci* **1071**:313–323.

90 Toichi M, Kubota Y, Murai T, Kamio Y, Sakihama M, Toriuchi T, Inakuma T, Sengoku A, Miyoshi K (1999). The influence of psychotic states on the autonomic nervous system in schizophrenia. *Int J Psychophysiol* **31**: 147–154.

91 Ul'yaninskii LS (1995). Emotional stress and extracardiac regulation. *Neurosci Behav Physiol* **25**: 257–65.

92 Umegaki H, Yamamoto A, Suzuki Y, Iguchi A (2006). Stimulation of the hippocampal glutamate receptor systems induces stress-like responses. Neuro Endocrinol. Lett. **27**: 339–43.

93 van der Kolk BA and van der Hart O (1989). Pierre Janet and the breakdown of adaptation in psychological trauma. *Am J Psychiatry* **146**: 1530–40.

94 Wittling W and Pfluger M (1990). Neuroendocrine hemisphere asymmetries: Salivary cortisol secretion during lateralized viewing of emotion-related and neutral films. *Brain Cogn* **14**: 243–265.