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AUTONOMIC AND CENTRAL STRESS-REGULATION DISINTEGRATION IN STRESS-RELATED ANXIETY DISORDERS

Olga Kara[1,3(A,B,D,E,F)], **Olli Polo**[1,2(A,B,D,E,F)]

[1] Department of Pulmonary Medicine Tampere University Hospital, Tampere, Finland
[2] Unesta Research Center, Tampere, Finland
[3] Brain Fitness Center BFC, Tampere, Finland

SUMMARY

Anxiety disorders related with central and autonomic stress-regulation systems insufficiency. The broad range of anxiety symptoms includes among others signs of neuroendocrinological stress-control faulty. The inherent psychological traits of anxiety are genetically predetermined and can be assigned by the physiological measurements of HRV, QEEG and ERP, which can be used as functional biomarkers in differential diagnostics and prognostics within anxiety disorders. This multidisciplinary review summarizes the current state of knowledge existing within anxiety research and proposes the idea of disturbed coordination between autonomic and central stress-regulation networks as a basis for anxiety disorders development.

Key words: anxiety, stress, self-regulation, ANS, HPA, biomarkers, QEEG, ERP

INTRODUCTION

Anxiety disorders fall into the group of stress-related and somatoform disorders (ICD-10). This disability represents significant functional and occupational impairment and sizeable economic costs. Every second visit to points of primary care with symptoms of chest pain, tachycardia, dizziness, abdominal complains and dyspnea is related to anxiety as opposed to the real physical illnesses (Kroenke and Mangelsdorff, 1989; Somers et al., 2006;Kessler et al., 2012). Common symptoms reported in anxiety include an excessive irrational fear; avoidance of anxiety triggers; anxious, black/white thinking; catastrophizing; fortunetelling; intolerance of uncertainty; need for control; safety behavior and rituals, and are often accompanied by severe sleep disturbances (Gardner, 1996; Falsetti and Resnick, 1997; Nardi et al., 1999; Dratcu, 2000; Kessler et al., 2003; First et al., 2004).

Both biological and psychological theories have been proposed to disclose the cause of anxiety disorders, nevertheless the role of the stress and self-regulation systems at fault in the development of this pathological condition remains uncertain.

The psychological theory of emotional learning suggests that anxiety is a result of fear conditioning where the structures involved in emotional regulation, learning, memory and self-control form abnormal neuronal circuits, which can cause the range of reactions presented within the anxiety disorders (Ressler and Mayberg, 2007, Quirk and Mueller, 2007). This was supported by neurobiological researches, where functional and anatomical abnormalities were found in the brain structures involved in stress – control, self-regulation, emotion control, learning and memory (Bizara et al., 1998; Vythilingam et al., 2000; Chen et al., 2006; Ferrari et al., 2008; Chen and Shi, 2011).

Genetic studies have claimed that anxiety is genetically predetermined as a form of psychological traits. This results in an inadequate response to stress (hyper-reactivity) and in insufficient coping strategy coming from a controversy between individual demands (obtained by cognitive appraisal) and the resources available to manage the stress (Lazarus and Folkman, 1984; Friedman and Thayeravos et al., 2012).

Neurobiological data also support the trait theory. Particularly, the individual, trait-related pattern of brain electrical activity associated with hemispheric asymmetry measured by quantitative electroencephalography (QEEG) (for a review see Dickter and Kieffaber, 2013). Event-related potential (ERP) studies found that the ERP components associated with response inhibition are influenced by the anxiety trait (Sehlmeyer et al., 2010).

The physiological symptoms of anxiety including tachycardia, chest pain, dizziness etc. and sleep disturbance are the signs of an autonomic stress-regulation faulty. At the same time, the same features are linked with anxiety trait. For example, Heart Rate Variability (HRV) is an index of self-regulation capacity and autonomic control strength, which is connected with an anxiety and emo-

tional sensitivity trait and predicts the long-term outcome of cardiac diseases (Segerstrom and Nes, 2007; Carpeggiany et al., 2005). Autonomic control measured by HRV is mediated by executive emotional regulation, and is positively associated with calmness, life satisfaction and other positive components controversial to the anxiety state (Geisler et al., 2010).

Autonomic stress-regulation system merged with the hormonal stress-control route. Hormonal control influences circadian rhythms, and has a different pattern of activity in males and females, which may explain the gender prevalence and sleep disturbances reported for anxiety disorders (Swaab et al., 2005).

Regardless of the extensive efforts made by researchers from different disciplines, there is a lack of understanding the integrative power of central and autonomic stress-regulation routes in anxiety disorders development.

The present review attempts to fill the gap between the different disciplines in order to highlight the complexity of anxiety disorders and the role of the stress-regulation systems at fault as a biological basis of anxiety.

AUTONOMIC STRESS-REGULATION ROUTE IN ANXIETY

Anxiety symptoms such as sweating, shaking, chest pain, tachycardia etc. are a usual reaction to stress that is controlled by the autonomic nervous system (ANS). ANS is a primary controlling path of internal “vital” physiological functions consisting of two interrelated parts: sympathetic and parasympathetic. The unified functioning of these systems represents the level of the central nervous system (CNS) activation on a continuum between deep sleep to alertness and excitement.

The sympathetic branch of ANS performs a sufficient level of arousal to execute the physiological, behavioral, and cognitive performance (motivation, emotions, memory, and attention). The sympathetic system is engaged in a reflective, immediate “survival” reaction to the potentially danger situation - the fight or flight response. Activation of this branch can also be triggered by the non-physical or “psychogenic” events launched by the innate program or previous experience appraised as a threat, which is often presented in patients with anxiety (Ulrich-Lai and Herman, 2009). The hyper-activation of this system induces physical excitement and augments energy expenditure with a reciprocal inhibition of other power consuming processes e.g. the reproductive functions, immune and thyroid systems responses and has a subsequent negative influence on the cognitive functioning. The sympathetic stress-response is mediated through the release of catecholamines: norepinephrine (noradrenalin) and epinephrine (adrenaline). Noradrenergic neurons arise from the locus coeruleus (LC) within the brainstem with dense projections to the different brain regions including the thalamus, the prefrontal cortex (PFC), the hippocampus, and the amygdala (Ramos and Arnsten, 2007). The activity of the LC determines the level of arousal by encouraging the excitatory influence on wakefulness-promoting regions: the cholinergic neu-

rons of the basal forebrain, the serotonergic neurons of the dorsal raphe nuclei, and the cortically projecting neurons of the thalamus with subsequent inhibition on sleep – promoting GABAergic neurons in the basal forebrain and the ventrolateral preoptic area of the hypothalamus (Carter et al., 2010; Samuels and Szabadi, 2008). The stimulation of the LC results in a sympathetic influence on the physiological functions (increases activity in the tissues that receive sympathetic innervations and decreases activity in tissues with parasympathetic innervations). The hypothalamic and brainstem centers including locus coeruleus are in turn regulated by the descending pathways that arise from the orbitofrontal cortex, the medial prefrontal cortex (mPFC) and limbic system (i.e. anterior cingulate (ACC), the medial temporal cortex (mTC), insula and amygdala) (Critchley, 2005) (Fig. 1).

The regulatory influence of the brain structures on LC. LC is receiving dense projections from different brain structures, which modulate its activity. At the same time, the noradrenaline secretion in LC suppresses LC neurons via α-adrenoceptors. LC activity is regulated by the amygdala and hypothalamus (Pace-Schott et al., 2003; Tasman et al., 2011)

The parasympathetic division of ANS dominates during sleep and in contrast to the sympathetic branch controls the duration of the autonomic responses and serves for energy conservation, relaxation, regeneration, and other healing processes. Stress or emotional stimulation inhibits the parasympathetic axis and activates the sympathetic, thus it increases arousal, affects sleep and reduces reparative functions (Cohen et al., 2000). Parasympathetic acetylcholine fibers are derived from the brainstem motor nuclei to implement precise, tissue-specific

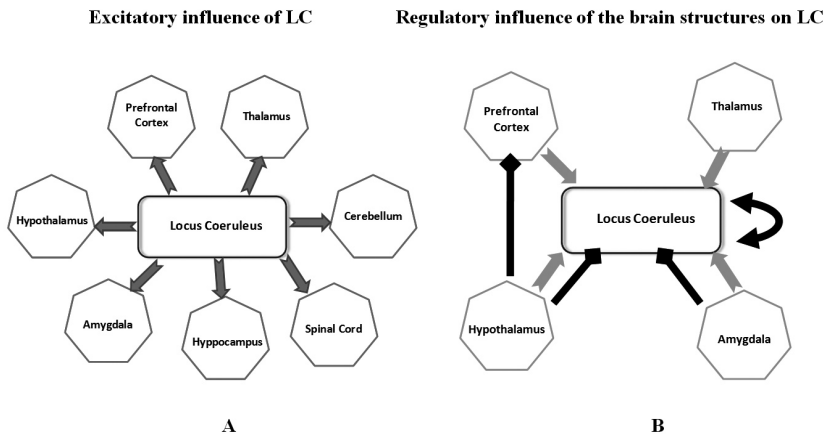

Fig. 1. The central role of Locus Coeruleus (LC) in Sympathetic Regulation
(A) Excitatory influence of LC on brain structures.
(B) The regulatory influence of the brain structures on LC. LC is receiving dense projections from different brain structures, which modulate its activity. At the same time, the noradrenaline secretion in LC suppresses LC neurons via α-adrenoceptors. LC activity is regulated by the amygdala and hypothalamus (Pace-Schott et al., 2003; Tasman et al., 2011)

regulation of the various autonomic functions by the distinct ganglia located within the innervated tissue (glandular acini) (Leblanc AND Landis, 1998) Nevertheless, the functions of the parasympathetic axis are inclined by the long preganglionic axons projecting from the central nervous system, particularly from the medial prefrontal cortex (mPFC) (Owens and Verberne, 1996; Critchley, 2005 24). Interestingly, the mPFC are often described as a "visceromotor" cortex that performs the top-down control of the autonomic functions through the direct projections to the nucleus of the solitary tract (NTS). Lesions studies have shown that the ventromedial part of the medial prefrontal cortex (vmPFC) does not affect resting blood pressure and heart rate variability, but plays a key role in the regulation of parasympathetic outflow under stressful or emotional conditions (Hänsel and von Känel, 2008; Goswami et al., 2011; Ferreira-Junior et al., 2011). In addition, the stimulation of this area provokes cardiovascular depression and suppression of the sympathetic control (Verberne et al., 1998; Hilz et al., 2006). Thus, the executive autonomic control is an interaction between the sympathetic and parasympathetic centers at the midbrain and hypothalamus, which regulate groups of target-specific output pathways. These regulation routes include premotor neurons, which in turn affect the preganglionic neurons with both excitatory and inhibitory inputs from spinal interneurons, the brain stem, and hypothalamus, and the ganglion cells innervating the particular tissue (Jänig and McLachlan, 1992; Morrison, 2001). However, an emotional stimulation or stressful life event will engage the higher brain control, where the left vmPFC is related with the parasympathetic activation and the right vmPFC is linked to the sympathetic inhibition. The lesion studies demonstrate that the right vmPFC deficiency may be related with the sympathetic hyperexcitability (Hiltz et al., 2006). Anxiety symptoms such as palpitation, chest pain, sweating, trembling, flushing, muscle twitching, and insomnia are the main components of stressfulness that represent the imbalance in the ANS regulation (Drake et al., 2004; Vahtera et al., 2007; Tyrer and Baldwin, 2006).

NEUROENDOCRINOLOGICAL REGULATION OF STRESS

The hypothalamic-pituitary-adrenocortical (HPA) axis is usually activated within 3-5 minutes after a stressor presentation. At this time the corticotropin-releasing hormone (CRH) (as well as arginine vasopressin (AVP), and oxytocin) is released by the hypothalamic paraventricular nucleus (PVN) neurons and triggers the secretion of the corticotropin (ACTH) into the systemic circulation by means of the anterior pituitary gland, which then stimulates the synthesis of glucocorticoids by the adrenal glands (Herman et al., 2005). The secreted glucocorticoids have a negative inhibiting feedback that suppresses a HPA axis cascade (Fink, 2007).

The basal concentration level of glucocorticoids is a precipitating factor for stress-response intensity. If the initial level of glucocorticoids is low, the suprachi-

asmatic nucleus (SCN) inhibits its responsiveness to stress, but if the glucocorticoids level is high – it will bypass the hypophysis and reaches the adrenals to facilitate the release of ACTH (Sage et al., 2001).

The HPA axis activation has well described circadian (light-dark cycle) and ultradian (once in an hour) patterns, which maintain the basal level of cortisol. The circadian and ultradian rhythms are superimposed with the stress-related increase in the glucocorticoids concentration that defines the intensity of the stress-response. The alterations in the basal cortisol concentration have been found in anxiety and depression (Deuschle et al., 1997; Takahashi et al., 2005), where the high pre-stress basal value of the stress hormones seems to be persistent due to the hyperactivity of the HPA system.

It is important that the brain tissue is a major target for free glucocorticoids. After stressor exposition the peak concentration of glucocorticoids in the brain is reached about 20 minutes later than in plasma (due to a blood/brain barrier), but rapidly returns to the baseline when the stress-reaction is abolished. The type and duration of the stress influences the level of free glucocorticoids in the brain tissue. It is important to add here that the mild psychological stress elicits a short-lasting (max. 60 min) elevation in hippocampal corticosterone, whereas explosive, continued, and combined stress (psychological plus physical) has a prolonged effect (up to 110 min) (Droste et al., 2008). Prolonged, supraphysiological elevation in adrenal glucocorticoid secretion and concentration has a neurotoxic effect on hippocampal neurons, causes the atrophy of pyramidal cells, shuts down neurogenesis, and may induce mental disorders development (Sapolsky, 1996;McEwen , 1999: McEwen , 2000).

The activation of the HPA axis is regulated by a complex higher-order control of the hippocampus, amygdala, anterior cingulate and prefrontal cortex – structures that are deeply related with ANS control.

It has been shown that hippocampal stimulation inhibits the HPA axis and decreases the cortisol level in humans (Dunn and Orr, 1984). Lesions of amygdala reduce the level of corticosterone or ACTH in response to stress, whereas stim-

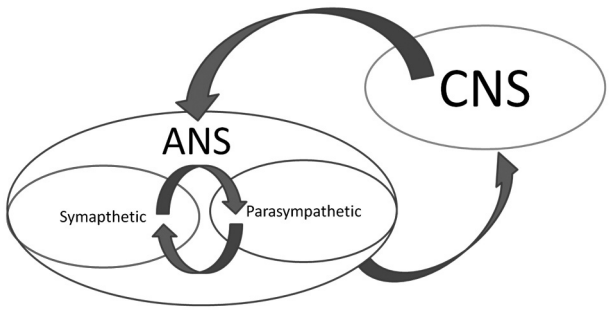

Fig.2 Autonomic and central stress-regulation integration

ulation of this structure increases the HPA axis activation (Herman et al., 2005). Lesions in anterior cingulate increase ACTH and corticosterone secretion in rats and induce corticotrophin release hormone CRH production after forced restraint (Figueiredo et al., 2003). On the other hand, the acute administration of the cortisol and prednisolone has an anxiogenic effect on the prefrontal cortex and is linked with right frontal EEG alpha activation among healthy participants (Schmidt et al., 1999; Tops et al., 2005).

Dysfunctions in the HPA axis are connected with psychosomatic and psychiatric disorders (Raison and Miller, 2003). Whereas the hyperactivation of the noradrenergic system in response to stress has been found in anxiety disorders and in major depression (Björntorp, 1996), and hypoactivation was associated with autoimmune processes such as the lupus erythematosis, multiple sclerosis, neurodermatitis, fibromyalgia, chronic fatigue, and rheumatoid arthritis (Kudielka and Kirshbaum, 2005). Additionally, hyperactivation of the sympathetic axis and increased arousal affect sleep which, in turn, decreases cortisol-mediated inhibition and further suppresses the stress regulation system (Chrousos and Kino, 2009).

GENDER PREVALENCE IN ANXIETY DISORDERS

Mood and anxiety disorders more often affect women (Kessler et al., 2003; Somers et al., 2006), which seem to have a strong relation with the endogenous fluctuations of neurosteroids, whereas both acute administration and withdrawal have anxiolytic effects (Akwa et al., 1999). An estrogen enhances the vagal tone, suppresses the sympathetic activation, and inhibits arousal in women during the early follicular phase (Goldstein et al., 2005). Cyclic fluctuations in the estrogen/progesterone level modulate hippocampal excitability in dentate gyrus especially in the CA3 area and can modulate cognitive functioning (memory) (Scharfman et al., 2003). Though, estrogen attenuates the influence of glucocorticoids and reduces their response to stress by decreasing the norepinephrine spillover and noradrenergic vascular reactivity, which in turn decreases the risks of cardiovascular diseases in women (Sudhir et al., 1997; Komesaroff et al., 1999). The estrogen deficit is related to anxiety, whereas a dominance of estrogen causes the symptoms of depression (Newhouse et al., 2010; Paskova et al., 2012).

Progesterone deficiency is linked with increased irritability, anxiety and panic attacks. The reason for this is that progesterone acts as a glucocorticoid antagonist and can bind to glucocorticoids and mineralocorticoids receptors, thus it increases the rate of dissociation of the glucocorticoids from the receptor. Progesterone modulates the number of receptors in the hippocampus and can diminish the effectiveness of cortisol feedback on stress responsiveness (Ahima et al., 1992; Kudielka and Kirshbaum, 2005).

The studies of Kirschbaum have showed the elevation in the stress-related level of ACTH in men in comparison with women, independent of their follicular phase or oral contraceptive intake. At the same time, the level of free cortisol re-

mains the same for both men and women in the luteal phase, but was lower in women in the follicular phase and under oral contraceptive intake (Kirschbaum et al., 1999). It was also stated that men respond to stress with the greater increase in cortisol when compared to women. This can be a reason for HPA axis hyperactivation and the increased risk of cardiovascular diseases or diabetes. A low cortisol level in women may lead to hypoactivation of the HPA axis and raises the risks of autoimmune reactions, which coincide with the epidemiologic results on the gender prevalence in the mentioned disorders (Kudielka and Kirshbaum, 2005).

The structures involved in the control of the ANS and HPA response to stress, i.e. anterior insula, anterior cingulate, the orbitofrontal cortex and amygdala, also represent a significant sexual dimorphism. Hippocampal projections to central amygdala modulated by vasopressin and oxytocin. The vasopressin is involved in anxiety, stress, aggression, and playing a role in mediating the “fight-or-flight” response in men. Oxytocin is responsible for women’s “tend-to-be-friend” stress-response (Nugent et al., 2011). The connectivity between amygdala and the frontal lobe can be altered by testosterone (van Wingen et al., 2011).

Taken together it can be seen that endocrinological deficiency itself can cause a range of symptoms related with anxiety. In turn prolonged or extensive stress may result in neuroendocrinological abnormalities, which are often co-morbid with anxiety disorders (Hall and Hall, 1999).

NEUROANATOMY OF ANXIETY

Neuroanatomical studies revealed structural abnormalities in the volume characteristics of the amygdala, hippocampus, parahippocampus, bilateral insula, mPFC, ACC, the temporal lobe and precuneus (Bisaga et al., 1998; Vythilingam et al., 2000; Ferrari et al., 2008; Chen et al., 2006; Chen and Shi, 2011). The listed structures are components of the limbic system that processes socially and emotionally relevant information and stimulates the subsequent coordinated physiological and behavioral responses. These structural deviations underlie the anxiety disorders in general and are essential parts of the so-called “fear network” that plays a central role in the negative emotion regulation (Gorman et al., 2000; Woodward et al., 2006; Ruiz et al., 2007). The central part of this system is amygdala, which consists of subnuclei with distinct afferent and efferent interconnections that form separate brain networks to control a particular process. The basolateral complex of amygdala (BLA) receives sensory information from sensory and executive cortices, thalamus and hippocampus, defines the importance of stimulus and projects this information to other brain regions involved in response to a threat. The central nucleus of amygdala projects itself to the brainstem, hypothalamus and forebrain and stimulates the specific defensive fight-or-flight response of the sympathetic nervous system (Etkin et al., 2009; Ziemann et al., 2009). Amygdala plays a primary role in forming memories of events that induce strong emotions (Maren , 2008; Morrison and Salzman , 2010; Adolphs,

2010; Sabattinelli et al., 2011) and is involved in the learning, storage, and expression of both acquired (conditioned) and innate (unconditioned) fears (Büchel and Dolan, 2000; Rosen, 2004).

Additionally, it was discovered that amygdala functions as a central chemosensor that detects changes in CO_2 level, stimulates the sympathetic branch of ANS for the fight-or-flight response and activates the fear-circuit for the appropriate response to threat (Ziemann et al., 2009). CO_2 stimulates acid-activated respiratory chemoreceptors in the brain stem and triggers the breathing to exhale CO_2 and increase the systemic pH. Provocative CO_2 inhalation or abnormal patterns of breathing increases the partial pressure of CO_2 in the blood and lowers pH throughout the body (Wemmie, 2011). This important result explains another anxiety related symptom - hyperventilation and abnormal chemoreactivity, which can cause or be a result of the decreased left amygdala volume within anxiety patients (Milham et al., 2005). The insular cortex (IC) receives, integrates and processes inputs from all sensory modalities, and participates in sensorymotor integration, pain perception, emotional recall, cognitive and memory processing (Phan et al., 2002; Chen et al., 2009). The IC has extensive reciprocal connections with other parts of the limbic system such as the amygdala, the entorhinal cortex, and the frontal and temporal lobe (Augustine , 1996), and implicates itself in the subjective awareness, represents the internal state of arousal, and plays a role in the suppression of consciousness thoughts (Wyland et al, 2003; Craig, 2009; Critchley, 2009; Coen et al., 2009). The volumetric reduction of IC disrupts the process of emotional suppression that causes the symptoms of hyperarousal in patients with anxiety and a declarative memory deficit in PTSD (Giuliani et al., 2011). The hippocampus is involved in the pathogenesis of Panic disorder (PD), specific phobias, and in the recurrent re-experiencing of traumatic events in PTSD (Bremner et al., 1997; Stein et al., 1997; Villarreal et al., 2002). The decreased gray matter density in the hippocampus was shown for PD, social anxiety disorder, generalized anxiety disorder and PTSD (Chen et al., 2006; van Tol et al., 2010).The hippocampus receives afferent projections from most of the cortical and subcortical structures directly or via the entorhinal cortex and plays a central role in memory processing, special and contextual learning, continues the encoding of ongoing experience, and in anxiety/behavioral inhibition (Kubik et al., 2007). The synergetic amygdala-hippocampal activation is involved in the forming and encoding of emotional memories and thus may underlie the memory processing disturbances associated with PTSD (Richter-Levin and Akirav, 2000; Dolcos et al., 2004). The medial wall of the frontal lobe consists of the ACC and mPFC, and is often referred as a “limbic lobe” (Etkin et al., 2011). The ACC has dense reciprocal connections from the multiple cortical and subcortical brain structures (midline thalamus, the brainstem nucleus, PFC, the motor cortex, the orbitofrontal cortex, ventral striatum, amygdala, PAG) and is implicated in emotion, memory, attention, learning, cognitive processing, pain, conflict and error detection and monitoring, as well as in executive motor control, autonomic control, and monitoring the bodily arousal state (Critchley et al., 2003; Mansouri et

al., 2009). The ACC is a complex multimodal area that can be subdivided into ventral (pregenual and subgenual portions) and dorsal (anterior and posterior) areas. The ventral and anterior parts of the dorsal ACC (dACC) are interacting with the limbic system, while the dorsal parts are connected with the frontal areas and are included in top-down regulation (Etkin et al., 2011). There is an evidence of the direct involvement of the dACC in the control of autonomic arousal during volitional behaviors, including effortful cognitive processing. Particularly, the work of Critchley and colleagues has demonstrated the role of ACC in the volitional control of autonomic arousal (Critchley et al., 2001; Critchley et al., 2005). A significant gray matter volume reduction of the right dorsal ACC has been found in patients with panic disorder, anxiety and depression (Gusnard et al., 2001).

The medial prefrontal cortex is comprised of ventral (VMPFC) and dorsal (DMPFC) parts, where the VMPFC is involved in the emotional and affective processing, and the DMPFC is associated with complex cognitive operations (Asami et al., 2008). The mPFC is directly connected with the amygdala, hypothalamus, and with central autonomic structures within the brainstem: the solitary nucleus, periaqueductal gray (PAG), dorsal raphe, ventral tegmental area and locus coeruleus. These structures are involved in the perception of fearful stimuli, and in the coordination between emotion-related behavior and autonomic responses in complex emotional situations (Barbas, 2003; Gabbott et al., 2005; Vertes, 2006; Bishop, 2007; Benarroch, 2012). The mPFC downregulate the reactivity of amygdala (Urry et al., 2006), that is why the enhance connectivity between these structures is predicting the lower anxiety (Kim et al., 2011). The volumetric reduction of the left dorsal and the medial prefrontal cortex has been found in patients with PTSD, OCD and bipolar disorder, who had experienced chronic stress in childhood (Almeida et al., 2009; Koprivová et al., 2009; van Harmelen et al., 2010).

The ACC plays mostly an evaluative role and is involved in generating autonomic changes, while the insula and orbitofrontal cortices are attached to visceral responses mapping. Moreover, the reciprocal connections between the ACC and the amygdala form a network that is involved in the rapid orienting of attention to threat and is hyper-responsive in anxiety disorders (Carlson et al., 2012). At the same time, the VMPFC is recognized to support the processes of internal self-reference that predominant in the states of rest and disengagement and putatively serves as a benchmark for dynamic interactions with the environment (Etkin et al., 2011; Critchley 2003) (Fig. 3).

TRAITS AND GENETIC PREDISPOSITION OF ANXIETY DISORDERS

The psychological theory claims that certain traits are associated with hyperarousal and a liability to anxiety, which can predispose individual reactivity to negative life events or stressors and result in subsequent sleep disturbances (van Dongen et al., 2005). Thus neuroticism with negative affectivity, low self-

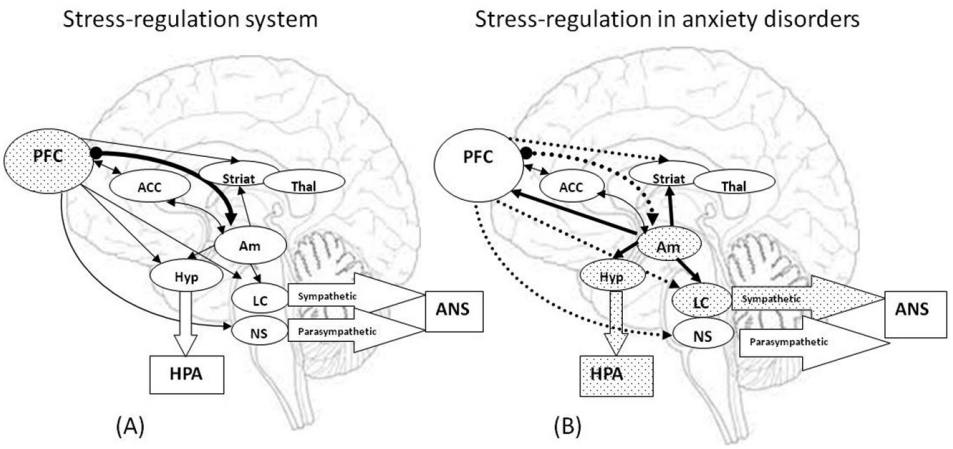

Fig. 3. Stress-regulation system in norm and in anxiety disorders
(A) Stress-regulation system in normal condition. Prefrontal cortex (PFC) is directly connected with the anterior cingulate cortex (ACC), the amygdala (Am), striatum, hypothalamus (Hyp), locus coeruleus (LC), and the nucleus of the solitary tract (NS). PFC downregulates (solid arrow) the amygdala reactivity, influences the sympathetic outflow and has an effect on the HPA axis control, thus it adjusts the level of anxiety.
(B) The disruption of the PFC circuits in stress-related anxiety disorders leads to the hyperactivation of Am, which in turn additionally suppresses the prefrontal executive circuits; triggers the autonomic arousal, activates the HPA axis and disrupts the central self-regulation control

esteem, life dissatisfaction and pessimism and introversion with the high level of arousal, low sociability and the tendency to experience the negative emotions, are found to be risk factors for the development of mood disorders and panic attacks (Freire et al., 2007). In support of this assumption, it was shown that young adults with trait anxiety accompanied by a high level of shyness show a volumetric reduction in the left amygdala and in the left dorsal and the medial prefrontal cortex (Blackmon et al., 2011; Kühn et al., 2011) and have a higher relative right frontal asymmetry (Davidson et al., 2000; Blackhart et al., 2006; Beaton et al., 2008).

Some data has defined the linkage between behavioral inhibition (BI) and the tendency to be shy, and avoidant and behaviorally-restrained in novel and unfamiliar situation with the predisposition to stress-related disorders (Smoller et al., 2005). It was proposed that neuroticism may be a result of the malfunctioning of the aversive motivational system (behavioral inhibition system) normally involved in the inhibiting behavior and stimulation of autonomic arousal to protect an individual from harm (Clark et al., 1994).

Genetic researches further support the trait predisposition theory and define anxiety as a complex genetic disability that has a significant familial aggregation with the etiological influence of biological as well as environmental or psychological factors, respectively (Domschke et al., 2009; Hettema et al., 2001). The contribution of genetic factors has been found with an estimated heritability of

up to 67%, where genetic variations in enzymes regulated catecholamines (dopamine, epinephrine, and norepinephrine) and monoaminergic neurotransmitters (serotonin, adrenaline, noradrenalin, and melatonin) are restricted to the female subgroup (Stein et al., 2004). The molecular genetic studies support the psychophysiological theory of traits and show functional variations in the corticotrophin releasing a hormone gene and the serotonin transporter gene in animals and humans with BI and neuroticism (Smoller et al., 2005; Jacobs et al., 2006). The extraversion and related personality traits are linked with beta-1 adrenergic receptor variants (Stein et al., 2004).

FUNCTIONAL BRAIN BIOMARKERS IN ANXIETY DISORDERS

The trait theory of anxiety is supported by neurobiological researches aimed at identifying specific functional brain variations associated with particular disorders (Pogarell et al., 2006; Bosl, et al., 2011; Steiger and Kimura , 2010; Iosifescu, 2011). Functional brain biomarkers are objective measures that serve in the evaluation of the essential causes of illnesses, its clinical course, and adjustment by treatment (Wiedemann et al., 1999). These measures provide information on the functional connectivity between structures that can be used to disclose the pathological loops involved in a particular disorder, and facilitate a personal treatment strategy. A growing number of research reports identify genetic, psychological, anatomical and functional characteristics of anxiety that can be used as potential biomarkers.

Functional neuroimaging studies concur with the neuroanatomical deviations discussed above, but provide information on the degree of activation or deactivation of a particular structure and its network. For instance, the hyperactivation of amygdala, insula and anterior cingulate, with simultaneous hypoactivation of the dorsal and ventral regions of the mPFC was reported for all anxiety disorders excluding obsessive compulsive disorder. These structures are at the same time involved in the regulation of emotions and fear throughout the limbic-medial prefrontal circuit and “fear network” (Kent and Rauch, 2003; Rauch et al., 2003; Bremner, 2004; Damsa et al., 2009; Shin and Liberzon, 2010; Holzschneider and Mulert, 2011).

EEG and ERP measures represent the dynamic features of the brain with an extremely high temporal resolution, and may be used as objective biomarkers to evaluate the unique feature of a particular disorder and predict the effect of treatment. The quantitative EEG or QEEG method is a mathematical processing of digitally recorded EEG. QEEG transforms EEG into a format or domain that elucidates relevant information or associates numerical results with the EEG data for a subsequent review or comparison (Nuwer, 1997). QEEG analysis includes the statistical comparison of individual QEEG parameters, such as amplitude, frequency and coherence with the normative database to identify the areas of significant deviations in individual brain functioning (Hammond, 2005;

Tab. 1. Functional brain mapping and applied neurofeedback (NFB) protocols in anxiety patients

Disorder	Hyperactivation	Hypoactivation	EEG	Asymmetry	Connectivity	NFB protocols
General Anxiety Disorder (GAD)	The left orbital frontal lobe, mPFC, right VLPFC, left DLPFC, left parietal area, cingulate, bilateral insula, and amygdala (Glabus, 2005; Mathew et al., 2004; Engel et al., 2009).	Medial, middle frontal and temporal lobe and the left basal ganglia (Chen and Shi, 2011).	EEG studies defined reduce alpha suppression over the occipital lobe, reduced delta and alpha bands over the left posterior temporal cortex	Decreased left frontal alpha or the frontal lobe alpha asymmetry (Glabus, 2005).	Disrupted connectivity within PFC and between amygdala and posterior cingulate, precuneus and the mPFC were reported (Strawn et al., 2012).	Increased alpha or alpha-theta bands (8-13, 4-8 Hz) with either eyes open or closed condition (Hammond, 2005). the activation protocols aimed to augment frontal activation and decrease interhemispheric asymmetry by increasing the beta and/or decreasing alpha activity with electrodes placed at Fz/Pz, Fp1/Fp2, F3/F4; F7/F8, F7/T5, F8/T6, and C4/C4 was successfully applied for GAD and chronic anxiety (Thomas and Sattlberger, 1997; Kerson et al., 2009).
Panic Disorder (PD)	Left hippocampus, amygdala, thalamus, pons, and medulla (Gorman et al., 2000; Hahn et al., 2011)	Left inferior parietal, posterior temporal, inferior parietal areas and cerebellum (De Cristofaro et al., 1993; Bisaga et al., 1998)	Repeated slow (theta) waves over the parietal occipital areas (Hayashi et al., 2010). During the panic attack - relative decrease of theta activity over the entire cortex with the increase in the right frontal alpha and augmented fronto-central and right temporal beta activity (Lopes et al., 2010; Engelbregt et al., 2012).	Significant frontal asymmetry with increased right frontal activation	Increased functional connectivity between left anterior and right posterior cingulate; right amygdala and the bilateral precuneus. Altered connectivity at the dACC network with frontal, parietal and occipital areas was also shown (Han et al., 2008, Pannekoek et al., 2013)	Increase alpha or alpha-theta bands (8-13, 4-8 Hz) with either eyes open or closed condition (Moore, 2003; Hammond, 2005).

Tab. 1. Functional brain mapping and applied neurofeedback (NFB) protocols in anxiety patients (cont,)

Social Anxiety Disorder (SAD)	Visual association cortex, amygdala, insula, right hippocampus, right DLPFC, left parietal cortex, thalamus, striatum, supplementary motor cortex (Ziv et al., 2013)	Amygdala, ACC and PFC (Demenescu et al., 2013; Ziv et al., 2013)	Decrease in absolute and relative delta, theta power, and slow beta with dominant alpha frequency (Sachs et al., 2004),	Increase in relative right alpha asymmetry (Moscovitch et al, 2011).	Left amygdala, medial orbitofrontal cortex and precuneus and reduced functional connectivity between the medial orbitofrontal and anterior cingulate cortices was reported (Hahn et al., 2011)	Alpha-theta protocols (Gruzelier, 2009)
Post Traumatic Stress Disorder (PTSD)	Ventral anterior and dorsal posterior parts of amygdala, insula, the posterior cingulate cortex, and the motor areas (Etkin and Wager, 2007; Francati et al., 2007)	Rostral ACC, dorsal anterior cingulate, thalamus, hippocampus, and the vmPFC (Etkin and Wager, 2007; Sripada et al., 2012)	Increased theta band at the central regions, augmented beta activity over the frontal, central and left occipital areas, reduction of alpha frequency (Begić et al., 2001; Jokić-Begić et al, 2003).	Significantly lower theta activity over frontal and in the right temporal areas in patients with PTSD in comparison with norm (Todder et al., 2010)	The increased functional connectivity over the left fronto-parieto-temporal regions, decreased connectivity in the right fronto-parieto-occipital areas (Kim et al, 2011).	Increase alpha or alpha-theta bands (8-13, 4-8 Hz) with either eyes open or closed condition (Hammond, 2005).
Obsessive Compulsive Disorder (OCD)	Lateral OFC, ACC, PFC, caudate nucleus, putamen, and hypoactivation in striatum (Baxter et al., 1988; Perani et al., 1995; Stern et al., 2013)		Diffuse excessive alpha and beta power over frontal, central and mid-temporal areas, or increased theta power over frontal and posterior temporal areas (Sürmeli and Ertem, 2011).	Significant fronto-temporal dysfunction predominantly in th left hemisphere (Ischebeck et al., 2014)	Abnormal functional integration in the cortical-striatum-thalamic-cortical circuits and default mode network (Hou et al., 2013)	qEEG-guided protocols (Surmeli and Ertem, 2011)

Prichep, 2005). The normative reference database allows the multivariate description of QEEG abnormalities in patients when compared to age appropriate normative values, and the exploration of neurophysiological heterogeneity within populations (Thatcher and Lubar, 2008).

Based on the QEEG evaluation it was found that anxiety disorders linked with greater relative right frontal asymmetry at rest and after provocation was found in all anxiety disorders patients independent of their age (Heller et al., 1995; Wiedemann et al., 1999; Avram et al., 2010). Anxious patients displayed paradoxical enhance in slow theta band activity in the prefrontal and fronto-temporal cortical areas, possibly related to desynchronization in the autonomic and somatic arousal levels (Knott and Lapierre, 1988; Knott, 1990; Hayashi et al., 2010). The increase in the beta frequency band in the right prefrontal and temporal cortex at rest with overall augment in arousal was also reported (Dantendorfer et al., 1996; Guerrero Figueroa et al., 2001). These data are consistent with Davidson's EEG-asymmetry-emotion model, where high levels of relative left frontal asymmetry are associated with the expression and experience of positive approach-related emotions. While high levels of relative right frontal activity are coupled with the experience and expression of negative or withdrawal-related emotions. The degree of activation is inferred from the spectral power in the alpha band (8-12 Hz), with lower values in alpha power being allied with a higher degree of activity (Davidson et al., 2000).

In addition, the elevated right frontal-brain activity during rest or in response to emotional provocation has been shown among non-clinical and clinical samples of socially anxious individuals (Beaton et al., 2008; Moscovitch et al., 2011).

ERP studies on anxiety patients (Table 1) reported an enhancement in the amplitudes and decrease in the latencies of early ERP components (Hanatani et al., 2005; Kolassa et al., 2007; Weinberg et al., 2010; Weinberg et al., 2012; Pachalska et al., 2014). Enhanced amplitude of the response monitoring component defined in anxiety patients is also linked with a high level of behavior inhibition (McDermott et al., 2009). This data are coincided with the idea of disrupted sensory-gating, and insufficient, rapid, pre-consciousness allocation and deployment of attention in anxiety (Clark et al., 2009; Paul et al., 2012).

CONCLUSION

The theory of stress-regulation system being faulty in anxiety disorders concurs with the ancient philosophical view of stress and its relation with different forms of health conditions, where the stress and a stressful life experience predispose the development of anxiety disorders (Ströhle and Holsboer, 2003). Stress-regulation is a complex multi-component hierarchical system that includes structures involving emotional, attentional, motivational, executive and other higher brain functions. Depending on the nature, strength, duration and the degree of stress, different levels of the stress-regulation system are involved and the set of responses is launched through the autonomic (sympathetic and

parasympathetic branches) and hypothalamic-pituitary-adrenocortical (HPA) axes to perform an immediate, intermediate, or prolonged reaction, and can diminish the adaptation capacities and the ability to cope with stress (Seaward, 2006). The sympathetic and parasympathetic ANS balance is important for the optimal level of arousal. The disrupted coordination between those systems may result in hypersensitivity or the hyper-reactivity of autonomic stress-regulation systems and the development of anxiety symptoms.

The neuroendocrinological bases of anxiety disorder defined the role of the HPA axis in stress-regulation system sensitivity, where the basic level of stress hormones may increase or inhibit its reactivity and is allied with the appearance of psychosomatic and psychiatric disorders (Sage et al., 2001; Raison and Miller, 2003). The hyperactivation of the HPA axis was found in anxiety disorders and major depression (Björntorp, 1996), whereas hypoactivation was associated with autoimmune processes such as lupus erythematosis, multiple sclerosis, neurodermatitis, fibromyalgia, chronic fatigue syndrome, and rheumatoid arthritis (Kudielka and Kirshbaum, 2005). Gender prevalence of anxiety disorders in the population seems to be related with women's cyclic estrogen/progesterone level fluctuation, which modulates HPA axis sensitivity. This system protects women from cardiovascular diseases, but increases their vulnerability to anxiety disorders. Genetic studies further clarify the reasons for gender prevalence by the identification of genetic polymorphism in serotonergic, dopaminergic and noradrenergic systems being restricted for the female subgroup. From psychological studies it is known that anxiety disorders are linked with neuroticism, negative affectivity, high level of shyness and avoidance (Clark et al., 1994; Freire et al., 2007). This, in turn, can be a result of malfunction in the aversive motivational system (behavioral inhibition system) normally involved in inhibiting behavior and stimulating the protective autonomic arousal. In addition, genetic researches have defined the link between gene variants and behavioral inhibition (Domschke and Deckert, 2009).

The hippocampus, amygdala, anterior cingulate and the prefrontal cortex regulate the stress-related responses of the ANS and HPA axes, and at the same time are involved in emotional, executive and cognitive self-regulation. This supports the idea of unified systems that sub serve stress- and self-regulations. This multilevel loop provides the selective control of autonomic and behavioral responses in according with an apprised threat level and its potential danger for the organism.

To understand the complexity of anxiety and to provide differential diagnostics and prognostics it is necessary to analyze all the elements of this system in conjunction. Successful treatment outcome will depend on personalization and a multidimensional approach, which will include indexes of each of the subsystems discussed above.

The present review has demonstrated that the pathophysiology of anxiety is linked with biological, genetic, neuroendocrinological and functional deficiency in circuits involved in stress- and self-regulation, where the stress- and self-reg-

ulation systems sensitivity increases personal vulnerability to stress-related disorders development.

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Address for correspondence:
Olga Kara
Lintuviidankatu 18, 33340 Tampere
Finland
+358 40 5591439
kara.olga@gmail.com