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Psychophysiological Markers of Anxiety Disorders and Anxiety Symptoms

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1. Introduction

In anxiety research, relative few psychophysiological studies have been conducted. In this chapter, we presented previous studies that used different psychophsiological markers that can be further utilized in future research. However, there are a few things to be considered when psychophysiological markers are used in anxiety studies, first of which may be genetic factors. Genetic factors influence vulnerability to anxiety disorders. There are several genetic polymorphisms associated with anxiety disorders among which are the serotonin-transporter-linked polymorphic region (*5-HTTLPR*), the Catechol-O-methyltransferase (*COMT*), and the brain-derive neurotrophic factor (*BDNF*) gene variants. We first presented studies that invsestigated the relationship between these genetics variants and anxiety disorders. Also, it has been suggested that anxiety disorders are characterized by abnormal neural activity—amygdala hyperactivity and dysfunctional prefrontal activity—and cognitive bias favoring threat-relevant stimuli (Cisler et al., 2010; McClure et al., 2007; Nitschke et al., 2009; Whalen et al., 2008). We will present different psychophysiological markers that have been used to study dysfunctional neural, serotonergic, cognitive and autonomic activites associated with anxiety disorders. They include: (1) a loudness dependence of the auditory evoked potential (LDAEP) which is proposed to be associated with serotonin activity, (2) various components of the event-related potentials [P1, P2, N300, P3b, early posterior negativity (EPN), late positive potential (LPP), and error-related negativity (ERN)] that reflect altered neural activity in anxiety disorders and (3) the reduced heart rate variability (HRV) which indicates autonomic dysregulation associated with increased sympathetic and decreased vagal control of the heart. Particularly, in this chapter, we introduced the loudness of the auditory evoked potential (LDAEP) as a possible psychophysiological marker that can be utilized in anxiety research. Our previous studies revealed that patients with different subtypes of anxiety disorders produced distinctive LDAEPs and that the LDAEP could play an important role in predicting the efficacy of selective serotonin reuptake inhibitor (SSRI) treatment in anxiety disorders (Park et al., 2010, 2011). We suggest that utilizing the LDAEP along with other various ERP components indicating neural and cognitive dysfunctions associated with anxiety disorders may enhance our understanding of the etiology and maintenance of anxiety disorders. Also, it is important to understand how they interact with each other and with other environmental stressor to reinforce or to exacerbate anxiety symptoms (see Figure 1). Of clinical relevance is whether these psychophysiological markers may play a role in predicting clinical outcome of different treatment.

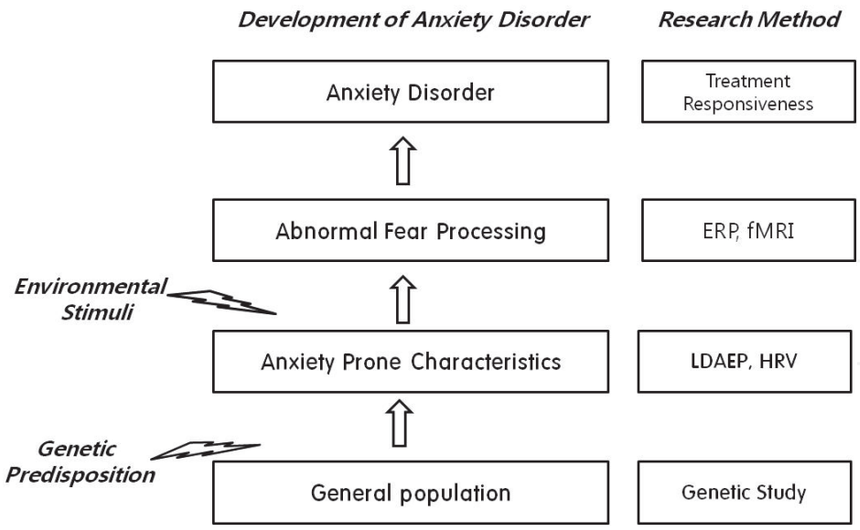

Fig. 1. Development of anxiety disorders and research methods that can be used in each stage.

2. Genetic predispositions of anxiety symptoms

Anxiety disorders have genetic predispositions and it is critical to consider individuals' genetic predispositions to develop anxiety prone characteristics and anxiety disorders. Several anxiety-related genetic markers have been identified, one of which includes the serotonin transport promoter polymorphism (*5-HTTLPR*). The dysfunctional serotonergic system (5-hydroxytryptamine or *5-HT*) is known to be implicated in anxiety and fear (Harmer et al., 2004). In human, serotonergic raphe neurons project to different brain structures (e.g., cortex, amygdala, hippocampus) and are associated with integrating various functions including emotion, cognition, motor function, pain, circadian and neuroendocrine functions such as food intake, sleep and sexual activity (Lesch et al., 1997). The 5-HT transporter (*5-HTT*) plays a vital role in regulating serotonergic neurotransmission by facilitating the reuptake of 5-HT from the synaptic cleft (Lesch et al., 1996; Hariri et al., 2002). Lesch and colleagues (1996, 1997) identified a relatively common polymorphism in the promoter region of the serotonin transporter gene, which results in two different alleles—the short (*s*) and long (*l*). Research has showed that the *5-HTTLPR* plays a functional role in regulating *5-HTT* expression and *5-HTTLPR* genotype may modulate *5-HTT* expression (Lesch et al., 1996; Lesch et al., 1997). Individuals carrying one or two copies of the *s* form of *5-HTTLPR* were associate with almost 50% reduction in *5-HTT* availability compared to individuals homozygous for the *l* variant (Lesch et al., 1996; Lesch et al., 1997; Hariri et al., 2002). As a result, it has been reported that *s*-carriers were associate with increased anxiety-related behaviors and greater risk for developing anxiety in stressful life situations compared to individuals homozygous for the *l* variant (Lesch et al., 1996; Lesch et al., 1997; Hariri et al., 2002). Research also indicated that allelic differences in the 5-HTT may modulate activity of neural circuits (Heinz et al., 2005; Pezawas et al., 2005). Health individuals carrying one or two copies of the *s* allele showed greater activity in the amygdala in response to fearful stimuli (Heinz et al., 2005). Also, individuals with the *s* allele showed altered coupling of prefrontal-amygdala feedback circuit—which may lead to dysfunctional amygdala regulation in response to fearful stimuli—compared to individuals homozygous of the *l* allele (Heinz et al., 2005; Pezawas et al., 2005).

Another gene associated with anxiety disorders is the Catechol-O-methyltransferase (*COMT*) genetic variation (Funke et al., 2005). *COMT* is an enzyme that plays an important role in the metabolism of brain dopamine and norepinephrine (Gadow et al., 2009). The *COMT* gene can be found in chromosome 22q11 and contains several single nucleotide polymorphisms (SNPs) that are functionally important. For example, *Val158Met* (rs4680)—associated with encoding either valine (*Val*) or methionine (*Met*)—plays an important role in modulating *COMT* activity in the prefrontal cortex (Harrison et al., 2008). Current evidences suggest that *Val158Met* may be associated with anxiety disorders, particularly bipolar disorder, via controlling dopamine activity in the prefrontal cortex (Funke et al.,2005). Individuals with Val158 homozygous showed 35-50% higher *COMT* activity in human dorsolateral prefrontal cortex than those with Mel158 homozygous (Harrison et al., 2008). Although *Met-COMT* is considered to play an important role in the development of bipolar disorder, there exists evidence that *Val-COMT* is also associated with bipolar disorder (Funke et al., 2005).

Lastly, the brain-derived neurotrophic factor (*BDNF*) gene variants are suggested to be linked with anxiety disorders (Chen et al., 2006; Gadow et al., 2009). *BDNF* is a neurotrophin that plays an important role in neuronal growth, differentiation, and synaptic plasticity (Chen et al., 2006; Gadow et al., 2009; Rasmusson et al., 2002). BDNF is also associated with learning and memory and modulates aggression (Rasmusson et al., 2002). It has been reported that BDNF plays a role in mediating effects of stress (Rasmusson et al., 2002). Reduced BDNF expression in the hippocampus was observed in response to stress, which may contribute to hippocampus-dependent memory deficits and the decreases in hippocampal volume associated with patients with post-traumatic stress disorder (PTSD; Rasmusson et al., 2002). Recent studies investigated the relationship between a SNP in the *BDNF* gene, *Val66Met*, and psychopathology, which yielded conflicting results (Jiang et al., 2005). In an animal study, when exposed to stress, *BDNF* Met/Met mice demonstrated anxiety-related behaviors and were not responsive to the antidepressant, fluoxetine (Chen et al., 2006). Studies showed that *Val66* allele were associated with greater neuroticisim scores, suggesting that individuals with the Val allele may have increased risk for developing anxiety or depression (Hünnerkopf et al., 2007; Sen et al., 2003). However, no association between *BDNF Val66Met* genotypes and neuroticisim was observed in Asian female participants (Tsai et al., 2004). *BDNF Met66* allele was found to be a risk allele for anxiety and depression (Jiang et al., 2005) whereas other found it to be a protective allele for obsessive-compulsive disorder (OCD; Hall et al., 2003). In sum, *BDNF* may be related to anxiety disorder though it is yet to be determined which specific variant is responsible for the pathogenesis of anxiety disorders (Gadow et al., 2009).

So far, we have presented different candidate genetic marker of anxiety disorders. To have better understanding of anxiety disorders, it would be important to identify genetic polymorphisms associated with anxiety disorders and study together with psychophysiological markers which will be discussed later.

3. Neurophysiological and cognitive characteristics of anxiety disorders

Anxiety disorders are characterized by altered neurophysiological and cognitive functions. Various psychophysiological markers used in anxiety research may reflect these altered neural and cognitive characteristics of anxiety disorders. Here, we briefly described altered neural activity and dysfunctional cognitive processing of threat-relevant information in people with anxiety disorders.

3.1 Amygdala hyperactivity and reduced PFC function

Amygdala hyperactivity has been considered as an important neural characteristic of anxiety disorders (Bar-Haim et al., 2005; Dannlowski et al., 2007; McClure et al., 2007). Previous functional brain imaging studies indicated that anxiety disorders are linked with hyperactivity of the amygdala in response to anxiety provoking tasks (e.g., public speaking), fear-conditioning, and viewing face pictures with emotionally negative expressions (Phan et al., 2006). Also, functional magnetic resonance imaging (fMRI) studies revealed that effective treatment produced significantly reduced amygdala activity in patients with social phobia (Kilts et al., 2006; Furmark et al., 2002). Patients characterized with greater amygdala hyperactivity before treatment responded better to treatments such as SSRI medications and cognitive behavioral therapy (CBT; McClure et al., 2007). More recently, fMRI studies also revealed that high-trait anxiety individuals showed reduced activity in anterior cingulate cortex (ACC)—associated with conflict monitoring—and lateral prefrontal cortex (lateral PFC)—related with attentional control over threat-relevant distractors (Bishop et al., 2004). Patients with generalized anxiety disorder (GAD) patients who showed greater activation in ACC in response to or in anticipation of aversive pictures were associated with better treatment outcome (Nitschke et al., 2009; Whalen et al., 2008). In addition, GAD patients who showed greater activation in the ventrolateral prefrontal cortex—associated with emotional regulation by exerting inhibitory control over subcortical structures—had fewer anxiety symptoms (Monk et al., 2006). Therefore, anxiety disorders may be characterized by amygdala hyperactivity—associated with heighten sensitivity to motivation-relevant stimuli—and reduced PFC activity—resulting in the lack of top-down attentional control and emotional regulation (Bishop et al., 2004; McClure et al., 2007; Monk et al., 2006).

3.2 Cognitive characteristics of anxiety disorders

It has been well established that anxious individuals exhibit attentional biases toward threat-relevant stimuli (Cisler et al., 2010; Mathews et al., 1997). Anxiety-related attentional biases are typically observed in three different ways: (1) faster detection to threat-relevant stimuli relative to nonthreat stimuli, (2) difficulties in disengaging attention away from threat stimuli (sustained attention to threat stimuli), and (3) attentional avoidance of where threat-relevant stimuli are presented (Cisler et al., 2010; Fox et al., 2001; Koster et al., 2004; 2005). Initially, anxiety-related attentional biases were studied in the emotional Stroop task. In the task, threat or neutral words were written in different colors and participants were instructed to name the color of ink while ignoring the meaning of the word (Cisler et al., 2010). Research showed that high-trait anxiety participants were slower to name the color of ink in which threaten words were written, particularly to items relevant to their anxiety conditions. For instance, Vietnam combat veterans with Post-Traumatic Stress Disorder (PTSD) and without PTSD were asked to name the color of PTSD-related words,OCD-related words, positive words, and neutral words (McNally et al., 1993). Veterans with PTSD took longer to name the color in which PTSD-related words were written relative to veterans without PTSD who showed no difference in reaction times across different types of the words. Similarly, slower responses were observed to read threat-relevant words in patients with GAD (Mathews & MacLeod, 1985) and panic disorder (McNally et al., 1994). Highly anxious non-clinical participants showed negativity bias even though they could not consciously aware of the presence of threat-relevant stimuli (MacLeod and Rutherford, 1992). Moreover, performances on the masked emotional Stroop task predicted later emotional reactivity (Den Hout et al., 1995).

Fox and her colleagues (2001) adapted Posner's spatial cuing task to systematically investigate different components of anxiety-related attention bias (Posner & Petersen, 1990). In the spatial cuing task, a target is preceded by a cue which can be either "central" (e.g., an arrow presented at the center of the display pointing one of two peripheral boxes in which the target would subsequently appear), or "peripheral" (e.g., an abrupt luminance of one of the peripheral boxes; Posner et al., 1990; Posner et al., 2007; Bartolomeo et al., 2001). When the cue appears on the same display that a target appears, it is considered to be a valid trial because the cue correctly predicts the location in which the target appears. However, when the cue fails to predict where the target will appear, it is considered to be invalid. In valid trials the detection of targets is facilitated (cuing benefits) whereas the detection of targets is delayed in invalid trials (cuing costs). In the modified emotion spatial cuing task, emotionally charged words or pictures were used as cues (Fox et al., 2001; Vuilleumier et al., 2009). If high-trait anxiety participants automatically draw their attention to threat-relevant stimuli, their response to targets following valid threat-relevant cues should be fast (Fox et al., 2001). If high-trait anxiety participants have a difficulty in disengaging their attention from threat-relevant stimuli, then their responses to targets following invalid threat-related stimuli should be slow (Fox et al., 2001). In the first study, Fox et al. (2001) found that attentional disengagement from threat-relevant words took longer compared to neutral or positive words. However, there was no difference between high and low-trait anxiety participants. In the second study, they used schematic faces with 'angry,' 'neutral,' and 'happy' facial expressions. When a cue duration period increased to 250 ms, only high anxious individuals showed the delayed attentional disengagement from angry faces. Fox and colleague (2001) suggested that regardless of anxiety level, people were initially drawn to threat-relevant information for a brief period of time (about 100 ms). However, low-trait anxiety participants were capable of quickly disengaging their attention from threat-relevant, positive and neutral information whereas high-trait anxiety participants were less successful in disengaging their attention from the location in which threat-related information was presented.

Recent studies suggested that high-trait anxiety is associated with the "vigilance-avoidance" attentional patterns in response to threat-relevant information, which may account for the maintenance of anxiety (Koster et al., 2006). The initial attention to mildly and highly threatening information may trigger the constant processing of fearful information and interfere with engaging in goal-directed behaviors (Koster et al., 2006). Faster detection of mildly and highly threatening information trigger anxious conditions in high-trait anxiety participants, which reinforces them to avoid threatening information in an attempt to reduce anxiety (Koster et al., 2006). However, this strategic attentional avoidance may not be a good coping strategy because it can lead to a failure of habituation to threaten stimuli and constantly remind of fear (Koster et al., 2006). Koster and colleagues (2005, 2006) used neutral, mildly and highly threatening pictures as cues and reported that when picture cues were presented at 100 ms, high-trait anxiety participants exhibited faster attentional engagement and slower attentional disengagement in response to highly threatening pictures compared to low-trait anxiety participants. However, when picture cues were presented longer, 500 ms, high-trait anxiety participants showed slower attentional engagement to highly and mildly threatening cues, which may suggest attentional avoidance to highly threatening stimuli (Koster et al., 2006).

Interestingly, there is evidence suggesting that the *5-HTTLPR s* allele—genetic predispositions to anxiety—may be related with anxiety-related cognitive bias (Beck, 2008). Twenty-seven psychiatric inpatients who carried *s* allele of the promoter region of the *5-HTTPR* showed anxiety-related attentional biases favoring threat-relevant words compared to patients with homozygous for the *l* variant (Beevers et al., 2007). Fox and colleagues recently showed that healthy individuals with homozygous for the *l* allele were characterized by a marked avoidance of negative stimuli and a vigilance for positive stimuli whereas *s*-allele carriers did not show such protective attentional pattern (Fox et al., 2009). Therefore, allelic variation of the promoter region of the serotonin transporter gene may influence the way in which an individual processes emotional materials.

4. The event-related potentials (ERP) components used to study anxiety disorders

Several ERP components have been used to study serotonergic, neural, and cognitive dysfunctions associated with anxiety disorders. We provided underlying mechanisms of the loudness dependence of the auditory evoked potential (LDAEP) and presented studies that used the LDAEP in anxiety research. Also, researchers have studied other ERP components that reflect neural mechanisms of cognitive bias toward threat-relevant stimuli commonly observed in patients with anxiety disorders.

4.1 Loudness of the auditory evoked potential

It has been proposed that the LDAEP—which measures activity in the primary auditory cortex in response to different tone intensities—indicates the functioning of the central serotonergic system (Hegerl et al., 1993; Juckel et al., 1999). More specifically, the LDAEP is defined as the linear regression slope calculated from five amplitudes of N1/P2 components in response to increasing five auditory tones (Senkowski et al., 2003; see Figure 2). Research has indicated that the LDAEP is inversely related to central serotonergic activity: a stronger LDAEP indicates lower serotonergic neurotransmission and vice versa (Juckel et al., 1999, Park et al. 2010).

Initial evidence that linked the LDAEP and the serotonergic system came from animal studies (O'Neill et al., 2008). Administrating quipazine maleate—a 5-HT_2 receptor agonist—reduced the amplitude of N1/P2 components whereas administrating spiperone—a 5-HT_{1A} receptor antagonist—increased the N1/P2 amplitude in rats (Manjarrez et al., 2005). Administrating the precursor of 5-HT, L-tryptophan, was associated with the reduced amplitude of N1/P2 components (Manjarrez et al., 2005). Other studies showed that the LDAEP was inversely correlated with the concentration of 5-hydroxyindoleacetic acid (main metabolite of serotonin) in cerebrospinal fluid (von Knorring et al, 1981). High scores in the serotonin syndrome scale were associated with weaker LDAEPs and vice versa in depressive patients who underwent SSRI treatment (Hegerl et al., 1998). Individuals scored high on measures of sensation seeking and impulsiveness were associated with stronger LDAEP—potentially indicating reduced serotonergic function (Brocke et al., 2000; Hegeral et al., 1995). So far, there have been three studies that investigated the relationship between allelic variants of the seroton transporter gene and the LDAEP. It has been found that individuals homozygous for the *l* variant exhibited lower LDAEP (Gallinat et al., 2003) whereas others (Strobel et al., 2003; Hensch et al., 2006) reported that the *l* allele carriers

showed stronger LDAEP. These studies provide evidence that the LDAEP is linked with the serotonin transporter polymorphism although there are inconsistencies in predicting directional changes in serotonin neurotransmission (O'Neill et al., 2008).

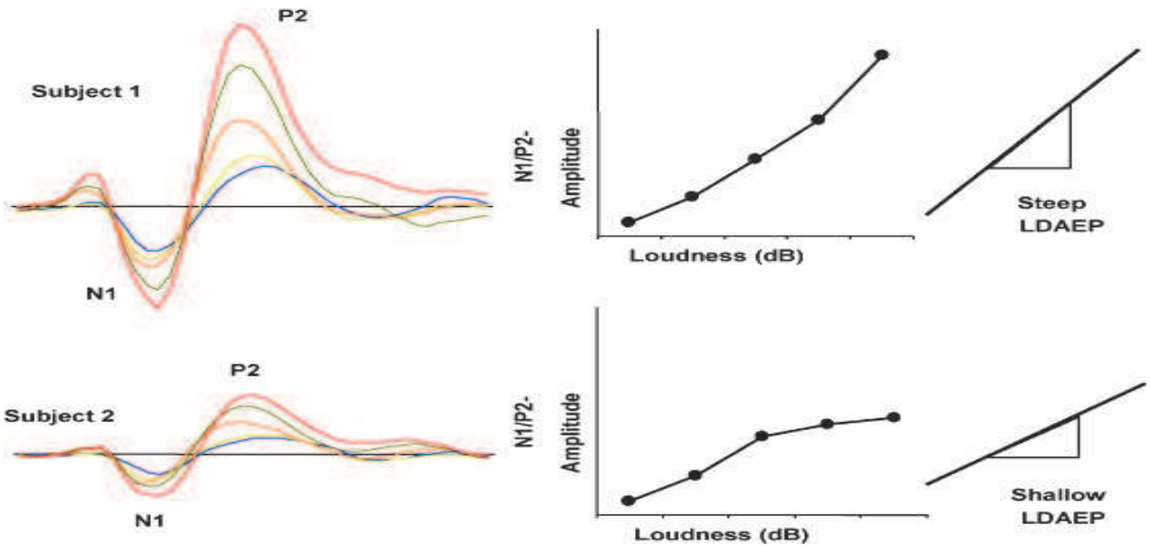

Fig. 2. Subject 1 possesses a steep LDAEP (a large increase in N1/P2 amplitude with increasing loudness) whereas subject 2 shows a shallow LDAEP (a small increase in N1/P2 amplitude with increasing loudness). Adapted from O'Neill et al., 2008. (Reprinted by permission of author and publisher).

There is evidence suggesting that the LDAEP is also modulated by dopaminergic neurotransmission (Juckel et al., 2008). High intensity dependence of auditory and visual evoked potentials were associated with low levels of dopamine metabolites (i.e., homvanillic acid) in cerebrospinal fluid and urine (Pogarell et al., 2004; O'Neill et al., 2008). Pogarell and colleagues (2004) used single photon emission computed tomography (SPECT) and showed that the LDAEP was positively associated with both serotonin and dopamine transporter availabilities in patients with OCD. Recently, Juckel and colleagues (2008) found that the LDAEP is also related with the genetic variants of the c*COMT*—implicated in the inactivation of synaptic dopamine (Stein et al., 2005; Samochowiec et al., 2004). Reduced *COMT* activity caused by genetic polymorphisms was associated with a weaker LDAEP (Juckel et al., 2008).

The LDAEP has been utilized to study dysfunctional serotonergic and dopaminergic activity in patients with GAD (Senkowski et al., 2003), PTSD (Park et al., 2010), schizophrenia (Juckel et al., 2003) or depression (Gallinat et al., 2000). Recently, Park and colleagues (2010) compared the results of the LDAEP in a variety of psychiatric patients including GAD, PTSD, panic disorder, bipolar depression, major depressive disorder (MDD), and schizophrenia. Individuals with different anxiety disorders produced different strengths of LDAEPs (see Fig. 3), which raised a possibility that the differences in the LDAEP may be associated with distinctive anxiety symptoms and cognitive impairments that characterize different subtypes of anxiety disorders. However, further studies are needed to explicate the relationship between different anxiety disorders and the strength of LDAEP.

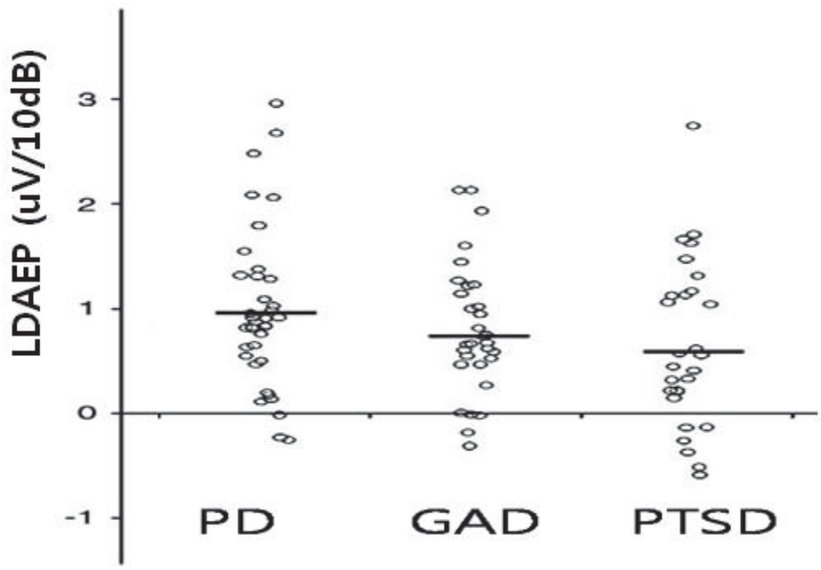

Fig. 3. Comparison of the LDAEP among panic disorder (PD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD). Note: Adapted and modified from Park et al. (2011). (Reprinted by permission of publisher).

Furthermore, evidence suggests that the LDAEP can serve as a predictor of responses to SSRI treatment in GAD patients, which phenomenon was previously observed in patients with MDD (Gallinat et al., 2000; Linka et al., 2004). Research has indicated that a strong LDAEP— indicating lower serotonergic activity and turnover rate—is associated with a favorable response to SSRI treatment in patients with depression (Gallinat et al., 2000; Linka et al., 2004). Our study (Park et al., 2011) also showed that GAD patients who had stronger LDAEPs responded favorably to SSRI (escitalopram) treatment. Park et al. (2011) also confirmed this finding in the brain source activity of the LDAEP, which was measured using a standardized low resolution brain electro-magnetic tomography (*sLORETA*; Pascual-Marqui, 2002). GAD patients who showed greater loudness dependence source activity in the primary auditory cortex were more responsive to the escitalopram treatment (see Fig. 4). The study (Park et al., 2011) implies that source activity of the LDAEP, as well as the cortical LDAEP, may play an important role in predicting the efficacy of SSRI treatment in GAD patients, which can be used in clinical settings.

4.2 Other ERP components that are associated with neural mechanisms of cognitive bias

Because of high-temporal resolution, the event-related potentials (ERP) method can be particularly useful to capture the time course of anxiety-related attentional biases (Mercade et al., 2009) and has been utilized in some studies (Holmes, et al., 2008; Bar-Haim et al., 2005). Researchers have studied the P1—the first major positive voltage deflection occurring 50-165 ms after the onset of stimulus—and the early posterior negativities (EPNs)—showing negative deflection over the temporo-occipital sites within a time window between 150 (200) and 300 ms—in response to emotional stimuli (Schupp et al. 2006; see Figure 5). A number of studies reliably found that negative faces elicited the significantly higher amplitude of the

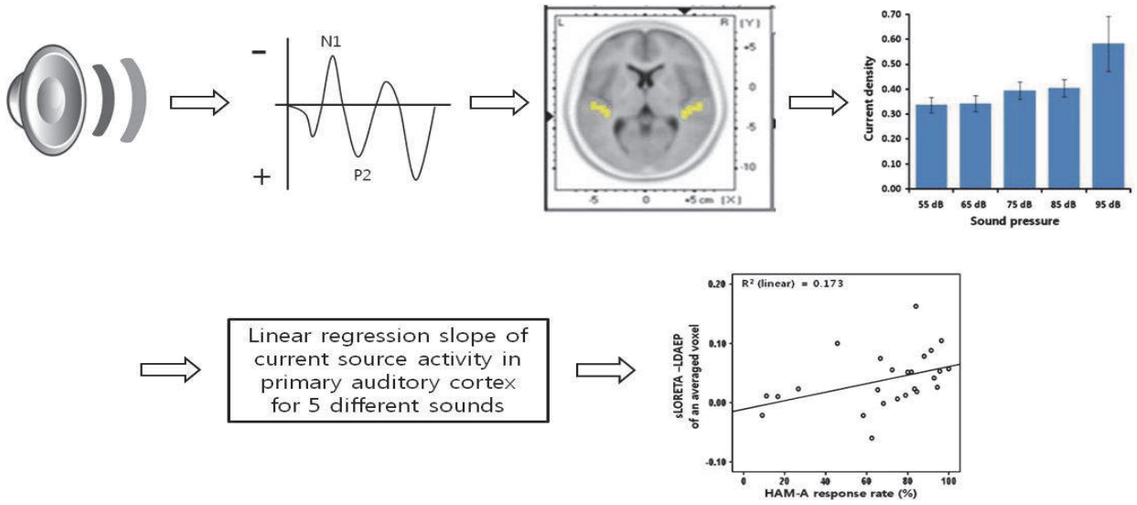

Fig. 4. The source activities of ERP components (N1-P2) on the primary auditory cortex were obtained by the *sLORETA* program. And the linear regression slope of the source activities of five ERP components was considered as the sLORETA - loudness dependence of the auditory evoked potential (*sLORETA-LDAEP*). The *sLORETA-LDAEP* showed the significant positive correlation [Spearman's rho = 0.54 (p=0.005)] with symptom response rates measured by Hamilton Anxiety Rating Scale (HAM-A) in patients with generalized anxiety disorder treated with escitalopram. Note: Adapted and modified from Park et al. (2011). (Reprinted by permission of publisher).

exogenous visual P1 component (Pourtois et al., 2005; Holmes et al., 2008). Greater EPNs were observed in response to negative faces compared to positive and neutral faces over lateral posterior and occipital areas (Schupp et al., 2004b; Holmes et al., 2008). Similarly, Bublatzky and colleagues (2010) reported that emotional pictures elicited an enlarged EPN. The P1 and the EPNs are particularly useful because they are associated with the preferential attentional processing of negative facial expressions in extrastriate visual cortex, which is extensively modulated by the amygdala and attentional networks in fronto-parietal cortex (Homles et al., 2008). Also, the EPN may be associated with a transient stage at which motivationally relevant stimuli are 'tagged' for prioritized processing, which can be useful to study preferential processing of motivationally relevant stimuli commonly observed in patients with anxiety disorders (Cuthbert et al. 2000; Michalowski et al. 2009; Schupp et al., 2006). In Holmes et al. (2008), high-trait anxiety participants who performed a variant of the emotional spatial cuing task showed an enhanced early P1 component to fearful faces relative to neutral faces at occipital electrode sites (Holmes et al., 2008). However, high-trait anxiety participants did not show greater lateral parietal negativities (or EPNs) in response to fearful faces, which may indicate attentional avoidance following the initial attentional vigilance or the failure to differentiate threat from non-threat stimuli (Holmes et al., 2008). In contrast, Wieser and colleagues (2010) reported that that healthy participants who expected to make public speaking produced enhanced EPN responses for angry facial expressions, suggesting enhanced early perceptional processing of angry faces.

Furthermore, Bar-Haim and colleagues (2005) used the emotional spatial cuing task similar to Fox et al., (2001) and reported high-trait anxiety participants had greater amplitudes of

the P2 component—the following major positive voltage deflection occurring 50-165 ms after the onset of stimulus—to angry faces compared to low-trait anxiety participants. Greater P2 components indicate greater attentional allocation to threat-related stimuli, which is frequently exhibited in individuals with anxiety disorders (Holmes et al., 2008).
Rossignol and colleagues (2005) used an emotional oddball task in which participants were asked to detect an infrequent emotional target stimulus among a series of frequent neutral standard stimuli and provided evidence that anxiety modulated the amplitude of N300, a negative deflexion peaking at central sites around 300ms, and the latency of the P3b component, occurring at parietal situes around 450 ms. N300 is associated with affective processing and P3b reflects decision-making and premotor response-related stage (Rossignol et al., 2005). High-trait anxiety participant showed the reduced amplitude of N300 suggesting that they were less able to process the emotional content of faces. However, faster detection of infrequent emotional target stimuli as suggested by faster reaction time latency and the P3b latency indicated that high-trait anxiety participants made fast decisions and preparation for actions (Rossignol et al., 2005).

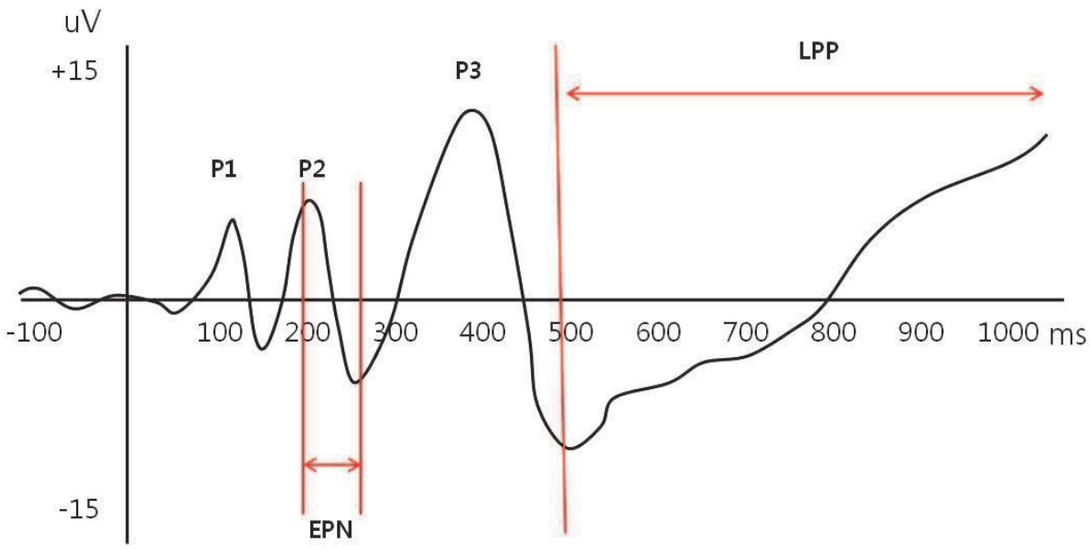

Fig. 5. Illustration of P1, P2, P3, early posterior negativity (EPN), and late positive potential (LPP) in response to fearful target stimuli in the odd ball task.

Another ERP component that has been used to study the abnormal processing of threat-relevant stimuli in anxious individuals is the late positive potential (LPP)—which becomes apparent approximately 300 ms after stimulus onset (Hajcak et al., 2010). Research indicated that greater LPPs are observed in response to emotional compared to neutral stimuli and do not habituate to stimuli that are repeatedly presented (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Dillon, Cooper, Grent-'t-Jong, Woldorff, & LaBar, 2006; Foti, & Hajcak, 2008; Hajcak, Dunning, & Foti, 2007; Hajcak & Nieuwenhuis, 2006; Hajcak & Olvet, 2008; Moser, Hajcak, Bukay, & Simons, 2006; Schupp et al., 2000; Schupp, Cuthbert et al., 2004a; Schupp, Ohman et al., 2004b; Schupp, Junghöfer, Weike, & Hamm, 2003). The LPP is associated with sustained attention toward, and elaborative processing of, motivationally relevant stimuli, which phenomenon is commonly observed in patients with anxiety

disorders (Hajcak et al., 2010). The source activity of the LPP may be traced to occipital activation resulting from elevated amygdala activity to motivationally relevant stimuli (Hajcak et al., 2010). It has been suggested that the LPP may reflect activity in the locus coeruleus (LC)-Norepinephrine (NE) system that innervates large areas of the cortex in response to motivationally relevant stimuli (Hajcak et al., 2010). Research indicated that patients with anxiety disorders had larger LPP than health controls (Leutgeb et al., 2010; MacNamara & Hajcak et al., 2010). For instance, spider phobia patients showed enhanced LPP amplitude in response to spider pictures (Leutgeb et al., 2010). Also, GAD patients had larger LPPs to aversive targets presented with neutral distrators compared to healthy controls (MacNamara & Hajcak, 2010).

There is an ERP component that can reflect prefrontal activity. For example, research has indicated that the error-related negativity (ERN), a negative deflection observed at fronto-central sites, is generated in the anterior cingulate cortex (ACC; Olvet and Hajcak, 2008). The ERN arises around the time when an erroneous response is made and peaks at 50-100 ms after stimulus onset (see Figure 6). The ERN has been found across different types of the tasks that employed various stimuli and response modalities (Hajcak et al., 2003; Weinberg et al., 2010). Significantly larger ERN component has been associated with anxiety (Xiao et al., 2011). Undergraduate students who scored high on the Penn State Worry Questionnaire

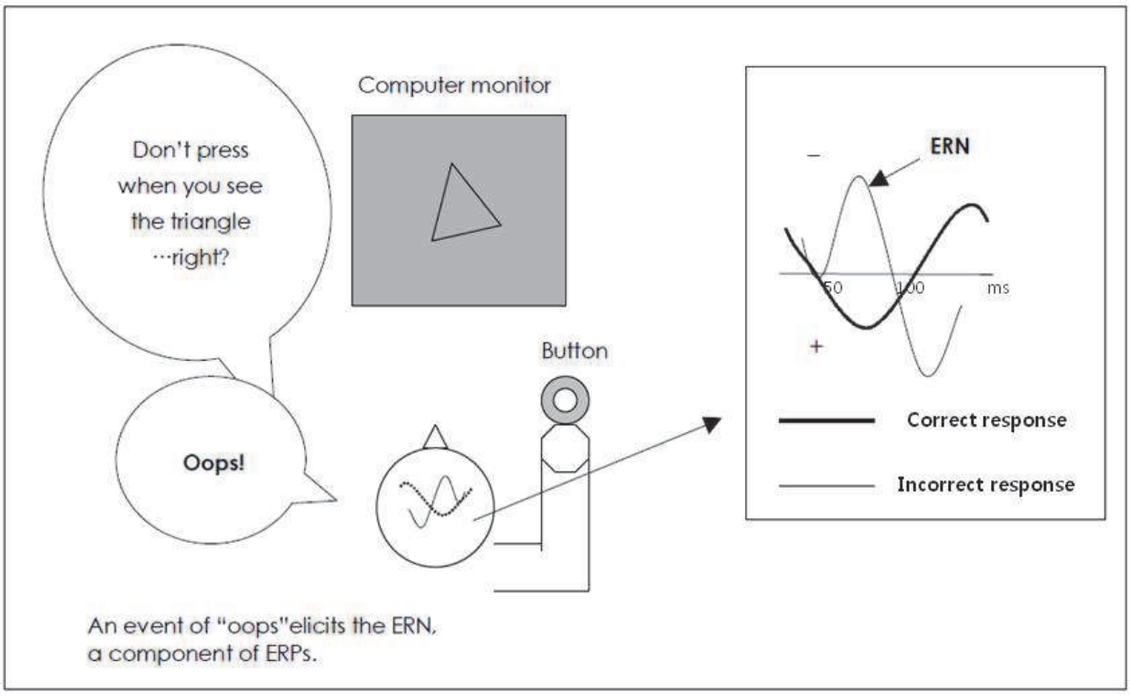

Fig. 6. Incorrect response is involved with the generation of ERN (error-related negativity). The ERN is negative-going deflection in averaged electrical brain activity that is time-locked to the execution of an incorrect response. Note that the ERN is absent for correct response. Note: Adapted and modified from Kim and Lee (2008). (Reprinted by permission of author and publisher).

Had significantly greater ERN compared to both phobic and non-anxious participants when making errors in the Stroop task (Hajcak et al., 2003). Also, significantly larger ERN

amplitudes were observed in individuals who had high scores on negative affect scores on negative affect compared to those with low scores on NA (Hajcak et al., 2004). Administrating anxiolytics such as oxazepam and alprazolam has decreased ERN amplitudes (Johannes et al., 2001; Riba et al., 2005). Several studies showed that patients with OCD have been associated with enhanced ERN amplitudes which did not change after successful treatment (Endrass et al., 2010; Gehring et al., 2000; Hajcak et al., 2008). A recent study showed that GAD patients showed larger ERN relative to healthy controls (Weinberg et al., 2010). Olvet and Hajcak (2008) have proposed that error monitoring activity of the ACC indexed by the ERN may play a role as an endophenotype of anxiety disorders.

5. Heart rate variability

Patients with anxiety disorders are characterized by reduced heart rate variability (HRV; Ost et al., 1984; Friedman, 2007). HRV—which refers to the differences in beat-to-beat alterations in heart rate—indicates the dynamic interplay between sympathetic and parasympathetic (vagal) activity in the heart (Berntson et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Thayer and Lane, 2000). Under resting conditions, the heart is predominately under the control of the parasympathetic activity (Levy, 1971). Although the intrinsic heart rate is approximately 105 beat per minute, resting heart rate is only 6o-80 beats per minute, indicating that the heart is under the strong vagal control ("vagal dominance"; Brownley et al., 2000; Ellis & Thayer, 2010)

There is converging evidence suggesting that reduced HRV—indicating autonomic dysregulation associated with elevated sympathetic activity and reduced vagal activity of the heart—is commonly observed in patients with panic disorder, GAD, and even children of patients with panic disorder (see Friedman, 2007 for a review; Friedman and Thayer, 1998; Srinivasan et al., 2002). Research has indicated that reduced HRV is associated with predispositions to various physical and psychological illnesses and considered to be a predictor of all-cause mortality (Thayer and Lane, 2000). Also, reduced HRV is associated with reduced attentional control, poor emotional regulation, decreased response to various stimuli, and antisocial behavior in adolescents (Mezzacappa et al., 1997; Friedman, 2007; Thayer et al., 2000). Patients who experienced severe panic attacked frequently exhibited reduced HRV in various situations (e.g., quiet rest, shock avoidance, face immersion, isoproterenol infusions; Friedman et al., 1993; Yeragani et al., 1995). High trait anxiety was associated with autonomic dysreguation indexed by reduced HRV (Miu et al., 2009). Thus, reduced HRV may play a critical role in the development of anxiety disorders and can be considered as an important endophenotype of anxiety (Friedman, 2007; Crişan et al., 2009). In a recent review of the literature, Friedman (2007) provided a number of studies that linked reduced HRV with a variety of anxiety disorders over the past 15 years and provided the summary of the Neurovisceral Integration model of anxiety.

5.1 The Neurovisceral Integration Model of anxiety

Several researchers have identified neural networks in the central nervous system associated with autonomic, emotional, and cognitive self-regulatory responses, one of which is the central autonomic network (CAN; Benarroch, 1993; Thayer and Lane, 2000; 2002). The structures of the CAN include the anterior cingulate, insula, ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the

hypothalamus, the periaquaductual gray matter, the parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguous, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field (for reviews, Ellis and Thayer, 2010; Thayer and Lane, 2002). Reciprocally interconnected components in the CAN allow information to flow in both top-down and bottom-up fashions (Theyer and Lane, 2000, 2002). Also, these components are loosely connected so that it is possible to recruit additional structures when it is necessary to make specific behavioral adaptations (Thayer and Lane, 2000, 2002).

In the CAN, the prefrontal cortical structures—including the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC)—modulates cardiovascular, autonomic, and endocrine responses by exerting tonic inhibitory control on subcortical structures, such as the central nucleus of the amygdala (Thayer and Lane, 2000; Thayer et al., 2009). In emotionally stressful and threatening situations, sympathoexcitatory subcortical circuits are activated to produce the fight or flight response (Thayer and Lane, 2000; Thayer and Seigle, 2002). However, the constant activation of sympathoexcitatory subcortical activity is not suitable for many other situations and will eventually wear and tear the system down. Therefore, sympathoexcitatory subcortical activity has to be controlled, and research indicated that the PFC—typically associated with governing higher cognitive functions—is involved in regulating activity in sympathoexcitatory subcortical circuits (Thayer et al., 2009). In emotionally stressful situations, the prefrontal cortex disinhibits its inhibitory control over sympathoexcitatory subcortical circuits and lets subcortical neural structures such as the amygdala make autonomic and prepotent responses to situations (Thayer et al., 2009). However, when identifying certain safety signals, the PFC exerts its inhibitory control over sympathoexcitatory subcortical circuits and makes responses that are appropriate for contexts in which the signals occur. Therefore, the inhibitory cortical-subcortical circuit is critical for self-regulation (Thayer and Lane, 2000; 2002). On the other hand, the breakdown of the inhibitory mechanism can result in the constant activation of sympathoexcitatory subcortical circuits, which may lead to emotional, attentional, and autonomic dysreguation and the emergence of perseverative behavior such as worry. Neurochemically, tonic inhibitory control is achieved by γ-aminobutyric acid (GABA) activity within the NTS and reduced GABA activity has been also associated with anxiety, perseverative cognition and poor habituation (Malizia et al., 1998; Friedman, 2007; Thayer and Lane, 2000).

The complex neutral circuits link the inhibitory cortical and subcortical pathways with the heart via the vagus nerve (for reviews, see Benarroch, 1993; Ellis & Thayer, 2010; Thayer et al., 2009). High vagally-mediated HRV indicates an exertion of good cognitive, emotional and physiological self-regulation, which is associated with highly integrated cortical-subcortical circuits (Thayer et al., 2009). In contrast, low HRV is associated with poor regulatory systems resulting from the lack of prefrontal regulation over subcortical activity, which is behaviorally manifested through hypervigilance, the failure to habituate to novel, nonthreatening stimuli, and perseverative behavior such as worry (Friedman, 2007; Thayer et al., 2009).

There exists the relationship between serotonergic activity and HRV. HRV is positively related to serotonin turnover (DePetrillo et al., 1999). Individuals carrying *s* allele of serotonin transporter gene showed reduced HRV compared to *l*-homozygotes (Crişan et al., 2009). Lower levels of serotonin induced by tryptophan depletion were associated with reduced HRV in remitted depressed patients (Booij et al., 2005). Thayer and Ruiz-Padial (2006) suggested that reduced HRV may also indicate the altered coupling or breakdown of the connectivity between the PFC and the amygdala typically exhibited in individuals

carrying *s* allele (Heinz et al., 2005; Pezawas et al., 2005). Increased vagally-mediated HRV was observed after SSRI treatment in panic patients (Tucker et al., 1997) and PTSD (Cohen et al., 2000).

6. Conclusion

In this chapter, we presented potential psychophysiological markers that have been studied in anxiety research. A weak LDAEP may indicate dysfunctional serotonergic activity associated with patients with anxiety disorders. Patients with different subtypes of anxiety disorders may be associated with distinctive LDAEPs and that the LDAEP may serve as a predictor of SSRI treatment outcome in patients with GAD. Also, other ERP components (e.g., P1, P2, N300, P3b, EPN, LPP and ERN) have been useful in studying attentional biases favoring threat-relevant stimuli in highly anxious individuals. Patients with anxiety disorders typically show reduced HRV—indicating autonomic dysfunction caused by elevated sympathetic and reduced vagal cardiac control (Friedman, 2007). Accumulated evidence suggests that reduced HRV—linked with anxiety disorders—may contribute to poor emotional and cognitive self-regulation, the failure of inhibition at multiple levels and perseverative cognition such as worry (Friedman, 2007).

The genetic, cognitive, and psychophysiological characteristics may interact with each other and with other environmental factors such as stress to produce or exacerbate different symptoms in anxiety disorders. Future work may benefit from integrating these markers and exploring the relationships with genetic predispositions to the psychopathology. Of clinical importance is whether these potential psychophysiological markers may play a role in predicting the efficacy of psychological and medical treatments, which is yet to be determined.

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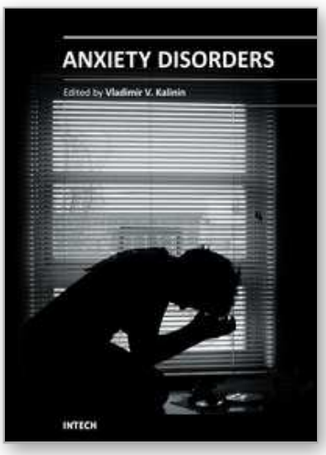

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During the last 2-3 decades drastic research progress in anxiety issues has been achieved. It concerns mostly the study of different subtypes of anxiety and their treatment. Nevertheless, the data on anxiety pathogenesis is less elaborated, although here a multidimensional approach exists. It includes neurochemistry, pathophysiology, endocrinology and psychopharmacology. Again, we are able to recognize the multifarious sense of anxiety, and the present collective monograph composed of 16 separate chapters depicting the different aspects of anxiety. Moreover, a great part of book includes chapters on neurochemistry, physiology and pharmacology of anxiety. The novel data on psychopathology and clinical signs of anxiety and its relationship with other psychopathological phenomena is also presented. The current monograph may represent an interest and be of practical use not only for clinicians but for a broad range of specialists, including biochemists, physiologists, pharmacologists and specialists in veterinary.

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