REVIEW ARTICLE

Electroencephalography and panic disorder

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Submitted: 2013-09-06 Accepted: 2013-12-12 Published online: 2014-07-28

Key words: **electroencephalogram; panic disorder; QEEG; LORETA; frontal asymmetry; polysomnography**

Act Nerv Super Rediviva 2014; **56**(1–2): 3–8 ANSR561214R01

Abstract

INTRODUCTION: Panic disorder is frequent psychiatric disorder characterized by sudden and unexpected onset of a panic attack, characterized by terror or impending doom, and associated with many somatic symptoms.
METHODS: A literature review was performed using the National Library of Medicine PubMed database and Web of Science, including all resources within the period 1991–2011, additional references was found through bibliography reviews of relevant articles.
MAIN FINDINGS: Studies of patient with panic disorder regularly show frontal asymmetry. Changes in absolute power in beta 1 (12,5–16Hz) and beta 2 (16.5–21.5 Hz) frequency bands in lateral prefrontal cortex were found when using LORETA.
CONCLUSIONS: Although there are many studies monitoring changes in EEG of patients with panic disorder, there are no specific findings for panic.

Introduction

Panic disorder is characterized by the occurrence of spontaneous panic attacks, resulting in persistent worry about having another attack and avoidance of situations in which an attack is felt likely or feared. Spontaneous panic attacks are often interspersed with situationally predisposed panic attacks involving supermarkets, subways, public transport, crowds, bridges etc. Panic attacks are the central feature of panic disorder. Panic attacks usually last from 5 to 20 minutes and rarely takes one hour. Panic attacks are accompanied by intense autonomous, especially cardiovascular and respiratory, reaction. Several groups of associated symptoms, mostly physical, are experienced: palpitations, chest pain or discomfort, dizziness or unsteady feelings, dyspnea, trembling and shaking, choking or smothering, sweating, paraesthesias, hot and cold flashes, feelings of unreality (derealization, depersonalization), and fear of dying, going crazy, or losing control of oneself (Hollander and Simeon 2008). It is clear that most of the physical symptoms of a panic represent massive hyperstimulation of the autonomous nervous system. A lot of patients continue to feel agitated and fatigued for several hours after the main attack has finished.

Methods

A literature review was performed using the National Library of Medicine PubMed database and Web of Science, including all resources within the period 1991–2011, additional references was found through bibliography reviews of relevant articles.

Electroencephalogram and anxiety

The EEG (electroencephalogram) is the assessment of regional cerebral cortical electrical activity. The EEG is a recording of brain wave electrical activity from the surface of the scalp. Deep structures, such as the amygdala or the hippocampus, do not contribute to the EEG as much as cortical structures (Grillon 2008). The EEG is usually used in psychiatry to rule out non-psychiatric disease, such as seizure disorders of delirium, as a cause of psychiatric symptoms. Because anxiety has been considered a state of hyperarousal, the EEG has a prominent place in anxiety studies. It is inexpensive and non-invasive functional tool with excellent temporal resolution that cannot be matched by any other techniques. The main disadvantage of EEG is poor spatial resolution.

Power spectral analyses of EEG can be performed to provide and objective quantification of the EEG signal. After digitalization, the raw signal is submitted to a fast Fourier transform that computes power for the traditional EEG frequency bands, delta (0.5 to 4.0 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), and beta (13 to 30 Hz) (Grillon 2008).

Computer-transformed EEG data is the creation of color-coded two-dimensional maps of summaries of the EEG data.

EEG is an excellent tool for the assessment of CNS arousal. The general observation is that greater cerebral arousal is associated with reduced alpha and increased beta activity power in the EEG (Grillon 2008). This EEG pattern is reliably observed during fear and anxiety.

An important development in recent years is the assessment of asymmetrical patterns of EEG activity. Differential hemispherical activation is associated with basic emotions. Activation commonly refers to a reduction in alpha power. It is calculated as the difference in alpha power over homologous sites of the two hemispheres. Anterior asymmetry is an index of responses to positive and negative emotions, including fear and anxiety (Grillon 2008). Because fear can lead to active withdrawal and behavioural inhibition, it is believed that right anterior activation is a marker of aversive states.

Neural circuitry of panic disorder

There are many neuroanatomical hypothesis of panic disorder. Advantageous way to study structures, that take part in panic reaction, is using animal models. But analogy of panic attacks to animal fear is imperfect and further more animals cannot tell us about the experience of anxiety. Gorman *et al* (1989) presented their hypothesis, where the sensory stimulus goes through anterior part of thalamus to lateral nucleus of amygdala and than to central nucleus of amygdala. Central nucleus of amygdala plays dominant role in regulation of autonomous and behavioral response. Efferent neurons from central amygdalar nucleus influence many other structures: lateral hypothalamus (responsible for activation of sympathetic part of autonomic nervous system), paraventricular nucleus of hypothalamus (control releasing of corticosteroids), locus coeruleus (responsible for norepinephrine release), parabrachial plexus (regulating breathing frequency), periaqueductal gray matter (responsible for behavioural response). The amygdala also receives information from the brain stem, sensoric part of thalamus a cortical regions. Important are also interconnections between amygdala, prefrontal cortex, insula, sensory thalamus and primary somatosensory cortex (Gorman *et al* 2004)

Extracranial measurements of EEG are generated by cortical pyramidal neurons undergoing post-synaptic potentials. These neurons are oriented perpendicular to the cortical surface. Using statistical analysis and computer imaging it is possible to measure also coherence and concordance of neurons (qEEG) or make 3D model of neural activity in cortex (LORETA, Low Resolution Brain Electromagnetic Tomography).

As mentioned above Gorman *et al* (1989) were first authors who proposed a neuroanatomical model specific of panic disorder and also logically accounted for various clinical features of panic disorder. The model covered clinical phenomena of unexpected panic attacks (discharge of brain stem nuclei), anticipatory anxiety (limbic activation and kindling) and avoidance (medial prefrontal cortical activation). A seminal component of the neuroanatomical hypothesis integrated observations that both pharmacological and cognitive-behavioural treatment could be effective in treating panic disorder. Medication were hypothesized to work through stabilization of brainstem nuclei and cognitive therapy through modification of the catastrophic cognitions (cortical processing), which presumably occurred at the level of the prefrontal cortex and hippocampus. Although it has been hypothesized that cognitive-behavioral therapy exerts its effect in panic disorder by behavioral desensitization of hippocampal-mediated contextual conditioning, or by cognitive techniques of strengthening the medial prefrontal cortex inhibition of amygdala (Gorman et al, 2000), the relevant empirical studies are at the beginning. In the past fifteen years since neuroanatomical hypothesis was proposed our knowledge has advanced and Gorman's hypothesis was revisited and refined (Grove *et al* 1997, Goddard and Charney 1997, Coplan and Lydiard 1998, Gorman *et al* 2000).

The goal of Prasko *et al* study (2004) was to identify brain structures in patients with panic disorder (PD) that show changes in ^{18}FDG PET during the treatment with cognitive behavioural therapy (CBT) or antidepressants. Twelve patients suffering from panic disorder were studied with [^{18}F]-2-fluoro-deoxyglucose positron emission tomography (^{18}FDG PET) scanning during resting state (condition of random episodic silent thinking, REST). After PET examination patients

were randomly assigned to either cognitive behavioural treatment group (6 patients) or antidepressants treatment group (6 patients). There are increases of ^{18}FDG uptake mostly in the left hemisphere in prefrontal, temporoparietal and occipital regions and in the right hemisphere in posterior cingulum. The decreases were prominent in the left hemisphere in frontal regions, and in the right hemisphere in frontal, temporal and parietal regions. They did not find any changes in ^{18}FDG uptake subcortically. Changes in brain metabolism (^{18}FDG uptake) after the treatment either with CBT or with antidepressants were similar in a number of brain regions, with considerable right-left difference. This is in concordance with asymmetry of brain activity noted in patients with PD according to PET (and SPECT) studies.

With regard to the general fear neurocircuitry described above, potential deficits in frontal cortical processing could lead to the misinterpretation of body sensory information known to be a hallmark of panic disorder, resulting in inappropriate activation of the fear network via misguided excitatory input to the amygdala. It seems likely that there is a deficit in the coordination and processing of top-down (cortical) and/or bottom-up (brain stem) sensory information, activating what may be a hyperresponsive amygdala. Both CBT and SSRIs help with coordination of these processing. We speculated that CBT improve processing of top-down and SSRIs of bottom-up.

Quantitative eeg correlates of panic disorder

Quantitative electroencephalography is a laboratory method that allows measurement of brain activity. It is based on principal of computer-assisted imaging and statistical analysis. Compare with other methods studying functional activity of the brain has qEEG many advantages (no ionizing radiation, milisecond time domain characteristic of procesing neural information, do not study changes of hemodynamic processes but neuronal activity itself). qEEG is just a complement. Each raw EEG should be at first read by qualified electroencephalographer, qEEG may help to identify some abnormalities that were overlooked. There are evidences that attest applicability for disorders of childhood, mood disorders, dementia, anxiety, panic and schizophrenia. Unfortunately although exist many studies showing significant statistical differences on measure between groups of patients, qEEG do not allow to classify individuals into their respective groups with any useful degree of accuracy. Possibility how to classify patients into the concrete diagnostic and prognostic group is using combination of unvaried measurement (symmetry, coherence, absolute or relative power, phase and spectral ratios) and multivariate measures. It is very likely, that when being aware of the limits, qEEG could be used for prediction of response to pharmacological treatment and clinical course of the disease.

Quantitative analysis of electroencephalographic (EEG) signals recorded from multiple scalp sites was used to compare panic disorder patients (n=34) with normal healthy controls (Knott *et al* 1996). Patients exhibited greater overall absolute power in the delta, theta, and alpha frequency bands and less relative power in the beta band. Discriminant analysis of absolute power indices correctly classified 75% of the subjects, while relative power indices exhibited a 69% correct-classification rate. Absolute delta and theta power were positively correlated with observer ratings of anxiety, while relative beta power was related to self-ratings of anxiety.

Based on previous reports of relaxation-induced panic attacks in panic disorder patients, quantitative electroencephalographic (EEG) profiles and subjective anxiety ratings were assessed in panic disorder patients and normal controls listening to neutral and relaxation audiotapes (Knott *et al* 1997). Regardless of tape condition, patients exhibited a greater frequency and severity of panic-related symptoms. Relaxation failed to alter panic-related symptom ratings or anxiety ratings in patients and controls. Theta and alpha increments were observed during relaxation, but only in normal controls. High frequency beta activity was less evident in patients, regardless of tape conditions.

Using qEEG Wiedemann *et al* (1999) describes an asymmetry in frontal alfa activity in patients with panic disorder. Panic patients show lower interhemispheral functional connectivity in bilateral frontal areas (Hanaoka 2005). Likewise PET studies usually detect left-right asymmetry in hippocampal region (hyperactivity in the right side), parahippocampal region and low prefrontal cortex activity (Reiman et al., 1986, De Cristofaro *et al* 1993, Bisaga *et al* 1998). These findings confirm PET study of Prasko *et al* (2004), in which the treatment by SSRI and CBT leads to right-left changes in ^{18}FDG PET in prefrontal and temporal lobes (Prasko *et al* 2004).

The aim of our study was to identify functional changes in patients with panic disorder drug naive or treated by SSRI (Sos *et al* 2007; Prasko *et al* 2007). 33 patients with panic with or without medication were involved. Control group consisted of 33 healthy volunteers. We observed inter an intra hemispheral koherence between 19 electrodes. When comparing medication naive patients with panic and control group we found lower inter-hemispheral frontal coherence and intra-hemispheral prefronto-frontolateral coherence. If we compared patients treated by SSRI and healthy controls, we found lower inter-hemispheral frontal coherence, interhemispheral frontolateral coherence, intra-hemispheral fronto-temporal coherence on the right and left side and intra-hemispheral prefronto-frontolateral coherence bilateral.

LORETA

sLORETA is a widely used inverse solution technique that estimates the intracranial distribution of electrical activity in the cortex based on a head model (Pascual-Marqui 2002). ICA (independent component analysis) is a data-driven (i.e. model-free) technique widely used to decompose the multivariate EEG signal into sources as independent as possible (Congedo *et al* 2008; Onton *et al* 2006). The assumption of EEG source independence is consistent with the fact that the cortex is organized into functionally distinct areas and that neighbouring and highly connected regions (e.g. via corpus callosum) are likely to fire in synchrony (Onton *et al* 2006). Physical and statistical principles supporting the use of decomposition methods based on second-order statistics for EEG data have been reviewed in Congedo *et al* (2008). Koprivova *et al* (2009) studied 14 patients with panic disorder; results were compared with group of 14 healthy controls. EEG was measured in rest state with closed eyes, using standard 10–20 montage with 19 electrodes. Patients with panic disorder showed higher absolute power in beta1 (12.5–16 Hz) and beta2 (16.5–21.5 Hz) frequency bands in lateral prefrontal cortex. There was significant predominance in right hemisphere.

Gerez *et al* (2011) presented case study of two patients with panic disorder that were partly responsive to first line treatment. They were examinated by EEG. Patients developed panic symptoms in response to bag-hyperventilaton and LORETA Z-score source correlation analysis showed increased current source densities at the right amygdala in both subjects during the induced panic symptoms.

Anticipatory anxiety

Patients with panic disorder typically exhibit increased baseline physiological arousal in laboratory setting; they exhibit abnormal respiratory measures, increased heart rate, heightened EMG activity, and enhanced levels of skin conductance (Lader 1967; Leyton *et al* 1996). It is unknown whether increased physiological activity is a persistent trait marker of chronic arousal or a transient change associated with laboratory context. Physiological features of elevated arousal have been found in some studies but not in others (except for respiratory instability) (Stones *et al* 1999, Parente *et al* 2005, Garcia-Leal *et al* 2005).

Startle reflex in panic disorder and possible relation to EEG

Regardless of whether physiological arousal is or is not a chronic feature of panic disorder, there is substantial evidence showing that patients with panic disorder are overly sensitive to challenging or stressful context. The startle reflex is exaggerated in threatening contexts in which they anticipate future exposure to unpleasant shocks (Grillo, 2002). The startle response is defined as "an immediate reflex response to sudden, intense stimulation" measured by the eye-blink reflex component of the startle response (Landis & Hunt 1939). The eye-blink component of the acoustic startle response was measured using an electromyographic (EMG) startle system. Some studies have reported that the acoustic startle reflex, a rapid escape response elicited by a sudden and intense auditory stimulus, is increased in patients with anxiety disorders (Koch 1999) and in healthy subjects viewing aversive pictures (Lang *et al* 1990). One study in medicated patients with panic disorder showed that prepulse inhibition (PPI) is reduced (Ludewig *et al* 2002). Startle habituation is deficient in patients with panic disorder (Ludewig *et al* 2005). Unmedicated patients with PD exhibited increased startle reactivity, reduced habituation and significantly reduced prepulse inhibition (PPI) in the 30-ms, 60-ms, 120-ms and 240-ms prepulse conditions. Furthermore, in unmedicated patients with panic disorder, increased startle response and decreased habituation were correlated significantly with higher cognitive dysfunction scores.

Potentiated startle may reflect activation of a negative emotional state. This view is supported by measures of basic dimensions of emotion provided by EEG studies of anterior brain asymmetry (Davidson 1998). Patients with panic disorder exhibit EEG asymmetry with a pattern of right anterior activation (i.e. avoidance-withdrawal response)(Grillon 2008). This laterality pattern is present only before and during exposure to anxiety and panic-relevant situations.

Sleep polysomnography in panic disorder

The physiology of alteration of sleep function in anxiety disorders is still a relatively young field of research. Sleep is very sensitive to stress and emotional distress. Sleep disturbance is a symptom found in a variety of anxiety disorders. Patients suffering with panic disorder often complain of insomnia (Sheehan *et al* 1980). Panic disorder does not appear to produce the typical abnormalities seen in major depression such as shortened REM latency. In fact, there are no consistent specific differences between the sleep parameters of patients with anxiety disorder. Mellman and Uhde (1990) found that 67% of patients with panic disorder report insomnia as a regular and pervasive problem. Polysomnographic research with patients with panic disorder showed increased sleep latency, decreased sleep time and efficacy, as is seen in patients with GAD (Cervena *et al* 2005; Mellman & Uhde 1989). More alertness should affect the patient by generating more problems in resting and falling asleep. In the literature, there is disagreement among various authors regarding the severity of sleep disturbances in patients with panic disorder (Cervena *et al* 2005). But most of the reports

are based on subjective statements of the patients and unfortunately, the results of polysomnographic studies in these patients are inconsistent. Thus Uhde (1994) reports that these patients have remarkably normal sleep. Strambi *et al* (1996) reported no difference between healthy controls and patients with panic disorder for sleep induction and maintenance parameters, but the percentage of non-REM sleep stage 1 was increased in patients when compared with controls. Further, polysomnographic studies demonstrated a decrease of sleep efficiency, total sleep time and amount of non-REM sleep stage 4 in patients with panic disorder compared with controls (Saletu-Zyhlarz *et al* 2000; Sloan *et al* 1999; Arriaga *et al* 1996; Stein *et al* 1993). Cervena *et al* (2004) studied polysomnographic sleep patterns in 20 patients with panic disorder before and after the standard therapy (cognitive behavioral therapy in combination with SSRIs). The subjective total sleep time after therapy was longer and the sleep latency was shorter after treatment, but the differences were not statistically significant. In contrast, the sleep quality score showed a small but significant improvement after treatment. Pretreatment sleep efficiency obtained by polysomnography was slightly subnormal, and the sleep stage 1 percentage was rater high, compared with normal values previously published for a healthy population of this age. This finding is in agreement with the patient´s reports of impaired sleep quality. Following therapy, sleep stage 1 was shortened and the sleep stage 4 was prolonged, both in absolute time units and in percentage. The sleep onset latency, sleep efficiency and total sleep time did not show significant changes. The main outcome was that a significant improvement of the panic disorder is not accompanied by a corresponding improvement of major sleep variables.

Nocturnal panic attacks

Nocturnal panic attacks were recorded only during synchronic sleep (non-REM period). Panic attacks typically occur at the onset of sleep or during stage 2-stage to 3-stage transition (Sloan *et al* 1999). It means that panic attack is no a consequence of the dream or nightmare (Lesser *et al* 1985).

Panic and epilepsy

There was described higher incidence of epileptogenic EEG abnormities in patients with panic disorder (Hughes 1996), that occurred 4 times more frequent than in patients with depression. When using brain mapping (BEAM) there were found also abnormities in EEG in temporal regions. Other autors though do not confirm these finding of epiteptiform abnormities in patients with panic. Stein and Uhde (1989) find EEG abnormities just in 14% of patients. These findings were non specific and do not confirm epilepsy. Lepola *et al* (1990) studied 54 patients with panic using extensive EEG recording and CT. 28% of these patients were treated for temporal epilepsy or other neurological disease. Majority of the patients had normal EEG findings. Only in 23% of the patients were found the abnormity in slow waves. Unlike Jabourian *et al* (1992) found during 24 hours EEG monitoring of 150 patients with panic attacks abnormities in 63% of patients, where about ¾ had epileptiform abnormities.

Conclusions

Although there is an anatomical hypothesis of the panic disorder, there are no specific EEG findings in patients with panic. Most of the studies are concentrated on searching for EEG abnormities in frontal lobes using qEEG, the very frequent finding is frontal asymmetry in alfa activity. LORETA study showed changes in beta1 and beta2 activity in prefrontal cortex in patients with panic disorder. Future research should be done.

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