

Review

# Different patterns of freezing behavior organized in the periaqueductal gray of rats: Association with different types of anxiety

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## Abstract

Freezing defined as the complete absence of body movements is a normal response of animals to unavoidable fear stimuli. The present review presents a series of evidence relating different defensive patterns with specific anxiety disorders. There are at least four different kinds of freezing with specific neural substrates. The immobility induced by stimulation of the ventral column of the periaqueductal gray (vPAG) has been considered a quiescence characteristic of the recovery component of defense–recuperative processes. There is an isomorphism between freezing response to contextual stimuli paired with electrical shocks and generalized anxiety disorder. Besides, two types of freezing emerge with the electrical stimulation of the dorsal aspects of the periaqueductal gray (dPAG): the dPAG-evoked freezing and the dPAG post-stimulation freezing. Evidence is presented in support of the hypothesis that whereas dPAG-evoked freezing would serve as a model of panic attacks, the dPAG post-stimulation freezing appears to be a model of panic disorder. It is also proposed that conditioned freezing plus dPAG electrical stimulation might also mimic panic disorder with agoraphobia. A model of serotonergic modulation through on- and off-cells of the defense reaction generated in the dPAG is also presented. The understanding of how the periaqueductal gray generates and elaborates different types of freezing is of relevance for our better knowledge of distinct types of anxiety such as panic disorder or generalized anxiety disorder.

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**Keywords:** Animal models of anxiety; Freezing behavior; Generalized anxiety disorder; Panic attacks; Panic disorder without agoraphobia; Panic disorder with agoraphobia

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## 1. Introduction

Anxiety disorders are among the most prevalent mental health problems across the individual life span. Animal modeling has been crucial in dissecting pathophysiological mechanisms and designing more effective therapies. A difficulty in modeling psychiatric disorders has been limited information about their origin and underlying neural mechanisms. Although anxiety research is no different from any other psychiatric disease this is likely in better position to be modeled than any other psychiatric disease, given that the circuitry is well-understood and maintained in many ways between humans and rodents [48]. Based on these animal models, experimental studies suggest that different defensive patterns, which involve well-defined neural circuitries, might be associated with specific anxiety disorders [18,40,41]. Thus, it has been possible to find correlation between these disorders and defensive responses that animals present when facing with dangerous situations. The purpose of the present article is to review some of these studies, which point out that the neural systems underlying distinct patterns of defensive freezing behavior might be associated with different anxiety disorders.

The first section of this review makes an appraisal of how anxiety disorders are currently classified according to nosological categories. The second and third sections discuss how different animal defensive behaviors and their respective neural circuitries might be related to generalized anxiety disorder (GAD) and panic disorder (PD). The fourth section describes a series of results showing that there are at least four types of freezing behavior associated with different patterns of defensive behaviors. A hypothesis is also discussed that proposes that the dorsal periaqueductal gray (dPAG)-evoked freezing is a model of panic attacks, whereas the dPAG post-stimulation freezing is a model of PD. It is also suggested that freezing behavior triggered by contextual cues previously associated with dPAG electrical stimulation might be a model of PD with agoraphobia. The fifth section presents pharmacological results obtained with animal models of anxiety designed to examine the chemical mediation of the several types of freezing associated with the PAG. The last section summarizes the reviewed evidence and states the conclusions.

## 2. Historical background

To make an integrative appraisal of the neural circuits proposed to underlie the different types of anxiety, we start with important changes that took place in the classification of anxiety disorders during the 1970s. During that time, most psychiatrists viewed anxiety as a single construct that ranged in intensity from normal to pathological or neurotic levels. Accordingly, anxiolytic drugs were the main prescription to treat this single disorder. A major shift to this view occurred in the beginning of 1980, with the publication of the 3rd edition of the American Psychiatric Classification (DSM-III) [1]. Some years later, the revised version of this classification established PD as an independent nosological category [2]. This new classification delineated distinct nosological entities, namely, GAD, PD, agoraphobia, simple phobias, social phobia, post-traumatic stress

disorder, and obsessive–compulsive disorder. In general, the same proposal remained in the DSM-IV classification, being also adopted by the ICD-10 classification of the World Health Organization of 1992 [85].

Among the diverse types of anxiety, GAD and PD, with and without agoraphobia, are the nosological entities focused in this review. GAD is diagnosed when a patient worries excessively about a variety of everyday problems. The worry construct has received considerable attention since the diagnostic of GAD shifted from a residual category in the DSM-III [1] to an independent anxiety disorder type in the 4th edition of the DSM [3]. According to the DSM-IV, worry is generally associated with several symptoms such as muscle tension, feeling tired and restless, concentration difficulties and irritability. These worries are generally associated with impairments in academic, social, or personal functioning and related to multiple domains or activities. In order to be considered a pathological feature of GAD, worry must occur (more days than not) for a period of at least 6 months.

Panic attacks are sudden surges of intense fear or terror, desire of fleeing and feeling of imminent death or losing control. These subjective symptoms are accompanied by major neurovegetative changes, such as palpitation, hypertension, difficulty in deep breathing, sweating, urge to void the bladder and increased peristalsis. Panic disorder, with or without agoraphobia, is a psychiatric illness that can have a chronic course and be associated with significant morbidity. PD is characterized by recurrent panic attacks, either unexpected or associated with particular situations, and persistent concern about having another attack or worry about the implications and consequences of the panic attacks. This leads to worry about the next attack or anticipatory anxiety, and avoidance of places where a panic attack would be embarrassing [40,41].

Panic disorder, with agoraphobia, may lead to the loss or disruption of interpersonal relationships, especially as individuals struggle with the impairment or loss of their social role and the issue of responsibility for symptoms. Patients with PD frequently fear that panic attacks represent catastrophic medical events despite the evaluation indicating the absence of a medical problem. Patients also fear that the attack is an indicator of a life-threatening illness. In addition, they may live in a nearly constant state of apprehension and may be severely limited by phobic avoidance. Patients with PD with agoraphobia experience anxiety and avoidance of places or situations where escape or help may be unavailable if they have panic symptoms. Typical situations eliciting agoraphobia include traveling on buses, subways, or other public transportation and being on bridges, in tunnels, or far from home. Many patients who develop agoraphobia find that situational attacks become more common than unexpected attacks. Some patients might experience severe attacks so that they might take extreme actions such as quitting a job to avoid the possibility a new attack. Others may become so anxious that they eventually avoid most activities outside their homes [3].

Panic attacks are among the most prominent symptoms in PD, but they might occur in other anxiety disorders. Panic attacks are discrete periods of intense fear or discomfort, accompanied by at least 4 of the 13 somatic or cognitive symptoms defined

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