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Review

Updating freeze: Aligning animal and human research

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ABSTRACT

Freezing is widely used as the main outcome measure for fear in animal studies. Freezing is also getting attention more frequently in human stress research, as it is considered to play an important role in the development of psychopathology. Human models on defense behavior are largely based on animal models. Unfortunately, direct translations between animal and human studies are hampered by differences in definitions and methods. The present review therefore aims to clarify the conceptualization of freezing. Neurophysiological and neuroanatomical correlates are discussed and a translational model is proposed. We review the upcoming research on freezing in humans that aims to match animal studies by using physiological indicators of freezing (bradycardia and objective reduction in movement). Finally, we set the agenda for future research in order to optimize mutual animal–human translations and stimulate consistency and systematization in future empirical research on the freezing phenomenon.

Contents

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1. Introduction

Freezing behavior has been used as a main outcome measure for fear for decades in animal studies. It has been described as a highly heritable fear response that is relatively stable over time (De Castro Gomes and Landeira-Fernandez, 2008; Rogers et al., 2008). Human research has recently also recognized the importance of freezing as part of the human defense cascade (Hagenaars et al., 2012; Hermans et al., 2012; Lang et al., 1997, 2000; Marx et al., 2008; Mobbs et al., 2009). Knowledge about freezing in humans is of great importance, as freezing has been linked to the development of psychopathology. That is, freezing is considered to play a role in the etiology of threat-related disorders such as posttraumatic stress disorder (PTSD; e.g., Hagenaars et al., 2008; Rizvi et al., 2008) and social phobia (Buss et al., 2004).

Human defense-models are largely based on findings from animal studies (e.g., Lang et al., 1997). Unfortunately, definitions, instruments, and methods of animal and human studies vary, thereby hampering comparisons and mutual knowledge transfer, as well as empirical testing of animal models in humans. Also, although numerous animal studies have used freezing as an index of fear, research on the nature and phenomenology of freezing responses themselves is scarcer.

We therefore aim to clarify the conceptualization of freezing in order to optimize mutual translations. Several neurophysiological correlates are discussed and human research is reviewed that used the main objective indicator for freezing, similar to animal studies: bodily immobility. Finally, we aim to define gaps in our knowledge and point out directions for future research in order to align animal and human approaches and stimulate a systematic investigation of freezing behavior.

2. Definition and boundaries

2.1. Definition and main characteristics

In the present review, we use the freezing definition that was originally referred to as crouching (Blanchard et al., 1968) and is widely used in animal research: a complete absence of movement, except for that associated with respiration, and a tense body posture (e.g., Fanselow, 1984; Kalin and Shelton, 1989). Note that a tense body posture implies increased muscle tonus. We extend this definition with a third characteristic: reduced heart rate (bradycardia). Bradycardia was found to be consistently associated with freezing in several well-controlled animal studies (Vianna and Carrive, 2005; Walker and Carrive, 2003), and has been widely recognized as an important indicator of freezing in humans (Lang et al., 2000; Marx et al., 2008). Reduced (ultrasonic) vocalization has also been reported during freezing (Jelen et al., 2003; Takahashi and Rubin, 1993). Note that in rats decreases were found for freezing associated with fear or acute threat, whereas increases were found for freezing associated with anxiety or potential threat. Also note that vocalization is not a fruitful indicator of freezing in human experiments, as in most setups participants are expected not to talk during assessments.

Freezing is associated with a typical physiological response. When a stimulus or a situation is perceived as threatening, the brain activates many neuronal circuits to adapt to the demand, the most well-known being the autonomic nervous system and the glucocorticoid stress system (the latter is discussed at the end of Section 3.2). During freezing the two opposing parts of the autonomic nervous system, the sympathetic and parasympathetic nervous systems, become activated (Iwata et al., 1987). Physiological parameters of freezing therefore consist of both sympathetic and parasympathetic features, which vary depending on which system is dominant at a certain point in time. Sympathetic nervous system activity is expressed by increased arousal and physical symptoms that support the freezing response: increased arterial pressure (Carrive, 2000), increased muscle tonus (Azevedo et al., 2005), reduced (followed by a slower increase in) body temperature (Vianna and Carrive, 2005), and a pronounced reduction in cutaneous temperature in the extremities (Vianna and Carrive, 2005), hyper-responsiveness and potentiated startle (Fendt and Fanselow, 1999), and pain suppression (Finn et al., 2006). The sympathetic nervous system would lead to heart rate acceleration. However, involvement of the parasympathetic nervous system during freezing causes heart rate deceleration (Hunt et al., 1998; Schenberg et al., 1993), or reduced heart rate acceleration (Vianna and Carrive, 2005), as well as changes in vocalization (e.g., Takahashi and Rubin, 1993).

2.2. Freezing as a defense response

Freezing is seen in many species as part of a repertoire of species-specific defense responses. It is a universal fear response, used as an indicator of conditioned fear in learning paradigms (i.e., when the animal associates a previously neutral stimulus with harm, thus in reaction to anticipated danger), and also occurs as an unconditioned fear response (i.e., in reaction to current threat; Rosen, 2004). Freezing is considered to have several evolutionary advantages such as avoiding detection by the predator (Whishaw and Dringenberg, 1991), optimizing perceptual and attentional processes (Kapp et al., 1992; Lang et al., 2000), and preparation for rapid escape or defensive fighting (Butler et al., 2007; Griebel et al., 1996; Kalin, 1993).

Animals select appropriate defense responses on the basis of innate and learned response options. Whether or not they respond with freezing depends on several variables. First, defense responses are considered to be species-specific (Bolles, 1970), with some species having an innate preference for freezing and others that hardly ever freeze. Obviously, this hampers the interpretation of findings of studies using different species. Second, between-subject trait characteristics (e.g., behavioral inhibition, trait anxiety) and state factors within the animal (e.g., incubation, age) seem to play a role in the selection of a particular defense response. For example, high trait anxious rats spend more time freezing than low trait anxious rats (Frank et al., 2006). Incubating hens typically show bradycardia, whereas non-incubating hens show tachycardia (Steen et al., 1988) during freezing. Young rats show bodily freezing but do not yet inhibit heart rate acceleration (Hunt et al., 1998). Third, time courses of defense responses vary and animals switch between different defense responses, resulting in constantly changing physiological parameters. Fourth, fear responses (including freezing) may be different for discrete versus contextual stimuli (Carrive, 2000). Fifth, environmental factors (e.g., presence of escape routes, distance from predator) shape defense behavior. With escape routes available, animals will show shorter freezing durations and instead they will flee (Blanchard and Blanchard, 1989). Also, distal threat evokes different defense behavior then proximal threat (Blanchard et al., 2011; Mobbs et al., 2007). Obviously, all these factors affect defense behavior, and should therefore be taken into account when comparing and interpreting research findings.

2.3. Related concepts and boundaries

2.3.1. Fear and anxiety

As described above, freezing is a threat-related defense strategy. It is therefore also closely associated with *fear*. Fear has to be distinguished from another threat-related emotion: *anxiety*. Blanchard and Blanchard (1988) made a clear distinction between