



## Habituation and sensitization of protective reflexes: Dissociation between cardiac defense and eye-blink startle

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### ABSTRACT

We examined the habituation and recovery of two protective reflexes, cardiac defense and eye-blink startle, simultaneously elicited by a white noise of 500 ms as a function of the time interval between stimulus presentations. Participants were 90 volunteers (54 women) randomly distributed into 6 inter-trial interval (ITI) conditions. They all received three presentations of the stimulus with a time interval of 30 min between the first and third noise. The timing of the second noise was manipulated in six steps, using a between-group design, in order to increase the ITI between Trials 1 and 2 and symmetrically decrease the ITI between Trials 2 and 3. Cardiac defense showed fast habituation at the shortest ITI (2.5 min), but reduced habituation and increased recovery at the longest ITI (27.5 min). In contrast, eye-blink startle showed sensitization irrespective of the ITI. This pattern of findings highlights dissociations between protective reflexes when simultaneously examined. The results are discussed in the context of the cascade model of defense reactions.

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### 1. Introduction

Defense reactions are essential mechanisms for survival. They are not only important in traumatic, life-threatening situations (Schauer et al., 2005) but also in everyday life. Thus, protection of the body surface from collision is a daily defense mechanism that requires continuous sensory-motor coordination to avoid potentially dangerous objects (Graziano and Cooke, 2006). Defense reactions are closely linked to fear and anxiety, the typical emotional responses to the presence of danger or threat. Advances in the neurophysiology of fear and anxiety have primarily derived from animal research into defense responses such as freezing, startle and escape-attack behaviours (Davis, 1992; LeDoux, 2000; Blanchard and Blanchard, 1988; Fanselow, 1994).

Defense reactions do not constitute separate entities. Rather, a dynamic sequence or cascade of defense responses, from increased attention to protective actions, seems to take place depending on the type and severity of the danger, its spatial and temporal proximity and the success or failure of the initial responses to cope with it (Gallup, 1977; Marks, 1987; Gray, 1988;

Blanchard and Blanchard, 1988; Fanselow, 1994; Lang et al., 1997a,b; Bracha, 2004; Facchinetti et al., 2006). In non-human mammals, a sequence of four defense responses has been well established as a function of proximity of the danger and availability of escape: *attentive freezing* (when danger is first encountered at a safe distance), *flight* (when danger is approaching and an escape route is available), *fight* (when attack is imminent and no escape route is available), and *tonic immobility* (when a dominant predator has already made direct physical contact with the prey).

Although there is increasing evidence that the same sequence applies to humans (Marx et al., 2008), research on defense reactions has traditionally focused on somatic and autonomic protective reflexes such as motor startle and cardiac defense. This tradition is rooted in the work of Pavlov and Cannon. Pavlov (1927) used the term *defense reflex* to refer to unconditioned responses elicited by noxious stimulation such as hand withdrawal to an electric shock or eye-blink to a puff of air. Cannon (1929) used the term *fight or flight* to refer to a sympathetically mediated cardiovascular response to emergency situations aimed at facilitating adaptive behaviours such as attack or escape. Since then, motor startle and cardiac defense have been extensively studied in both animals and humans (Strauss, 1929; Landis and Hunt, 1939; Bond, 1943; Sokolov, 1963; Graham and Clifton, 1966; Davis, 1984; Turpin, 1986; Graham, 1992; Lang, 1995;

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Ramírez et al., 2005; Vila et al., 2007) and have made a widely recognised contribution to knowledge on the neurophysiology and psychology of fear and stress (Davis, 1992; Koolhaas et al., 1999; LeDoux, 2000; Lang and Davis, 2006; Lissek et al., 2007; Waters et al., 2008).

The eliciting stimuli used in the first descriptions of motor startle and cardiac defense were unexpected loud sounds of a pistol shot just behind the individual's or animal's head (Strauss, 1929; Bond, 1943). Strauss, a German psychiatrist, was one of the first to systematically study the startle reflex in humans, which involved a quick closing of the eyes accompanied by stiffening of the head, dorsal neck, body wall, and limbs, as if to protect from a predator (see Graziano and Cooke, 2006). This response pattern rapidly habituates on repeated stimulus presentations, although some components of the reflex, such as the eye-blink, tend to persist and habituate more slowly. As regards cardiac defense, Bond (1943), a student of Cannon, was the first to describe in cats and dogs a complex response pattern to intense noises (*made by a pistol shot or by hitting a table top with an iron rod several times in less than 2 s*) characterized by an initial heart rate acceleration that lasted for 4–6 s, followed by a sudden fall and then a second acceleration with a more gradual slope reaching its peak between 20 and 40 s. This response pattern also showed habituation with stimulus repetition (faster for the second acceleration), although in separate sessions the response was *remarkably constant and repeatedly demonstrable for the individual* (Bond, 1943, page 89).

Subsequent research on cardiac defense in humans has confirmed Bond's findings and advanced knowledge on many aspects of this response pattern, including individual differences, characteristics of the eliciting stimulus and its physiological and psychological functionality (see Vila et al., 2007 for a review). Nevertheless, although a fundamental issue in the theoretical debate on cardiac reflexes, the rapid habituation of this response has been inadequately investigated (Graham, 1979, 1992). According to Graham's classic model, cardiac defense is differentiated from cardiac startle in the transient/sustained characteristics of the eliciting stimulus and their response habituation rate, among other criteria. Transient high-intensity stimuli are reported to elicit startle whereas sustained high-intensity stimuli are said to elicit defense, and the defense reflex is said to be more resistant to habituation in comparison to startle.

Graham's model has been widely investigated (see, for instance, Kimmel et al., 1979; Siddle, 1983; Lang et al., 1997b; Dawson et al., 1999) but has also been the subject of continuous debate and reformulation (Barry and Maltzman, 1985; Cook and Turpin, 1997; Graham and Hackley, 1991; Graham, 1997; Öhman et al., 2000; Turpin et al., 1999; Vossel and Zimmer, 1992; Barry, 2006). As regards startle and defense, the data have never supported the assumed higher resistance to habituation of cardiac defense (Turpin and Siddle, 1978, 1983; Turpin et al., 1999; Ramírez et al., 2005). In fact, when eye-blink and cardiac defense were simultaneously examined using an acoustic stimulus capable of eliciting both reflexes, a faster habituation was observed for cardiac defense than for eye-blink startle (Ramírez et al., 2005; Fernández et al., 2008).

Besides the theoretical implications of the differential habituation of cardiac defense and eye-blink startle, it also poses methodological difficulties for research into the relationship among protective reactions in relation to the above-mentioned defense cascade. It has been suggested (Turpin et al., 1999; Vila et al., 2007) that the complex response pattern that characterizes cardiac defense reflects the succession of two defensive phases: an attentional protective phase linked to short-latency acceleration/deceleration and a motivational

defensive phase linked to long-latency acceleration/deceleration. The attentional protective phase would be equivalent to a *startle/freezing* response (interruption of ongoing activity and heightened attention to the potential danger), whereas the motivational protective phase would be equivalent to the *fight/flight* response (preparation for active defense, either escape or attack). This idea is supported by data showing that cardiac defense (a) also includes a decelerative component after the first acceleration (Vila et al., 1992), (b) is positively correlated with attentional tasks of sensory intake (Vila et al., 1997; Pérez et al., 2000; Fernández and Vila, 1989a), and (c) is physiologically mediated by both vagal and sympathetic mechanisms: the first acceleration/deceleration is controlled by parasympathetic influences, whereas the second acceleration/deceleration is controlled by reciprocal sympathetic and parasympathetic influences (Bond, 1943; Fernández and Vila, 1989b; Reyes del Paso et al., 1993, 1994).

Confirmation of this attention–motivation model of cardiac defense requires comparative studies with other protective reflexes differentially associated with attention (e.g., startle) or motivation (e.g., fight/flight). In the case of startle, however, the fast habituation of cardiac defense limits the test to a few trials, reducing the possibilities of comparative studies with experimental procedures (e.g., the pre-pulse inhibition or the startle probe paradigms) that use large numbers of trials and a repeated-measures design. Examination of the differential habituation/recovery of cardiac defense and eye-blink startle within a single laboratory session is therefore a relevant theoretical target, but numerous methodological difficulties must be overcome.

Cardiac defense and eye-blink startle belong to two different response systems (cardiovascular and motor) with different sensitivities to experimental manipulations. Thus, acoustic stimulation can elicit both reflexes but the optimal parametric characteristics of the eliciting stimulus are different (see Ramírez et al., 2005). Whereas the whole pattern of cardiac defense requires an eliciting stimulus of long duration (around 500 ms and over) but no specific rise time (even long rise times of around 240 ms can evoke cardiac defense), motor startle can be elicited with short and long stimulus durations (50 ms and over) but requires very short rise times (less than 24 ms). The response latency is a further differential characteristic that affects the interval between stimulus presentations. Cardiac defense requires a minimum of 80 s for the response to be fully developed, whereas eye-blink startle is initiated and completed within a window of 20–150 ms. Therefore, the short inter-trial intervals (10–20 s) typically used in eye-blink startle studies would rule out examination of cardiac defense. Hence, the simultaneous examination of both reflexes necessarily implies using experimental procedures that might be optimal for one reflex but not for the other.

The aim of the present study was to examine similarities and differences in habituation and recovery between cardiac defense and eye-blink startle by using a single laboratory session. We followed an optimal experimental procedure to study the habituation and recovery of cardiac defense: three presentations of an intense white noise of 500 ms duration and instantaneous rise time, capable of eliciting both reflexes, within a time interval of 30 min. The interval between stimulus presentations was manipulated, using a between-group design, by increasing the time interval between the 1st and 2nd stimulus, from 2.5 to 27.5 min, and symmetrically decreasing the time interval between the 2nd and 3rd stimulus. It was hypothesized that increasing the time interval between the 1st and 2nd stimulus would reduce habituation, whereas increasing the time interval between the 2nd and 3rd stimulus would facilitate recovery.

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