Neuroscience and Biobehavioral Reviews 149 (2023) 105163

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Fear-induced bradycardia in mental disorders: Foundations, current advances, future perspectives

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ARTICLE INFO

Keywords:
Fear-induced bradycardia
Fear conditioning
Heart rate
Psychiatry
Biomarker
Mental disorders
Societal burden

ABSTRACT

Fear-induced bradycardia, a transient heart rate deceleration related to a threatening event, is a powerful technique used to assess fear conditioning in humans. During the last century, studies highlighted its usefulness, even when applied to patients with various psychiatric disorders. Here, we provide an insight into these first steps in the field as well as modern works, which helped in refining the methodology. As data is still limited, future endeavors will continue to deepen the knowledge on fear-induced bradycardia and ensure its use as a biomarker to expedite and improve psychiatric interventions, thus lowering the socio-economic burden associated with these disorders.

1. Fear conditioned changes of heart rate

Fear conditioning is a highly flexible and widely used paradigm in neuroscience, both in humans and animals, which led to countless insights in the field of psychiatric disorders in the last century. It is grounded on the theoretical principle that a neutral stimulus, when paired repeatedly with a threatening or painful outcome, which takes the name of unconditioned stimulus (US), elicits specific physiological changes in the observer, thus becoming a conditioned stimulus (CS) (Fig. 1). These changes can be observed in animals and humans in different paradigms, as simple signals (cue conditioning) or even the entire setting (contextual conditioning) can function as a CS. These changes can be measured by heart rate (HR), which signals the instantiation and expression of fear conditioning. Notably, the typical physiological marker in this framework is called *fear-induced bradycardia*, as threatening stimuli elicit a temporary heartbeat deceleration, meaning a lower heart rate for a couple of seconds (Battaglia et al., 2022). Besides its relevance in traditional research contexts, its singularity can also shine when the focus is shifted towards psychiatric populations. A considerable number of psychiatric patients responds poorly to treatments, which results in economic burdens on the healthcare system (Howes et al., 2022). A deeper understanding of such disorders will lead to better treatment and therefore reduce socio-economic pressure, beside an improvement in well-being and a reduction of suffering for patients.

2. Insights from the past

The pivotal study on fear-bradycardia in psychiatric populations comes from Hare and Quinn (1971), which recruited inmates from a penitentiary and classified them based on their psychopathy levels, characterized by a lack of emotional responses and empathy, impulsivity, and antisocial behavior (see Table 1 for further details). The results revealed a pattern of cardiac deceleration to the CS+ regardless of psychopathy levels, thus suggesting that fear-induced bradycardia is present in psychopathic individuals as well. It is important to highlight, however, that psychopathic individuals did not show a difference between CSs when measured with skin conductance resistance (SCR). Importantly, this reveals that while electrodermal responses are absent in this population, it is possible to assess fear conditioning by means of fear-induced bradycardia.

Distressing or painful stimuli have a detrimental effect on individuals

Abbreviations: CS, Conditioned stimulus; HR, Heart rate; SAD, Social anxiety disorder; SCR, Skin conductance resistance; US, Unconditioned stimulus.

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https://doi.org/10.1016/j.neubiorev.2023.105163
Received 16 January 2023; Received in revised form 21 March 2023; Accepted 4 April 2023
Available online 6 April 2023

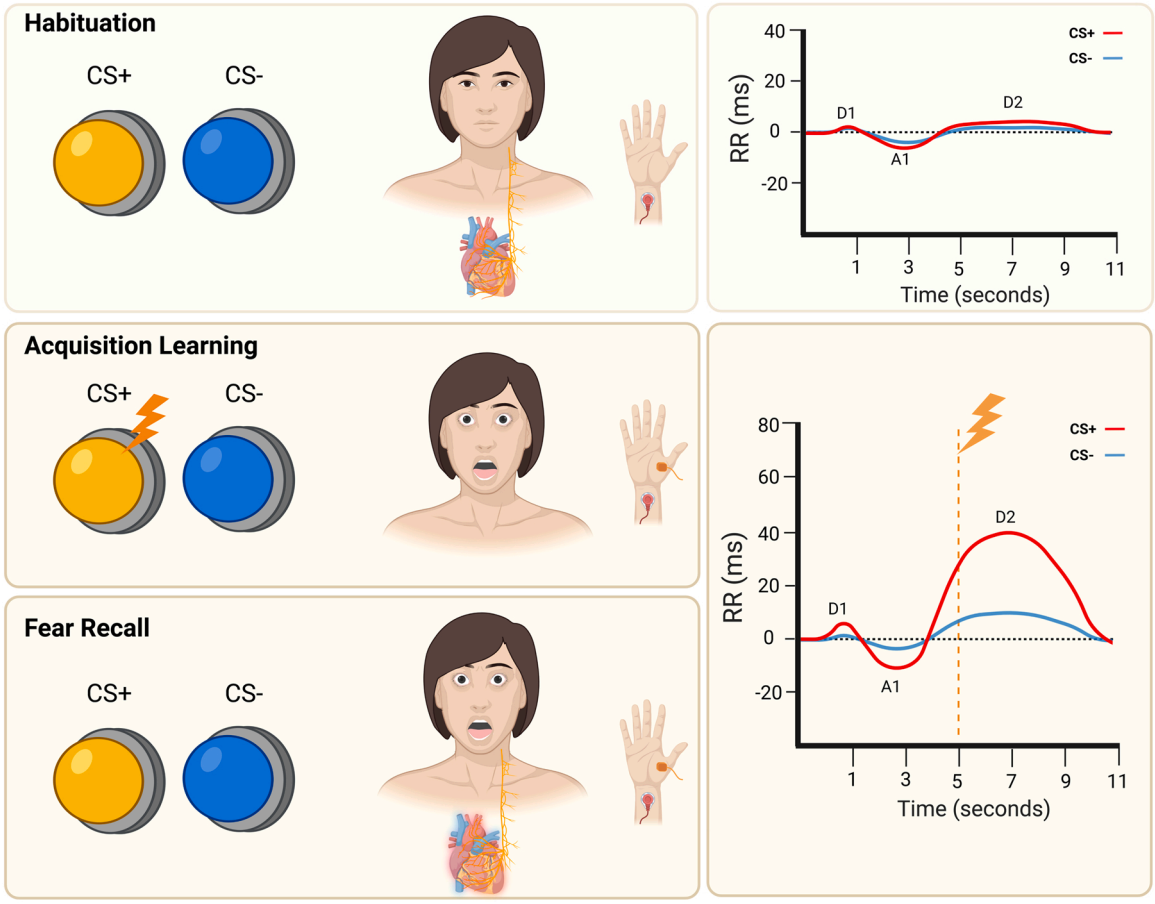

Fig. 1. Fear conditioning paradigm. In fear conditioning studies, participants usually first undergo a habituation phase, during which two neutral stimuli (NS) are presented to familiarize with them. Subsequently, during what is referred to as acquisition learning phase, repeated NS presentations paired with an unconditioned stimulus (US), like a shock to the hand, cause the NS to become a conditioned stimulus (CS+), able to exert conditioned responses, while the other remains neutral (CS-). Physiological activation to the CS+ persists beyond the acquisition phase as evidenced by fear recall phase, whereby conditioned responses are elicited even in the absence of the original US. Such responses can be observed thanks to heart rate modulation measurements by calculating the difference in milliseconds from one heartbeat to the following one. This highlights fear-induced bradycardia, a transient deceleration (D2) that manifests near the time of expected US administration, following a previous initial deceleration (D1) and acceleration (A1). The figure was created using BioRender.com.

Table 1
Summary of findings on fear-induced bradycardia in psychiatric populations.

Study	*Participants (N)*	*Fear Conditioning Paradigm*	*Psychophysiological Measures of Fear*	*CS*	*US*	*Analysis Method*	*Main Findings*
Hare and Quinn (1971)	54 (psychopathic inmates and controls)	Delay conditioning	HR, SCR	Acustic tones	Shock pulse	BPM	Bradycardia for CS+
Fredrikson (1981)	24 (phobics patients and controls)	Delay conditioning	HR, SCR	Visual stimuli (fear-relevant and fear-irrelevant pictures)	Shock pulse	BPM	Bradycardia for CS+ in the first trials of acquisition, then tachycardia
Rothemund et al. (2012)	22 (Psychopathic patients and controls)	Delay conditioning	HR, SCR, FPS, EMG	Visual stimuli (neutral faces)	Shock pulse	BPM	No difference in HR
Ahrens et al. (2016)	62 (SAD patients and controls)	Partial reinforcement Delay conditioning	HR, SCR	Visual stimuli (neutral faces)	Loud Sound (human scream)	BPM	Bradycardia for both CS+ and CS- in social anxiety disorder

with genetic and environmental predispositions, leading to the development of specific phobias. Based on these features, Fredrikson (1981) aimed at assessing if reactions to phobia-inducing pictures in phobic participants could be comparable to fear conditioned responses (see Table 1 for further details). The phobic group viewed pictures of spiders and snakes, one of them being the object of their phobia, and two other neutral pictures, while the control group underwent a fear conditioning paradigm. Results showed that the phobic group displayed greater cardiac acceleration, an increased heart rate, to the phobic stimulus and deceleration to the non-feared stimulus. On the other hand, the control group showed greater fear-induced bradycardia in response to the CS+ during the first half of the acquisition phase. Results from the recall phase on the following day reveal a familiar pattern of fear-induced bradycardia to the CS+ and no modification from baseline in response to the CS- presentation. Based on these results, it is possible to deduce that a highly feared stimulus in phobics can exert tachycardia, a brief

heart rate acceleration.

3. From neuroscience to psychiatry: current advances

In recent years, Rothemund et al. (2012) proposed a modern take on the subject investigated by Hare and Quinn's study described above, thanks to more refined methodologies as a result of technological advances that took place during the several decades between the two studies (see Table 1 for further details). To this aim, they recruited psychopathic and control individuals which underwent a classical fear conditioning experiment. Both groups showed a reduction in heart rate to both stimuli, and both during acquisition and extinction. This data then reveals a general pattern of heart rate deceleration, possibly due to the very large number of trials during both phases.

Overgeneralization of learned fear to unharmful stimuli is a common feature of anxiety disorders, but the lack of specific evidence regarding social anxiety disorder (SAD) led Ahrens et al. (2016) to investigate fear generalization in patients suffering from said condition (see Table 1 for further details). A sample of SAD patients and healthy controls underwent a fear generalization paradigm, where two female faces served as CSs. The US was the CS+ face displaying a fearful expression, accompanied by a loud human scream. Different versions of the two faces were created, morphing them in 20 % steps and were presented during the generalization phase along with the two original CSs. HR data revealed that SAD participants showed greater cardiac slowing to both CSs when compared to controls, while no differences between groups emerged in the SCR analysis. Moreover, only SAD patients generalized to other stimuli, as expressed by greater cardiac deceleration to the CS+ and the morph most similar to it. Therefore, it is possible to suggest that SAD patients show fear generalization that can be observed by fear-induced bradycardia. To summarize, current evidence reveals that psychopathic individuals display an HR trend similar to that of healthy controls. Moreover, fear generalization in SAD patients can only be observed with HR but not with SCR. Taken together, these findings may suggest that HR modulations rely on different neurobiological pathways than SCR, which should be intact in psychiatric patients.

4. Future perspective: promises or pitfalls?

Classical and recent studies on different psychiatric disorders reveal promising results, suggesting that in some cases the analysis of HR may reveal intact or pathological mechanisms behind fear conditioning when other physiological techniques are not able to detect it (Ahrens et al., 2016; Hare and Quinn, 1971). In any case, data collected to this day is still not enough to claim definitive conclusions on specific fear-induced bradycardia dynamics in psychiatric populations.

Notwithstanding, substantial improvements need to be made to enhance the quality of the data collected. For instance, using heart period instead of beats per minute to assess cardiac variations is desirable, as it is more precise. Moreover, the use of neutral stimuli instead of threatening ones will help in preventing participants from showing physiological activations purely based on their predispositions to threatening cues. Even the analysis method needs to be homogenized, in order to create a more streamlined series of results that can complement each other, with model-based estimates representing a solid starting point (Battaglia et al., 2022). Notwithstanding, fear-induced bradycardia is a valuable methodology in the study of psychiatric disorders, as it can detect the presence of intact fear learning when other techniques fail to do so. However, it generally requires a higher number of trials to develop, which may be taxing for psychiatric patients.

Even though limited, this evidence is promising and may lead to the use of fear-induced bradycardia as a valuable biomarker in the detection and study of psychiatric illnesses. The studies presented here highlight that, both in psychopathic and anxiety disorder patients, HR measurements can detect physiological changes that SCR fails to acknowledge. Thus, future endeavours focusing on HR modulation will allow the development of more accurate diagnoses and monitor treatment efficacy, as well as eventual subsequent follow-ups. Finally, this knowledge enrichment will help in developing and identifying new biomarkers for such highly debilitating mental conditions, which will positively alleviate the socio-economic implications of these disorders.

Funding

This work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022) to Simone Battaglia.

Declaration of Competing Interest

The authors declare no competing interests.

References

Ahrens, L.M., Pauli, P., Reif, A., Mühlberger, A., Langs, G., Aalderink, T., Wieser, M.J., 2016. Fear conditioning and stimulus generalization in patients with social anxiety disorder. J. Anxiety Disord. 44, 36–46. https://doi.org/10.1016/j.janxdis.2016.10.003.

Battaglia, S., Orsolini, S., Borgomaneri, S., Barbieri, R., Diciotti, S., di Pellegrino, G., 2022. Characterizing cardiac autonomic dynamics of fear learning in humans. Psychophysiology 59, e14122. https://doi.org/10.1111/psyp.14122.

Fredrikson, M., 1981. Orienting and defensive reactions to phobic and conditioned fear stimuli in phobics and normals. Psychophysiology 18, 456–465. https://doi.org/10.1111/j.1469-8986.1981.tb02480.x.

Hare, R.D., Quinn, M.J., 1971. Psychopathy and autonomic conditioning. J. Abnorm. Psychol. 77, 223–235. https://doi.org/10.1037/h0031012.

Howes, O.D., Thase, M.E., Pillinger, T., 2022. Treatment resistance in psychiatry: state of the art and new directions. Mol. Psychiatry 27, 58–72. https://doi.org/10.1038/s41380-021-01200-3.

Rothemund, Y., Ziegler, S., Hermann, C., Gruesser, S.M., Foell, J., Patrick, C.J., Flor, H., 2012. Fear conditioning in psychopaths: event-related potentials and peripheral measures. Biol. Psychol. 90, 50–59. https://doi.org/10.1016/j.biopsycho.2012.02.011.