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Karita E. Ojala, Dominik R. Bach

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Measuring learning in human classical threat conditioning: translational, cognitive and methodological considerations

Karita E. Ojala[1, 2] and Dominik R. Bach[1, 2, 3,*]

[1] Computational Psychiatry Research, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital, University of Zurich. Lenggstrasse 31, 8032, Zurich, Switzerland. [2] Neuroscience Center Zurich, University of Zurich. Winterthurerstrasse 190, 8057, Zurich, Switzerland. [3] Wellcome Centre for Human Neuroimaging and Max-Planck UCL Centre for Computational Psychiatry and Ageing Research, University College London. 12 Queen Square, WC1N 3BG, London, UK.

* Corresponding author:
Dominik R Bach
Max Planck UCL Centre for Computational Psychiatry and Ageing Research
10-12 Russell Square
London WC1B 5EH
United Kingdom
d.bach@ucl.ac.uk

Highlights

- At least 10 different measures of human threat conditioning exist in the literature
- Measures are highly variable in translational, cognitive and methodological aspects
- Evidence of the measures reflecting amygdala-dependent learning in humans is scarce
- Formal learning models have mostly been studied for skin conductance responses
- Startle eye-blink and pupil size seem to best differentiate CS+/CS−

Abstract

Threat conditioning is a laboratory model of associative learning across species that is often used in research on the etiology and treatment of anxiety disorders. At least 10 different conditioned responses (CR) for quantifying learning in human threat conditioning are found in the literature. In this narrative review, we discuss these CR by considering the following questions: (1) Are the CR indicators of amygdala-dependent threat learning? (2) To what components of formal learning models do the CR relate? (3) How well can threat learning be inferred from the CR? Despite a vast literature, these questions can only be answered for some CR. Among the CR considered, heart period, startle eye-blink and Pavlovian-to-instrumental transfer are most clearly related to amygdala-dependent threat learning. Formal learning models have mostly been studied for skin conductance responses, which are likely to reflect threat prediction and its uncertainty. Startle eye-blink and pupil size appear to best differentiate CS+/CS−, although few direct comparisons between CR exist. We suggest future directions for improving the quantification of threat conditioning.

Key words: fear conditioning; associative learning; implicit learning; psychophysiology; inverse inference; conditioned responses; retrodictive validity

1 Introduction

Classical or Pavlovian threat conditioning, also termed fear conditioning (LeDoux, 2014), is a laboratory model for learning to predict threat through association of initially neutral stimuli (conditioned stimuli, CS) with aversive outcomes (unconditioned stimuli, US). By themselves, US elicit defensive responses, such as activation of the autonomic nervous system and escape behavior (unconditioned responses). Over the course of learning, CS come to elicit anticipatory conditioned responses (CR), such as freezing in rodents, or autonomic activation in many species. Observation of

such CR is commonly taken as evidence that a CS-US association has been established. Various CR are observed in different species, and several are commonly used in humans. For researchers in the field, this multiplicity raises a question as to which measures are most appropriate, possibly depending on the research question. In this narrative review, we seek to provide a comprehensive overview of different types of CR elicited in humans. After first recapitulating the motivation for threat conditioning research and the experimental protocols used, we ask three questions for each CR: (1) Translational: Does the CR reflect amygdala-dependent threat learning, as standardly investigated in non-human species? (2) Cognitive-computational: What component of an associative learning process does the CR relate to? (3) Methodological: What are the psychometric properties of the CR for inferring CS-US association? In contrast to a recent methodological review on threat conditioning protocols (Lonsdorf et al., 2017), we exclusively focus on CR, but cover a wider array of CR and provide more in-depth discussion of these three questions. We review skin conductance, pupillary, cardiac, respiratory, startle eye-blink, limb withdrawal, and gaze direction responses, as well as reaction time, Pavlovian-to-instrumental transfer and explicit report of CS-US contingencies (see Table 1 for an overview). We do not cover eye-blink conditioning which is established to depend on cerebellum rather than amygdala (Medina et al., 2002). For each CR, we briefly introduce how it is measured and quantified, and how it has been used until now.

The main motivation for research into amygdala-dependent threat conditioning is clinical as well as comparative. Regarding the clinical motivation, there are at least two perspectives. First, threat conditioning is sometimes considered as an etiological model of pathological fear and anxiety. In other words, it is assumed that the clinical condition arises through learning, for example by associating a traumatic event with sensory cues that preceded it (Foa et al., 1989). The second aspect is independent of the etiology of fear and anxiety disorders. Once a threat memory is established in the laboratory, reduction of this existing memory can serve as a pre-clinical testbed to investigate treatment strategies such as exposure therapy (Hofmann and Smits, 2008) or various interventions meant to block memory reconsolidation (e.g., Bach et al., 2019; Brown et al., 2009; Kindt et al., 2009; Kroes et al., 2016; Schiller et al., 2010).

In addition to its clinical face validity, threat conditioning is a simple model of associative learning with comparable experimental setups across species, ranging from aplysia (Walters et al., 1981) to humans. Much of what we know about neural circuits relevant for threat conditioning stems from rodent experiments (Herry and Johansen, 2014; Milad and Quirk, 2012; Tovote et al., 2015; Yau and McNally, 2018) although this translation is not always straightforward (e.g., Flores et al., 2018; LeDoux and Pine, 2016; Lonsdorf et al., 2017).

Crucially, theories of clinical conditions, or of neurobiological memory mechanisms, are usually not formulated at the observation level of the CR but on the cognitive or neural level of the CS-US association. This is an abstract construct that cannot be directly observed. Therefore, CR are used to make inference on whether a CS-US association was acquired (see e.g. Bach et al., 2020, 2018a; Cacioppo and Tassinary, 1990 for a general discussion of this inverse inference problem in psychological research). The three questions we ask for each CR reflect three different perspectives on the quality of this inference.

To answer our first question, we review evidence across species on whether the CR is generated by amygdala synaptic plasticity-dependent learning (Duvarci and Pare, 2014), which we contrast with hippocampus- or cerebellum-dependent learning. We discuss anatomy and neural stimulation evidence for a role of these structures in generating the response outside conditioning paradigms, correlation of neural activity with CR during threat conditioning, and lesion studies that suggest a necessary function of a structure for generation of CR. Where available, we consider research in non-human animals and humans, the latter mainly using functional magnetic resonance imaging (fMRI) and clinical lesion models. As a limitation, sample sizes in clinical lesion studies are often small. Additionally, we discuss the role of declarative memory on each CR. According to some theoretical accounts, declarative memory is acquired in a process that is separate from the acquisition of other CR (dual-process model; Lovibond and Shanks, 2002; see section 2.10) and amygdala-independent (Bechara et al., 1995). Even if amygdala-dependent synaptic plasticity is demonstrated to generate a CR, the inverse inference, that is, inferring amygdala-dependent synaptic plasticity from the CR, is ambiguous if declarative memory depends on a different learning mechanism that can generate the same CR. Indeed, instructed CS-US associations that were never experienced can generate responses that are indistinguishable from CR in threat conditioning (Atlas, 2019; Dunsmoor et al., 2012; Dunsmoor and LaBar, 2012; Mertens and Engelhard, 2019), and this implies a possibility that also declarative CS-US memory emerging during threat conditioning contributes to generation of these CR. In many cases, amygdala lesion studies do not solve the puzzle. For instance, amygdala lesions impair responses generated by instruction alone, suggesting amygdala is part of an output pathway for instructed responses. In these cases, the observation that amygdala lesion diminish the CR could be due to lesion of an amygdala-dependent learning circuit, or due to lesion of an output relay from an amygdala-independent learning circuit. We will conclude in these cases that the relative contribution of possibly different learning systems to the generation of the CR cannot be answered conclusively.

To answer the second question, we discuss how cognitive components of the learning process relate to the CR. This is important because it may allow for specific measurement of these

components, particularly so in the context of formal (computational) learning models (see Box 1 for an introduction to computational models and a description of the learning models and quantities discusses in the text). Importantly, formal learning models contain several quantities that, on average, differ between a threat-predictive CS+ and a safety-predictive CS− in standardly used partial reinforcement schedules. Obviously, US prediction is higher for a CS+ compared to CS-, but in many paradigms, uncertainty of that prediction will also be higher for CS+ compared to CS-. While condition differences in the CR still support an inference that learning has occurred, one cannot distinguish between different learning quantities from condition averages alone. To allow such distinctions, we mainly discuss studies that leverage the trial-by-trial trajectory of CR. In one approach, the CR trajectory is fitted with computational learning models to give a full account of the data, and model evidence used to select the most appropriate description of the data. In another approach, the CR trajectory is related to particular learning quantities, and linear regression used to establish an impact of that quantity, irrespective of the contributions of other quantities.

Finally, we assess quantitatively how well a CR allows inference that a CS-US association has been established. This is of practical importance for study planning and ensuring reproducibility. Our primary criterion is retrodictive validity, i.e. the effect size to distinguish CS+/CS− (Bach et al., 2018a, 2020). This criterion jointly captures accuracy and precision of the inference on CS-US association (Bach et al., 2020). Crucially, different CR possibly index different components of a learning process, and CS+/CS−differences in these components depend on the experimental paradigm. Hence retrodictive validity can depend on experimental settings in different ways for different CR. Thus, we discuss to what extent a CR is expressed in different paradigms or phases thereof. Where available, we also report reliability, with the caveat that test-retest reliability depends on measurement precision but also on inter-individual variability, which may be different between different CR (Brandmaier et al., 2018). Because many studies require assessing memory retention, usually under extinction (i.e., no reinforcement), we discuss how quickly the measure extinguishes and whether post-learning retention has been demonstrated. Where applicable, we list experimental design features that may impact the quality of inference on CS-US association.

We refer the reader to other sources regarding individual differences in threat conditioning (Lonsdorf and Merz, 2017; Van Well et al., 2012), methodological considerations for designing and analyzing threat conditioning studies (Lonsdorf et al., 2017), statistical considerations in the analysis of psychophysiological data for threat conditioning (Bach et al., 2018a, 2020; Bach and Melinscak, 2020; Ney et al., 2018), neural circuits involved in threat conditioning (in humans: Fullana et al., 2016; Greco and Liberzon, 2016; and in rodents: Yau and McNally, 2018; Herry and Johansen, 2014; Tovote

et al., 2015), and the relationship of threat conditioning to episodic memory (Dunsmoor and Kroes, 2019) and to subjective feeling of fear (Raber et al., 2019).

Box 1. Computational learning models of threat conditioning.

- Computational models formalize the learning process in a biological or artificial system.
- Many models entail parameters with values that may differ between contexts, or between individuals.
- Such models can be fitted to experimental data, whereby an optimization algorithm identifies the most likely parameter values, given the data.
- Predictions generated from computational learning models can be compared to experimental data. For example, a normative (parameter-free) model, or a model fitted to trial-wise psychophysiological responses, generates predictions that can be compared to, for example, neural responses.
- Various learning models have been proposed in the field of threat conditioning, including classical associative learning models, reinforcement learning models from computer science, statistically normative models, and combinations of these (see e.g. Gershman, 2015).

Reinforcement learning models

Learning takes place as updating of associative strength of CS to US (reflecting US prediction) depending on the difference between US prediction and actual outcome ('prediction error').

Rescorla-Wagner model (Rescorla and Wagner, 1972)
On each trial, US prediction is updated by a constant fraction (learning rate) of the signed prediction error. Worse than predicted outcomes increase the value for US prediction and better than predicted outcomes decrease it.

Temporal difference model (Sutton, 1988)
An extension of the Rescorla-Wagner model, where learning can occur continuously and is not constrained to one update per trial – a property which can account for second-order conditioning.

Pearce-Hall model (Pearce and Hall, 1980)
On each trial, US prediction is updated by a variable fraction of the US value, and this fraction is termed 'associability' of a CS. Associability on each trial is computed as a constant fraction of the unsigned (absolute) prediction error of the previous trial, reflecting magnitude of surprise regardless of whether the outcome was better or worse than predicted. In this model, US prediction asymptotes to the same value for partial or full reinforcement.

Hybrid Rescorla-Wagner-Pearce-Hall model
On each trial, US prediction is updated by a variable fraction (associability) of the signed prediction error; and associability is a constant fraction of the absolute prediction error of the previous trial.

Bayesian learning models

US prediction is represented as a probability distribution over different possible values of the US prediction. This inherently includes uncertainty estimation. Current evidence (experienced US outcome) is integrated with prior information (US prediction) to arrive at a subjective belief of US prediction. The term 'uncertainty' here is used to denote US outcome uncertainty (how surprising CS-US transitions are on average, highest for 50% reinforcement), uncertainty of US prediction (subjective belief of CS-US probabilities, highest at the beginning of an experiment), and stability of US prediction (volatility of CS-US probabilities). See Bach & Dolan (2012) for further examples.

Hierarchical Bayesian model
A model that consists of several levels of hierarchy, which represent different types of beliefs as separate probability distributions; for example, beliefs about US prediction (first level), belief on how likely different values of these predictions are (second level), and belief on how stable the second-level belief is (third level). Estimates at each level influence belief updating at the level below, e.g. making learning faster in uncertain environments by higher weighting of prediction errors.

Normative Bayesian model
Learning is assumed to be statistically optimal and model predictions can be generated without fitting the model to experimental data. However, this does not account for individual differences in learning.

Central quantities in learning models

- US prediction: probability of US occurrence after a CS, also termed associative weight of a CS (reflecting CS-US association)
- US prediction: mean of the prior distribution over US probability

• Associability: malleability of current US prediction • Signed prediction error: difference between the experienced and predicted outcome, with sign depending on whether the outcome was worse (+) or better (−) than expected. • Unsigned prediction error: absolute difference between the experienced and predicted outcome (unexpectedness regardless of outcome sign)	• Uncertainty of US prediction: e.g. variance of the prior distribution over US probability (large if US probability is unknown) • Uncertainty of US outcome: e.g. variance of the distribution over US outcomes (large if estimated US probability is close to 50%) • Volatility: e.g. variance of the prior probability distribution reflecting changeability of CS-US contingencies • Uncertainty-weighted prediction error: the effect of prediction errors on belief updating is scaled by US outcome uncertainty (larger effect with less uncertainty) • 'Surprise' as unsigned prediction error

2 Threat conditioning measures

2.1 Skin conductance responses

2.1.1 Background

Sweating increases the electrical conductance of the skin, which can easily be measured. Sweating is primarily a thermoregulatory mechanism (Boucsein, 2012), but various other internal and environmental stimuli (Dawson et al., 2007b) also induce phasic firing of sympathetic sudomotor nerve fibers (e.g., Gerster et al., 2018). Different from sympathetic innervation of other effector organs, sudomotor fibres release acetylcholine, which cause opening of eccrine sweat glands across the body. Highest sweat gland density is found on fingers, palms, and plantar arc. These thus constitute the most common measurement sites (Boucsein, 2012; Stevens and Landis, 1987). While not specific to threat, phasic skin conductance responses elicited during CS+ presentation are typically higher than those during CS− (see for review Boucsein, 2012).

2.1.2 Translational: Amygdala-dependent learning

Skin conductance responses are observed not only in humans but also in other mammals with eccrine glands on the palm or sole, including rats (Lykken, 1962; Stevens and Landis, 1987), cats (Lang et al., 1964) and non-human primates (Bagshaw and Coppock, 1968; Laine et al., 2009). Across species, amygdala projects to the sudomotor system via hypothalamus and brainstem (Boucsein, 2012). Stimulation of basolateral amygdala in lightly anesthetized cats generated skin conductance responses (Lang et al., 1964). During threat conditioning, selective bilateral amygdala lesions in rhesus monkeys have been shown to attenuate skin conductance responses evoked by CS+ (Bagshaw and Coppock, 1968; Pribram et al., 1979).

In humans, electrical stimulation of the amygdala in awake epileptic patients elicited skin conductance responses (Mangina and Beuzeron-Mangina, 1996). A number of human neuroimaging studies have suggested a correlation between amygdala blood oxygen level-dependent (BOLD) signal and threat-conditioned skin conductance responses (Büchel et al., 1998; Carter et al., 2006; Cheng et al., 2007, 2006, 2003; Furmark et al., 1997; Knight et al., 2005; Morris et al., 1998; Petrovic et al., 2008; Phelps et al., 2001; Spoormaker et al., 2011; Tabbert et al., 2006), although a meta-analytic summary is lacking and the localization of these activations within the temporal lobe may not always allow distinction between amygdala and hippocampus. Clinical lesion studies have provided mixed evidence on the role of temporal lobe structures for threat-conditioned skin conductance responses. On the one hand, unilateral temporal lobectomy (including removal of both amygdala and hippocampus) was associated with diminished CS+/CS− difference, or CS+ response, in overall N > 50 patients (Coppens et al., 2010; LaBar et al., 1995; Peper et al., 2001; Phelps et al., 1998). Reduced threat-conditioned skin conductance responses have also been demonstrated in patients with Alzheimer's disease and frontotemporal lobar degeneration, conditions with significant atrophy of the hippocampus and amygdala (Barnes et al., 2006; Cuénod et al., 1993; Poulin et al., 2011). On the other hand, one study with unilateral temporal lobectomy patients did not report significantly diminished differential skin conductance responses (N = 28) (Åhs et al., 2010). As yet, meta-analytic summary of these studies is lacking. To disambiguate amygdala and hippocampal contribution, one patient with selective bilateral amygdala damage due to Urbach-Wiethe disease showed impaired threat-conditioned skin conductance responses (Bechara et al., 1995). We note that this single-case study did not assess differential threat conditioning and only reported skin conductance responses elicited by CS+. Overall, it appears that medial temporal lobe structures are probably required for threat-conditioned skin conductance responses, but human evidence for amygdala-dependent learning as underlying mechanism is weak.

In addition, differential skin conductance responses (CS+ vs. CS−) can be elicited and extinguished in instructed threat protocols without threat conditioning (Atlas, 2019; Luck and Lipp, 2016; Sevenster et al., 2012). This raises a possibility that skin conductance responses elicited during threat conditioning are generated or modulated by declarative CS-US contingency knowledge that also emerges during conditioning. Furthermore, unilateral lesions of the left amygdala appear to impair skin conductance responses to instructed threat cues (Masaoka et al., 2003), suggesting that the output pathway for skin conductance responses generated by instructed knowledge involves amygdala. If this were the case, then the observation of diminished threat-conditioned skin conductance responses after amygdala lesions allows no unambiguous interpretation. To resolve this puzzle, a single-case lesion study suggested that hippocampus lesion impairs declarative CS-US

contingency learning but not threat-conditioned skin conductance responses to the CS+ (Bechara et al., 1995). This seems to be the most specific human evidence to date suggesting that threat-conditioned skin conductance responses are at least partly generated by amygdala-dependent rather than declarative hippocampus-dependent learning.

A circumstantial argument in support of amygdala dependence of conditioned skin conductance responses would be a demonstration that they occur in experimental preparations that preclude declarative memory, or even CS identity awareness. A plethora of studies have reported conditioned skin conductance responses when the CS were masked or below sensory detection threshold (Balderston et al., 2014; Esteves et al., 1994; Knight et al., 2006, 2003; Morris et al., 1998; Schultz and Helmstetter, 2010). On the other hand, when using supra-threshold CS and comparing participants who were aware of the CS-US contingency to those who were unaware of it, a similar number of studies suggested that lack of CS-US contingency awareness precludes conditioned skin conductance responses in healthy individuals (Dawson et al., 1986, 1979; Dawson et al., 2007a; Hamm and Vaitl, 1996; Tabbert et al., 2011, 2006; Weike et al., 2007 for a review of earlier evidence, see Dawson and Furedy, 1976) and in unilateral temporal lobe lesion (Coppens et al., 2009; Weike et al., 2005). However, the methods for defining “awareness” in both types of studies have been discussed critically (e.g., Lovibond and Shanks, 2002; Mertens and Engelhard, 2019; Singh et al., 2013). A recent meta-analysis (Mertens and Engelhard, 2019) reported a medium effect size in favor of CR in the absence of CS awareness, but with evidence for substantial publication bias. Stronger designs and larger studies would be required to support this argument.

Taken together, human fMRI and lesion studies tentatively suggest temporal lobe contribution to generation of threat-conditioned skin conductance responses, but meta-analytic summary of the considerable literature is lacking. Most human studies do not allow disambiguating amygdala and hippocampus contribution. There is meta-analytic evidence for conditioned skin conductance responses in the absence of declarative memory, but methods in this field have been critically discussed. Direct evidence for amygdala dependence of threat-conditioned skin conductance responses is relatively weak and comes from two monkey lesion experiments and one single-case lesion study in humans.

2.1.3 Cognitive-computational: Underlying learning components

Looking at the trial-by-trial CR trajectory, several studies have conducted Bayesian model comparison to infer the underlying learning model. They have consistently shown that the associability term from a hybrid Rescorla-Wagner-Pearce-Hall model describes the trajectory of skin conductance responses better than the US prediction term in this model, or in a standard Rescorla-Wagner model

(Homan et al., 2019; Li et al., 2011; Seymour et al., 2005; Tzovara et al., 2018; Zhang et al., 2016). Two of these studies investigated further learning models. One found that a weighted mixture of associability and US prediction from the hybrid model best described the skin conductance responses (Homan et al., 2019), while another found that skin conductance responses were best described by a mixture of uncertainty and US prediction from a normative Bayesian model (Tzovara et al., 2018). A regression study reported that conditioned skin conductance responses were related to the uncertainty of the US prediction, defined as the variance of a subjective belief distribution over CS-US probabilities in a hierarchical learning model (de Berker et al., 2016). It has been suggested that the trial-by-trial trajectory of conditioned skin conductance responses is different from that of explicit US prediction ratings (Blechert et al., 2008), which supports the notion that these two measures index different learning quantities, different learning systems, or both. A crucial data feature that favors the contribution of US uncertainty is that skin conductance responses diminish over the course of learning (Codispoti et al., 2006) – as uncertainty does. This phenomenon is not caused by peripheral habituation (Gerster et al., 2018). However, such central habituation is observed in many experimental preparations that involve stimulus repetition (Rankin et al., 2009). Although this can be generally thought of as generated by a learning process, it is not established whether this reflects a domain-general process or should be seen as part of the threat learning mechanism.

Collectively, these studies demonstrate that skin conductance responses most likely reflect a mixture of US prediction and its uncertainty, but the most appropriate formulation of uncertainty is unclear.

2.1.4 Methodological: Psychometric properties

Skin conductance responses are not specific to any particular psychological or cognitive process. They are generated or modulated by many internal, external, and motor processes that may spontaneously occur during learning experiments (Dawson et al., 2007b). This places theoretical constraints on effect size to distinguish CS+ and CS−, i.e. retrodictive validity (Bach et al., 2020). Retrodictive validity is variable across the literature and appears to depend on participant exclusion criteria, CS-US interval, and CS sensory modality. Only a few studies have directly compared skin conductance responses with other CR in the same sample or setup. A study using a peak-scoring approach reported higher retrodictive validity for skin conductance than pupil size responses (Leuchs et al., 2018). However, in a paradigm with short CS-US interval (3.5-5 s), analyzed in the framework of psychophysiological modelling (PsPM; Bach et al., 2018a; Bach and Friston, 2013; Bach and Melinscak, 2020), pupil size responses had higher retrodictive validity than skin conductance responses (Korn et al., 2017). Using the same short CS-US interval paradigm and model-based analysis, retrodictive

validity for skin conductance responses during threat acquisition was approximately equal to that of heart period responses (Castegnetti et al., 2016), and higher than for respiratory amplitude responses (Castegnetti et al., 2017). For threat memory retention under extinction, retrodictive validity for skin conductance responses was lower than for fear-potentiated startle and heart-period responses (Khemka et al., 2017). In summary, skin conductance responses appear to have moderate retrodictive validity. Reported test-retest reliability of the individual CS+/CS− difference is between (intra-class correlation) 0.43 at 8-12 weeks and 0.33 at 8 months (Torrents-Rodas et al., 2014; Zeidan et al., 2012). Conditioned skin conductance responses are retained over time (e.g., Phelps et al., 2004), decrease under extinction and reappear under reinstatement, recovery and renewal (Haaker et al., 2014; Vervliet et al., 2013). Threat-conditioned skin conductance responses appear highly variable across individuals and are affected by many factors such as sex, genetic polymorphisms, personality traits, brain morphology, and stress (Lonsdorf et al., 2017; Lonsdorf and Merz, 2017). Finally, skin conductance response tails are relatively long (more than 30 s; Bach et al., 2010a) such that conditioned and unconditioned skin conductance responses overlap, and responses from subsequent trials overlap in many common paradigms. Model-based analysis (Bach et al., 2018a; Bach and Melinscak, 2020) allows disentangling overlapping responses, and trial-by-trial skin conductance responses are sufficiently informative to distinguish between computational learning models (see 2.1.3).

2.2 Pupil size responses

2.2.1 Background

Pupil size mainly depends on illuminance but is modulated by a number of cognitive processes (Korn and Bach, 2016). Changes in pupil size are mediated by a midbrain circuit from which sympathetic innervation dilates, and parasympathetic innervation constricts, the pupil (Loewenfeld, 1999; McDougal and Gamlin, 2008). Threat-conditioned pupil dilation is a well-established phenomenon (Korn et al., 2017; Leuchs et al., 2017; Reinhard et al., 2006; Reinhard and Lachnit, 2002; Visser et al., 2016, 2015, 2013). CS− of different sensory modalities can elicit rather dissimilar changes in pupil size, ranging from dilation to constriction, while added influence of a CS+ appears to be rather stereotypical (Korn et al., 2017). Pupil constriction due to increased illumination by a CS, and dilation of the pupil specifically due to the CS+ gives rise to the phenomenon of 'threat-inhibited pupillary light response' (Bitsios et al., 2004, 1996; see also Korn et al., 2017).

2.2.2 Translational: Amygdala-dependent learning

Threat-conditioned pupil size responses are reported in non-human species (e.g., in mice; Dalmay et al., 2019). Stimulating the medial amygdala nucleus in cats (Koikegami and Yoshida, 1953) or the central nucleus amygdala in rabbits (Applegate et al., 1983) appears to elicit pupil dilation. To our knowledge, no non-human or human studies have addressed whether threat-conditioned pupil size responses reflect amygdala-dependent or other types of learning.

2.2.3 Cognitive-computational: Underlying learning components

To our knowledge, only one study has used the trial-by-trial trajectory of pupil size during threat conditioning to disambiguate formal associative learning models. Tzovara et al. (2018) reported that threat-conditioned pupil size responses were best described by US prediction (corresponding to associative weight in traditional associative learning terminology) from a probabilistic learning model, rather than by uncertainty of US predictions or a combination thereof. However, several regression studies have suggested that pupil size is also influenced by uncertainty of US prediction in a hierarchical learning model (de Berker et al., 2016), by US outcome uncertainty (e.g., Koenig et al., 2017; Leuchs et al., 2017), and by the estimated rate of change in the environment, also called volatility (Browning et al., 2015). Possibly reconciling these accounts, it has been tentatively suggested that pupil size indexes US prediction early during learning and uncertainty of US prediction later on (Koenig et al., 2018).

2.2.4 Methodological: Psychometric properties

The literature on evaluating psychometric properties of pupil size responses or comparing pupil size responses to other measures is scarce. In a paradigm with short CS-US interval (3.5-5 s), analyzed in the framework of psychophysiological modelling (PsPM; Bach et al., 2018a; Bach and Friston, 2013; Bach and Melinscak, 2020), retrodictive validity of pupil size was higher than for skin conductance, heart period, and respiratory amplitude responses during threat acquisition (Korn et al., 2017). We are not aware of a comparison to other CR during post-learning retention, or an assessment of reliability. Threat-conditioned pupil size responses are retained over time (Visser et al., 2013), decrease during extinction learning (Visser et al., 2015), and re-appear after reinstatement (Leuchs et al., 2017). Pupil size responses are affected by various individual and situational factors, such as age, fatigue, alertness and information processing load (Tryon, 1975). Due to its short response tail (Korn et al., 2017), pupil size responses of each trial can be estimated separately as it does not overlap with other trials. Furthermore, the conditioned pupil size response is fully separable from the US response (Korn et al., 2017). Trial-by-trial pupil size responses have successfully been used to distinguish between computational learning models (see section 2.2.3).

2.3 Heart period responses

2.3.1 Background

The cardiovascular system is innervated by both sympathetic and parasympathetic branches of the autonomic nervous system. Sympathetic activity accelerates the heartbeat, and parasympathetic activity decelerates it (Berntson et al., 2007). In cats and dogs, sympathetic stimulation frequency linearly scales with heart period, not heart rate, changes (Parker et al., 1984; Rosenblueth and Simeone, 1934; see for a comprehensive comparison Berntson et al., 1995). Therefore, quantifying changes in heart rhythm as heart period responses, rather than heart rate, is more likely to allow linearly inferring autonomic nervous system activity.

Threat conditioning elicits conditioned cardiovascular responses in a wide range of animal species, such as mammals, birds and fish (Cohen and Randall, 1984). Among these is a short-latency stimulus-evoked deceleration of heartbeat (bradycardia) in humans (Furedy and Poulos, 1976; Headrick and Graham, 1969; Klorman and Ryan, 1980), rabbits (Gallagher et al., 1981; Gentile et al., 1986) and rats (Supple and Leaton, 1990). Heartbeat can easily be assessed with electrocardiography (ECG), or with photoplethysmography, which is often used in MRI scanners (Abi-Abdallah et al., 2007; Berntson et al., 2007). Blood pressure can also be threat-conditioned in rodents (Dworkin and Dworkin, 1990), non-human primates (Klose et al., 1975), and humans (Reiff et al., 1999), but the human literature is scarce such that we do not discuss this in detail.

2.3.2 Translational: Amygdala-dependent learning

Neural firing in central amygdala nucleus occurs concomitantly, and correlates with, conditioned bradycardia in rabbits (Applegate et al., 1982; McEchron et al., 1995; Pascoe and Kapp, 1985) and in rats (Rorick-Kehn and Steinmetz, 2005). In the latter study this relationship was also observed in the basolateral amygdala. Central amygdala lesions attenuate threat-conditioned heart period responses in rabbits (Gentile et al., 1986; Kapp et al., 1979) and rats (Roozendaal et al., 1991; Sananes and Campbell, 1989; Young and Leaton, 1996). Bilateral selective amygdalectomy appears to abolish threat-conditioned bradycardia in rhesus monkeys (Pribram et al., 1979). In humans, we are not aware of stimulation, activation, or lesion, studies that have assessed the relation of threat-conditioned heart period responses and amygdala-dependent learning. Similar to skin conductance responses, bradycardia is also observed after instructed threat cues (Costa et al., 2015), pointing to a potential influence of declarative learning on heart period responses. Heart period responses to instructed threat cues were reduced in patients with amygdala lesions (Masaoka et al., 2003).

Taken together, there is convergent evidence from several non-human mammal species that amygdala is involved in the generation of threat-conditioned heart period responses. Evidence from human studies is lacking, and declarative (possibly amygdala-independent) memory in humans may potentially generate or modulate heart period responses as well.

2.3.3 Cognitive-computational: Underlying learning components

To our knowledge, there are no studies assessing the cognitive-computational learning process underlying conditioned heart period responses. Because of the impact of respiratory arrhythmia (Yasuma and Hayano, 2004), it is difficult to obtain trial-by-trial estimates of heart period responses (see section 2.3.4 below), which is the most important source of evidence for such investigations.

2.3.4 Methodological: Psychometric properties

There is no large literature on the psychometric properties of heart period responses. In a paradigm with short CS-US interval (3.5-5 s), analyzed in the framework of psychophysiological modelling (PsPM; Bach et al., 2018a; Bach and Friston, 2013; Bach and Melinscak, 2020), heart period responses had lower retrodictive validity than pupil size responses (Korn et al., 2017), similar to skin conductance responses (Castegnetti et al., 2016), and better than respiratory amplitude responses (Castegnetti et al., 2017) during threat acquisition. For threat memory retention under extinction, retrodictive validity for heart period responses was lower than for fear-potentiated startle and higher than for skin conductance responses (Khemka et al., 2017). Taken together, heart period responses appear to have moderate retrodictive validity. We are not aware of studies on the reliability of heart period responses, or their robustness to situational factors. Heart period responses have been shown to be retained over time (Castegnetti et al., 2016) and extinguished (Panitz et al., 2015). Single-trial estimation of heart period responses has not been reported.

2.4 Respiratory responses

2.4.1 Background

Brainstem centers regulate breathing and are under control of other brain areas as well as autonomic nervous system input (Barnes, 1986; Hlastala and Berger, 1996; Kreibig, 2010; Lorig, 2007). Breathing patterns are influenced by emotional arousal in humans (Abelson et al., 2010; Boiten et al., 1994; Homma and Masaoka, 2008; Lorig, 2007), but have been rarely used in threat conditioning experiments. Conditioned respiratory disruptions (acceleration, deceleration, irregularity) have been

observed in rhesus monkeys (Pribram et al., 1979). In rats, threat-predictive CS have been shown to induce respiratory slowing (Hegoburu et al., 2011) and stabilization of the respiration rate (Moberly et al., 2018). In contrast, one human study (N > 40) reported a threat-conditioned respiration rate increase as well as a decrease in end-tidal carbon dioxide pressure (Van Diest et al., 2009). Another study showed that threat-predictive CS induced a decrease and later increase in respiration amplitude across five independent samples (overall N > 100) (Castegnetti et al., 2017). Respiration amplitude responses thus appear to be the best replicated threat-conditioned respiratory response. Notably, for precise measurement of respiration amplitude, a double-belt system is required (Binks et al., 2007), but an approximation is possible using a single-belt system if there is a relatively constant ratio of abdominal and thoracic contributions to respiration within an individual (Bach et al., 2016). This is of interest because such single-belt systems are available in most MRI facilities. The aforementioned report on respiratory amplitude responses used a single-belt system (Castegnetti et al., 2017).

2.4.2 Translational: Amygdala-dependent learning

In rhesus monkeys, bilateral amygdalectomy caused a reduction in the number of threat-conditioned respiratory disruptions (acceleration, deceleration, and irregularities) (Pribram et al., 1979). Furthermore, specific cryogenic blockade of the central amygdala decreased threat-conditioned respiratory response (diaphragmatic electromyography signal) in cats (Zhang et al., 1986). To our knowledge, there are no human studies investigating the amygdala-dependence of respiratory responses in general, and no non-human or human studies on amygdala-dependence of respiratory amplitude responses specifically. Also, there are no reports of respiratory amplitude or other phasic respiratory responses in instructed threat paradigms. Taken together, there is no direct evidence for or against amygdala-dependence of conditioned respiratory responses in humans.

2.4.3 Cognitive-computational: Underlying learning components

To our knowledge, there are no studies assessing the cognitive-computational learning process underlying conditioned respiratory responses.

2.4.4 Methodological: Psychometric properties

A study using short (3.5-5 s) CS-US interval, analyzed in the framework of psychophysiological modelling (PsPM; Bach et al., 2018a; Bach and Friston, 2013; Bach and Melinscak, 2020), has reported lower retrodictive validity for respiratory amplitude than for pupil size, skin conductance or heart period responses during threat acquisition (Castegnetti et al., 2017). Reliability of threat-conditioned respiratory responses has not been assessed. To our knowledge, there are no reports of retention or extinction of threat-conditioned respiratory responses. Unlike other autonomic measures discussed

in this review, respiration is at least partly under conscious control (Lorig, 2007), which may engender systematic confounds in some experimental paradigms. Single-trial estimation of respiratory amplitude responses has not been reported.

2.5 Startle eye-blink responses

2.5.1 Background

A fast defensive startle reflex is elicited by a sudden unexpected loud sound or an intensive tactile or vestibular stimulus (Landis and Hunt, 1939; Yeomans et al., 2002). This reflex entails a change in posture where the head is withdrawn, the shoulders elevated, and the eyes closed (Landis and Hunt, 1939; Yeomans et al., 2002). This defensive whole-body startle reflex might serve to protect an organism from a blow to the head or upper body (Yeomans et al., 2002). In humans, startle reflex is most commonly measured as startle eye-blink response, quantified from surface electromyography (EMG) of the orbicularis oculi muscle under either eye (Blumenthal et al., 2005). The neural pathway underlying the startle reflex has been extensively studied in non-human species (for reviews, see e.g. Davis, 2006; Walker et al., 2003).

Crucially, the startle reflex is increased during presentation of CS+ compared to CS−, a phenomenon classically termed fear-potentiated startle (Brown et al., 1951). Fear-potentiated startle response has been demonstrated in mice (Falls et al., 1997), rats (Brown et al., 1951; Chi, 1965; Davis and Astrachan, 1978), rhesus monkeys (Antoniadis et al., 2007; Winslow et al., 2002), and humans (Ameli et al., 2001; Bradley et al., 2005; Grillon et al., 1991; Grillon and Davis, 1997; Hamm et al., 1993; Spence and Runquist, 1958). Conceptually similar phenomena are observed in non-mammal species (e.g., aplysia: Walters et al., 1981). Fear-potentiated acoustic startle response is arguably the most widely translated CR across multiple mammal species.

2.5.2 Translational: Amygdala-dependent learning

Across species, there are direct projections from the central nucleus of the amygdala as well as indirect projections from the central and the medial nucleus of the amygdala, to the pontine reticular nucleus in the startle reflex pathway (Davis, 2006; Rosen et al., 1991). Electrical stimulation of the central, medial, basolateral, and intercalated nuclei of the amygdala, of the pathway from the amygdala to the acoustic startle brain stem (Rosen and Davis, 1988), and of the lateral and basolateral nuclei of the amygdala (Rosen et al., 1996) lead to enhanced startle amplitude in rats. Lesions of the basolateral amygdala (Sananes and Davis, 1992; Walker and Davis, 1997) or central amygdala (Hitchcock and Davis, 1986; Kim and Davis, 1993; Walker and Davis, 1997) abolish the acquisition and expression of the fear-potentiated startle in rats.

In humans, functional magnetic resonance imaging (fMRI) studies suggest a correlation of BOLD signal with fear-potentiated startle (Kuhn et al., 2019; Van Well et al., 2012; but also see Lindner et al., 2015). There is no meta-analytic summary of these studies yet. Clinical lesion studies in patients with unilateral temporal lobectomy (N = 30) (Weike et al., 2005) or specific bilateral lesions of the basolateral amygdala due to Urbach-Wiethe disease (N = 4) (Klumpers et al., 2015) suggest that amygdala lesions impair fear-potentiated startle. On the other hand, a study in patients with unilateral (left or right) medial temporal lobe resections (N = 28) (Åhs et al., 2010) showed no such impairment.

As for skin conductance and heart period responses, startle eye-blink potentiation is observed during instructed threat anticipation (Costa et al., 2015; Grillon et al., 1993; Mertens and De Houwer, 2016); although in one study, SEBR potentiation was not suppressed by instruction (Sevenster et al., 2012). Thus there is a possibility that startle amplitude in humans is modulated by declarative CS-US contingency knowledge. Clinical lesion studies in patients with left temporal lobectomy (N = 28) (Åhs et al., 2010) and left temporal lobectomy with partial amygdala resection (N = 6) (Funayama et al., 2001) suggested that startle potentiation by instructed threat is reduced in amygdala lesion patients. In the latter study, right temporal lobectomy with partial amygdala resection had no impact (N = 8) (Funayama et al., 2001).

Circumstantial evidence for amygdala-dependent learning underlying fear-potentiated startle would be the demonstration that this CR can be observed in the absence of declarative learning. There are a few reports of fear-potentiated startle in the absence of contingency awareness (Hamm and Vaitl, 1996; Jovanovic et al., 2006; Sevenster et al., 2014; Weike et al., 2007), while others did not observe this (Dawson et al., 2007a; Grillon, 2002; Purkis and Lipp, 2001). A meta-analysis (which pooled 26 skin conductance and 4 fear-potentiated startle studies for the calculation of effect size) highlighted substantial publication bias and methodological difficulties (Mertens and Engelhard, 2019), such that it appears premature to draw strong conclusions.

To summarize, there is good direct non-human evidence that amygdala-dependent learning underlies fear-potentiated startle. Lesion evidence in humans is weaker, and there is a possibility that declarative memory modulates fear-potentiated startle responses via a pathway that passes through amygdala.

2.5.3 Cognitive-computational: Underlying learning components

To our knowledge, there are no empirical studies assessing the cognitive-computational learning process underlying conditioned startle. We note a theoretical suggestion that fear-potentiated startle does not directly relate to US prediction, but represents a balance between the metabolic cost of the startle reflex and its benefit in terms of predator escape, both of which also

depend on contextual factors (Bach, 2015). This is supported by the observation that startle reflex amplitude in rats non-monotonically depends on US magnitude: startle amplitude becomes smaller when very strong US is predicted (Davis and Astrachan, 1978). Finally, we note that during instructed anticipation of threat, startle magnitude in one study related to outcome uncertainty rather than outcome probability (Bennett et al., 2018).

2.5.4 Methodological: Psychometric properties

Compared to the large literature on startle eye-blink responses, relatively few studies have directly compared them to other CR. In one study using short (3.5-5 s) CS-US interval, with all CR analyzed in the framework of psychophysiological modelling (PsPM; Bach et al., 2018a; Bach and Friston, 2013; Bach and Melinscak, 2020), startle eye-blink responses discriminated CS+/CS− better than skin conductance or heart period responses during threat acquisition and retention (Khemka et al., 2017). In contrast, another study reported that peak-scored skin conductance responses discriminated CS+/CS− better than startle eye-blink responses (Leuchs et al., 2018); retrodictive validity for startle eye-blink responses in this sample was less than half of what was reported in three independent samples in Khemka et al. (2017). Threat-conditioned startle eye-blink potentiation is retained, extinguished and reinstated (Norrholm et al., 2006), and recovers after 24 hours (Norrholm et al., 2011). The startle eye-blink response is affected by various individual and situational factors, such as attention and arousal (Bradley et al., 1993; Graham, 1975; Grillon and Baas, 2003; Lang et al., 1990; Lipp et al., 1998, 1997; Vanman et al., 1996). Due to its very short duration, startle eye-blink responses can be estimated on a single-trial level and distinguished from responses elicited by US (Blumenthal et al., 2005; Khemka et al., 2017). In contrast to passively measured responses, such as skin conductance, pupil size, heart period and respiratory amplitude, startle-eye blink requires elicitation by an acoustic startle probe. Startle probes have been shown to interfere with threat learning to CS+ as measured with skin conductance (Sjouwerman et al., 2016) and with safety learning to CS– as measured with pupil size (de Haan et al., 2018).

2.6 Limb withdrawal responses

2.6.1 Background

Withdrawal of a limb is an immediate protective skeletal muscle response to a noxious (unconditioned) stimulus. It can also be observed as consummatory CR to avoid harm in the specific limb to which a nociceptive US will be administered (Dimitrova et al., 2004; Schlosberg, 1928; Zhang et al., 2016). In humans, limb withdrawal responses can be measured with electromyography from the tibialis anterior muscle in the shin, when electric shock US is administered to the foot (Dimitrova

et al., 2003; Kolb and Timmann, 1996), or from the brachioradialis and biceps-brachii muscles of the arm on which a US is administered (Zhang et al., 2016). Limb withdrawal responses have been observed when US was unavoidable, that is, in the absence of instrumental reinforcement (Baumbauer et al., 2009; Timmann et al., 2000; Zhang et al., 2016).

2.6.2 Translational: Amygdala-dependent learning

Conditioned limb-withdrawal responses are observed in several species. There is no direct non-human evidence for or against amygdala-dependent learning to underlie limb withdrawal. In dogs, conditioned leg flexion response was initially abolished after bilateral amygdala lesions, but responses recovered over time (Fonberg et al., 1962). In cats, cerebellar lesion (Kolb et al., 1997) and inactivation (Voneida, 2000) impaired conditioned withdrawal responses. There is a suggestion that spinal cord-dependent learning enables conditioned limb withdrawal responses in several non-human species (Culler, 1938; Grau et al., 1990; Illich et al., 1994; Patterson, 1975), but it appears unclear to what extent this contributes to limb withdrawal conditioning in intact, awake animals (Nordholm et al., 1991).

In humans, fMRI suggests that limb withdrawal magnitude relates to ipsilateral BOLD activity in the cerebellum (Zhang et al., 2016). Furthermore, a human lesion study reported impaired conditioned limb withdrawal in patients with cerebellar lesions (N = 10) (Timmann et al., 2000).

To summarize, there is direct evidence in non-humans and humans that conditioned limb withdrawal reflects cerebellum-dependent learning, with no evidence for or against amygdala-dependent learning, and limited evidence for spinal cord dependent-learning. It thus appears that limb withdrawal conditioning is more akin to eyeblink conditioning than to the other CR discussed (see for review Bracha and Bloedel, 1996; Timmann et al., 2010).

2.6.3 Cognitive-computational: Underlying learning components

One human fMRI study suggested that the associability term from a hybrid Rescorla-Wagner/Pearce-Hall learning model correlates with BOLD fMRI responses in cerebellar regions that also related to conditioned limb withdrawal (Zhang et al., 2016). However, to our knowledge, there are no studies directly assessing the cognitive-computational learning process underlying conditioned limb withdrawal.

2.6.4 Methodological: Psychometric properties

As far as we are aware, psychometric properties of limb withdrawal have not been quantitatively studied or compared with other CR. Conditioned limb withdrawal has been shown to

extinguish in dogs (Antal and Gantt, 1970), rats (Ginn et al., 1983) and spinalized cats (Beggs et al., 1983). Based on a comparison of many studies across species, it has been suggested that conditioned withdrawal responses require more repetitions of the CS-US pairings to emerge, compared to skin conductance and pupil size responses (Lennartz and Weinberger, 1992).

2.7 Gaze direction responses

2.7.1 Background

From the point of view of survival, it may be important for an organism to attend to threat signals. When CS were presented in competition with distractors during threat conditioning, several studies reported CS+/CS− differences in fixation time (Austin and Duka, 2010; Koenig et al., 2017) and in first saccade latency (Koenig et al., 2017). Other studies did not report such differences (Eippert et al., 2012) or found longer fixation time for both CS+ and CS− compared to the distractors (Hopkins et al., 2015). In a different type of attentional task, performed after threat conditioning, CS serve as distractor items. Mulckhuyse et al. (2013) had participants perform an oculomotor selection task in which they made saccades to a target stimulus. These saccades deviated more toward CS+ than CS− distractors early (200 ms) after trial start but deviated away from the CS+ later on (> 260 ms). Nissens et al. (2017) found very similar results with more saccades to the CS+ distractor than CS− distractor, especially for early saccades, and this persisted when looking at the CS+ was punished (by triggering US delivery). Moreover, Koenig et al. (2017) found that in a visual search task, early attentional bias (frequency of fixations) to CS distractors was stronger for cues with higher shock association. In yet another setup, CS are used as distractor and target items after conditioning in an instructed saccade task. Here, instructed saccades towards CS+ were faster than towards neutral cues (Schmidt et al., 2015a), and there were more erroneous saccades towards CS+ (Hopkins et al., 2016; Schmidt et al., 2015a). To summarize, there is limited evidence for differential fixation duration and saccade latency when CS are presented together with distractors during learning, as well as some evidence for differential gaze patterns when CS are distractors in a task after threat conditioning.

2.7.2 Translational: Amygdala-dependent learning

To our knowledge, there are no studies investigating the neurobiological learning mechanisms underlying conditioned gaze direction responses in humans or other species.

2.7.3 Cognitive-computational: Underlying learning components

We are not aware of empirical studies assessing the cognitive-computational learning process underlying conditioned gaze patterns.

2.7.4 Methodological: Psychometric properties

In a threat-conditioning experiment with a visual display of either a CS+ or a CS− and distractor stimuli, retrodictive validity to distinguish CS+/CS− by gaze dwell time was smaller than for pupil size responses (Koenig et al., 2017). We are not aware of other studies investigating psychometric properties of threat-conditioned gaze responses, or their retention and extinction.

2.8 Reaction time

2.8.1 Background

Reaction time is a common measure of attention and processing speed for perception, decision and motor action. Studies that measure the effect of threat conditioning on reaction times can be broadly divided into those where reaction times are measured (1) to the CS during (or directly after) acquisition in a threat conditioning experiment or (2) to other target stimuli in an attentional task during or after threat conditioning, where the CS can be a location cue or a distractor stimulus.

Regarding studies of type (1), the direction of reported effects is rather inconsistent between studies (Critchley et al., 2002; Eippert et al., 2012, 2008; Geuter et al., 2017; Gottfried et al., 2002; Lawson et al., 2014; Morris and Dolan, 2004; Padmala and Pessoa, 2014; Prévost et al., 2013; Romaniuk et al., 2010; Seymour et al., 2005). We are not aware of systematic investigations or meta-analyses.

Studies of type (2) have consistently reported shorter reaction times for target stimuli that were cued by CS+ compared to CS− (Armony and Dolan, 2002; Pischek-Simpson et al., 2009; Schmidt et al., 2015b; Van Bockstaele et al., 2010; Van Damme et al., 2004; however, see Purkis and Lipp, 2009), shorter reaction times for validly cued and longer reaction time for invalidly cued targets when the cue is CS+ rather than CS− (Koster et al., 2005, 2004; Notebaert et al., 2011; Van Damme et al., 2006; however, see Stormark et al., 1999), and longer reaction times to auditory or vibrotactile cues in the presence of visual CS+ (Dawson et al., 1982; Dirikx et al., 2007, 2004; Hermans et al., 2005; Lipp et al., 1993). To summarize, this indicates faster reaction when the CS+ is correctly cueing the location of a following target stimulus (attentional capture; the first moving of attention to a stimulus), and slower later reactions to other target stimuli when a CS+ is present (attentional holding; longer-lasting focus of attention on a stimulus), compared with a CS−.

2.8.2 Translational: Amygdala-dependent learning

To our knowledge, there are no studies investigating the neurobiological learning mechanisms underlying conditioned attentional capture or holding in humans or other species. A report of attentional capture during instructed threat (Deltomme et al., 2018) suggests a potential influence of declarative learning.

2.8.3 Cognitive-computational: Underlying learning components

We are not aware of studies investigating which associative learning component is reflected in conditioned attentional capture or holding. A study on reaction times to CS during threat learning (Prévost et al., 2013) appears difficult to interpret in the light of the conflicting literature on the sign of reaction time differences between CS+ and CS−.

2.8.4 Methodological: Psychometric properties

Psychometric properties of conditioned attentional capture or holding have not been reported or directly compared to other CR. Conditioned attentional capture can be extinguished (Dirikx et al., 2007, 2004; Hermans et al., 2005; Koster et al., 2005; Van Bockstaele et al., 2010; Van Damme et al., 2006), reinstated (Dirikx et al., 2004; Van Damme et al., 2006; but see: Dirikx et al., 2007; Hermans et al., 2005), as well as reacquired (Van Bockstaele et al., 2010).

2.9 Pavlovian-to-instrumental transfer

2.9.1 Background

Pavlovian-to-instrumental transfer is the impact of a Pavlovian CS that predicts a particular outcome on instrumental actions performed to achieve the same (specific Pavlovian-to-instrumental transfer) or a different (unspecific Pavlovian-to-instrumental transfer) outcome (Bouton, 2007; Cartoni et al., 2016). In non-human species, threat-conditioned stimuli inhibit instrumental responses to obtain a reward (conditioned suppression; Estes and Skinner, 1941) and facilitate instrumental responses to avoid a different aversive outcome (conditioned facilitation; Lolordo, 1967). Outcome-unspecific conditioned facilitation of avoidance response rate by threat-conditioned CS+ compared to CS− has also been demonstrated in humans (Xia et al., 2019). Similar paradigms include setups in which a motor response is instrumentally trained and simultaneously incentivized by explicit goals in a computer game; in such a setup, both outcome-specific and outcome-unspecific conditioned facilitation by threat-conditioned stimuli have been reported (Garofalo and Robbins, 2017). Furthermore, conditioned suppression by threat-conditioned cues has been observed on instructed motor responses (i.e., responses that do not lead to explicit rewards; Allcoat et al., 2015; Bond, 1979;

Di Giusto and Bond, 1979; Di Giusto et al., 1974; Punch et al., 1976). Threat-conditioned stimuli also interact with subsequent goal-directed behavior when the CS become predictive of new outcomes (Lindström et al., 2019), or when participants are instructed to approach the CS (Krypotos et al., 2014). Overall, there is good evidence that threat-conditioned cues interfere with goal-directed behavior both in classical Pavlovian-to-instrumental transfer paradigms and in other experimental situations, although not all studies have reported such effects (Hebart and Gläscher, 2015; Rigoli et al., 2012).

2.9.2 Translational: Amygdala-dependent learning

Pavlovian-to-instrumental transfer can be measured in various non-human species. In rats, conditioned facilitation was disrupted after lateral and central amygdala but not basal amygdala lesions (Campese et al., 2014), and after medial amygdala lesions (McCue et al., 2014). Also in rats, conditioned suppression was impaired by lateral and central amygdala lesions (Campese et al., 2015) but not basolateral amygdala lesions (McDannald and Galarce, 2011). In contrast, medial amygdala lesions did not affect conditioned freezing (McCue et al., 2014) while basolateral amygdala lesions did impair freezing (McDannald and Galarce, 2011), suggesting that either the plasticity sites or output relays are partly different for these two types of CR. To our knowledge, there are no human studies on the neurobiological mechanisms underlying aversive Pavlovian-to-instrumental transfer.

2.9.3 Cognitive-computational: Underlying learning components

We are not aware of studies investigating which associative learning component is reflected in aversive Pavlovian-to-instrumental transfer.

2.9.4 Methodological: Psychometric properties

In one study using short (3-3.5 s) CS-US interval, with all other CR analyzed in the framework of psychophysiological modelling (PsPM; Bach et al., 2018a; Bach and Friston, 2013; Bach and Melinscak, 2020), Pavlovian-to-instrumental transfer discriminated CS+/CS− less well than skin conductance, heart period and pupil size responses (Xia et al., 2019). However, this comparison was biased against Pavlovian-to-instrumental transfer because psychophysiology was acquired during learning (with ongoing reinforcement) and Pavlovian-to-instrumental transfer during extinction. A Pavlovian impact on latency of instructed approach towards CS has been shown to be sensitive to extinction and renewal in one human study (Krypotos et al., 2014). We are not aware of studies investigating retention or extinction with a classical Pavlovian-to-instrumental transfer paradigm.

2.10 Explicit report of CS-US contingencies

2.10.1 Background

Explicit memory, or declarative knowledge, of the CS-US contingency is measured with free verbal report, via various questionnaires, or by visual analogue scale. Contingency knowledge can be measured continuously or intermittently during and/or after the experiment. A multitude of threat-conditioning studies have shown that participants report higher US expectancy after CS+ than CS− both during and after learning (e.g., Knight et al., 2003; MacNamara et al., 2015; Sevenster et al., 2014; review: Lovibond and Shanks, 2002). How the emergence of declarative contingency knowledge relates to other CR has been discussed for decades but is still unclear. Three models have been suggested: (1) contingency awareness causes other CR (strong single-process model of threat conditioning), (2) declarative knowledge and other CR are caused by the same underlying learning process (weak single-process model), and (3) declarative knowledge and other CR reflect entirely separate learning processes (dual-process model; Lovibond and Shanks, 2002). Instructed CS-US contingencies can elicit various CR (Atlas, 2019; Dunsmoor et al., 2012), a necessary but not sufficient condition for the strong single-process model. On the other hand, CR in the absence of CS awareness (and consequently, in the absence of CS-US contingency knowledge) would be a sufficient (but not necessary) condition for the dual-process model. In a meta-analysis including various CR, Mertens and Engelhard (2019) found a medium effect size for unaware conditioning with significant publication bias, which rendered the meta-analytic evidence inconclusive. Hence, the question cannot be answered at present. Finally, declarative contingency knowledge forms part of a wider array of episodic memory of CS and US encounters; for further discussion of episodic memory in the context of threat conditioning we refer to Dunsmoor and Kroes (2019).

2.10.2 Translational: Amygdala-dependent learning

Declarative memory can only be assessed in humans. Declarative memory in many tests requires hippocampus integrity (Eichenbaum, 2004), and so it is suggested that explicit report of CS-US contingency knowledge in threat conditioning also depends on hippocampus. A single-case study in a patient with selective bilateral hippocampal lesion found impaired contingency learning (but unimpaired skin conductance responses) whereas another patient with selective bilateral amygdala damage showed unimpaired CS-US contingency learning (but diminished conditioned skin conductance responses; Bechara et al. 1995). We note this study did not assess discriminant conditioning and the delayed contingency recall test may have underestimated contingency learning during the task. Similar results were found in another single-case study with a bilateral amygdala lesion patient (Phelps et al., 1998). fMRI studies reported a relationship between accuracy of contingency

reports and BOLD signal in bilateral middle frontal gyrus and parahippocampal gyrus (Carter et al., 2006), and a relation of contingency awareness with hippocampal BOLD responses on a trial-by-trial basis (Knight et al., 2009), while aware and unaware participants differed in ventral striatal BOLD signal elicited by CS+ vs. CS− (N > 110) (Klucken et al., 2009). A human lesion study in patients with unilateral temporal lobectomy reported unimpaired CS-US contingency learning (N = 22) (LaBar et al., 1995).

To summarize, there are circumstantial arguments that hippocampal, but not amygdalar, learning underlies contingency reports, with direct evidence from one single-case human study.

2.10.3 Cognitive-computational: Underlying learning components

One may assume that contingency ratings reflect US prediction, although the precise wording of the instructions may influence this. In one study, trial-by-trial US expectancy ratings were better explained with the US prediction term from a hybrid Rescorla-Wagner/Pearce-Hall model than from a standard Rescorla-Wagner model (Boll et al., 2013).

3.10.4 Methodological: Psychometric properties

Retrodictive validity for explicit reports has been reported much higher than for autonomic or attentional conditioned responses (e.g., gaze direction: Hopkins et al., 2015; skin conductance: MacNamara et al., 2015; Sevenster et al., 2014). We are not aware of studies on the reliability of contingency ratings. According to one study, declarative contingency knowledge in the form of trial-by-trial US prediction can be retained, extinguished, spontaneously recovered, reinstated and counter-conditioned (Kang et al., 2018). To our knowledge, no studies have reported extinction of post-experiment CS-US contingency ratings. For further considerations regarding the measurement of explicit CS-US contingency knowledge, we refer the reader to Lovibond and Shanks (2002).

Table 1. Summary of the reviewed findings for each conditioned response.

	Observed in non-human species	Amygdala-dependent learning in humans (quality of evidence)	Amygdala-dependent learning in non-human species (quality of evidence)	Declarative memory modulation	Effect size to distinguish CS+/CS− *	Retention	Extinction
Skin conductance	Yes	Yes (single case study)	Yes (one monkey study)	Possible	Moderate	Yes	Yes
Pupil size	Yes	NA	NA	NA	High	Yes	Yes
Heart period	Yes	NA	Yes (several studies)	Possible	Moderate	Yes	Yes
Respiration	Yes	NA	NA	NA	Low	Yes	NA
Startle eye-blink	Yes	Yes (conflicting results)	Yes (several studies)	Possible	High	Yes	Yes
Limb withdrawal	Yes	No (circumstantial)	No (circumstantial)	NA	NA	NA	Yes
Gaze direction	NA	NA	NA	NA	Moderate/high	Yes	NA
Reaction time	NA	NA	NA	Possible	NA	NA	Yes
PIT	Yes	NA	Yes (several studies)	NA	Low	Yes	NA
Explicit memory	-	No (single case study)	NA	-	High	Yes	Yes

NA = Not Available, i.e. no published studies identified. PIT = Pavlovian-to-instrumental transfer. * However, different CR may reflect different underlying learning quantities, and therefore, effect size to distinguish CS+/CS− can depend on the specific experimental paradigm.

3 Conclusions

In this review, we summarized some of the vast literature on the use of various CR to index threat conditioning mainly in humans, but also in other species. While sometimes taken as equivalent, it turns out that the reviewed measures differ in functional, neural, cognitive, and methodological aspects. Indeed, some of these measures are only weakly inter-correlated on trial-by-trial basis during threat learning (Leuchs et al., 2018).

From the functional perspective, skin conductance, pupil size, and respiratory amplitude are valence-unspecific measures that do not directly relate to active defensive or escape behaviors (Bradley et al., 2008, 2001; Lipp et al., 1994). Limb withdrawal, on the other hand, is a consummatory defensive response specific to the aversive stimulus, directly protecting the organism from threat (Zhang et al., 2016). Finally, gaze direction is related to information gathering about the potential threat; threat-relevant stimuli attract attention because it is important to observe them in order to be able to avoid the following threat.

On the neural level, it seems that amygdala-dependent learning is involved in the generation of some CR. Based on our review of the literature, evidence for a role of amygdala-dependent learning is most robust for startle reflex across species, good for heart period responses and Pavlovian-to-instrumental transfer in non-human species, while it is relatively weak for skin conductance responses. We note that the reviewed human lesion studies can only provide limited information on this question: specific lesion cases are rare, non-specific lesions usually cannot separate amygdala and hippocampus involvement, and surgical lesions usually leave one hemisphere intact. Furthermore, there may be adaptation to the lesion and possible restoration of function over years (Müller and Knight, 2006; Rorden and Karnath, 2004). At the time of writing, the neurobiological processes underlying threat-conditioned pupil size, respiratory, gaze direction responses, attentional capture and holding have not been investigated. Limb withdrawal conditioning appears to be dependent on the cerebellum and possibly the spinal cord, but an involvement of the amygdala has not been excluded. Circumstantial evidence and a single-case lesion study suggest that explicit report of CS-US contingencies represents declarative knowledge that might rely on hippocampal learning.

On the cognitive level, there is a dearth of studies addressing the relation of formal associative learning models and the trial-by-trial trajectories of CR. Skin conductance and pupil size responses have been associated with different computational quantities across studies, although some of these quantities were not used in a formally equivalent manner across studies. Therefore, we believe that more systematic investigation of the computational mechanisms underlying threat-learning, using a variety of CR, a larger model space and larger sample sizes, is warranted.

In terms of methodology, despite attempts to standardize the measurement of some CR (e.g., Blumenthal et al., 2005; Boucsein, 2012), for most CR there is a marked lack of consensus. Recent papers have provided an overview across research fields (Lonsdorf et al., 2017) as well as tractable criteria on how to decide between measures. One of these is retrodictive validity, the effect size to discriminate CS+ and CS−, which quantifies the quality of inference on CS-US association (Bach et al., 2018a, 2020). However, no comprehensive comparison of the different CR exists at this moment. For the model-based approaches reviewed by Bach et al. (2018a), it seems that pupil size (for acquisition of threat responses) and startle-eye blink responses (for retention) provide the highest retrodictive validity, translating into the fewest participants needed to achieve the same statistical power to discriminate CS+ and CS− (Bach et al., 2020). However, an important consideration is that different CR may reflect different learning quantities. To what these quantities differ between CS+ and CS− trials can depend on the experimental design, such that some designs may favor one CR and other designs a different CR. Regarding the influence of experimental design on inference in associative learning experiments, we refer the reader to Melinscak and Bach (2020).

Several, but not all, CR provide the possibility for quantifying the trial-by-trial learning trajectory, which allows investigation of the underlying computational threat learning mechanism. Since it is not known precisely which measures depend on synaptic plasticity in the amygdala, and whether they index the same cognitive quantities, measuring different CR simultaneously may be advantageous, even if some of them are noisier than others. This would also allow better comparisons of psychometric properties between CR. Of course, each measure brings along a variety of practical considerations that have been touched upon only cursorily here and have been covered extensively in other sources (Cacioppo et al., 2007; Lonsdorf et al., 2017).

The selection of CR is crucial for quantifying success of experimental memory interventions. Extinction is thought to form inhibitory memory (Dunsmoor et al., 2015) and thereby suppress the expression of CR, although threat memory may persist. This is why a range of interventions are discussed that may reduce latent threat memory and may possibly be used for clinical application (Phelps and Hofmann, 2019). Several interventions were successful in reducing some CR but not others (Bach et al., 2018b; Kredlow et al., 2016; Soeter and Kindt, 2010). To translate experimental interventions to clinical practice, it would be important to understand which learning or memory system is targeted by these drugs, which in turns requires understanding which learning systems are indexed by the different CRs. In the light of such translational controversies, it appears that investigating the neural and cognitive underpinnings of different threat conditioning measures is not only of methodological and academic interest but will yield tangible benefits to clinical application as well.

To this end, we have summarized the most pressing research questions arising from our review in Table 2. With this work, we hope to have contributed to a more rational and broader choice of conditioned responses for future threat conditioning experiments in humans.

Table 2. Most pressing open research questions for the study of CR in human threat conditioning.

Research question	Necessary studies to answer the question
1) Is amygdala necessary for threat-conditioned pupil size, heart period, respiratory amplitude, limb withdrawal, reaction time and gaze responses in humans?	• Selective amygdala lesion patient studies
2) What is the involvement of declarative CS-US contingency memory in the various CR, especially startle eye-blink and skin conductance responses?	• Comparison of CS-US contingency unaware vs. aware participants with better methodology
3) Do hippocampus lesions affect threat-conditioned startle eye-blink and skin conductance responses, or other CR, in humans or in other species?	• Hippocampus lesion patients • Hippocampus lesions in rodents
4) Do the different CR reflect different learning components?	• Large computational modelling studies with multiple CR and learning models • Studies on the effects of behavioral/pharmacological memory interventions on multiple concurrent CR
5) What is the retrodictive validity (CS+ vs. CS− effect size) of each CR? Which CR has the best properties across the board or in a given experimental design?	• Comprehensive measurement of multiple CR and comparison of retrodictive validity for different experimental designs and in large samples

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