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Making translation work: Harmonizing cross-species methodology in the behavioural neuroscience of Pavlovian fear conditioning

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ABSTRACT

Translational neuroscience bridges insights from specific mechanisms in rodents to complex functions in humans and is key to advance our general understanding of central nervous function. A prime example of translational research is the study of cross-species mechanisms that underlie responding to learned threats, by employing Pavlovian fear conditioning protocols in rodents and humans. Hitherto, evidence for (and critique of) these cross-species comparisons in fear conditioning research was based on theoretical viewpoints. Here, we provide a perspective to substantiate these theoretical concepts with empirical considerations of cross-species methodology. This meta-research perspective is expected to foster cross-species comparability and reproducibility to ultimately facilitate successful transfer of results from basic science into clinical applications.

1. Introduction

In the biomedical research enterprise, the term “translation” often decorates review articles, original publications and grant applications. It promises, for instance, the elegant transfer of mechanisms in rodents to complex human functions and vice versa. In behavioural neuroscience, specifically, translation entails the mapping of synapse-specific processes in animal models onto neurobiological systems in humans. However, the potential of translational research comes with major challenges, most importantly methodological disparities that are inherent to experimental protocols in non-human animals and humans. Consideration of such methodological disparities has been suggested to aid potential translation of findings in biomedical sciences (Freedman et al., 2015; Kola and Landis, 2004; Macleod et al., 2014). Here, we provide such considerations for fear conditioning research across species.

Although translational work in neuroscience is challenging, there have been some successes. For example, decades of research on the basic mechanisms of emotional learning and memory in animals has yielded significant insight into novel therapeutic approaches for clinical

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disorders of fear and anxiety in humans (e.g., Fenster et al., 2018; Griebel and Holmes, 2013,Mataix-Cols et al., 2017; Ressler et al., 2004; Singewald et al., 2015; Walker et al., 2002). Indeed, one form of emotional learning -Pavlovian fear conditioning- has been promoted as *the* prime example of a "translational" paradigm (Kandel et al., 2014; Milad and Quirk, 2012). Although the importance of translational work has been emphasised from a theoretical perspective, the practical implementation to realize translational research in fear conditioning experiments has been neglected so far. While translation of findings is often not the primary goal in fear conditioning experiments, translational implications are often inferred without further considering how and if such promises can be met in practice. We argue that it is important to consider the impact of methodological differences on translational research in rodents and humans in order to provide orientation how to evaluate translational research in practice.

Here, we will compile the practical, methodological considerations for cross-species research in Pavlovian fear conditioning, derived from discussion across ten different international labs working on fear conditioning in rodents or humans. To this end, we aim to initiate a discussion on cross-species challenges and provide methodological consideration for translational research that we expect to ultimately advance progress in fear conditioning research. We also intend to go beyond theoretical ideas of translation by informing mechanistic insights across species with an evidence-based methodological comparison to ultimately foster translational progress.

1.1. Pavlovian fear conditioning — a simple protocol?

Across species, learning to identify and predict danger is key for survival. Animals, including humans, are equipped with an evolutionary-conserved (neuro)physiological machinery that mobilizes defensive responses to mitigate current threats as well as mediates learning to anticipate future threats (Blanchard, 2017; Blanchard et al., 1989; Fanselow, 1994; LeDoux, 2012; Maren, 2001). Theoretically, these conserved circuits allow for the examination of the behavioural and biological basis of learned threat responses in rodents (such as rats and mice) to infer how these processes operate in humans.

The study of learned defensive behaviour has relied upon Pavlovian fear conditioning, a fundamental form of associative learning that exhibits similar properties in a range of species, including rodents to humans. In the laboratory, Pavlovian fear conditioning procedures typically involve several phases, including acquisition training, extinction training and retrieval tests of learned responses (for an overview see Lonsdorf et al., 2017). In brief, during *acquisition training*, individuals learn to associate a distinct cue (conditioned or conditional stimulus, CS +) or a whole context (conditioned or conditional context, CXT+) with the occurrence of an aversive event (unconditioned or unconditional stimulus, US). As a result, the presence of the CS + or CXT + elicits a conditioned or conditional response (CR), which manifests as a number of physiological responses and species-specific defensive reactions. Collectively, these diverse CRs are often termed "fear" CRs, as a useful way to aggregate a number of different defensive responses (freezing, tachycardia, hypertension, sweating, etc.). Although it is not known whether non-human animals experience a subjective state of fear (e.g., LeDoux, 2014), there are clearly similarities in the nature of the CRs to aversive CSs across mammalian species and these responses likely reflect a central state of fear (whether experienced subjectively or not; Fanselow and Pennington, 2018). During a subsequent *extinction training* phase, the CS + or CXT + is presented without the US, which leads to a decrease in the magnitude and/or frequency of the CR. The expression (and inhibition) of CRs can be probed during *retrieval tests*.

Although Pavlovian fear conditioning procedures can be performed in both rodents and humans, translation of results across species is challenged by inherently different procedural and methodological instantiations of Pavlovian fear conditioning protocols in rodents and humans. In the following, we describe these differences and their relevance to cross-species comparisons between rodents (here restricted to mice and rats) and humans. In particular, we aim to raise awareness on how methodological differences might impact interpretation of results, in order to promote valid cross-species comparisons of existing findings, as well as to improve translational designs of future studies. The overarching aim of this overview is to equip readers from diverse backgrounds with a basic set of tools to evaluate cross-species methods employed in fear conditioning research to enable them to correctly interpret findings. We further provide advice how to consider and overcome cross-species methodological differences to utilize the full potential of translational research in fear conditioning. First, we discuss and compare key elements entailed in the fear conditioning paradigm across both species. Second, we describe the most important dependent measures within each species and third, comment on individual differences. Detailed "what to consider" key-points summarizing the key take-home messages provide practical guidelines for the reader.

2. Paradigm

While this description of the fear conditioning paradigm sounds straightforward, the specific methodological instantiation (e.g., which stimulus types for the CS, CXT, US are used; timing of acquisition and extinction training) can heavily affect the outcomes, as well as comparability across species. Hence, consideration of methodological details of species-specific protocols is central to inform cross-species comparability of results. Here, we will compare essential elements of fear conditioning paradigms that are shared across species (e.g., CS, CXT, US) or species-specific elements (e.g., instruction of human participants).

2.1. Conditioned stimuli (CS): cues and control conditions

Cues of different modalities have successfully been employed as CSs across species. In rodents, auditory cues are typically employed (for an overview see Wotjak, 2019), whereas in humans, visual cues are common (for a comparison of visual and auditory CSs on fear-potentiated startle see Norrholm et al., 2011 and for a discussion see Lonsdorf et al., 2017). Despite inherent differences in underlying sensory processing, learning-related mechanisms are considered comparable (Delgado et al., 2006; Maren, 2001; Whalen and Phelps, 2009; cf. Bergstrom and Johnson, 2014; Tazumi and Okaichi, 2002). Typically, stimuli that are neutral prior to fear acquisition training are used as CSs, but in some cases stimuli that inherently signal threat-relevant information have been employed. Importantly, threat-relevant cues can be species-specific, including pictures of angry facial expressions in humans (Mineka and Ohman, 2002; Öhman and Dimberg, 1978) or contact with conspecifics in animals (Toth et al., 2012; Toth and Neumann, 2013).

Fear conditioning paradigms typically include control conditions to discriminate associative from non-associative processes (such as habituation, dishabituation and sensitization, see Rescorla, 1967). These control conditions, however, often consist of different procedures in rodents and humans. In rodent work, *single-cue protocols* with a single CS + are typically employed that include a separate control group in a *between-subject* design. Typical control groups either receive the same number of CS and US presentations as the experimental group that are however either explicitly unpaired (Pearce and Dickinson, 1975; Sevelinges et al., 2007) or presented randomly (i.e., 'truly random control'; e.g., Barnet and Hunt, 2005; Jüngling et al., 2015; Rescorla, 1967; Rogan et al., 1997) or CSs are presented in the absence of any US (CS alone paradigm; Do-Monte et al., 2015; Maren, 2001; Rescorla, 1967). In research in humans, fear conditioning is typically conducted with *differential protocols,* in which a CS- that is not paired with the US is presented interleaved among paired CS+/US trials in a *within-subject* design (see Norrholm et al., 2008 as an example for the use of single- *and* differential-cue protocols in humans). Additionally, another

common within-subject condition in human experiments that focus on extinction training includes two CS+, one of which is presented during extinction training (CS + E) while the other CS + is not (CS + U) and serves as an unextinguished control (Milad et al., 2007, 2009a, 2009b; Zeidan et al., 2011).

Importantly, control conditions used in animals and humans need to be interpreted with caution, since these controls may not always function as unambiguous neutral conditions (as discussed by Lissek et al., 2005a, 2005b; Lonsdorf et al., 2017; Rescorla, 1967; Wotjak, 2019). Control conditions including explicitly unpaired CS/US presentation in single-cue protocols for example can increase the salience of the context and may allocate safety signal properties to the unpaired cue (Baas and Heitland, 2015; Heitland et al., 2016; Norrholm et al., 2008; Rogan et al., 2005; Tang et al., 2001; Wotjak, 2019). Similarly, the CS- in differential protocols may also acquire safety signal properties (Gerber et al., 2014; Kong et al., 2014; Lohr et al., 2007; Rogan et al., 2005) and hence may imbue associative learning processes – yet inhibitory (i.e., CS/'no US') rather than excitatory in nature (Cándido et al., 2004; Seligman and Binik, 1977; Wendt et al., 2015; but see Chauveau et al., 2012; Jüngling et al., 2008). These additional learning processes recruited in differential protocols include not only safety learning (as discussed above), but also stimulus habituation (Thompson and Spencer, 1966) and learned irrelevance (Baetu et al., 2005; Baker, 1976; for discussion see Ohman, 2009).

Differential conditioning protocols in rodents often include presentations of the CS + and CS- on separate days (Chauveau et al., 2012; Jüngling et al., 2008; Tang et al., 2003), a procedure rarely employed in fear conditioning experiments in humans, where CS + and CS- are presented interleaved within the same training session (for an overview see Lonsdorf et al., 2017). In protocols that include CS- presentation on the same day as the CS+, the sequence of the CS presentation in rodents can either be fixed (e.g., all CS- trials always precedes the CS+, Goosens et al., 2003; Herry et al., 2008; Letzkus et al., 2011), or pseudo-randomized, (e.g., Likhtik et al., 2014; Stujenske et al., 2014), which resembles CS presentation procedures that are commonly used in humans.

In conclusion, experiments in rodents and humans use fear conditioning procedures that reliably engage excitatory learning to a CS that predicts an aversive US. However, differences typically exist with respect to the employment of control conditions (e.g., between vs. within-subject designs, sequence of CS presentations). As these procedural differences may result in the engagement of different or additional learning mechanisms (e.g., safety learning, see above) they potentially hinder direct comparison of results between (and within) species. Moreover, recruitment of such additional learning mechanisms can induce more individual variance in fear learning. For example, safety learning is reduced within individuals with high trait anxiety (e.g., Gazendam et al., 2013; Haaker et al., 2015; Haddad et al., 2012; for an overview see Lonsdorf and Merz, 2017) and diagnoses of anxiety related disorders (Duits et al., 2015; Jovanovic et al., 2010; Lissek et al., 2005a, 2005b). Hence, even though fear conditioning protocols across species share similar operationalization of learned threat anticipation to the CS+, the specific operationalization (e.g., if and when a CS- was presented) of control conditions and their underlying mechanisms needs to be considered to make a valid interpretation of translational results.

2.2. Context conditioning

Context in Pavlovian fear conditioning experiments has been defined as the internal (physiological and cognitive, i.e., interoceptive) or external (environmental and social, i.e., exteroceptive) background in which associative learning and retrieval takes place (Bouton, 2004; Maren et al., 2013). Contexts are configural representations of numerous multimodal cues, and they can be separated from discrete cues based on their modality, duration, complexity and temporal arrangement (Fanselow, 2010; Rudy, 2009). A context can be associatively learned as a predictor for a US (here termed as CXT+) and/or setting the occasion for CS/US associations that have been learned during acquisition and extinction training. As such, the context plays a central role in gating the expression or inhibition of CRs across species (Bouton, 2002; Goode and Maren, 2014).

In animal research, a multisensory manipulation of external contexts is common practice (Maren, 2001). This is often accomplished by manipulating specific features of the physical chambers (e.g., size, floor textures, visual patterns, odors, background noise, ambient illumination, or a combination of all) in which animals undergo acquisition training, extinction training, and retrieval testing (Bouton, 2002). In addition to these exteroceptive stimuli, internal stimuli create interoceptive contexts that influence fear conditioning. Interoceptive contexts can include drug or hormonal state (Acca et al., 2017; Bouton et al., 1990; Cunningham, 1979), deprivation state (e.g., hunger), as well as the passage of time (Bouton, 2002; Maren et al., 2013). In humans, exteroceptive contexts typically consist of visual stimuli (Alvarez et al., 2008; Andreatta et al., 2015; Kroes et al., 2017; Marschner et al., 2008) including colours of computer background screens (Haaker et al., 2013a, 2013b; 2017; Kalisch et al., 2006; Pohlack et al., 2012), complex images of environments (Lonsdorf et al., 2014; Milad et al., 2007), or virtual visual contexts (Glotzbach-Schoon et al., 2013; Huff et al., 2010; Kroes et al., 2017). Investigations in humans that employ two *physically* different rooms (to mirror the context manipulations in animals) are rare in humans (LaBar and Phelps, 2005a, ; Schiller et al., 2008). Moreover, in contrast to work in animals, interoceptive contexts (e.g., drug state) in humans and their influence on fear conditioning processes have not been investigated in detail. In particular, while interoceptive states in humans have been manipulated (e.g., stress-manipulation or administration of cortisol), such interoceptive states have not been used as a contextual manipulation of fear conditioning processes (e.g., enhanced cortisol during acquisition training *and* retrieval testing).

In sum, Pavlovian fear conditioning in humans occurs in contexts that are differentiated by subtle changes in visual stimuli, rather than wholesale changes of the surrounding multisensory environment, as employed in rodents. In the last decade, computer-generated contexts in virtual realities that are either presented on large screens or through (immersive) head-mounted displays have gained increasing popularity (Baas et al., 2004; Glotzbach et al., 2012; Grillon et al., 2006; Huff et al., 2010; Kroes et al., 2017). Nonetheless, despite their clear advantage to easily construct different contexts with more complex environmental features, these virtual contexts are typically limited to visual stimuli (Kroes et al., 2017; Maren et al., 2013). It should moreover be considered that acquisition of neural responses in humans (e.g., functional magnetic resonance imaging (fMRI), magnetoencephalography, electroencephalography) typically restricts the physical context (e.g., the bore of an fMRI scanner; Maren et al., 2013).

Despite the procedural differences in context operationalization, there is translational evidence for basic contextual influences on the expression and inhibition of conditioned fear, which is mediated by converging neural networks across species (Haaker et al., 2013a, 2013b; Maren et al., 2013; Milad et al., 2007). However, the effects of such simple instantiation of contextual features in human experiments (e.g., screen background) are limited, since contextual features from the testing room might override contextual learning (Kroes et al., 2017). Moreover, subtle changes in screen backgrounds can induce unintended contextual effects, which has been discussed with respect to reinstatement of CRs in humans (Haaker et al., 2014; Sjouwerman et al., 2015). When presenting reinstatement US, experiments in humans often employ diverse visual contextual features (e.g., black background screen, fixation cross, background screen without cues, etc.), without considering how these subtle differences can impact the contextual modulation of reinstated CRs during a later test. In contrast, contexts presented dur ing reinstatement in rodents often entail well defined,

multisensory features. So far, only one study in humans used different rooms to test the contextual influence on reinstatement of CRs in humans (LaBar and Phelps, 2005a,). It is plausible that future experiments that employ more holistic operationalization of contexts in humans may induce contextual gating of the expression and inhibition of CRs that is more comparable to research in rodents and allow for investigation of more fine-grained contextual effects. Hence, operationalization of contexts as holistic environments in humans would overcome the gap to research in rodents and allow for a better cross-species investigation of contextual influences on CRs.

2.3. Unconditioned stimuli (US)

Across species, the most commonly employed US in Pavlovian fear conditioning designs is electrical stimulation. Other cross-species US-types include high-intensity white noise bursts and air blasts (see Lonsdorf et al., 2017 for more details on US employed in humans and Wotjak, 2019 for rodents). Naturalistic USs in turn, are typically species-specific and consequentially more difficult to translate between species. Naturalistic USs in rodents include, for instance, predator odour (Takahashi et al., 2008) and in humans videos of actors that insult human participants (Reichenberger et al., 2017; Wieser et al., 2014) or fearful human faces paired with screams (Glenn et al., 2012).

The sensory quality of electric stimulation is considered to be comparable across species (see Wotjak, 2019 for a discussion on nociceptive comparability in rodents), despite different operationalization: In rodents, electric stimulation is usually given as a brief scrambled AC shock to the feet (Curzon et al., 2009) delivered through a metallic grid floor. In human participants, a DC shock is commonly applied to the hand or forearm through attached electrodes (Lonsdorf et al., 2017). Usually, in both species, the intensity of the electric stimulation is chosen to be an aversive, but only mild nociceptive signal.

Even if we here assume comparable nociceptive qualities, there exist major differences across species with respect to controllability and previous experience of the US. More precisely, human volunteers typically have some control over the US intensity (at least for electric stimulation), which is, for ethical reasons, typically adjusted to tolerable levels ("unpleasant, but not painful" or "unpleasant and painful, but bearable"). The precise procedure to reach such a criterion varies however between laboratories (see Lonsdorf et al., 2017 for more details). These pre-experimental calibration procedures naturally involve pre-exposure to the US. As a consequence, human participants, in contrast to rodents, are neither naïve to the intensity nor the imminence of the threat. Importantly, pre-exposure to the US has been found to attenuate learning of the CS+ as predictors for the US in rodents (Kamin, 1961) as well as in humans (Meulders et al., 2012; Taylor, 1956). US pre-exposure within the experimental *context* might yield excitatory learning, which might impact subsequent learning about the CS/US contingencies, including blocking learning about the CS (Kamin, 1968; Yau and McNally, 2019; but see Maes et al., 2016). It has further been shown in rodents that an acquired context-US association (i.e., first learning) changes the neurochemical substrates that underlie subsequent acquisition training to a CS+ (i.e., second learning; Finnie et al., 2018). In addition, human participants are informed that the experiment involves administration of an electric stimulation prior to the experiment. Hence, prior to fear acquisition training, participants are provided with instructions about the US (cf. details on instructions) in addition to directly experiencing the US during the calibration procedures.

Yet, the electrical stimulation USs are essential to fear conditioning protocols across species. In rodents, the magnitude of the US tends to produce monotonic increases in CRs, such as freezing behaviour (Fanselow and Bolles, 1979) although this relationship is not reflected by increasing acoustic startle responses (Davis and Astrachan, 1978). In rodents, US intensities are commonly between 0.4–1.0 mA for mice and 0.5–1.0 mA for rats with durations of 0.5–2.0 s. To properly interpret these intensities, they should be related to the pain threshold of the animal (same strain and in the same setup, Wotjak, 2019). In humans, physical US intensities are often not informative, because participants rate their subjectively experienced unpleasantness, which typically corresponds to values of 5 or 7 on a 10 point scale (from 0 "I feel nothing" to 10 "maximally unpleasant"; e.g., Andreatta et al., 2015; Haaker et al., 2013a, 2013b; Lonsdorf et al., 2017; Pohlack et al., 2012). Importantly, in rodents high US intensities promote the generalization of conditioned responding. In rodents, generalization has been described to stimuli that are not directly associated with the US such as freezing to the context (Baldi et al., 2004) or CS- (Ghosh and Chattarji, 2015; Laxmi et al., 2003), as well as it might lead to general sensitization of fear responses (Kamprath and Wotjak, 2004; Siegmund and Wotjak, 2006; for an overview see Riebe et al., 2012). Converging findings in humans are sparse (for initial studies on neurobiological US processing see Goodman et al., 2018; Knight et al., 2010), but there is some evidence that highly aversive multisensory USs (electric stimulation combined with white noise and looming snake pictures) induce generalization of skin conductance responses to novel cues as compared to an electric US alone (Dunsmoor et al., 2017).

Experiments in rodents generally employ US presentations that follow presentations of the CS+, so called continuous paring or 100% contingency, whereas human experiments employ continuous, but also partial pairings that include unpaired CS+ presentations (contingencies vary from 100% to below 20%, for review see Lonsdorf et al., 2017; Lonsdorf and Merz, 2017; Sehlmeyer et al., 2009). Lower contingencies have been associated in humans with diminished SCR differential (CS + > CS-) responses (Grady et al., 2016) and reduced amygdala responses (Dunsmoor et al., 2007, but see Sehlmeyer et al., 2009), as well as reduced freezing to an auditory CS + in mice (saline group in experiment 3 in Cain et al., 2005). Similarly, reducing the CS-US contingencies by additional insertion of USs is reflected by decreased freezing to an auditory CS+ in mice (saline group in experiment 2 in Cain et al., 2005). Rred Reduced contigenczy between Re diminished correlates of synaptic plasticity (long-term potentiation) in the basolateral amygdala in rats, when contigency between excitatory postsynaptic potentials (EPSP, mimiking CS signals) and depolarisation (mimiking US signal) is reduced (Bauer et al., 2001). Hence, as postulated by animal work in operant conditioning (Rescorla and Wagner, 1972), contingency between the CS and US scales the processes that underlie learning of CS-US association and the resulting CRs. Studies in humans often employ lower contingencies to slow down CS-US learning, for example to probe learning processes along a larger number of trials, or to analyse unpaired CS presentations (without any US signal) or to slow down extinction learning that follows upon acquisition. Evidence for prolonged CRs during extinction training after partial pairings during acquisition training has mostly been provided from animal studies that used operant protocols (Bouton et al., 2014; Capaldi, 1967). In human experiments, the separation between acquisition and extinction training might also be less pronounced (i.e., a clear start of extinction training is not clear to the participants) when acquisition training employed low CS-US contingencies and extinction follows immediately after acquisition training (without a gap, see *Timing of experimental phases*). Clear separation between acquisition and extinction training, which might be induced in transitions from continuous pairings during acquisition to immediate extinction training, might signal new learning phases (due to a strong violation of expectations) and thereby influence context-dependent extinction learning processes (Dunsmoor et al., 2018; Gershman et al., 2017).

In sum, the use of electric stimulation as US in fear conditioning protocols is considered to induce comparable nociceptive effects across species. Yet, differences across species with respect to the controllability, pre-exposure and expectations about the US exist, which influences threat learning processes in rodents and humans differently (e.g., by expectancy-driven adaption or the impact of instructions about the US). More cross-species research on how procedural factors might

shape US expectancy could help to enhance translation of results across species.

2.4. Instructions

An essential challenge to translational research is that human participants are always verbally informed about the upcoming experiment, while rodents are not. Information about the experiment (typically referred to as instructions) have a powerful impact on fear and safety learning (e.g., Atlas, 2019; Atlas et al., 2016; Duits et al., 2017; Mertens et al., 2018a, 2018b, 2016; Sevenster et al., 2012) and therefore have consequences on the interpretation of findings in humans and translatability of results across species.

In humans, instructions vary from explicit CS/US contingency information ('Only the blue square will be followed by the aversive stimulus, the yellow square will never be followed by the aversive stimulus') to no information about contingencies ('Attend to the visual material on the screen') with varying instantiations in between ('One of the two pictures presented on the screen will be followed by the aversive stimulus, the other not. You will be able to figure out which one by paying close attention'; for an overview see Lonsdorf et al., 2017). Such instructions concerning CS/US contingencies or changes thereof may or may not be provided prior to every experimental phase (i.e., acquisition and extinction training, retrieval tests). In addition to instructions, probing ratings of fear and US expectancy might further enhance awareness for the CS/US contingency and affect conditioned responses (Boddez et al., 2013; Lipp, 2006; Mertens et al., 2018b; Razran, 1955; Sjouwerman et al., 2016; Warren et al., 2014).

Instructions have been employed, for instance, to minimize individual differences in awareness about CS/US contingencies. For example, when extinction learning is of primary interest, instructions about CS/US contingencies during fear acquisition may minimize individual differences prior to extinction. It should, however, be considered that such type of instructions has the potential to affect subsequent phases. Furthermore, some paradigms rely completely on instructions (i.e., 'threat of shock', e.g., Bublatzky et al., 2018; Grillon et al., 1991; Phelps et al., 2001) to produce anticipatory threat responses without providing direct US experiences.

Importantly, instructions affect the temporal dynamics of (conditioned) responding over trials. More precisely, explicit CS/US contingency instructions induce US anticipation to the CS+ as well as discrimination from safety signals (i.e., CS-) already in the first acquisition training trial (i.e., expression of instructed knowledge rather than learning by direct experiences). In contrast, learning from direct experiences (without explicit CS/US contingency instructions) involves a gradual development of US anticipation (Duits et al., 2017; Sjouwerman et al., 2015; Tabbert et al., 2006) and hence CS discrimination typically evolves over time during acquisition training.

Furthermore, the biological substrates recruited and learning processes involved in socially transmitted verbal information (i.e., instructions) as opposed to direct learning experiences have been shown to be distinct (Atlas, 2019; Atlas et al., 2016; Braem et al., 2017; Mechias et al., 2010; Mertens et al., 2018a; Olsson and Phelps, 2007; Phelps et al., 2001; Tabbert et al., 2011).

In sum, instruction of human participants (about the CS/US contingencies) critically determines the process that is probed within a fear conditioning protocol (i.e., learning from direct experiences vs. expression of instructed associations). Since instructions are never part of experiments in rodents, these procedures in humans needs to be critically examined (type and timing of instructions) when comparing and interpreting results across species (Fig. 1)

2.5. Timing of experimental phases

The timing of extinction training with respect to acquisition training does matter, as both associative learning processes require synaptic (across hours) and systemic (across days) consolidation processes to enable long-term memory storage (for a review see for example Baldi and Bucherelli, 2015; Johansen et al., 2011; McGaugh, 2000; Orsini and Maren, 2012).

The time-delay between acquisition and extinction training however typically differs between studies in humans and rodents. While animal experiments often separate acquisition and extinction training by days (*delayed extinction*), it is more common in human research to use *immediate extinction* protocols, i.e., extinction training that follows directly after acquisition training. Research in rodents and humans has shown that immediate extinction training interferes with consolidation of the previously acquired CS/US association memory (Chang et al., 2011; Golkar et al., 2013; Maren and Chang, 2006; Merz et al., 2016; Myers et al., 2006; Norrholm et al., 2008; for an overview see Maren, 2014, but see Kim and Richardson, 2009; Schiller et al., 2008). Interestingly, such interference was found in rats when extinction either followed directly after acquisition training (without a gap) or if both phases were separated by a 15 min gap (Totty et al., 2019). This finding is opposed by a study in humans, revealing that a short break (10 s as opposed to no break), which separates acquisition from extinction training, reduced interference between acquisition and extinction training (Dunsmoor et al., 2018). Hence, gaps between acquisition and extinction training in rodents and humans might be not directly comparable, probably due to a higher stress level after acquisition training in rats (Totty et al., 2019).

Likewise, retrieval tests that probe reinstatement or renewal of CRs typically take place on separate experimental days in rodents, but often occur immediately after extinction training in human experiments (for an overview see Lonsdorf et al., 2017). The time point of retrieval testing, relative to extinction training, however, has an impact on the expression of CRs in rodents (Archbold et al., 2013; Kim and Richardson, 2009) including differences in the underlying neuronal matrix (Kitamura et al., 2017; Sacco and Sacchetti, 2010; Vetere et al., 2017; Wheeler et al., 2013). Hence, it is plausible that extinction memory processes interfere with retrieval testing, yet this has not been addressed in human experiments.

In sum, the timing of experimental phases needs to be considered when comparing results across species. Immediate or delayed extinction or retrieval procedures may recruit different consolidation machineries and map onto different real world experiences: Learning safety (e.g., getting therapeutic treatment) either delayed or following immediately after salient aversive events.

WHAT TO CONSIDER: PARADIGM

Conditioned Stimuli

- Check if a CS- was employed as a CS+ control (within-subject design), or if a between group design was chosen.
- In differential protocols: Check how and when the CS- was presented (*e.g.,* prior to acquisition training or intermixed with the CS+).
- Consider the different (or additional) processes probed by single-cue (mostly excitatory learning) or differential (excitatory and inhibitory learning) protocols.

Context

- Check how "context" is defined. In rodents, contexts are usually defined as different chambers (which might include change at multisensory level such as visual, olfactory and tactile stimuli), whereas contexts in human experiment are often operationalized by different visual stimuli.
- Check if changes in visual features (e.g., background screen) in human experiments are used for contextual modulation. Even subtle, unintended, changes can impact contextual gating of CRs.

Unconditioned Stimuli

- Check the sensory properties of the US (electrical stimulation, loud noise or perhaps species-specific naturalistic stimulus). Shock USs are typically applied to the feet in animals and the forearm, finger, or hand in humans. Despite sensory differences this US type is considered to generate a comparable nociceptive input across species.
- Check the US intensity in animal and human experiments. Moderate US intensities that are associated with discriminative learning in animals (check freezing responses to the CS+ as compared to the CS- or context) may be more comparable to human procedures. High US intensities may induce generalization of CRs (to the context or CS-) and are usually (on average) not employed in experiments with human volunteers.

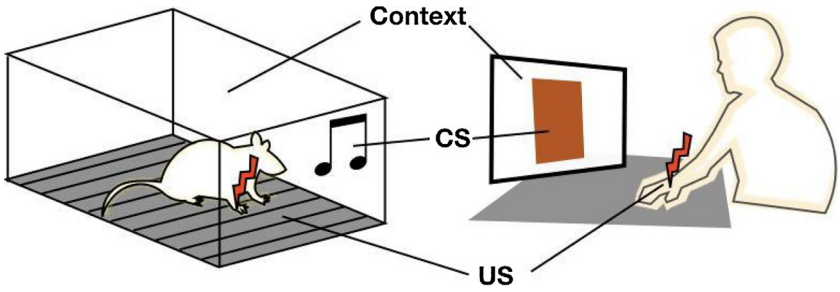

Fig. 1. Schematic illustration depicting key elements within an exemplified cued fear conditioning protocol in rodents (left) and humans (right). CS = conditioned stimulus, US = unconditioned stimulus.

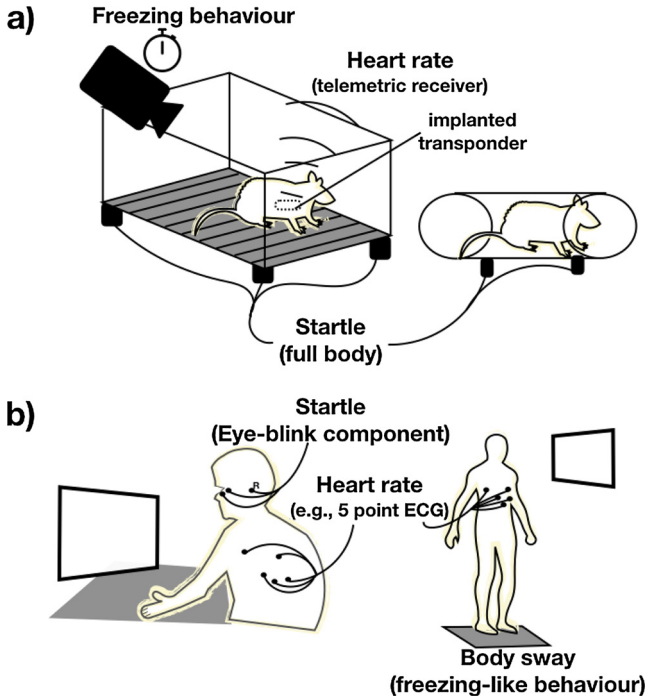

Fig. 2. Schematic illustration of outcome measures in (a) freely moving animals (left), restrained animals (right), (b) humans in sitting positions (left) and on a stabilometric platform (right). R = reference electrode.

- Check the calibration procedure in experiments involving human volunteers. Calibration of the US intensity prior to the experiment can be considered a signaled pre-exposure to the US. Hence, human participants are not naïve to the intensity and imminence of the US during fear conditioning experiments.

Instructions

- Check if human participants have received instructions about the CS/US contingencies and changes thereof (and in what detail). Human experiments, in which participants receive minimal or no instructions (i.e., learning depends mainly on experiences) more closely resemble animal experiments.

Timing of experimental phases

- Check timing between acquisition training, extinction training and retrieval test phases. Animal research often follows a 'delayed' schedule with a day to weeks between the different phases, thus allowing for long-term consolidation processes to take place. Human experiments use "immediate" or (less often) "delayed" schedules. Even short gaps (10 s) might alter memory processes that are initiated by acquisition and extinction training in humans (as compared to no gaps).

3. Outcome measures

Conditioned responses can be examined across species on different levels of analysis, which encompass behavioural and physiological, including neurophysiological, responses. Additionally, experiments in humans allow for studying verbal reports of subjective emotional experiences, such as fear, distress, and (US) expectations. These different response levels reflect different defensive processes (Anderson and Adolphs, 2014; Bechara et al., 1995; Lang et al., 2000; LeDoux, 2012; LeDoux and Pine, 2016) and thus do not necessarily converge (for a discussion see Lonsdorf et al., 2017). As a consequence, research across species needs to carefully consider the processes that are reflected by these measurements employed within each species.

Within the following paragraphs, we introduce the most commonly used behavioural and physiological outcome measures for fear conditioning studies that have been employed in both, rodents and humans. We have excluded measures of neural activity here, since comprehensive translational reviews on neural systems that mediate the acquisition and extinction of CRs in rodents and humans exist (Delgado et al., 2006; Gunaydin et al., 2014; Johansen et al., 2011; LeDoux, 2012; LeDoux and Daw, 2018; Maren, 2001; Maren and Quirk, 2004; Milad and Quirk, 2012; Parsons and Ressler, 2013; Tovote et al., 2015 ; see Sevenster et al., 2018 for a recent review of advances and challenges that results from this cross-species research). In general, the techniques to record neural activity usually differ substantially between species, with respect to the level of detail and invasiveness, for example, intracranial single cell recordings in animals vs. local field potentials and hemodynamic systems in humans. Recent studies in rodents, however, have examined hemodynamic responses (by fMRI) during retrieval test (Brydges et al., 2013; Harris et al., 2016, 2015). This dependent measure is commonly used to investigate neurobiological mechanisms of fear conditioning in humans and might help to bridge neural substrate across species in the future. This promising example for translational research, however, highlights the constraints of methodological differences between species. In particular, rodents in the aforementioned experiments had to be extensively habituated to the fMRI environment across several days and were restrained during testing, whereas humans can be naïve to fMRI environment before acquisition training and are not restrained, but instructed to minimize their movement.

The following paragraphs provide cross-species comparisons of dependent measures that are used in both species (cf. Fig. 2).

3.1. Fear-potentiated startle

The acoustic startle response has been widely used as an outcome measure in fear conditioning studies in both rodents and humans (Fendt and Fanselow, 1999). Startle responses that are elicited for example by a sudden, loud noise (so called startle probe) include the contraction of facial, neck and skeletal muscles, resulting in eye-lid-closure, and a disruption of on-going behaviours to protect the organism from a potential threat (Landis et al., 1939).

Startle responses in fear conditioning experiments in both humans and rodents are commonly elicited by short acoustic stimuli [e.g., 20–90 ms white noise, typically with intensities between 90–105 dB (A) and a steep rise/fall time (0–2 ms)] presented via speakers (in rodents) or headphones (majority of studies in humans).

In both species, startle response amplitudes can be modulated by different internal and external variables, resulting in a decrease or increase from a non-zero baseline (Fendt and Koch, 2013). As such, startle responses increase (compared to baseline) in response to threat

predicting CS + and decrease to conditions that are safe (Gerber et al., 2014; Hamm et al., 1993). The startle potentiation during anticipation or exposure to conditioned and unconditioned threats (i.e., CSs and USs) in rodents (Davis et al., 1997) and humans (Grillon, 2002; Grillon and Baas, 2003; Hamm and Weike, 2005; Norrholm et al., 2006, 2011, 2014) is called fear-potentiated startle (FPS). Experiments in both, rodents and humans, require habituation of startle responses to the acoustic probe prior to acquisition training to observe FPS.

In rats (Brown et al., 1951) and mice (Daldrup et al., 2015; Falls et al., 1997; Falls, 2002) FPS is usually indexed by a whole body response (i.e., whole-body startle), measured by automatic procedures using startle chambers (plexiglas cylinders positioned on a stabilimeter, see Fig. 2) or motion-sensitive platforms (unrestraint behaviour of freely moving animals). Startle responses in rodents are not monotonically related to US intensity, as is the case for freezing responses (Davis and Astrachan, 1978). Mice exhibit less pronounced and more variant startle responses compared to rats (Lauer et al., 2017; Paylor and Crawley, 1997) and FPS is less commonly used in mice (but see for example: Daldrup et al., 2015; Falls, 2002; Smith et al., 2011).

In humans, the eye-blink component of the startle reflex is measured through recording of electromyographic (EMG) activity measuring the contraction of the *orbicularis oculi* muscle (Landis et al., 1939, see Fig. 2) - the most reliable component of the startle response in humans (Koch, 1999).

Because the eye-blink startle response is a component of the whole body startle, it is assumed that both share a common neurobiological pathway (Koch, 1999). Primary and modulatory neuroanatomical and biochemical circuits are well studied in rodents (primarily in rats, e.g., Koch, 1999; Lauer et al., 2017 and non-human primates, e.g., Davis et al., 2008; Winslow et al., 2002). In humans, however, studies on the neurobiological pathways of startle responses have just recently emerged, enabled by new technical advances allowing to combine EMG and fMRI recordings (Kuhn et al., 2019 Lindner et al., 2015). These studies hold promise to provide the yet missing link for a translational understanding on the neural basis of startle responses.

It should be kept in mind that startle responses are responses that are triggered by the presentation of (potentially mildly aversive) stimuli (i.e., startle probes). As such, the startle probe has been conceptualized as an additional aversive stimulus (Lissek et al., 2005a, 2005b) and has been shown to impact on the learning process during acquisition training in humans (e.g., as examined in SCRs by Sjouwerman et al., 2016 and pupillometry by de Haan et al., 2018).

In conclusion, FPS (measured as whole body startle in rodents and as eye-blink startle responses in humans) represents a cross-species measurement of defensive CRs (Davis et al., 2010; Fendt and Koch, 2013; Grillon and Baas, 2003).

3.2. Freezing and freezing-like behaviour

In rodent experiments, changes in the animals' observable behaviour in response to the CSs are common outcome measures indexing conditioned responding. The most common behavioural index in fear conditioning protocols is freezing, though the CRs also include changes in risk-assessment, flight, grooming, exploration, rearing, and quiescence (see Remmes et al., 2016). Freezing behaviour is a defensive response elicited by both conditioned and unconditioned threats (Blanchard, 2017; Hagenaars et al., 2014; Roelofs, 2017; Volchan et al., 2017). It is defined as the absence of movement (except for breathing) with increased muscle tension that demarks attentive immobility towards distal threats or immobility under imminent threat, if escape is not possible (Blanchard et al., 1989). Freezing is commonly reported in rodents as the percentage of a defined time-window (e.g., CS presentation or time freezing in the CXT) within the animal exhibited freezing behaviour. While freezing is the typically recorded response to conditioned and unconditioned threats in mice and rats, it is only one response amongst a rich behavioural repertoire of defensive responding in animals (Bolles, 1970; Perusini and Fanselow, 2015). Thus, the lack of freezing does not necessarily indicate the lack of conditioned fear, since exaggerated fear responding may result in panic-like flight behaviour (Fadok et al., 2017; Tovote et al., 2016).

In human fear conditioning experiments, naturally occurring behavioural responses are commonly not examined (or possible), because participants are usually tested in a sitting position in front of computer screens or positioned in the MRI scanner. Moreover, several outcome measures (e.g., physiological signals and neural measures) demand participants to refrain from body movements. Recent studies in humans, however, have started to measure behavioural responses to threats, which might mirror freezing. In particular, decreased postural body sway on a stabilometric force platform was found during anticipation of threats (Azevedo et al., 2005; Bastos et al., 2016; Gladwin et al., 2016; Roelofs et al., 2010; Stins et al., 2011; for reviews see Blanchard, 2017; Hagenaars et al., 2014; Roelofs, 2017; Volchan et al., 2017), including anticipation of electric shock USs (Gladwin et al., 2016) and presentations of CSs (Van Ast and Roelofs, personal communication). This initial evidence that anticipation of threats can be examined by freezing-like behaviour through means of body sway in humans is underlined by bradycardic changes in the heart rate (cf. next chapter) during reduced body sway (Azevedo et al., 2005; Bastos et al., 2016; Gladwin et al., 2016) which mirrors simultaneously occurring freezing and bradycardia in rodents (Vianna and Carrive, 2005; Walker and Carrive, 2003).

In general, when comparing "behaviour" across species within fear conditioning experiments, it should be noted that fear conditioning protocols in rodents often allow for expression of a range of defensive responses, while behaviour in human participants is commonly restricted to key presses or body sway in fixed positions. Moreover, human participants are aware of the possibility to ultimately discontinue and hence escape from the aversive testing situation, which furthermore impacts the choice of defensive responses that can be measured in human experiments.

In sum, freezing behaviour in rodents is a common outcome measure in fear conditioning experiments and studies on body movements in humans, as a measure of freezing-like responses, have recently emerged. These new developments in humans hold the promise to develop into a translational measure of defensive behaviours that can be employed in future fear conditioning studies.

3.3. Heart rate

Alterations of heart rate in responses to CSs and CTXs have been described across species as an index of psychophysiological arousal. Both, deceleration and acceleration have been observed due to simultaneous parasympathetic and sympathetic involvement in the CR (mice: Stiedl and Spiess, 1997; Stiedl et al., 2004, rats: Iwata and LeDoux, 1988; Roozendaal et al., 1991, humans: Graham and Clifton, 1966; Hamm et al., 1993; Headrick and Graham, 1969; Lipp and Vaitl, 1990; Öhman and Dimberg, 1978; for detailed information on heart rate measurement in rodents see Morgan and Paolini, 2012; Stiedl et al., 2009 and in humans see Jennings et al., 1981; Lonsdorf et al., 2017). Measurements in humans are non-invasive and feasible in different testing environments (e.g., in front of computer screens or during fMRI scanning). In rodents, heart rate measurements require implantation of telemetric devices (Carrive, 2000; Dielenberg and McGregor, 2001) in order to avoid restraining the animal during measurements, which has been used in earlier studies. Restraining of the animal, can elicit stress responses itself (Iwata and LeDoux, 1988), which impacts on the changes in the heart rate to the CS (as discussed by Iwata and LeDoux, 1988): higher basal heart rate (often in restrained animals) favours deceleration, whereas lower basal rates are often followed by acceleration. In humans, the divergence between acceleration and deceleration has been related to different CS processing. Heart rate acceleration during acquisition training was linked to affective responses

(paralleled by enhanced startle potentiation and subjective experiences of unpleasantness) and preparation of avoidance, whereas deceleration was associated with the learned anticipation of threats (Hamm et al., 1993; Hamm and Vaitl, 1996; Hodes et al., 1985; Roelofs, 2017).

Taken together, heart rate analysis offers a cross-species measurement of the sympathetic and parasympathetic part of the CR. When interpreting acceleration and deceleration, the basal levels and the specific operationalization of the measurement in rodents (i.e., restraining vs. free-moving) needs to be considered.

WHAT TO CONSIDER: OUTCOME MEASURES

Fear potentiated startle

- Consider that startle responses are measured as whole body startle in rodents and as the eye-blink component in humans.
- Consider that startle responses are triggered (in contrast to continuous measures of freezing and SCRs, for example) by mildly aversive stimuli, which delays learning about the CS/US association.

Freezing and freezing-like behaviour

- Check if freezing behaviour is the only behavioural measure of CRs in rodents, since it accounts for only one part of a complex defensive response pattern. In humans, reduced body sway (as a measure of freezing-like behaviour) has recently been employed to examine defensive responses in anticipation of threats.
- Check how expression of behavioural responses is defined in the experiment. The conditioning apparatus used in rodents often allows (relatively) free movement in a chamber, but is commonly restricted in humans (position in front of a computer screen).

Heart rate

- Check if animals were restrained to measure heart rate (in earlier studies) or if devices were used that allow free movements.
- Consider that sympathetic and parasympathetic signals interact in heart-rate measurements and thus might reflect different processes.

4. Individual differences

Fear conditioning research in both rodents and humans has generally focused on investigating common principles and mechanisms. This approach has generated invaluable knowledge on the canonical neural, behavioural, physiological and cellular mechanisms underlying fear and anxiety, which has provided a necessary framework for the study of individual differences. Heterogeneity within a population, however, was typically regarded as 'residual variance' in this context in both species. But a limited focus on average mechanisms deprives us from gaining crucial insights into the mechanisms beyond the average (Kosslyn et al., 2002) and may bias the field through wrong conclusions because the (artificial) sample mean may not describe any individual very well (Hedge et al., 2018; Kosslyn et al., 2002; Lonsdorf and Merz, 2017).

Hence, systematic investigations of differences between individuals (i.e., inter-individual differences) within fear conditioning experiments provides a strategy to infer on mechanisms beyond the average. In the following, we briefly outline and summarize some of the major sources of inter-individual differences in fear conditioning experiments and emphasize cross-species translational gaps with respect to methodological (i.e., procedural and analytical) issues.

4.1. Specific sources of individual differences across species

A plethora of specific sources of possible individual difference factors has been identified in rodents and humans. The most obvious factors that differ between individuals include sex and age - as a choice on specific inclusion or exclusion criteria regarding these factors is mandatory prior to each experiment, across species. Additional examples of factors impacting on conditioned responding include various stressors and life history events, genetic variations or personality characteristics in humans (for review see Lonsdorf and Merz, 2017) and rodents (for review see Holmes and Singewald, 2013).

Sex: Biological sex, varying sex hormone concentrations over the cycle as well as hormonal contraceptives impact on threat learning and extinction processes in humans (Glover et al., 2015; Merz et al., 2018) and rodents (Cover et al., 2014; Lebron-Milad and Milad, 2012). While rodent work has revealed important sex differences in fear conditioning (e.g., Gruene et al., 2015a, b; Maren et al., 1994; Milad et al., 2009a, 2009b; Zeidan et al., 2011), experiments are commonly conducted in males only (Cover et al., 2014; Lebron-Milad and Milad, 2012). These sex differences are often used as an explanation for excluding female animals in experiments, in order to reduce variance in the results. Results derived from male populations are, however, often not generalizable to female individuals (Cahill, 2012), which is problematic from a translational perspective: Human samples in fear conditioning are often mixed sex samples (Lonsdorf and Merz, 2017) and women are overrepresented in clinical populations that suffer from pathological responses to threats in anxiety related disorders (Breslau, 2002; Cover et al., 2014; Reed and Wittchen, 1998). Recent policies by the National Institute of Health call for inclusion of female animals in future experiments (Clayton and Collins, 2014), which will likely affect gender-distribution in fear conditioning research. These mixed sex samples in rodents would get closer to sex distributions in human experiments (women are slightly overrepresented; cf. Lonsdorf and Merz, 2017). Yet, even though mixed samples are investigated in human experiments, sex differences are often not explicitly considered.

Despite being often neglected, there are specific translational challenges that need to be considered when comparing work between rodents and humans. First, when comparing female individuals, the temporal dynamics of sex hormone concentrations over the course of the estrus cycle (4 days) in rodents and menstrual cycle (28 days) in humans matter: In multiple-day experiments, the faster fluctuation of hormones in rodents inevitably results in different sex hormone levels within different experimental phases. Second, differences across species further include the common use of hormonal contraceptives in women (Merz et al., 2018). Third, the impact of the sex of the experimenter (who has contact to the human participants and rodents during testing) has hitherto not been addressed in fear conditioning research, although there is evidence for these participant-experimenter interactions in other stress related tasks (for a discussion of general effect in humans see Chapman et al., 2018 and experimenter-animal interaction see Bohlen et al., 2014; Sorge et al., 2014).

Age and development: In rodent work, developmental studies revealed evidence for acquisition of CRs already at an early age (Richardson and Fan, 2002) whereas extinction learning seems to emerge only later in life – possibly mirroring the development of involved prefrontal brain regions (Kim and Richardson, 2010; Shechner et al., 2014). Notably, fear conditioning studies in adolescent or even younger individuals are rare in both, rodents (Shechner et al., 2014) and humans (for a review see Lonsdorf and Merz, 2017). Typically, rodents are tested during adulthood (i.e., 2–6 months postpartum), which corresponds to the typical age of participants in human fear conditioning studies (i.e., 21–25 years; cf. Lonsdorf and Merz, 2017; Sengupta, 2012; Spear, 2000; see www.translatingtime.org/translate for a tool to translate age between different species). However, directly translating age between rodents and humans represents a challenge, since adolescence is characterized by different features across species and changes in sex hormones across developmental phases (e.g., puberty, pregnancy or menopause) are not necessarily comparable between species. Yet, these difference are also not well studied (e.g., Milligan-Saville and Graham, 2016).

Another translational challenge when investigating young individuals are ethical considerations regarding the employed US: Electrical stimulations, as usually employed in rodents and adult humans, cannot be used in children. Instead, air-puffs or loud and aversive sounds or screams are typically implemented (Shechner et al., 2014). Thus, despite differences in US intensities in general (see above), US types and intensities diverge between rodents and humans in particular when young individuals are studied. For a comprehensive review of methodological consideration of fear conditioning protocols in developing rodents we refer to Cowan and Richardson, 2018.

Stressors: The investigation of individual differences with respect to stressors poses a challenge for translational attempts mostly due to ethical constraints. First, acute stressors that are experimentally induced differ substantially between species. In rodents, this typically involves potentially life-threatening events (i.e., restraint stress, underwater trauma, tail shocks, social defeat, exposure to cat or fox odours; Schöner et al., 2017). In humans, in turn, acute stress typically involves physiological challenges (e.g., cold-pressor task) or social as well as self-evaluative threat (e.g., Trier Social Stress Test; Kirschbaum et al., 1993; see Dickerson and Kemeny, 2004 for a meta-analysis). However, for ethical reasons, these challenges neither cause physical harm, nor are they potentially life-threatening. Importantly, exposure to natural or man-made disasters, which are potentially life threatening (but not under experimental control), have been conceptualized as stressors (Luo et al., 2012; Steudte et al., 2011). Second, stressors in early life can be investigated in rodents under experimental conditions (Pryce et al., 2005), including experimentally generated life-histories (Bodden et al., 2017; Remmes et al., 2016; Tsoory et al., 2007). In human research, in contrast, the assessment of critical life events in fear conditioning (McLaughlin et al., 2016; Scharfenort et al., 2016) is often based on retrospective questionnaires such as the Childhood Trauma Questionnaire (Bernstein et al., 2003). Interview-based measures or ascertainment of events through official records -which could be more valid measures of such events- might provide further insights in future fear conditioning studies (Li et al., 2016; Monroe, 2008). Third, also chronic stress can be experimentally manipulated in rodents (Hoffman et al., 2015; Maren and Holmes, 2016), yet this is again not applicable in humans due to ethical reasons.

Despite these different methodological approaches between species to induce stress, the resulting increases in relevant stress hormones may provide similar read-outs. For example, biological markers for chronically elevated stress hormones, such as the assessment of hair cortisol concentrations (Stalder et al., 2017). Such biological markers, in contrast to questionnaires, might serve as a translational tool, to assess endocrine responses retrospectively over longer periods and across species (Yu et al., 2015). It should, however, be considered that the interaction between stress-related neurotransmission and neuromodulation (e.g. by monoamines and hormones, respectively) with emotional arousal evoked by fear conditioning protocols might affect learning and memory processes in a non-linear (e.g., inverted-U shape) fashion (Baldi and Bucherelli, 2005).

Genetic variation: Both human (Hettema et al., 2003; Merrill et al., 1999) and animal studies (Royce, 1972) report considerable influence of genetic variation on inter-individual variability in the ability to acquire and extinguish CRs. More precisely, one third of the variance in human fear conditioning (Hettema et al., 2003) has been attributed to genetic factors.

In humans, the majority of studies have investigated associations of candidate variants (i.e., polymorphisms) of a single biologically plausible candidate gene (for reviews see Lonsdorf and Kalisch, 2011; Sumner et al., 2016) in association with fear conditioning processes. This approach has been criticized (e.g., Kendler, 2013), as it depends on knowledge about the pathophysiology underlying the disease/trait studied. More recently, genome-wide association studies are emerging in the field of (clinical) anxiety research, which provides novel candidates for more targeted investigations in experimental fear conditioning research (for example Deckert et al., 2017; Lueken et al., 2017).

In rodents in turn, genetic variation can be experimentally induced (e.g., gene knock-out/in, selective breeding), which allows to modify transmitter pathways that are also affected by naturally occurring genetic variants in humans (e.g., Bilkei-Gorzo et al., 2012). Importantly, the underlying biological alterations of single polymorphisms and knock-out/in procedures are not necessarily corresponding. Approaches, which mimic the genetic variant in humans by genetic modification in rodents might provide a closer match (e.g., Dincheva et al., 2015; Soliman et al., 2010). Recently developed advances in genome editing techniques (CRISPR/Cas; Jinek et al., 2012) hold the promise to facilitate such cross-species translation, e.g., by 'generating humanized mice'.

Personality factors: Personality traits such as trait anxiety, intolerance of uncertainty or neuroticism have been linked to different processes in fear conditioning paradigms in humans (for a review: Lonsdorf and Merz, 2017). In rodents, equivalent concepts can be subsumed under the umbrella term 'animal personality' (for reviews: Réale et al., 2010; Stamps and Groothuis, 2010), which has however rarely been applied to the field of fear conditioning to date (e.g., Borta et al., 2006; Walker et al., 2008). A major translational challenge with respect to personality traits comprises the question of how to translate specific personality facets from humans to rodents (e.g., conscientiousness or intolerance of uncertainty). A second translational challenge represents assessment of 'personality' across species. While personality traits in humans are typically assessed by means of self-report questionnaires requiring some introspection capability, animal 'personalities' are derived from behavioural indices (i.e., behaviour in the open field, the elevated plus maze or social interactions). To date, it remains unclear if 'personality characteristics' capture comparable concepts across species despite differences in assessment.

In sum, individual differences in fear conditioning experiments need to be carefully checked for their particular instantiation (e.g., which type of stressor was used?) when compared across species. Moreover, comparability of results could profit by reporting effects of individual differences like effects of sex in mixed samples (even if this effect is not at focus) or sex of the experimenter.

4.2. Methodological considerations for research on individual differences – cross-species translational gaps

The investigation of individual differences in both species requires specifically tailored methodological considerations with respect to selection of individuals, experimental design, data processing and statistics (for a discussion of the challenges in rodents see Richter and Hintze, 2019 and for the human field see Lonsdorf and Merz, 2017). Of note, sample selection, experimental design choices and data analysis strategies developed to investigate general mechanisms might not be appropriate for the investigation of sample heterogeneity (Hedge et al., 2018; Lonsdorf and Merz, 2017). In the following, a non-exhaustive number of experimental and data analytical challenges are discussed focusing on cross-species translation in fear conditioning research.

In most studies in humans and rodents alike, individuals are divided into subgroups based on study-specific, often cut-off-based, criteria. Importantly however, in humans, grouping (by means of e.g., median split or selection of extreme groups) is mostly based on individual difference variables (e.g., scores in questionnaires; reviewed in Lonsdorf and Merz, 2017) rather than performance in fear conditioning, extinction, retrieval or return of fear. Hence, grouping of participants is based on the factor of main interest (e.g., trait anxiety) and task-performance is usually treated as continuous variable.

In rodents in turn, grouping is often based on observed behaviour in fear conditioning experiments (Bush et al., 2007; Shumake et al., 2014) and study-specific mean-based cut-off criteria are employed - such as the upper and lower end of the distribution (Bush et al., 2007; Reznikov et al., 2015; Shumake et al., 2018; Walker et al., 2008), number of trials taken to reach a predefined extinction criterion (King et al., 2017) or data driven cut-off criteria in a probabilistic model (Shumake et al., 2018).

Critically, these cut-off criteria in human and rodent studies alike are mostly study-specific and hence, comparability of individuals labelled as for instance 'slow extinction' or 'high extinction phenotype' across studies is not always straightforward. Likewise, there have been some attempts in rodents to classify an individual as 'affected' or 'unaffected' based on cut-off criteria on a range of behavioural read-outs (Ardi et al., 2016; Cohen et al., 2003; Walker et al., 2008) in order to

mimic psychiatric procedures as employed in humans. The validity of psychiatric nosology in humans, however, has recently been challenged (Cuthbert and Insel, 2013; Hamm et al., 2016; Marquand et al., 2016) based on the massive within-diagnosis heterogeneity (Galatzer-Levy and Bryant, 2013). This gives such a backwards translational approach most likely limited promise.

Another methodological challenge for research on individual difference is the fact that fear conditioning protocols often employ 'strong experimental situations' (Lissek et al., 2006) and hence leave limited room for the manifestation of individual differences. This theoretical consideration has very recently been empirically demonstrated for seven classic tasks employed in cognitive neuroscience (Hedge et al., 2018). Importantly, the strength of the experimental situation may not be comparable across species in typical experimental set-ups.

An additional translational challenge exists with regard to differences in sample selection in rodents and humans. In general, human participants and laboratory animals in fear conditioning research are often homogenous groups. In the human field, work is primarily based on student samples between the ages of 21 and 25 (for review see Lonsdorf and Merz, 2017) without any history of psychiatric disorders (often excluding participants "at risk" for anxiety disorders and oversampling resilient individuals), which limits generalizability of these findings within a homogenous and possibly high functioning set of individuals to the general population (Henrich et al., 2010; Lonsdorf and Merz, 2017). Similarly, experiments in rodents typically avoid heterogeneous samples to reduce variability within experiments and thereby to increase power. As such, studies are typically performed in animals of the same inbred strain tested at exactly the same age and housed in the same environmental conditions (e.g., cage size, environmental enrichment, temperature, humidity, light intensity, time of day, etc.) . Consequently, recruitment strategies that focus on individual differences should be adjusted to induce systematic heterogeneity in humans (e.g., recruitment from the general population). Such a 'systematic heterogenization 'of the study sample would follow recent discussions in the rodent field that call for environmental or experimental 'heterogenization' rather than 'standardization' in order to produce robust findings (Richter, 2017; Richter et al., 2010, 2009; Voelkl et al., 2018). Studies on individual differences in fear conditioning research in rodents already included some (unsystematic) heterogeneity by using outbred rats (Bush, Sotres-Bayon, & LeDoux, 2007; Reznikov et al., 2015; Shumake et al., 2018; Walker et al., 2008) and tried to maximize (genetic) diversity in the sample by including crossing of rats that were provided by different suppliers (Shumake et al., 2018). To date, however, heterogenization with respect to sample selection is rarely applied in human research (Lonsdorf and Merz, 2017). Maximizing heterogeneity in a systematic way in the study population is thereby not only key for the investigation of individual differences in general, but can also be expected to facilitate generalization, replication and translation of results (Richter et al., 2009). Thorough statistical calculation of sample sizes and analytic strategies are further essential to align these efforts of study sample heterogenization with 1) the ethical point of view that experiments should be conducted in the smallest groups needed and 2) to provide sufficient power for statistical analyses (Button et al., 2013; Demétrio et al., 2013; Worp et al., 2010).

In sum, to foster research on individual differences across species and make study populations more representative at the same time, researchers may consider allowing more heterogeneous samples, employ dimensional characterisations rather than arbitrary groups and might re-design protocols tailored to allowing for the manifestation of individual differences.

4.3. Clinical perspective

Fear conditioning is a tool for the cross-species examination of basic affective learning mechanisms that shape adaptive, defensive responses against acute or imminent threats. Furthermore, in both, rodents and healthy human volunteers, fear conditioning is being used to study processes that contribute to maladaptive responses (for example in patients that suffer from anxiety-related disorders) as well as to offer insights on how to treat these disorders (Davis et al., 2006; Griebel and Holmes, 2013; Maren et al., 2013; Milad and Quirk, 2012; Morrison and Ressler, 2013; Singewald et al., 2015; Zuj and Norrholm, 2019). In particular, the development of pharmacological tools to augment therapies for anxiety related disorders rely on detailed mechanistic knowledge from translational work in rodents and humans.

One example is the enhancement of exposure therapy by augmenting NMDA-receptor activity via administration of d-cycloserine. The clinical application was based on initial findings in fear conditioning experiments (Davis et al., 2006; Ledgerwood et al., 2003; Ressler et al., 2004), and the efficiency and specificity was further guided by examination of extinction learning processes in basic fear conditioning experiments (Hofmann et al., 2015; Mataix-Cols et al., 2017; Norberg et al., 2008; Smits et al., 2013).

Similarly, the blockade of (nor)adrenaline transmission by propranolol has been examined as a prevention against the development of post-traumatic stress disorder (PTSD), based on the modulatory effect of noradrenaline on the acquisition and extinction of conditioned fear responses in rodents (Berlau and McGaugh, 2006; Fitzgerald et al., 2015). Yet, several controlled studies in humans revealed no effect of propranolol administration directly after trauma (McGhee et al., 2009; Nugent et al., 2010; Stein et al., 2007). Future mechanistic studies might provide insights into how noradrenaline modulation (maybe in combination with safety learning procedures) can be used to treat PTSD (Giustino et al., 2016; Pitman et al., 2002).

However, the inferences drawn from fear conditioning experiments will probably only shed light on partial processes that contribute to psychopathology, as for example avoidance tendencies are not assessed (Beckers et al., 2013). As such, in some cases promising findings from experimental fear conditioning studies cannot directly be applied in the clinic (e.g., Maples-Keller et al., 2019).

Our aim is to improve the understanding of general aversive learning mechanisms by fostering cross-species comparability. In the long run, we aspire that our methodological considerations of basic mechanisms inspire discussion about the methodological challenges of fear conditioning experiments to allow drawing valid inferences about psychopathology.

5. General discussion

Our aim in this perspective is to provide the missing methodological considerations on cross-species research in fear conditioning. Thereby, we address the central question whether the theoretical promises of translational research can actually be met in practice. To answer this question, we provide a cross-species comparison of key methodological elements within protocols in humans and rodents. We further highlight the implication of these methodological differences for the comparability of procedures between species.

We argue that raising awareness for methodological differences between species sets the stage for practical guidance to avoid pitfalls when drawing conclusions from published experiments across species. Furthermore, we hope to aid designing of experiments that employ methods for more comparable processes in human participants and laboratory rodents in fear conditioning protocols. These practical considerations provide the basis of *how* cross-species translation can actually work.

However, inherent differences in experimental demands in humans and rodents make translation of a protocol, in its literal sense, word by word, often impossible. We argue that alignment of protocols can only be achieved to a certain degree and we are not advocating for a gold standard how translational protocols should look like. Hence, simple alignment of superficial methodological details will not promote translational results. Instead, we are promoting to consider procedural

and methodological differences across species to guide the interpretation and comparison of *processes* that underlie the results in rodents and humans. These considerations should ultimately allow for identification of processes in fear conditioning protocols that are comparable between humans and rodents. Furthermore, it also sets boundaries for translation of findings that are derived from procedures that probe divergent processes. Identification of such procedural and methodological gaps across species that limit inferences from rodents to humans, or vice versa, are important. These gaps should not be downplayed, but rather highlighted with the same emphasis as comparable cross-species mechanisms are promoted.

We envision with this perspective to further foster cross-species exchange that enables new perspectives beyond the methodology that is commonly used within one species. In our view, learning from practical insights into research in other species is often helpful to recognize species-specific pitfalls and to interpret work in other species correctly. We aspire that our perspective equips researchers with these practical and methodological considerations across species to ultimately support the dialog between researchers in translational science and remove hurdles in designing “tandem-projects” across species.

In sum, we propose to consider translational research as a framework for conceptual rather than identical replications. Our perspective suggests that such translational research encompasses not only comparable processes within humans and rodents, but also place emphasis on processes that diverge between species. Methodological comparisons across species provide the basis to evaluate these common and species-specific processes to guide interpretation of findings across rodent and human research in order to lay the grounds for successful translational research.

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