Molecular Psychiatry
https://doi.org/10.1038/s41380-017-0006-0

PERSPECTIVE

# Lost in translation: how to upgrade fear memory research

África Flores[1] · Miquel À. Fullana[2,3] · Carles Soriano-Mas[4,5,6] · Raül Andero[1,7,8]

Received: 1 May 2017 / Revised: 30 October 2017 / Accepted: 3 November 2017


## Abstract

We address some of the current limitations of translational research in fear memory and suggest alternatives that might help to overcome them. Appropriate fear responses are adaptive, but disruption of healthy fear memory circuits can lead to anxiety and fear-based disorders. Stress is one of the main environmental factors that can disrupt memory circuits and constitutes as a key factor in the etiopathology of these psychiatric conditions. Current therapies for anxiety and fear-based disorders have limited success rate, revealing a clear need for an improved understanding of their neurobiological basis. Although animal models are excellent for dissecting fear memory circuits and have driven tremendous advances in the field, translation of these findings into the clinic has been limited so far. Animal models of stress-induced pathological fear combined with powerful cutting-edge techniques would help to improve the translational value of preclinical studies. We also encourage combining animal and human research, including psychiatric patients in order to find new pharmacological targets with real therapeutic potential that will improve the extrapolation of the findings. Finally, we highlight novel neuroimaging approaches that improve our understanding of anxiety and fear-based disorders.

## Introduction

Among all psychiatric pathologies, anxiety and fear-based disorders are the most prevalent in developed countries, affecting up to 30% of the population during their lifetime [1] and around 12% every year [2]. Such disorders are associated with a threefold increase rate of suicides [3] and represent a huge economic responsibility for society [4, 5]. So far the most effective treatments for anxiety and fear-based disorders include serotonin reuptake inhibitors and/or exposure-based psychotherapy. However, a significant proportion of patients does not respond to such treatments or relapse after treatment remission [6, 7], revealing a critical and urgent need to develop novel therapeutic approaches. We believe that a better understanding of the mechanisms in anxiety and fear-based disorders will help to improve therapeutic approaches.

Anxiety and fear-based disorders include a broad range of recognized clinical conditions, such as post-traumatic stress disorder (PTSD), panic disorder, or specific phobias, characterized by excessive anxiety and altered fear learning. Each of these conditions is unique with respect to the features of the fear or anxiety experienced as well as the type of stimuli that can induce it. Thus, patients with PTSD exhibit persistent recurring memories of traumatic events through intrusive thoughts, flashbacks, and nightmares, which the individual is unable to extinguish. In panic disorder, the subject experiences recurrent panic attacks (abrupt surges of intense fear accompanied by somatic symptoms) that are usually unexpected and uncued since they occur in the absence of any identifiable source of danger. Conversely, phobias are featured by cued panic attacks in which the sufferer experiences persistent and excessive fear in response to the presence of a clearly defined object, person, or situation. An important common

✉ Raül Andero
raul.andero@uab.cat

1 Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain
2 FIDMAG Germanes Hospitalàries–CIBERSAM, Sant Boi de Llobregat, Barcelona, Spain
3 Department of Psychiatry, Universitat Autònoma de Barcelona, Bellaterra, Spain
4 Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Hospitalet de Llobregat, Spain
5 CIBERSAM-G17, Barcelona, Spain
6 Department of Psychobiology and Methodology in Health Sciences, Universitat Autònoma de Barcelona, Bellaterra, Spain
7 CIBERSAM, Corporació Sanitaria Parc Taulí, Sabadell, Spain
8 Department of Psychobiology and Methodology in Health Sciences, Universitat Autònoma de Barcelona, Bellaterra, Spain

Published online: 03 January 2018

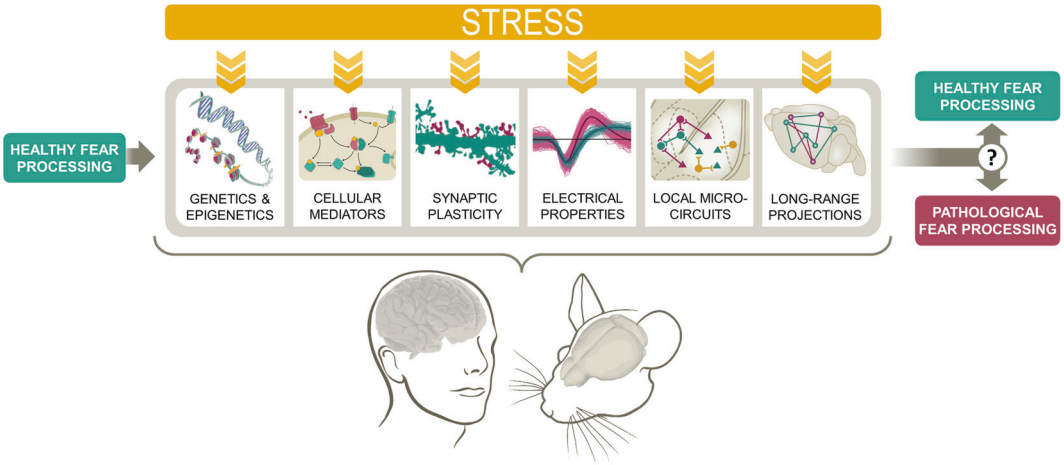


**Fig. 1** Stress can contribute to the transition from healthy to pathological fear processing at multiple levels in the brain. Fear is a physiological response that enables the subject to cope with threatening events. However, this healthy fear response can become pathologically persistent or intense, as in fear and anxiety disorders. Stress can affect fear processing by altering brain function at different levels. After stress exposure, some individuals will suffer from pathological fear, whereas others will remain unaffected, due to poorly understood mechanisms

characteristic of these disorders are that they present alterations in fear processing [6]. Whereas transient and appropriate fear responses allow the individual to cope with dangerous or stressful situations, anxiety and fear disorders present exaggerated fear responses that persist beyond the adaptive level [8]. The nature of these responses and their processing by fear memory circuits are crucial factors for the initiation and maintenance of the disorder [7].

Genetic and environmental factors strongly influence resilience and susceptibility to anxiety and fear-based disorders, being stress exposure among their most important modulators [9]. Exposure to certain forms of mild stress may act as a resilience factor by improving coping strategies in future stressful events [10]. However, chronic stress and acute trauma exposure can act as key factors in the initiation and maintenance of anxiety and fear-based disorders [11]. Thus, sustained moderate stressors (e.g., major changes at workplace, financial problems, health issues) as well as acute traumas (e.g., natural disasters, accidents, physical, or sexual assault) are able to alter memory circuits and brain plasticity at different levels [12, 13] (Fig. 1), and operate as vulnerability factors in certain subjects. We will be able to develop better treatments by understanding more about how stress interacts with other factors to cause these deleterious effects [14, 15].

Studying memory in both humans and laboratory animals has important limitations since the brains of these species process some forms of information quite differently [16], making it complicated to establish comparisons between them. An advantage when studying the neural circuitry underlying fear memory is the fact that some brain regions are involved in aversive processing across many mammalian species [17] (see Fig. 2 showing several key fear processing areas in rodents and humans), and its behavioral readout is both quick and robust, making it especially adequate for translational studies [18]. The formation of memory following laboratory fear tasks has been studied according to the Pavlovian learning paradigm both in animals and humans. This associative learning process consists of pairing a neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US) that elicits a conditioned fear response (e.g., freezing in rodents, skin conductance response in humans, among others). The CS can be a cue (e.g., a tone, auditory fear conditioning (FC)) or a context (e.g., a room, contextual FC). Also, a good fear measure in humans and rodents is fear-potentiated startle, consisting on the increase of the startle reflex elicited by a sudden noise in the presence of the CS (without US).

Unraveling the mechanisms of how stress alters fear memory circuitry may have implications for all anxiety and fear-based disorders. In fact, according to the new mainstream frameworks of brain disorders, Research Domain Criteria (RDoC, National Institute of Health, USA) and ROAMER (Horizon 2020, Europe), fear circuitry alterations in all anxiety and fear-based disorders should have a common core. Thus, finding treatments for pathological fear would potentially be beneficial to treat the fear component of all fear-related disorders. Insufficient knowledge of underlying mechanisms mediating fear processing limits the specificity and effectiveness of further therapeutic breakthroughs. Therefore, a greater understanding of the neural circuitry mediating altered fear processing will precipitate further progress in the development of more selective treatments for anxiety and fear-based disorders [6, 7].

In brief, the underlying mechanisms of anxiety and fear-based disorders might include aberrant functions and

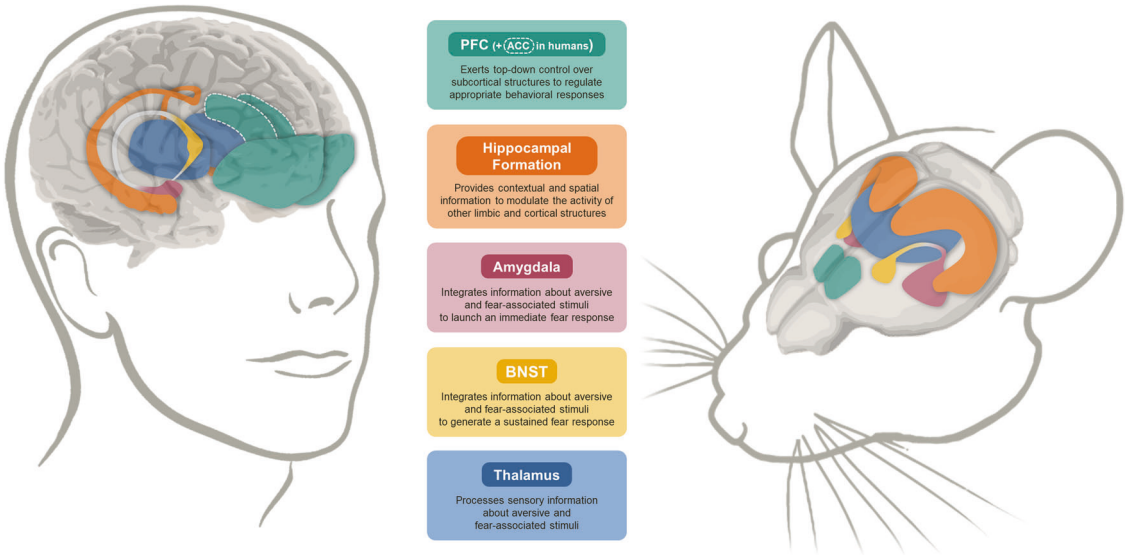


**Fig. 2** Key regions in the human and mouse brains involved in fear memory. Some of the main brain regions involved in fear memory processing display similar functions in rodents and humans, including the hippocampal formation, the amygdala, the bed nucleus of stria terminalis (BNST) and the thalamus. Some functions of the medial prefrontal cortex in mice and humans are equivalent. Certain functions of the anterior cingulate cortex (ACC; dashed line) in humans are located in the medial PFC in rodents

remodeling of neural circuitry caused, in part, by stress [19]. Although the neurocircuitry of stress and fear learning are well-characterized, the development of treatments resulting from this knowledge remains unsatisfactory. This reflects that the way in which animal models have been employed, despite providing tremendous advances in the field so far, has achieved limited translation of findings from the bench to the bedside. We believe that it is crucial to understand the molecular mechanisms of such malfunctioning in both animal models and humans concurrently so we can find better pharmacological treatments for anxiety and fear-based disorders (Fig. 2). Also, it is essential to include female subjects in both human and animal studies, since women are at a twofold higher risk for any anxiety-related disorder compared to men [20]. Considerable evidence [20, 21] indicates that sex differences in fear processing should be investigated more thoroughly, but how to address this factor is beyond the scope of this Perspective. See below our proposals on how to overcome some of the aforementioned limitations in order to achieve a more successful translation of studies focused on fear memory.

## How to improve translational research in fear memory

In this section, we argue that animal models of pathological fear learning are essential to find more effective treatments for anxiety and fear-based disorders, since neurobiological alterations present in these models might maintain a greater resemblance with these psychiatric conditions. Additionally, their combination with powerful emerging techniques would enhance our understanding of the molecular mechanisms of such malfunctioning in animals. Also combining animal and human research may help us find new targets with real therapeutic potential. Unifying methodological approaches in both animal and human studies would be highly beneficial in this regard. Finally, we highlight the contribution of theoretical frameworks that enable a better comprehension of anxiety and fear-based disorders.

### Using pathological—instead of healthy—fear models

The neurocircuitry of fear has been mostly studied in laboratory animals that present normal fear processing (similar to healthy individuals) [19]. Although these models provide invaluable information about fear circuits in the brain, they do not fully explain the mechanisms of pathological fear processing (as seen in diseased individuals) [19]. There are several animal models presenting altered fear processing that constitute suitable tools for modeling anxiety disorders. Certain anatomical manipulations, including chemical stimulation of the dorsomedial hypothalamus [22] or electrical stimulation of the dorsal periaqueductal gray [23], are used for modeling panic disorder. Specific transgenic mice and selected mouse strains (TgNTRK3 mice [24] and 129S1 mouse strain [25] as models of impaired fear learning and extinction) are useful for exploring the genetic basis of anxiety and fear-based disorders [26]. Also, those paradigms based on

**Table 1** Glossary of outstanding new techniques

| Technique | Application | Key elements | Technical basis | Advantages | Refs. |
|---|---|---|---|---|---|
| Optogenetics | Manipulation of neuronal activity | Opsins: light-sensitive ion channels (excitatory or inhibitory)<br><br>Optic fiber implants | Local expression of opsins by:<br>-Virus delivery containing cell-specific promoters<br>-Cre-inducible virus delivery (use in specific Cre-recombinase transgenic mice)<br><br>Activity controlled by light delivery through implanted optical fibers or LEDs | Region and cell-type specific<br><br>Specific pathway restriction<br>Allows neuronal inhibition and stimulation<br><br>Real-time activity manipulation | [35, 37] |
| Chemogenetics or DREADDs | Manipulation of neuronal activity | DREADDs: GPCRs (Gs, Gi/o or Gq coupled) engineered to exclusively respond to a synthetic small-molecule ligand | Local expression of DREADDs by analogous methods to optogenetics<br><br>Activity controlled by systemic or local administration of the specific synthetic ligand | Region and cell-type specific<br><br>Specific pathway restriction<br><br>Allows neuronal inhibition, stimulation, and control over other specific cellular pathways<br><br>Minimally invasive | [28, 43] |
| CRISPR/Cas system | Genome edition | Cas: DNA nuclease that employs RNA-based sequence recognition | Virus-mediated delivery of:<br>- Cas nuclease<br>- Single guide RNA (for site recognition)<br><br>Cas produces DNA double strand breaks, inducing cellular repair mechanisms and generating:<br>- Knock-outs (through small erroneous insertions or deletions)<br>- Knock-ins (inserting an external donor DNA template) | High-site specificity<br><br>Reduced off-target effects<br><br>Efficient multiplexing | [51, 54] |
| In vivo calcium imaging | Monitoring of neuronal activity | GECIs: genetically encoded calcium indicators (fluorescent reporters)<br><br>Optical imaging device | Local expression of GECIs by analogous methods to optogenetics, or use of GECIs transgenic mice<br><br>Optical visualization and monitoring through:<br>-Two photon microscopy (requires head fixation)<br>-Implantable optical devices (mini-epifluorescence microscopy and microendoscopy) | Cell-type specific<br><br>Direct visualization<br><br>Monitoring of large neuronal ensambles<br><br>Long-time period recordings | [57, 60] |

environmental manipulations (i.e., stress models) that alter fear processing are particularly useful to model some fear-based disorders like PTSD. Notably, although these paradigms are only modeling the environmental component, they may represent in some cases a more translational way to mimic the human situation because they elicit a myriad of genetic and epigenetic changes similar to those occurring in humans. One of these stress-based robust models of pathological fear is acute stress immobilization followed by auditory FC after 6 days [27, 28]. This procedure results in stressed mice presenting impaired fear extinction. Other models of acute stress also result in altered auditory fear extinction and morphological changes in the mPFC. Thus, a single 10 min of forced swimming in mice causes retraction of apical dendrites in infralimbic (but not prelimbic) cortex pyramidal neurons as evaluated 24 h after stress [29]. Interestingly, rats exposed to single prolonged stress (exposure to 2 h restraint followed by 20 min forced swimming and finally anesthesia with isoflurane) present enhanced contextual FC 14 days later [30]. Also in rats, inescapable tail-shock potentiates fear memory consolidation in footshock-induced FC both to a tone and to the context 7 days later in a differentiated environment [31]. All these models reflect many available procedures to induce pathological fear processing in rats and mice. Surprisingly, these models have not yet been combined with cutting-edge techniques such as in vivo calcium imaging, gene editing with CRISPR or powerful techniques to study neuronal projections including optogenetics and DREADDs (designer receptors exclusively activated by designer drugs) when studying fear memory. Also, surprisingly there are very few studies combining human data in anxiety and fear-based disorders with the interaction of stress and fear models. The question remains how can we find better treatments in anxiety and fear-based disorders if the animal models present normal fear processing and the data is often not directly associated with humans?

## Taking advantage of the new techniques in relevant models of pathological fear

A broad assortment of traditional techniques, including neuronal tracing, local lesions, pharmacological treatments, and electrophysiology, have been extremely useful to outline an elementary description of the normal and pathological fear circuitry so far [32–34]. Recent technical progress has provided us with a new repertoire of sophisticated tools (Table 1) that enable more direct and efficient monitoring of neural activity, as well as more specific and controllable manipulations of adaptive/maladaptive behaviors and their neural substrates. Unfortunately, although some of these techniques (mainly optogenetics) have already widely been used to study the fear circuit under physiological conditions [35, 36], there are seldom precedents using these cutting-edge procedures in rodent models presenting pathological fear learning.

Stimulating/inhibiting neurological pathways in animal behavior is key to establish causal links between the activity of specific brain circuits and particular behavioral and physiological outcomes. The emergence of optogenetics and chemogenetics (DREADDs) has allowed this manipulation to be region and cell-type specific, temporally precise and reversible [28, 37, 38]. This cell-type specificity is particularly useful to overcome the challenge of studying brain structures constituted by diverse subnuclei and cellular types (e.g., the amygdala [39, 40] or the BNST [41]) recruited during exposure to stressful life events and in anxiety and fear-based disorders. Additionally, this neuronal-type manipulation can be circumscribed to specific projections (by applying the laser or the inert ligand to an area different from that where the virus –either retrograde or anterograde– was injected), which refines possible conclusions to specific pathways. Pharmacological and gene inactivation approaches may achieve considerable spatial resolution as well, but their kinetics and reversibility are slow. Optogenetics allows millisecond-scale manipulation of neuronal activity, making it possible to drive brain circuits at specific frequencies of interest and precise timepoints within the learning process. This enables to detect, for instance, that cell-type-specific plasticity of phasic and tonic activity within the central amygdala gates fear expression and regulates fear generalization [42]. DREADDs otherwise is a more helpful tool when manipulating circuits in a sustained manner [43] (e.g., few hours, or weeks via minipumps). This permitted, for example, the identification of Thy-1 neurons of the basolateral amygdala as “fear-off” neurons through their tonic enhanced excitability during fear extinction [44]. A key advantage of optogenetics and DREADDs is their functional bidirectionality. This not only permits the stimulation but also the inhibition of neuronal activity, which allows us to assess both sufficiency and necessity of the tested pathway. Importantly, DREADDs act through G-proteins similarly to G-protein coupled receptors, and these are the most common targets of current therapeutic drugs in humans [45]. As a result, findings from animal studies using DREADDs might have translational implications [46], since DREADDs may control a portion of downstream signals targeted by known therapeutic drugs. However, translating DREADDs studies to humans is not direct due to the complexity of GPCR signaling among other issues. A recent work has highlighted the relevance of combining optogenetics with pathological models of fear [47]. This study reports that the vulnerability to heightened fear learning produced by repeated immobilization stress exposure emerges from a

serotonin-dependent fear memory consolidation process that is not present in unstressed mice [48]. Thus, optogenetic inhibition of the serotonergic dorsal raphe during conditioning is sufficient to prevent stress-induced enhancement of fear [47]. More studies following this or similar approaches are necessary in order to advance the use of animal psychiatric models presenting pathological fear processing.

Anxiety and fear-based disorders are considered multifactorial conditions involving complex gene-environment interactions [49, 50]. Thus, relying on technology that is able to finely manipulate gene expression is crucial to unravel key genes modified by exposure to stressful stimuli. The CRISPR/Cas system is among the most valuable genome editing tools developed during the last years, allowing for the introduction of double-stranded DNA breaks at nearly any specified sequence within the genome with nucleotide resolution in order to generate gene knock-outs or knock-ins on demand [51, 52]. The utilization is more user-friendly and affordable than other strategies to regulate gene expression (i.e., RNA interference), and presents higher efficiency and reduced off-target effects, even when simultaneously targeting multiple loci in the genome [53, 54]. Molecular genetic approaches, including genome-wide studies of genetic variation have identified a considerable number of genes associated to vulnerability/resilience to diverse anxiety and fear-based disorders [55, 56]. Using the CRISPR/Cas technology in rodent models of pathological fear might help to unravel which of these genes are indeed primary involved in aberrant fear memory processing, and more importantly, if their suppression/restriction could alleviate anxiety-related symptoms.

Another cutting-edge technique to take advantage of is optical imaging of neural activity. This technique has emerged to significantly improve cellular level recordings in behaving animals. Optical imaging methods overcome some of the limitations presented by extracellular electrophysiological methods, allowing genetic cell-type and connectivity specificity, stable long-term recordings, and simultaneous tracking of hundreds of cells in a single animal [57]. These features are particularly desirable when studying fear memory processing because of the large dynamics in neuronal ensembles that encode associative memories involved in FC and extinction [58, 59]. In fact, a recent work employing an intracellular calcium indicator to characterize the dynamics of amygdalar ensembles during FC and extinction has revealed a learning model that may have been unapparent in smaller recordings [60]. This model shows that the neuronal activation patterns representing the CS and the US become more similar throughout fear learning and return to be distinguishable again during fear extinction. However, the CS representation after fear extinction does not revert to its initial form. In addition, some studies using in vivo calcium imaging have already detected network disturbances in rodent models of brain diseases such as Alzheimer disease and synucleinopathies [61, 62]. This indicates that these tools may be helpful to uncover altered neuronal dynamics that orchestrate the transition to pathological disease states, as those produced by stress exposure in models of pathological fear.

## Combining animal and human data

Most research in anxiety and fear-based disorders is focused either on humans or on animal models [18]. This means that there is a clear lack of translational studies using both animals and humans in the same study, missing out on the advantages of this synergic combination. Of note, translational studies involving two or more species are not strictly necessary to advance research of new treatments for anxiety and fear-based disorders. In fact, there are many cases of promising new pharmacological approaches in fear-related disorders that emerged from only the human or the animal side. One example is the antibiotic and partial *N*-methyl-D-aspartate (NMDA) agonist D-cycloserine that was found to enhance fear extinction in rats that present either physiological or pathological fear processing induced by single prolonged stress [63, 64]. Later, some studies in humans have shown that D-cycloserine could also be effective in enhancing some exposure-based therapies in humans with a fear-related disorder (e.g., PTSD [65, 66], phobia [67]). Of note, a recent meta-analysis indicates that the clinical benefits of adding D-cycloserine to exposure-based therapies are relatively small and may easily dissipate over time [68].

Human research is often limited to observational and correlational studies for obvious ethical reasons. This results in being unable to establish causal effects and prove limited information about the cellular and molecular substrates underlying behavioral data. On its behalf, animal research overcomes these limitations, but is not always a good predictor of the human condition and most psychiatric symptoms can only be partially inferred in animal models. For this reason, its combination with human data magnifies the robustness, applicability and potential therapeutic relevance of findings from animal studies. Several publications have proven that mice are an optimal species for translational studies, and the comparison of both human and mouse pathological fear has resulted in the identification of common pathways that can be pharmacologically successfully targeted [69, 70]. For example, both transgenic mice and humans presenting a particular genetic variant BDNF polymorphism show impaired fear extinction [71]. Studies including psychiatric patients have shown that the opioid-receptor-like 1 has been associated with fear learning in

both mice and humans with PTSD [69]. Also, a study in humans has confirmed that extracellular signaling pathways involving matrix metalloproteinases are crucially required for fear learning [72], a role previously reported in rodents [73]. Of note, in some cases these common pathways might be detected only as a response to a challenge and not under basal conditions. This has been shown in a recent study identifying genetic variants associated with increased risk of psychiatric disorders, where an acute stress challenge unmasks an overlapping transcriptional profile in humans and mice [74]. Similarly, fear exposure may engage a specific transcriptional response (maybe not detectable in baseline conditions) that will be overlapping in human and mice [69, 74]. Thus, a critical point in future translational studies is to unify the fear procedures across species which would be helpful to obtain more relevant data.

## Unifying methodological approaches in animal and human research

The studies discussed in the paragraph above show the outstanding promises of translational models of fear learning that help us understand pathological fear, despite methods used to study fear learning in humans can be markedly different from those used in rodents. For example, most human studies use differential-cue paradigms where a CS is followed by the US (CS + ) and another CS is not followed by the US (CS-). In contrast, rodent *single-cue* paradigms (where only one CS is conditioned) are most often used. The reinforcement ratios during initial conditioning might differ between rodent and human studies as well and are often lower in humans. Also, fear extinction (and the return of fear) is often investigated within the same session (or after a very short time delay after conditioning) in human studies, mainly for practical reasons, whereas longer delays are often used in rodents. Moreover, although similar USs (e.g., electric shocks) can be employed in both humans and rodents, the intensity of such USs is typically much lower in humans for ethical reasons. In addition, some readout measures of fear learning can be used (i.e., easily "translated") in both humans and rodents (namely, the fear-potentiated startle), but some others cannot (e.g., skin conductance response in humans versus freezing in rodents) [75].

These differences between the methods used for evaluating fear learning in rodents and humans are likely masking conserved similarities across species. To uncover shared mechanisms of fear learning in different species it is necessary to use tests as similar as possible tackling the issues discussed in the paragraph above. Additionally, the translational value of new fear measures is also awaiting further research. In this regard, pupil dilation has been recently shown in humans to be a robust marker of fear learning that activates emotional areas in the brain [76, 77]. Studying pupil dilation in rodents is feasible [78], but it has not been tested yet in conjunction with fear learning paradigms. Thus, it is possible that recording the same psychophysiological measures in both rodents and humans may help to reduce the methodological gaps in fear paradigms across species.

Recent evidences indicate that it is also relevant to preserve certain conditions inherent to natural settings when translated to the laboratory. One of these factors present in most real fearful experiences is temporal unpredictability, generally omitted in both animal and human FC paradigms. Animal studies indicate that temporal ambiguity of aversive events greatly enhances fear [79], and certain neurons within the fear network show greater firing and activation in response to unpredictable stimuli than to predictable stimuli [80, 81]. This event results clinically relevant as well, since patients with fear and anxiety disorders have been reported to be highly affected by unpredictable aversive stimuli [82, 83] and more likely to interpret ambiguous stimuli as threatening [84]. Hence, employing more naturalistic conditions during FC might increase our chances to detect alterations in the fear circuitry involved with fear and anxiety disorders.

Finally, our ability to perform translational research is also constrained by methodological issues concerning neuroimaging studies in humans. In accordance with evidence from animal studies, it has been inferred from fMRI and PET studies that human FC and extinction involves the activation of a common core fear network including the amygdalar complex and regions of the cingulofrontal cortex among others [85, 86]. This view was further supported by studies in patients suffering from a rare genetic disorder, the Urbach-Wiethe disease, who present selective calcification of amygdalar tissue [87] correlating with impaired conditioning to a variety of fear-evoking stimuli [88, 89]. However, some neuroimaging studies report divergent findings with this regard. Indeed, recent meta-analyses of human fMRI studies could not confirm the well-established role of the amygdala on fear acquisition and extinction learning [90, 91]. The observed variance between these functional imaging studies may arise from the considerable methodological differences between them (e.g., contingency and timing parameters, modality of CS/US) [86, 90]. It may reflect as well technical (e.g., insufficient resolution, low signal-to-noise-ratio) or analytical limitations (e.g., mass-univariate approaches when analyzing the activity of sparse distributed neurons) in the assessment of brain function in humans in comparison to rodents [92, 93]. Thus, improving these methods and technology in human research will help to compare more accurately the results with animal data and improve translational research.

### Using theoretical frameworks: from humans to animals and back

Assessment of the neurobiological correlates of anxiety and fear-based disorders in humans has expanded beyond the mere translation of animal models to the human domain. Thus, concepts such as "emotional regulation" or "cognitive reappraisal" have burst into clinical psychology literature proposing novel research approaches that have been incorporated into neurobiological models of anxiety and fear-based disorders. These collection of concepts and ideas are aligned with cognitive formulations (which are difficult to model in animals) and refer to the downregulation of limbic activity by the cognitive processes dependent on the coordinated action of different parts of the prefrontal cortex [94]. In general, it is considered that emotional regulation is successful when engaged before emotional responses have been completely generated, rather than after the full development of the emotion [95]. Critically, patients with anxiety and fear-based disorders typically deploy maladaptive strategies to regulate or cope with their emotions, such as expressive suppression, or present less awareness of their emotions [96]. Likewise, neuroimaging studies have shown that in these patients prefrontal cortex circuits exert an ineffective top–down inhibitory control of limbic structures, which are characteristically hyperreactive [97, 98]. Importantly, such inefficient use of cognitive resources also has consequences for treatment response, since successful cognitive behavioral therapy (CBT) has been shown to associate with improvements in cognitive reappraisal abilities [99, 100]. The development of robust and fine-grained neuroimaging biomarkers [101] (i.e., based on the use of high-resolution functional magnetic resonance imaging and multivariate pattern-recognition techniques) may ultimately lead to the identification of the neural circuitry involved in successful emotion regulation and, therefore, provide a novel perspective of what is wrong in anxiety and fear-based disorders. Moreover, such neuroimaging biomarkers may provide the opportunity to develop novel therapeutic approaches, as can be inferred from emerging studies focused on reducing a certain aversive memory without explicit presentation of the fear-associated stimulus [102]. This strategy would avoid the unpleasant experience of repeated exposure to fear-evoking stimuli during CBT. Real-time decoding of multivariate fMRI signals has been recently employed to reduce fear memories by pairing rewards with the occurrences of induced activity patterns matching the fear-evoking stimulus in the absence of the stimulus itself [102]. Such network-level biomarkers could then be translated back to animal models where invasive research strategies aimed at the modulation of such circuits at the molecular or cellular level can potentially be developed. An elegant example of human-to-mouse translation in fear research can be found in a study in mice revealing how successful reduction of fear is achieved when the counter-conditioning reward is paired with the reactivation of a fear memory engram located in the dentate gyrus of the hippocampus, but not the one located in the amygdala [103]. This circuit dissection could not have been performed in humans, since specific manipulation of memory engram neurons was possible through optogenetic approaches. Furthermore, behavioral counterconditioning effectively reduces fear in both humans [104] and rodents [105], and, therefore, understanding the mechanisms behind counterconditioning could be particularly important.

## Conclusions

The focus of translational neuroscience in fear models can help us to further understand our brain in health and disease. Our view proposes that future studies need to unify methodologies in both animal and human research, and include novel technologies in animal models of pathological fear in combination with human data in anxiety and fear-based disorders. We also argue that the development of new technology will help us to test theoretical frameworks in both animals and humans. We predict that the results will be outstanding and contribute to the understanding of not only anxiety and fear-based disorders but also the brain.

**Acknowledgements** RA is supported by a NARSAD Young Investigator Grant #22434, Ramón y Cajal program RYC2014-15784, RETOS-MINECO SAF2016-76565-R and FEDER funds. MAF is supported by a PERIS contract from the Departament de Salud of Generalitat de (SLT002/16/00490). CSM is supported by a Miguel Servet contract from the Carlos III Health Institute (CPII16/00048). MAF and CSM are supported by grants (PI16/00144 and PI16/00889) from the Carlos III Health Institute and FEDER funds -a way to build Europe-. AF is supported by a Juan de la Cierva contract from the Spanish government's Economy and Competitiveness Ministry (FJCI-2016-29888). We would like to thank Nicole Gouws for proofreading the manuscript.

### Compliance with ethical standards

**Conflict of interest** RA declares intellectual property of the patent PCT/US2015/037629 "Methods of managing conditioned fear with neurokinin receptor antagonists". The remaining authors declare that they have no conflict of interest.

## References

1. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21:169–84.
2. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and

other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21:655–79.
3. Kanwar A, Malik S, Prokop LJ, Sim LA, Feldstein D, Wang Z, et al. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety. 2013;30:917–29.
4. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B. Group C study, et al. Econ Cost brain Disord Eur Eur J Neurol. 2012;19:155–62.
5. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialog- Clin Neurosci. 2015;17:327–35.
6. Farb DH, Ratner MH. Targeting the modulation of neural circuitry for the treatment of anxiety disorders. Pharmacol Rev. 2014;66:1002–32.
7. Clark DM. Anxiety disorders: why they persist and how to treat them. Behav Res Ther. 1999;37:S5–27.
8. Kindt M. A behavioural neuroscience perspective on the aetiology and treatment of anxiety disorders. Behav Res Ther. 2014;62:24–36.
9. Wermter A-K, Laucht M, Schimmelmann BG, Banaschewski T, Banaschweski T, Sonuga-Barke EJS, et al.From nature versus nurture, via nature and nurture, to gene x environment interaction in mental disorders. Eur Child Adolesc Psychiatry. 2010;19:199–210.
10. Plumb TN, Cullen PK, Minor TR. Parameters of hormetic stress and resilience to trauma in rats. Stress. 2015;18:88–95.
11. Pêgo JM, Sousa JC, Almeida OFX, Sousa N. Stress and the neuroendocrinology of anxiety disorders. Curr Top Behav Neurosci. 2010;2:97–117.
12. McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron. 2013;79:16–29.
13. Roozendaal B, McEwen BS, Chattarji S, Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10:423–33.
14. Kendler KS. Genetic epidemiology in psychiatry. Taking both genes and environment seriously. Arch Gen Psychiatry. 1995;52:895–9.
15. Franklin TB, Saab BJ, Mansuy IM. Neural mechanisms of stress resilience and vulnerability. Neuron. 2012;75:747–61.
16. Macphail EM. Cognitive function in mammals: the evolutionary perspective. Brain Res Cogn Brain Res. 1996;3:279–90.
17. Anderson DJ, Adolphs R. A framework for studying emotions across species. Cell. 2014;157:187–200.
18. Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends Neurosci. 2012;35:24–35.
19. Lüthi A, Lüscher C. Pathological circuit function underlying addiction and anxiety disorders. Nat Neurosci. 2014;17:1635–43.
20. Maeng LY, Milad MR. Sex differences in anxiety disorders: Interactions between fear, stress, and gonadal hormones. Horm Behav. 2015;76:106–17.
21. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. Front Neuroendocrinol. 2014;35:320–30.
22. Johnson PL, Truitt W, Fitz SD, Minick PE, Dietrich A, Sanghani S, et al. A key role for orexin in panic anxiety. Nat Med. 2010;16:111–5.
23. Brandão ML, Zanoveli JM, Ruiz-Martinez RC, Oliveira LC, Landeira-Fernandez J. Different patterns of freezing behavior organized in the periaqueductal gray of rats: Association with different types of anxiety. Behav Brain Res. 2008;188:1–13.
24. Santos M, D'Amico D, Spadoni O, Amador-Arjona A, Stork O, Dierssen M. Hippocampal hyperexcitability underlies enhanced fear memories in TgNTRK3, a panic disorder mouse model. J Neurosci. 2013;33:15259–71.
25. Hefner K, Whittle N, Juhasz J, Norcross M, Karlsson R-M, Saksida LM, et al. Impaired fear extinction learning and cortico-amygdala circuit abnormalities in a common genetic mouse strain. J Neurosci. 2008;28:8074–85.
26. Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, et al. Anxiety disorders. Nat Rev Dis Prim. 2017;3:17024
27. Sawamura T, Klengel T, Armario A, Jovanovic T, Norrholm SD, Ressler KJ, et al. Dexamethasone treatment leads to enhanced fear extinction and dynamic Fkbp5 regulation in amygdala. Neuropsychopharmacology. 2016;41:832–46.
28. Andero R, Dias BG, Ressler KJ. A role for Tac2, NkB, and Nk3 receptor in normal and dysregulated fear memory consolidation. Neuron. 2014;83:444–54.
29. Izquierdo A, Wellman CL, Holmes A. Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. J Neurosci. 2006;26:5733–8.
30. Takahashi T, Morinobu S, Iwamoto Y, Yamawaki S. Effect of paroxetine on enhanced contextual fear induced by single prolonged stress in rats. Psychopharmacol (Berl). 2006;189:165–73.
31. Baratta MV, Christianson JP, Gomez DM, Zarza CM, Amat J, Masini CV, et al. Controllable versus uncontrollable stressors bidirectionally modulate conditioned but not innate fear. Neuroscience. 2007;146:1495–503.
32. Maren S. Neurobiology of pavlovian fear conditioning. Annu Rev Neurosci. 2001;24:897–931.
33. Maren S, Quirk GJ. Neuronal signalling of fear memory. Nat Rev Neurosci. 2004;5:844–52.
34. Pape H-C, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev. 2010;90:419–63.
35. Belzung C, Turiault M, Griebel G. Optogenetics to study the circuits of fear- and depression-like behaviors: a critical analysis. Pharmacol Biochem Behav. 2014;122:144–57.
36. Dejean C, Courtin J, Rozeske RR, Bonnet MC, Dousset V, Michelet T, et al. Neuronal circuits for fear expression and recovery: Recent advances and potential therapeutic strategies. Biol Psychiatry. 2015;78:298–306.
37. Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. Nat Neurosci. 2015;18:1213–25.
38. Sternson SM, Roth BL. Chemogenetic tools to interrogate brain functions. Annu Rev Neurosci. 2014;37:387–407.
39. LeDoux J. The amygdala. Curr Biol. 2007;17:R868–74.
40. Gafford GM, Ressler KJ. Mouse models of fear-related disorders: Cell-type-specific manipulations in amygdala. Neuroscience. 2016;321:108–20.
41. Sparta DR, Jennings JH, Ung RL, Stuber GD. Optogenetic strategies to investigate neural circuitry engaged by stress. Behav Brain Res. 2013;255:19–25.
42. Ciocchi S, Herry C, Grenier F, Wolff SBE, Letzkus JJ, Vlachos I, et al. Encoding of conditioned fear in central amygdala inhibitory circuits. Nature. 2010;468:277–82.
43. Roth BL. DREADDs for neuroscientists. Neuron. 2016;89:683–94.
44. McCullough KM, Choi D, Guo J, Zimmerman K, Walton J, Rainnie DG, et al. Molecular characterization of Thy1 expressing fear-inhibiting neurons within the basolateral amygdala. Nat Commun. 2016;7:13149
45. Rask-Andersen M, Almén MS, Schiöth HB. Trends in the exploitation of novel drug targets. Nat Rev Drug Discov. 2011;10:579–90.
46. Zhu H, Roth BL. DREADD: a chemogenetic GPCR signaling platform. Int J Neuropsychopharmacol. 2014;18:pyu007.
47. Baratta MV, Kodandaramaiah SB, Monahan PE, Yao J, Weber MD, Lin P-A, et al. Stress enables reinforcement-elicited serotonergic consolidation of fear memory. Biol Psychiatry. 2016;79:814–22.

48. Meyer RM, Burgos-Robles A, Liu E, Correia SS, Goosens KA. A ghrelin-growth hormone axis drives stress-induced vulnerability to enhanced fear. Mol Psychiatry. 2014;19:1284–94.
49. Gillespie CF, Phifer J, Bradley B, Ressler KJ. Risk and resilience: Genetic and environmental influences on development of the stress response. Depress Anxiety. 2009;26:984–92.
50. Sharma S, Powers A, Bradley B, Ressler KJ. Gene × environment determinants of stress- and anxiety-related disorders. Annu Rev Psychol. 2016;67:239–61.
51. Yin H, Kauffman KJ, Anderson DG. Delivery technologies for genome editing. Nat Rev Drug Discov. 2017;16:387–99. https://doi.org/10.1038/nrd.2016.280.
52. Walters BJ, Azam AB, Gillon CJ, Josselyn SA, Zovkic IB. Advanced in vivo use of CRISPR/Cas9 and anti-sense DNA inhibition for gene manipulation in the brain. Front Genet. 2016;6:362.
53. Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, et al. Multiplex genome engineering using CRISPR/Cas systems. Science.2013;339:819–23.
54. Lee HB, Sundberg BN, Sigafoos AN, Clark KJ. Genome engineering with TALE and CRISPR systems in neuroscience. Front Genet. 2016;7:47.
55. Sheerin CM, Lind MJ, Bountress KE, Nugent NR, Amstadter AB. The genetics and epigenetics of PTSD: overview, recent advances, and future directions. Curr Opin Psychol. 2017;14:5–11.
56. Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology. 2016;41:297–319.
57. Hamel EJO, Grewe BF, Parker JG, Schnitzer MJ. Cellular level brain imaging in behaving mammals: An engineering approach. Neuron. 2015;86:140–59.
58. Buzsáki G. Large-scale recording of neuronal ensembles. Nat Neurosci. 2004;7:446–51.
59. Grewe BF, Helmchen F. Optical probing of neuronal ensemble activity. Curr Opin Neurobiol. 2009;19:520–9.
60. Grewe BF, Gründemann J, Kitch LJ, Lecoq JA, Parker JG, Marshall JD, et al. Neural ensemble dynamics underlying a long-term associative memory. Nature. 2017;543:670–5.
61. Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Wiederhold K-H, Haass C, et al. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. Science. 2008;321:1686–9.
62. Reznichenko L, Cheng Q, Nizar K, Gratiy SL, Saisan PA, Rockenstein EM, et al. In vivo alterations in calcium buffering capacity in transgenic mouse model of synucleinopathy. J Neurosci. 2012;32:9992–8.
63. Walker DL, Ressler KJ, Lu K-T, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci. 2002;22:2343–51.
64. Yamamoto S, Morinobu S, Fuchikami M, Kurata A, Kozuru T, Yamawaki S. Effects of single prolonged stress and D-cycloserine on contextual fear extinction and hippocampal NMDA receptor expression in a rat model of PTSD. Neuropsychopharmacology. 2008;33:2108–16.
65. Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. Am J Psychiatry. 2014;171:640–8.
66. de Kleine RA, Hendriks G-J, Kusters WJC, Broekman TG, van Minnen A. A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. Biol Psychiatry. 2012;71:962–8.
67. Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiatry. 2004;61:1136–44.
68. Mataix-Cols D, Fernández de la Cruz L, Monzani B, Rosenfield D, Andersson E, Pérez-Vigil A, et al. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: A systematic review and meta-analysis. JAMA Psychiatry. 2017;74:501–10. https://doi.org/10.1001/jamapsychiatry.2016.3955.
69. Andero R, Brothers SP, Jovanovic T, Chen YT, Salah-Uddin H, Cameron M, et al. Amygdala-dependent fear is regulated by Oprl1 in mice and humans with PTSD. Sci Transl Med. 2013;5:188ra73
70. Gunduz-Cinar O, MacPherson KP, Cinar R, Gamble-George J, Sugden K, Williams B, et al. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. Mol Psychiatry. 2013;18:813–23.
71. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science. 2010;327:863–6.
72. Bach DR, Tzovara A, Vunder J. Blocking human fear memory with the matrix metalloproteinase inhibitor doxycycline. Mol Psychiatry. 2017. https://doi.org/10.1038/mp.2017.65.
73. Brown TE, Wilson AR, Cocking DL, Sorg BA. Inhibition of matrix metalloproteinase activity disrupts reconsolidation but not consolidation of a fear memory. Neurobiol Learn Mem. 2009;91:66–72.
74. Arloth J, Bogdan R, Weber P, Frishman G, Menke A, Wagner KV, et al. Genetic differences in the immediate transcriptome response to stress predict risk-related brain function and psychiatric disorders. Neuron. 2015;86:1189–202.
75. Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, et al. Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neurosci Biobehav Rev. 2017;77:247–85. https://doi.org/10.1016/j.neubiorev.2017.02.026.
76. Korn CW, Staib M, Tzovara A, Castegnetti G, Bach DR. A pupil size response model to assess fear learning. Psychophysiology. 2017;54:330–43.
77. Leuchs L, Schneider M, Czisch M, Spoormaker VI. Neural correlates of pupil dilation during human fear learning. Neuroimage. 2017;147:186–97.
78. McGinley MJ, David SV, McCormick DA. Cortical membrane potential signature of optimal states for sensory signal detection. Neuron. 2015;87:179–92.
79. Amadi U, Lim SH, Liu E, Baratta MV, Goosens KA. Hippocampal Processing of ambiguity enhances fear memory. Psychol Sci. 2017;28:143–61.
80. Herry C, Bach DR, Esposito F, Di Salle F, Perrig WJ, Scheffler K, et al. Processing of temporal unpredictability in human and animal amygdala. J Neurosci. 2007;27:5958–66.
81. Belova MA, Paton JJ, Morrison SE, Salzman CD, Braus DF, Buchel C, et al. Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. Neuron. 2007;55:970–84.
82. Grillon C, Lissek S, Rabin S, McDowell D, Dvir S, Pine DS. Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiologic marker of panic disorder. Am J Psychiatry. 2008;165:898–904.
83. Holaway RM, Heimberg RG, Coles ME. A comparison of intolerance of uncertainty in analogue obsessive-compulsive

disorder and generalized anxiety disorder. J Anxiety Disord. 2006;20:158–74.
84. Dugas MJ, Gagnon F, Ladouceur R, Freeston MH. Generalized anxiety disorder: a preliminary test of a conceptual model. Behav Res Ther. 1998;36:215–26.
85. LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron. 1998;20:937–45.
86. Sehlmeyer C, Schöning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, et al. Human fear conditioning and extinction in neuroimaging: A systematic review. PLoS ONE. 2009;4:e5865
87. Quirici MB, da Rocha AJ. Teaching neuroimages: lipoid proteinosis (Urbach-Wiethe disease): typical findings in this rare genodermatosis. Neurology. 2013;80:e93.
88. Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science. 1995;269:1115–8.
89. Feinstein JS, Adolphs R, Damasio A, Tranel D, Naumann E, Bartussek D, et al. The human amygdala and the induction and experience of fear. Curr Biol. 2011;21:34–8.
90. Fullana MA, Harrison BJ, Soriano-Mas C, Vervliet B, Cardoner N, Àvila-Parcet A, et al. Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. Mol Psychiatry. 2016;21:500–8.
91. Harrison B, Albajes-Eizagirre A, Soriano-Mas C, Vervliet B, Cardoner N, Benet O, et al. 14. Fear extinction in the human brain: Four meta-analyses of fMRI studies. Biol Psychiatry. 2017;81:S6–7.
92. Bach DR, Weiskopf N, Dolan RJ. A stable sparse fear memory trace in human amygdala. J Neurosci. 2011;31:9383–9.
93. Boubela RN, Kalcher K, Huf W, Seidel E-M, Derntl B, Pezawas L, et al. fMRI measurements of amygdala activation are confounded by stimulus correlated signal fluctuation in nearby veins draining distant brain regions. Sci Rep. 2015; 5:10499
94. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci. 2012;1251: E1–24.
95. Gross JJ. Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. J Pers Soc Psychol. 1998;74:224–37.
96. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin Psychol Rev. 2010;30:217–37.
97. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164:1476–88.
98. Picó-Pérez M, Radua J, Steward T, Menchón JM, Soriano-Mas C. Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79:96–104.
99. Taylor SF, Liberzon I. Neural correlates of emotion regulation in psychopathology. Trends Cogn Sci. 2007;11:413–8.
100. Goldin PR, Ziv M, Jazaieri H, Hahn K, Heimberg R, Gross JJ. Impact of cognitive behavioral therapy for social anxiety disorder on the neural dynamics of cognitive reappraisal of negative self-beliefs: randomized clinical trial. JAMA Psychiatry. 2013;70:1048–56.
101. Woo C-W, Chang LJ, Lindquist MA, Wager TD. Building better biomarkers: brain models in translational neuroimaging. Nat Neurosci. 2017;20:365–77.
102. Koizumi A, Amano K, Cortese A, Shibata K, Yoshida W, Seymour B, et al. Fear reduction without fear through reinforcement of neural activity that bypasses conscious exposure. Nat Hum Behav. 2016;1:6
103. Redondo RL, Kim J, Arons AL, Ramirez S, Liu X, Tonegawa S. Bidirectional switch of the valence associated with a hippocampal contextual memory engram. Nature. 2014;513:426–30.
104. Paunović N. Prolonged exposure counterconditioning as a treatment for chronic posttraumatic stress disorder. J Anxiety Disord. 2003;17:479–99.
105. Correia SS, McGrath AG, Lee A, Graybiel AM, Goosens KA. Amygdala-ventral striatum circuit activation decreases long-term fear. Elife. 2016; 5. https://doi.org/10.7554/eLife.12669.