Post-traumatic stress disorder and beyond: an overview of rodent stress models

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Abstract

Post-traumatic stress disorder (PTSD) is a psychiatric disorder of high prevalence and major socioeconomic impact. Patients suffering from PTSD typically present intrusion and avoidance symptoms and alterations in arousal, mood and cognition that last for more than 1 month. Animal models are an indispensable tool to investigate underlying pathophysiological pathways and, in particular, the complex interplay of neuroendocrine, genetic and environmental factors that may be responsible for PTSD induction. Since the 1960s, numerous stress paradigms in rodents have been developed, based largely on Seligman's seminal formulation of 'learned helplessness' in canines. Rodent stress models make use of physiological or psychological stressors such as foot shock, underwater trauma, social defeat, early life stress or predator-based stress. Apart from the brief exposure to an acute stressor, chronic stress models combining a succession of different stressors for a period of several weeks have also been developed. Chronic stress models in rats and mice may elicit characteristic PTSD-like symptoms alongside, more broadly, depressive-like behaviours. In this review, the major existing rodent models of PTSD are reviewed in terms of validity, advantages and limitations; moreover, significant results and implications for future research—such as the role of FKBP5, a mediator of the glucocorticoid stress response and promising target for therapeutic interventions—are discussed.

PTSD is a disorder that may develop after exposure to a terrifying or catastrophic event involving actual or threatened death, serious injury or sexual violation. Typically, patients suffering from PTSD present symptoms of avoidance, intrusion and alterations in arousal, mood and cognition. Lifetime prevalence among adult Americans is 8.3% [1],

being twice as high in women (11.0%) than in men (5.4%). In 1980, the diagnosis of PTSD was added to DSM-3 [2], as the severe psychological consequences following combat exposure became increasingly apparent, for example, in returning Vietnam Veterans [3].

PTSD is often accompanied by psychiatric co-morbidities such as depression, substance abuse or anxiety disorders, which leads to a high level of functional disability. In addition, PTSD is a major risk factor for somatic diseases such as coronary heart disease [4] and stroke [5]. It imposes an enormous economic burden on health services and society: In terms of medical care, loss of productivity and

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suicide, the financial impact of PTSD and major depression in American troops has been estimated to range from $4 to $6.2 billion over a 2-year period post-deployment [6].

Although a substantial body of research has greatly improved our knowledge regarding prevalence, clinical symptoms and consequences of PTSD over the last decades, relatively little is known about underlying neurobiological abnormalities. This is why various animal models have been proposed.

General conditions for animal models in PTSD research

Willner [7] proposed three criteria to be considered regarding animal models: They should have a phenomenological resemblance to the modelled condition ('face validity'), show the same underlying mechanisms as the human disorder ('construct validity') and make correct predictions about treatment effects ('predictive validity'). Accordingly, as regard PTSD, the paradigms should include appropriate stressors which are able to provoke long-lasting behavioural symptoms similar to PTSD, for example, hyperarousal, hypervigilance, social withdrawal and cognitive alterations (face validity). Furthermore, these symptoms should be ameliorated by established psychopharmacological treatments, for example selective serotonin reuptake inhibitors (SSRI), in order to meet the criterion of predictive validity. The biological pathomechanisms of PTSD are still far from being understood, so it is difficult to define exact conditions of construct validity. However, emerging evidence indicates that a number of biological factors that have been implicated in the development of PTSD in humans, for example altered inflammatory signalling or increased amygdala reactivity, should also be looked for in a potential animal model.

As depression and PTSD share a variety of etiological factors, it is not an easy task to develop an animal model that exclusively reflects the one but not the other disorder. First, there is a considerable overlap of symptoms, especially as regards the symptom cluster of 'negative cognitions': for example, the inability to experience positive emotions, numbing or alterations of sleep and concentration. Moreover, co-morbidity between depression and PTSD is high [3], which, in practice, may make it quite difficult to make a clear distinction between the two disorders. Furthermore, it has been shown that psychosocial stress and adverse childhood events are not only risk factors for PTSD, but are also important contributors to the development of depressive disorders [8]. The mere presence of a stressor in an experimental paradigm is thus not necessarily sufficient to reproduce characteristic PTSD behaviours, as it might just as well lead to depressive-like symptoms. Yehuda and Antelman [9] proposed that the induction of a PTSD-like syndrome should include a brief and very intense stressor, in contrast to more chronic and mild stressors in animal models of depression.

There may also exist some important differences between the biological underpinnings of depression and PTSD: While both disorders have been linked with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, patients with depression typically display an increased level of plasma cortisol [10], whereas PTSD is associated with significantly lower concentration of plasma and urinary cortisol

[11, 12]. Therefore, it is hypothesized that PTSD leads to enhanced negative glucocorticoid feedback and hypocortisolism, a finding that may be highly specific for PTSD and, consequently, of major utility in the critical evaluation of experimental paradigms.

Animal stress models: differences between rats and mice

Rodents have been particularly useful in experimental modelling of human disease. In 2014, the great majority of the experimental procedures carried out in the United Kingdom involved mice (76%) and rats (7%) [13]. Rodents provide several advantages that make them convenient for researchers, for example easy housing and handling, a marked genetic resemblance to humans, fast reproduction and short lifespan. Although rats (Rattus Norvegicus) and mice (Mus Musculus) evolved from a common ancestor that lived 12–24 million years ago, they belong to different species that display numerous differences in anatomy, morphology, genetics and behaviour. Of special note, rat brains weigh approximately five times as much as mouse brains [14].

While rats have a clearly defined hierarchy system which finds expression through submissive posture or attack, mice do not typically present hierarchical behaviours [15]. This point gains added significance in animal stress models that rely on social defeat (SD) or unstable housing conditions [16]. In addition, rats and mice also seem to differ in how they cope with stress: Several studies have shown that stress models involving mice require comparably harsher stressors to reliably evoke anxiety-like or depression-like behaviours than stress models in rats [17]. In summary, it is of major importance to keep species-specific responses to stressors in mind when conceptualizing animal models of PTSD. Likewise, strain differences may play a crucial role in shaping behaviour and physiology and, therefore, also need to be taken into consideration.

History: learned helplessness

In the late 1960s, Seligman and Maier [18] developed the so-called 'learned helplessness' paradigm (LH), which is based on Pavlov's 'classical conditioning'. They demonstrated that dogs which had previously been given inescapable electric shocks failed to escape in a different setting afterwards. Instead of jumping over a low fence in order to avoid further shocks, pre-shocked dogs remained passive on the floor, which can be interpreted as a correlate of 'behavioural despair'. The decreased locomotion and the lack of response initiative of the pre-shocked animals can be conceptualized as a motivational deficit [19], which represents a core symptom of depressive disorders. This is why the LH procedure was primarily developed as a model of depression. Notwithstanding, different aspects of LH—namely, avoidance behaviour, numbing and the presence of a strong and inescapable stressor—were also recognized as closely linked with PTSD.

The concept of LH soon was extended to other species, especially rats and mice [20, 21]. Van der Kolk reintroduced LH as an

'Inescapable Shock-Learned Helplessness' (IS-LH) paradigm of PTSD [22]. Mice subjected to IS showed a relevant depletion of catecholamines and—putatively owing to changes in neurotransmitter concentrations—deficits in active motor responding performance [23]. Moreover, it was shown that some psychopharmacological agents are able to reverse the long-term sequelae of IS [24]. IS-LH has given rise to a controversial debate in the 1980s and early 1990s. Yehuda and Antelman [9], in particular, have called into question the usefulness of the paradigm since it fails to induce persisting behavioural changes, whereas long-term duration and chronicity of PTSD constitute characteristic features in humans [25] and represent a key aspect of the diagnosis according to DSM-5 [26]. This is why numerous modified models have emerged in the past decades, each offering a different approach to specific PTSD symptoms.

Time-dependent sensitization (TDS)

In 1988, Antelman described the TDS paradigm [27], which includes a very brief and intense stimulus, followed by a long-lasting and progressively amplified response to subsequent pharmacological and non-pharmacological stressors. Different types of stressor have been used in this model, mostly in rats: psychological stressors, for example, exposure to a black box [28] or immobilization [29, 30], as well as pharmacological stressors such as the injection of cocaine [29]. The common feature of all these experiments is sensitization: A dangerous, potentially life-threatening stimulus intensifies subsequent reactions to a similar or weaker stimulus, even if the second stimulus is applied much later [27]. Under natural circumstances, sensitization is a fundamental reaction to threat as it accelerates escape responses and thus may protect the subject from future danger. The effects of TDS may be observed at multiple levels including long-term changes in behaviour, neurotransmitter concentrations [31], neuroendocrine and immune-system responses [30] as well as altered susceptibility to pharmacological interventions [31, 32].

Foot shock (FS)

FS is a stressor broadly employed in animal models of anxiety, stress [21, 33–36] and depression [18]. FS elicits long-lasting behavioural and physiological effects that persist up to 3 weeks and may even intensify over time [21]. In general, animals are placed into a shock chamber on a metal-grid floor and subjected to a sequence of electric shocks of variable intensity and duration. The FS model reproduces some of the core symptoms of PTSD, including avoidance and anxiety behaviour [33], hyperarousal, aggression and re-experiencing [36], as well as alterations of sleep architecture [37]. Some studies combine the FS model with a situational reminder (SR) of the stressful experience which serves as contextual conditioned Pavlovian cue (*e.g.* re-exposure to the box where the shocks were administered). It has been shown that animals exposed to SR exhibit a distinct behavioural response (*e.g.* crouching near the back wall of the box, increase in respiratory rate, etc.) despite the absence of the stressor itself [36]. The incorporation of SR in rodent models provides an interesting new research perspective as it recalls human PTSD symptoms such as re-experiencing and intrusions.

Underwater trauma (UT)

Richter-Levin [38] developed a model of PTSD using UT. In this model, rats are forced to swim for 1 min. in a Morris water maze [39], from which the platform has been removed. Afterwards, they are held under water for 30 sec. with a metal net and then returned to a resting cage. Richter-Levin argues that this kind of stressor is more ethologically relevant than electric shocks since the threat of drowning is quite real in the life of a rat living in the wild. Learning in the Morris water maze is impaired as late as 3 weeks after UT [38], a finding which is in line with various studies reporting negative effects of stress on memory retrieval and learning [40, 41]. It also corresponds well to the 'negative alterations in cognition' criterion in DSM-5 [26].

Single prolonged stress (SPS) and restraint stress (RS)

In the SPS paradigm [42], rats are subjected to RS for 2 hrs, which is followed immediately by a forced swim for 20 min., and, after a brief rest period, by exposure to ether vapours until the experimental animal loses consciousness. Besides the conventional immobilization on wooden boards, RS can also be achieved through a special restraining syringe [43]. After a period of 7 days, rats are re-stressed in a brief session of RS. SPS is the first experimental paradigm that was able to reproduce PTSD-like alterations of the HPA axis [42]. In rats previously exposed to SPS, an increased sensitivity to glucocorticoid fast feedback was demonstrated after re-stress, a finding that recapitulates the HPA axis dysregulation commonly associated with PTSD: PTSD patients display significantly reduced urinary and salivary cortisol concentrations in tandem with increased suppression of cortisol in response to dexamethasone [11, 12]. In contrast to increased sensitivity to glucocorticoid feedback in the SPS paradigm, a chronic stress model in rats yielded decreased feedback [44], which accords well with neuroendocrine findings reported in major depression [45–47]. The stress–re-stress model thus appears to be particularly suitable to compare the specific neuroendocrine pathomechanisms of PTSD *versus* depression.

In addition to its effects on HPA axis regulation, SPS has also been shown to influence neurotransmitter signalling. In particular, SPS reduces hippocampal NMDA receptor density and leads to a dysregulation of inhibitory GABA pathways [48], which may contribute to impairments in spatial memory. At the behavioural level, SPS leads to diminished fear extinction [49], anxiety-like behaviour in the elevated plus maze and increased stress-induced nociceptive sensitivity [50], symptoms that seem to be reversed by administration of SSRI [51, 52].

Predator-based stress

The confrontation with a natural predator, for example, cats, ferrets, rats or foxes, has been shown to provoke high levels of intense fear and stress in rats and mice, followed by long-lasting behavioural and endocrine responses [53, 54]. Predators and predator-related stimuli such as the scent of predator urine are therefore highly effective tools for trauma induction in animal models. Typically, the rodent is exposed for a very brief period of time (5–10 min.) to the predator [16, 55] or to predator odorants, for example, soiled cat litter [56]. A 5-min. exposure of a rat to a cat leads to an increase in anxiety-like behaviour in the rat in the elevated plus maze that is still detectable after 3 weeks [55]. Zoladz and co-workers modified the predator-based stress model and devised the so-called 'predator-based psychosocial stress paradigm' (PPS) [16], which combines acute predator exposure with unstable housing conditions (*i.e.* randomly changing cage partners). The authors hypothesize that the chronic stress associated with unstable housing conditions exacerbates the psychological sequelae of predator exposure in much the same way that the likelihood of developing chronic PTSD is increased in trauma victims that lack social support [57]. Similar to the changes induced by SPS, PTSD-like glucocorticoid abnormalities with reduced corticosterone levels at baseline and following dexamethasone administration were observed in rats subjected to PPS [58].

Oxidative stress and chronic systemic inflammation constitute important risk factors for cardiovascular diseases such as myocardial infarction or stroke. Similar to PTSD patients [59], an increase in inflammatory cytokines and measures of oxidative stress has recently been demonstrated in rats subjected to PPS [60]. There is growing evidence in humans that PTSD increases the risk of cardiovascular events [5]. So far, few studies in experimental animals have addressed the effects of psychological trauma on cardio- and cerebrovascular vulnerability. Interestingly, a recent study documented increased sensitivity to ischaemic heart injury, that is, larger myocardial infarcts and attenuated post-ischaemic recovery, in male rats after PPS [61], suggesting that the PPS paradigm may be a useful tool to further explore the association between PTSD and cardiovascular disease.

Social defeat (SD)

The SD model has been widely used to examine behavioural and physiological sequelae of social stress, mainly in mice [62, 63]. SD leads to a long-lasting increase in social avoidance and submissive behaviour [62]. Hammamieh and co-workers adapted the model to investigate specific aspects of PTSD [64]. Mice are exposed to a trained aggressor conspecific for 6 hrs daily for 5 or 10 days in a 'cage-within-cage resident-intruder' protocol. It has been shown that animals subjected to SD present persisting PTSD-like behaviours such as increased freezing, lack of tail rattling [64], enhanced and prolonged response to acoustic startle [65], and weight loss [65]. Moreover, SD may produce pathological changes in the heart (inflammatory cardiac histopathologies) and brain (reduced spine density in medial prefrontal cortex) [64].

Social isolation

Long-term social isolation (SI) produces relevant behavioural and physiological disturbances in laboratory animals including hyperlocomotion, anxiety-like behaviour, aggression, cognitive alterations and neuroendocrine changes [66–68]. Mice exposed to 3–4 weeks of SI show increased contextual fear responses and impaired fear extinction [69].

Early life stress (ELS)

Early life stress (*e.g.* childhood abuse or neglect) significantly increases vulnerability to PTSD in humans [70]. ELS is mostly modelled using maternal deprivation. In rats, it has been shown that maternal separation for 3 hrs daily during the first 2 weeks of life leads to an increased acoustic startle reaction, increased anxiety-like behaviours and hypersecretion of corticosterone in response to mild handling stress in adulthood [71]. Moreover, the proportion of rats showing PTSD-like symptoms in the UT paradigm (see above) increases when the animals have been pre-exposed to juvenile stress [72].

Tail suspension

Some models of chronic stress include tail suspension (TS): Mice are suspended by the tail and left dangling in the air for a brief period up to several minutes. This can be combined with an assessment of the animal's behavioural response, which may consist of either struggling/climbing or passive hanging [73]. The latter is termed as 'immobility' and reflects behavioural despair. Importantly, anti-depressants may reduce the duration of immobility in the TS procedure [73]. Due to the higher body weight of rats, the TS procedure is only used in mice.

Chronic stress models

So far, chronic stress procedures have primarily been used to model depression [74]. However, it appears that chronic stress models may also be studied and interpreted fruitfully in the context of PTSD. Importantly, PTSD criterion A according to DSM-5 includes repeated traumatization, for example, repeated exposure to accidents in first responders such as firefighters or police officers [26]. In the 1980s, Katz and Hersh introduced a 21-day stress model of anhedonia in the rat [75], which consists of a variety of relatively severe stressors: exposure to 95 dB white noise, repeated unpredictable shock, 40 hrs of food and water deprivation, cold swim at 4.0°C, heat stress at 40°C, shaker stress, reversal of day–night cycle, switch of cage mates and increased housing density. Rats subjected to this chronic stress model show reduced sucrose consumption, a behaviour that is commonly interpreted as a correlate of anhedonia. Katz and co-workers were also able to demonstrate that anti-depressants ameliorate the behavioural alterations in their chronic stress model [75].

Willner and colleagues modified the above model slightly, using milder stressors (*e.g.* overnight illumination, shorter periods of food

or water deprivation over 4–23 hrs, 30° cage tilt) applied over a longer period of time (5–9 weeks) [76]. This so-called 'chronic mild stress model' (CMS) also leads to a decrease in sucrose consumption, disrupted sleep patterns, psychomotor alterations and weight loss, effects that may persist for several months. Again, the behavioural effects of CMS were shown to be reversed by anti-depressant pharmacotherapy (for review, see [77]).

More recently, Strekalova and co-workers devised a chronic stress model in mice that employs the following stressors over 28 days: exposure to a rat, RS and TS [17]. The authors found a strong decrease in sucrose preference in the stressed animals along with, among other things, weight loss, increased anxiety and hyperactivity [17]. Interestingly, the development of anhedonia in this stress paradigm was associated with reduced exploration of novelty and increased floating in the forced swim test [17].

Our group adapted this procedure to investigate the effects of chronic stress on mild brain ischaemia [43, 78]. We found that mice subjected to chronic stress showed impaired endothelium-dependent

Table 1 Rodent stress models

Model	Method	Behavioural and physiological response
Time-dependent sensitization (TDS) [27]	Different brief stressors (*e.g.* injection of pharmacological agents), followed by re-stress	Response to subsequent stressor↑, alterations of neurotransmitters, neuroendocrine and immune systems
Foot shock (FS)	Inescapable electric foot shocks, delivered through a steel grid floor, sometimes combined with situational reminder (SR), *e.g.* exposure to shock box	Anxiety behaviour↑, locomotion and rearing ↓, hyperarousal, re-experiencing [36], freezing response to acoustic triggers ↑ [21], sleep disturbances
Underwater trauma (UT)	Forced swim for 30 sec., followed by submersion for another 30 sec.	Spatial memory ↓ [94]
Restraint stress (RS)	Immobilization on wooden boards or in a restraint syringe	Anxiety ↑, nociception ↑
Single prolonged stress (SPS) [42]	Restraint for 2 hrs, followed by a forced swim of 20 min. and exposure to ether vapour until unconsciousness. Short session of RS after 7 days	Alterations of HPA axis [42], dysregulation of GABA pathways [48]. Freezing in response to contextual fear conditioning ↑, anxiety behaviour ↑, extinction of fear memory ↓ [95]
Predator-based psychosocial stress (PPS)	Exposure to a natural predator or predator-related stimuli, sometimes combined with instable housing conditions	Prefrontal cortex: serotonin ↓, norepinephrine ↑[96], inflammatory and oxidative stress markers ↑[60], anxiety ↑, cognition ↓, startle response ↑, freezing ↑, cognitive skills (*e.g.* memory for new information) ↓ [16]
Social defeat (SD)	Exposure to conspecific trained aggressors for 6 hrs daily for 5 or 10 days	Duration of grooming and freezing ↑, locomotion and tail rattling ↓ [64], weight ↓
Social isolation (SI)	Social isolation during 3–4 weeks	HPA system changes, hyperlocomotion, anxiety ↑, aggression, cognitive alterations, freezing ↑, fear extinction ↓ [69]
Early life stress (ELS)	Separation of animal pups from their mothers for several hours daily during postnatal days 1–10, followed by re-exposure to stressor in adulthood	Performance in spatial memory task ↓ [97], contextual freezing and anxiety ↑, startle reflex ↑, neuroendocrine response to subsequent stressors ↑
Tail suspension (TS)	Suspension of mice by the tail	Locomotor activity ↓
Chronic stress model (Katz)	21-day exposure to severe stressors, *e.g.* loud noise, shock, food and water deprivation, cold swim at 4.0°C, heat stress at 40°C, shaker stress	Sucrose consumption ↓
Chronic unpredictable mild stress (CMS) (Willner)	5–9 weeks exposure to mild stressors, *e.g.* overnight illumination, change of cage mates	Sucrose consumption ↓, disrupted sleep patterns, psychomotor alterations and weight ↓
Chronic mild stress (Strekalova *et al.*) [17]	28 days exposure to PPS, RS and TS	Sucrose consumption ↓, vasorelaxation ↓, larger infarct lesions [43]

vasorelaxation as well as significantly enlarged brain lesions after 30-min. middle cerebral artery occlusion (MCAo)/reperfusion [43, 78]. The deleterious effects of chronic stress were mediated, at least in part, by increased heart rate because heart rate reduction by ivabradine before stroke induction restored endothelial function and led to a marked reduction of infarct volume [78]. HPA system dysregulation in this model was illustrated by the fact that mice subjected to chronic stress showed significantly increased adrenal weights [43]. Furthermore, treatment with glucocorticoid receptor (GR) antagonist mifepristone reversed the harmful effects of stress on short-term stroke outcome at 72 hrs [43].

Future directions: the role of FKBP5

We are still a long way from understanding why some individuals display a higher vulnerability to develop PTSD after a traumatic event than others. Besides the specific aspects of the traumatic event, other factors such as childhood abuse or neglect, prior experience of trauma, lack of social support and a prior psychiatric history may make an individual more susceptible to PTSD. Genetic factors are also believed to exert an important influence on the risk of PTSD [79, 80]. Lately, FK506-binding protein 51 (FKBP5) has achieved increasing attention as an intracellular mediator of the stress response. Genetic variation and epigenetic modification of FKBP5 have been linked with the development of psychiatric disorders, in particular major depression and PTSD [81–84]. FKBP5 is a co-chaperone of the GR complex whose reactivity it modulates by decreasing ligand (*i.e.* corticosterone in rodents, cortisol in humans) binding and inhibiting translocation of the receptor complex from the cytosol to the nucleus. Activation of the GR leads to increased FKBP5 transcription, creating an ultra-fast negative feedback loop [85, 86]. The precise pathways through which FKBP5 affects the HPA axis and GR in PTSD and major depression are not fully understood although several recent studies in humans and in experimental animals are beginning to elucidate mechanisms that may underlie the neuroendocrine differences between both disorders.

In survivors of the World Trade Center attacks of 11 September 2001, reduced whole blood messenger RNA (mRNA) expression of FKBP5 has been shown to be associated with PTSD [87], a finding that might lead to enhanced GR responsiveness and explain the HPA axis dysregulation commonly associated with PTSD (*i.e.* lower basal cortisol levels as well as increased feedback sensitivity) [11, 12]. Furthermore, exciting findings from a cohort study by Elisabeth Binder and colleagues [81] suggest that polymorphisms of FKBP5 interact with history of childhood abuse to predict onset of PTSD symptoms in adulthood. Interestingly, the authors report that alleles associated with increased induction of FKBP5 confer increased GR resistance in healthy controls, whereas in PTSD patients, these same alleles were associated with increased GR sensitivity [81]. This pattern of effects suggests that the relationship between FKBP5 polymorphisms and GR responsiveness is critically dependent on context [88].

Investigations in experimental animals are also beginning to unravel the role of FKBP5 in the neurobiology of depression and PTSD:

Along with dysregulation of the HPA axis, SPS has been shown to acutely induce FKBP5 mRNA in prefrontal cortex, hippocampus and amygdala in rats [89]. Experiments in FKBP5 knockout mice have shown that these mice are less vulnerable to stress than wild-type controls [90]. Under basal conditions, exploratory drive, locomotor activity, anxiety-related behaviour, stress-coping and depression-like behaviour did not differ between young adult FKBP5$^{-/-}$ mice and littermate controls. However, after different acute stressors, lack of FKBP5 led to a more active coping behaviour [91]. Furthermore, FKBP5 deficiency decreased HPA axis reactivity and conferred mild GR hypersensitivity [90, 91]. Taken together, these findings suggest that modification of FKBP5 signalling may be a promising strategy for the development of future psychopharmacological agents to treat depression as well as stress-related disorders.

Conclusion

PTSD is a devastating psychiatric disorder of high prevalence and major socioeconomic relevance. The biological underpinnings of PTSD are in urgent need of further research. Over the last decades, a rich variety of rodent stress models have been established that faithfully recapitulate certain behavioural and physiological consequences of PTSD. Table 1 summarizes the most relevant experimental procedures, whereas Table 2 provides the comparison of DSM-5 criteria of PTSD and analogous behaviours in experimental rodents. Input from preclinical neuroscience will be key for further progress on questions related to biological (*e.g.* genetic or epigenetic) determinants of resilience or susceptibility. Of note, genetic models including FKBP5 knockout mice have already provided exciting new insights into the neurobiology of the stress response. Interactions of HPA axis regulation, FKBP5 signalling and the effects of SSRI have been identified in initial studies of chronically stressed animals and remain to be further

Table 2 DSM-5 criteria and corresponding behavioural phenotypes in animal models

DSM-5 criteria	Equivalent in animal model
Intrusion	• Fear memory: freezing, exaggerated response to mild stressor
Avoidance	• Anxiety-like behaviour in the elevated plus maze
Negative alterations in cognitions and mood	• Alteration of spatial memory (*e.g.* Morris water maze task) • Reduced social interactions • Reduced sucrose consumption • Immobility in forced swim test
Alterations in arousal and reactivity	• Exaggerated startling response to acoustic stimulus • Alterations of sleep • Increased locomotor activity • Increased aggressive behaviour

explored in PTSD [92]. Another important area for future experimental research will be to examine how traumatic events and, more broadly, untoward stress conditions, impact the body as a whole [43, 78, 93]. Here, interdisciplinary questions pertaining to the interplay between vascular disease (*e.g.* stroke, myocardial infarction) and stress-related disorders seem particularly pressing.

Authors' contributions

All authors participated in the drafting of the final manuscript.

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References

1. **Kilpatrick DG, Resnick HS, Milanak ME, et al.** National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. *J Trauma Stress*. 2013; 26: 537–47.

2. **American Psychiatric Association**. *Diagnostic and statistical manual of mental disorders*. 3rd ed. Washington DC: American Psychiatric Association; 1980.

3. **Kessler RC, Sonnega A, Bromet E, et al.** Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995; 52: 1048–60.

4. **Edmondson D, Kronish IM, Shaffer JA, et al.** Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J*. 2013; 166: 806–14.

5. **Sumner JA, Kubzansky LD, Elkind MS, et al.** Trauma Exposure and Posttraumatic Stress Disorder Symptoms Predict Onset of Cardiovascular Events in Women. *Circulation*. 2015; 132: 251–9.

6. **Tanielian T.** Assessing Combat Exposure and Post-Traumatic Stress Disorder in Troops and Estimating the Costs to Society: Implications from the RAND Invisible Wounds of War Study. 2009. 01.07.2016. http://www.rand.org/pubs/testimonies/CT321.html

7. **Willner P.** The validity of animal-models of depression. *Psychopharmacology*. 1984; 83: 1–16.

8. **Fava M, Kendler KS.** Major depressive disorder. *Neuron*. 2000; 28: 335–41.

9. **Yehuda R, Antelman SM.** Criteria for rationally evaluating animal models of posttraumatic stress disorder. *Biol Psychiatry*. 1993; 33: 479–86.

10. **Gold PW, Goodwin FK, Chrousos GP.** Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). *N Engl J Med*. 1988; 319: 348–53.

11. **Yehuda R.** Biology of posttraumatic stress disorder. *J Clin Psychiatry*. 2000; 61: 14–21.

12. **Yehuda R, Southwick SM, Krystal JH, et al.** Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. *Am J Psychiatry*. 1993; 150: 83–6.

13. **National Statistics Home Office**. Annual statistics of scientific procedures on living animals, Great Britain 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/469508/spanimals14.pdf

14. **Mink JW, Blumenschine RJ, Adams DB.** Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. *Am J Physiol*. 1981; 241: R203–12.

15. **Dixon AK.** The Social Behaviour of Mice and its Sensory Control. In: Hedrich H, editor. *The laboratory mouse*. London: Academic Press; 2004. pp. 287–300.

16. **Zoladz PR, Conrad CD, Fleshner M, et al.** Acute episodes of predator exposure in conjunction with chronic social instability as an animal model of post-traumatic stress disorder. *Stress*. 2008; 11: 259–81.

17. **Strekalova T, Spanagel R, Bartsch D, et al.** Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. *Neuropsychopharmacology*. 2004; 29: 2007–17.

18. **Seligman ME.** Learned helplessness. *Annu Rev Med*. 1972; 23: 407–12.

19. **Vollmayr B, Gass P.** Learned helplessness: unique features and translational value of a cognitive depression model. *Cell Tissue Res*. 2013; 354: 171–8.

20. **Seligman ME, Beagley G.** Learned helplessness in the rat. *J Comp Physiol Psychol*. 1975; 88: 534–41.

21. **Van Dijken HH, Van der Heyden JA, Mos J, et al.** Inescapable footshocks induce progressive and long-lasting behavioural changes in male rats. *Physiol Behav*. 1992; 51: 787–94.

22. **van der Kolk B, Greenberg M, Boyd H, et al.** Inescapable shock, neurotransmitters, and addiction to trauma: toward a psychobiology of post traumatic stress. *Biol Psychiatry*. 1985; 20: 314–25.

23. **Anisman H, Sklar LS.** Catecholamine depletion in mice upon reexposure to stress: mediation of the escape deficits produced by inescapable shock. *J Comp Physiol Psychol*. 1979; 93: 610–25.

24. **Glazer HI, Weiss JM, Pohorecky LA, et al.** Monamines as mediators of avoidance-escape behavior. *Psychosom Med*. 1975; 37: 535–43.

25. **Hamilton JD, Workman RH Jr.** Persistence of combat-related posttraumatic stress symptoms for 75 years. *J Trauma Stress*. 1998; 11: 763–8.

26. **American Psychiatric Association**. *Diagnostic and statistical manual of mental disorders*. 5th edn. Washington DC: American Psychiatric Association; 2013.

27. **Antelman SM.** Time-Dependent Sensitization as the Cornerstone for a New Approach to Pharmacotherapy - Drugs as Foreign Stressful Stimuli. *Drug Develop Res*. 1988; 14: 1–30.

28. **Antelman SM, Kocan D, Knopf S, et al.** One brief exposure to a psychological stressor induces long-lasting, time-dependent sensitization of both the cataleptic and neurochemical responses to haloperidol. *Life Sci*. 1992; 51: 261–6.

29. **Antelman SM, Degiovanni LA, Kocan D.** A single exposure to cocaine or immobilization stress provides extremely long-lasting, selective protection against sudden cardiac death from Tetracaine. *Life Sci*. 1989; 44: 201–7.

30. **Antelman SM, Cunnick JE, Lysle DT, et al.** Immobilization 12 days (but Not One Hour) earlier enhanced 2-Deoxy-D-Glucose-induced immunosuppression - evidence for stressor-induced time-dependent sensitization of the immune-system. *Prog Neuro-Psychoph*. 1990; 14: 579–90.

31. **Antelman SM, Caggiula AR, Kocan D, et al.** One experience with lower or higher intensity stressors, respectively enhances or diminishes responsiveness to haloperidol weeks later - implications for understanding drug variability. *Brain Res*. 1991; 566: 276–83.

32. **Antelman SM, Knopf S, Kocan D, et al.** One stressful event blocks multiple actions of diazepam for up to at least a month. *Brain Res*. 1988; 445: 380–5.

33. **Louvart H, Maccari S, Ducrocq F, et al.** Long-term behavioural alterations in female rats after a single intense footshock followed by situational reminders. *Psychoneuroendocrinology*. 2005; 30: 316–24.

34. **Louvart H, Maccari S, Lesage J, et al.** Effects of a single footshock followed by situational reminders on HPA axis and behaviour in the aversive context in male and female rats. *Psychoneuroendocrinology*. 2006; 31: 92–9.

35. **Maier SF.** Exposure to the stressor environment prevents the temporal dissipation of behavioral depression/learned helplessness. *Biol Psychiatry*. 2001; 49: 763–73.

36. **Pynoos RS, Ritzmann RF, Steinberg AM, et al.** A behavioral animal model of posttraumatic stress disorder featuring repeated exposure to situational reminders. *Biol Psychiatry*. 1996; 39: 129–34.

37. **Pawlyk AC, Jha SK, Brennan FX, et al.** A rodent model of sleep disturbances in posttraumatic stress disorder: the role of context after fear conditioning. *Biol Psychiatry*. 2005; 57: 268–77.

38. **Richter-Levin G.** Acute and long-term behavioral correlates of underwater trauma–potential relevance to stress and post-stress syndromes. *Psychiatry Res*. 1998; 79: 73–83.

39. **Morris R.** Developments of a Water-Maze procedure for studying spatial-learning in the rat. *J Neurosci Meth*. 1984; 11: 47–60.

40. **Diamond DM, Campbell AM, Park CR, et al.** Influence of predator stress on the consolidation *versus* retrieval of long-term spatial memory and hippocampal spinogenesis. *Hippocampus*. 2006; 16: 571–6.

41. **Roozendaal B, Okuda S, de Quervain DJ, et al.** Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience*. 2006; 138: 901–10.

42. **Liberzon I, Krstov M, Young EA.** Stress-restress: effects on ACTH and fast feedback. *Psychoneuroendocrinology*. 1997; 22: 443–53.

43. **Balkaya M, Prinz V, Custodis F, et al.** Stress worsens endothelial function and ischemic stroke *via* glucocorticoids. *Stroke*. 2011; 42: 3258–64.

44. **Young EA, Akana S, Dallman MF.** Decreased sensitivity to glucocorticoid fast feedback in chronically stressed rats. *Neuroendocrinology*. 1990; 51: 536–42.

45. **Carroll BJ, Curtis GC, Mendels J.** Cerebrospinal fluid and plasma free cortisol concentrations in depression. *Psychol Med*. 1976; 6: 235–44.

46. **Rubin RT, Poland RE, Lesser IM, et al.** Neuroendocrine aspects of primary endogenous depression. I. Cortisol secretory dynamics in patients and matched controls. *Arch Gen Psychiatry*. 1987; 44: 328–36.

47. **Reimold M, Knobel A, Rapp MA, et al.** Central serotonin transporter levels are associated with stress hormone response and anxiety. *Psychopharmacology*. 2011; 213: 563–72.

48. **Harvey BH, Oosthuizen F, Brand L, et al.** Stress-restress evokes sustained iNOS activity and altered GABA levels and NMDA receptors in rat hippocampus. *Psychopharmacology*. 2004; 175: 494–502.

49. **Knox D, George SA, Fitzpatrick CJ, et al.** Single prolonged stress disrupts retention of extinguished fear in rats. *Learn Mem*. 2012; 19: 43–9.

50. **Zhang Y, Gandhi PR, Standifer KM.** Increased nociceptive sensitivity and nociceptin/orphanin FQ levels in a rat model of PTSD. *Mol Pain*. 2012; 8: 76.

51. **Takahashi T, Morinobu S, Iwamoto Y, et al.** Effect of paroxetine on enhanced contextual fear induced by single prolonged stress in rats. *Psychopharmacology*. 2006; 189: 165–73.

52. **Lin CC, Tung CS, Liu YP.** Escitalopram reversed the traumatic stress-induced depressed and anxiety-like symptoms but not the deficits of fear memory. *Psychopharmacology*. 2016; 233: 1135–46.

53. **Masini CV, Sauer S, White J, et al.** Non-associative defensive responses of rats to ferret odor. *Physiol Behav*. 2006; 87: 72–81.

54. **Blanchard RJ, Nikulina JN, Sakai RR, et al.** Behavioral and endocrine change following chronic predatory stress. *Physiol Behav*. 1998; 63: 561–9.

55. **Adamec RE, Shallow T.** Lasting effects on rodent anxiety of a single exposure to a cat. *Physiol Behav*. 1993; 54: 101–9.

56. **Cohen H, Zohar J, Matar MA, et al.** Setting apart the affected: the use of behavioral criteria in animal models of post traumatic stress disorder. *Neuropsychopharmacology*. 2004; 29: 1962–70.

57. **Andrews B, Brewin CR, Rose S.** Gender, social support, and PTSD in victims of violent crime. *J Trauma Stress*. 2003; 16: 421–7.

58. **Zoladz PR, Fleshner M, Diamond DM.** Psychosocial animal model of PTSD produces a long-lasting traumatic memory, an increase in general anxiety and PTSD-like glucocorticoid abnormalities. *Psychoneuroendocrinology*. 2012; 37: 1531–45.

59. **von Kanel R, Hepp U, Kraemer B, et al.** Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. *J Psychiatr Res*. 2007; 41: 744–52.

60. **Wilson CB, McLaughlin LD, Nair A, et al.** Inflammation and oxidative stress are elevated in the brain, blood, and adrenal glands during the progression of post-traumatic stress disorder in a predator exposure animal model. *PLoS One*. 2013; 8: e76146.

61. **Rorabaugh BR, Krivenko A, Eisenmann ED, et al.** Sex-dependent effects of chronic psychosocial stress on myocardial sensitivity to ischemic injury. *Stress*. 2015; 18: 645–53.

62. **Pizarro JM, Lumley LA, Medina W, et al.** Acute social defeat reduces neurotrophin expression in brain cortical and subcortical

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areas in mice. *Brain Res.* 2004; 1025: 10–20.

63. **Siegfried B, Frischknecht HR, Waser PG.** Defeat, learned submissiveness, and analgesia in mice: effect of genotype. *Behav Neural Biol.* 1984; 42: 91–7.

64. **Hammamieh R, Chakraborty N, De Lima TC, *et al.*** Murine model of repeated exposures to conspecific trained aggressors simulates features of post-traumatic stress disorder. *Behav Brain Res.* 2012; 235: 55–66.

65. **Pulliam JV, Dawaghreh AM, Alema-Mensah E, *et al.*** Social defeat stress produces prolonged alterations in acoustic startle and body weight gain in male Long Evans rats. *J Psychiatr Res.* 2010; 44: 106–11.

66. **Brain P, Benton D.** Interpretation of physiological correlates of differential housing in laboratory rats. *Life Sci.* 1979; 24: 99–115.

67. **Kim JW, Kirkpatrick B.** Social isolation in animal models of relevance to neuropsychiatric disorders. *Biol Psychiat.* 1996; 40: 918–22.

68. **Hatch A, Balazs T, Wiberg GS, *et al.*** Long-term isolation stress in rats. *Science.* 1963; 142: 507.

69. **Pibiri F, Nelson M, Guidotti A, *et al.*** Decreased corticolimbic allopregnanolone expression during social isolation enhances contextual fear: a model relevant for post-traumatic stress disorder. *Proc Natl Acad Sci USA.* 2008; 105: 5567–72.

70. **Heim C, Owens MJ, Plotsky PM, *et al.*** Persistent changes in corticotropin-releasing factor systems due to early life stress: relationship to the pathophysiology of major depression and post-traumatic stress disorder. *Psychopharmacol Bull.* 1997; 33: 185–92.

71. **Kalinichev M, Easterling KW, Plotsky PM, *et al.*** Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long-Evans rats. *Pharmacol Biochem Behav.* 2002; 73: 131–40.

72. **Ardi Z, Albrecht A, Richter-Levin A, *et al.*** Behavioral profiling as a translational approach in an animal model of posttraumatic stress disorder. *Neurobiol Dis.* 2016; 88: 139–47.

73. **Steru L, Chermat R, Thierry B, *et al.*** The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology.* 1985; 85: 367–70.

74. **Heinz A, Mann K, Weinberger DR, *et al.*** Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcohol Clin Exp Res.* 2001; 25: 487–95.

75. **Katz RJ, Hersh S.** Amitriptyline and scopolamine in an animal model of depression. *Neurosci Biobehav Rev.* 1981; 5: 265–71.

76. **Willner P, Towell A, Sampson D, *et al.*** Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology.* 1987; 93: 358–64.

77. **Willner P.** Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology.* 1997; 134: 319–29.

78. **Custodis F, Gertz K, Balkaya M, *et al.*** Heart rate contributes to the vascular effects of chronic mental stress: effects on endothelial function and ischemic brain injury in mice. *Stroke.* 2011; 42: 1742–9.

79. **Nievergelt CM, Maihofer AX, Mustapic M, *et al.*** Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: a genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene. *Psychoneuroendocrinology.* 2015; 51: 459–71.

80. **Voisey J, Young RM, Lawford BR, *et al.*** Progress towards understanding the genetics of posttraumatic stress disorder. *J Anxiety Disord.* 2014; 28: 873–83.

81. **Binder EB, Bradley RG, Liu W, *et al.*** Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA.* 2008; 299: 1291–305.

82. **Ising M, Depping AM, Siebertz A, *et al.*** Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. *Eur J Neurosci.* 2008; 28: 389–98.

83. **Binder EB, Salyakina D, Lichtner P, *et al.*** Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet.* 2004; 36: 1319–25.

84. **Yehuda R, Daskalakis NP, Bierer LM, *et al.*** Holocaust exposure induced intergenerational effects on FKBP5 methylation. *Biol Psychiatry.* 2016; 80(5): 372–80. doi: 10.1016/j.biopsych.2015.08.005.

85. **Vermeer H, Hendriks-Stegeman BI, van der Burg B, *et al.*** Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: a potential marker for glucocorticoid sensitivity, potency, and bioavailability. *J Clin Endocrinol Metab.* 2003; 88: 277–84.

86. **Zannas AS, Binder EB.** Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes Brain Behav.* 2014; 13: 25–37.

87. **Yehuda R, Cai G, Golier JA, *et al.*** Gene expression patterns associated with post-traumatic stress disorder following exposure to the World Trade Center attacks. *Biol Psychiatry.* 2009; 66: 708–11.

88. **Binder EB.** The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology.* 2009; 34: S186–95.

89. **Nedelcovych MT, Gould RW, Zhan X, *et al.*** A rodent model of traumatic stress induces lasting sleep and quantitative electroencephalographic disturbances. *ACS Chem Neurosci.* 2015; 6: 485–93.

90. **Hartmann J, Wagner KV, Liebl C, *et al.*** The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. *Neuropharmacology.* 2012; 62: 332–9.

91. **Touma C, Gassen NC, Herrmann L, *et al.*** FK506 binding protein 5 shapes stress responsiveness: modulation of neuroendocrine reactivity and coping behavior. *Biol Psychiatry.* 2011; 70: 928–36.

92. **Wagner KV, Marinescu D, Hartmann J, *et al.*** Differences in FKBP51 regulation following chronic social defeat stress correlate with individual stress sensitivity: influence of paroxetine treatment. *Neuropsychopharmacology.* 2012; 37: 2797–808.

93. **Heinz A, Hermann D, Smolka MN, *et al.*** Effects of acute psychological stress on adhesion molecules, interleukins and sex hormones: implications for coronary heart disease. *Psychopharmacology.* 2003; 165: 111–7.

94. **Wang J, Akirav I, Richter-Levin G.** Short-term behavioral and electrophysiological consequences of underwater trauma. *Physiol Behav.* 2000; 70: 327–32.

95. **Yamamoto S, Morinobu S, Takei S, *et al.*** Single prolonged stress: toward an animal model of posttraumatic stress disorder. *Depress Anxiety.* 2009; 26: 1110–7.

96. **Wilson CB, Ebenezer PJ, McLaughlin LD, *et al.*** Predator exposure/psychosocial stress animal model of post-traumatic stress disorder modulates neurotransmitters in the rat hippocampus and prefrontal cortex. *PLoS One.* 2014; 9: e89104.

97. **Diehl LA, Alvares LO, Noschang C, *et al.*** Long-lasting effects of maternal separation on an animal model of post-traumatic stress disorder: effects on memory and hippocampal oxidative stress. *Neurochem Res.* 2012; 37: 700–7.