

Animal models for posttraumatic stress disorder: An overview of what is used in research

Bart Borghans, Judith R Homberg

Bart Borghans, Judith R Homberg, Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Centre, 6525 EZ Nijmegen, The Netherlands

Author contributions: Borghans B wrote and Homberg JR critically revised the manuscript.

Supported by The Netherlands Organisation for Scientific Research (NWO), No. 864.10.003 (awarded to Judith R Homberg).

Conflict-of-interest statement: The authors have no conflict of interest to report. Funding organisations had no further role in the design of the study, nor in the collection, analysis and interpretation of data.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Judith R Homberg, PhD, Associate Professor, Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Centre, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands. judith.homberg@radboudumc.nl
Telephone: +31-24-3610906

Received: June 9, 2015
Peer-review started: June 11, 2015
First decision: August 25, 2015
Revised: August 27, 2015
Accepted: October 23, 2015
Article in press: October 27, 2015
Published online: December 22, 2015

Abstract

Posttraumatic stress disorder (PTSD) is a common

anxiety disorder characterised by its persistence of symptoms after a traumatic experience. Although some patients can be cured, many do not benefit enough from the psychological therapies or medication strategies used. Many researchers use animal models to learn more about the disorder and several models are available. The most-used physical stressor models are single-prolonged stress, restraint stress, foot shock, stress-enhanced fear learning, and underwater trauma. Common social stressors are housing instability, social instability, early-life stress, and social defeat. Psychological models are not as diverse and rely on controlled exposure to the test animal's natural predator. While validation of these models has been resolved with replicated symptoms using analogous stressors, translating new findings to human patients remains essential for their impact on the field. Choosing a model to experiment with can be challenging; this overview of what is possible with individual models may aid in making a decision.

Key words: Post-traumatic stress disorder; Physical stressors; Animal models; Social stressors; Psychological stressors; Validity; Individual differences

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There are currently several widely accepted animal models being used in fundamental posttraumatic stress disorder (PTSD) research, and many publications using them have made valuable contributions to the collective knowledge on the subject. Still, the difference between models indicates that their suitability depends on the situation; each model has shown different amounts of success in replicating individual criteria or aspects of PTSD. Accordingly, the selection of the most suitable model for each experiment is important for optimally reliable results. This review offers relevant information to aid in that decision.

Borghans B, Homberg JR. Animal models for posttraumatic

stress disorder: An overview of what is used in research. *World J Psychiatr* 2015; 5(4): 387-396 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v5/i4/387.htm> DOI: <http://dx.doi.org/10.5498/wjpv5.i4.387>

INTRODUCTION

Anxiety disorders are a common problem world-wide. One of them is posttraumatic stress disorder (PTSD), characterised by hyper-arousal, disturbing flashbacks and numbing or avoidance of memories of an event^[1]. Ultimately only a subset of people experiencing trauma will develop PTSD, signifying the importance of individual variation. Treatment exists, but the psychological behavioural therapy lacks efficacy in many patients and medication is often no more than a temporary suppression of symptoms. PTSD is listed in the DSM-5 manual for mental disorders as a trauma or stressor-related trauma. The 8 criteria of PTSD according to DSM-5, labelled A through H, are: (1) A stressor must initiate the syndrome and symptoms; (2) Intrusive symptoms must be present; (3) Subjects must display increased avoidance; (4) Negative changes in cognition and mood must be present; (5) Changes in arousal and reactivity must occur; (6) Displayed symptoms must be persistent over time; (7) Symptoms must significantly affect the individual's functioning; and (8) Other factors that may cause the symptoms must be excluded.

Neurobiology

Despite the wide variety of symptoms found in PTSD, essentially all important hallmarks can be traced back to changes in the brain. Systematic reviews have analysed individual publications over the years, yet the causative process of PTSD remains far from understood. A literature study comparing findings regarding the brain volumes of patients and controls found several significant differences: PTSD was associated with reduced hippocampal and bilateral anterior cingulate cortex (ACC) volume, and a medium effect size reduction. However, no significant difference in amygdala volume was found^[2]. From these results it was proposed that the volume reductions in ACC underlie the attention and emotion modulation deficits found in PTSD. Another study found a volume reduction in the cornu ammonis 3 and dentate gyrus hippocampus subfields^[3]. Examining brain connectivity using resting state fMRI in PTSD patients and controls after an earthquake found decreased path length and increased clustering coefficient, global efficiency and local efficiency in patients. They displayed increased centrality in nodes involved in the default-mode and salience networks including posterior cingulate gyrus, precuneus, insular cortex, putamen, pallidum, and temporal regions. The study suggested that patients exhibit a shift towards a small-world network rather than towards randomisation^[4].

When children with PTSD caused by sexual assault and controls were tested for cortisol levels [output of the hypothalamus-pituitary-adrenal (HPA)-axis], it was found that cortisol levels increased with time after trauma^[5]. Blunted circadian cortisol oscillations are common in PTSD, and associated with hippocampal volume loss^[6]. The disrupted oscillations are thought to be driven by reduced circadian peaks and decreased overall cortisol secretion^[7]. This is consistent with animal models indicating that circadian cortisol cycling is needed for proper synaptic formation and pruning^[8]. PTSD patients having experienced the 2001 World Trade Center attack were found to have reduced circulating levels of endocannabinoid 2-arachidonoylglycerol (2-AG) than controls. Moreover, it was found that anandamide (AEA), another endocannabinoid, positively correlated with circulating cortisol content in PTSD patients. These findings support the hypothesis that deficient endocannabinoid signalling forms a component of PTSD's glucocorticoid dysregulation^[9]. While it is generally accepted that HPA function is altered, often assessed as increased cortisol suppression with the dexamethasone challenge, the exact relationship between PTSD and HPA function remains under discussion^[10]. Hyper-responsiveness of glucocorticoid receptors is also suggested by the increased circulating and cerebrospinal fluid concentrations of corticotropin releasing factor (CRF) neurotransmitter in PTSD patients, as well as depression and other mood disorders^[11].

Also neurotransmitter system functions are altered in PTSD. For instance PTSD patients exhibit increased dopamine transporter density^[12] and an association with serotonin transporter-linked polymorphic region (5-HTTLPR) genotype has been reported in cases of severe trauma exposure^[13]. Furthermore, the levels of chief inhibitory neurotransmitter gamma-aminobutyric acid (GABA) are decreased significantly in the right anterior insula of PTSD patients, and associated with increased state-trait anxiety inventory psychological classification^[14]. Glutamic acid decarboxylase (GAD65) is involved in memory consolidation, and consequently important for fear memory development^[15] as an enzyme essential for the production of GABA. Adrenergic receptors play an important role in stress response, and alpha-2B (ADR2B) receptor gene polymorphism was found to interact with childhood trauma in predicting adult symptoms of PTSD^[16]. The deletion variant selectively predicts enhancement of long-term memories induced by stress, in females at least^[17]. As a result, (Liberzon, 2014, Interaction of the *ADRB2* gene polymorphism with childhood trauma in predicting adult symptoms of PTSD) adrenergic receptors are popular targets for drug development. For instance, prazosin has been suggested to improve PFC function PTSD patients by blocking alpha-1 adrenoceptors^[18]. Similarly, alpha-2 adrenergic agonist guanfacine (extended release, GXR) has been shown to significantly alleviate symptoms of PTSD in children and adolescents^[19]. Yohimbine, another alpha-2 adrenergic agonist, is being

used successfully in clinical trials as an enhancer of exposure therapy^[20]. However, a clear consensus about the role of neurotransmitters in PTSD does not seem to be available yet.

An extremely extensive list of risk factors for PTSD has been found over the years, of which many fall within the genetics category. More recently the influence on epigenetics has been established as well. Given that epigenetic mechanisms are considered as an important channel by which the environment influences gene expression, and PTSD is a gene \times environment disorder, epigenetics may be even more interesting than genetic factors in understanding PTSD's neurobiological underpinnings^[21].

In sum, stress-based disorders obviously affect many different mechanisms in the brain, and more examples can be found whenever the effect of a new pathway on PTSD risk and treatment is observed. This forms a gradually improving model by which the workings and severity of the disorder can be assessed, as well as providing new targets for the development of pharmaceutical therapies.

MODELLING PTSD

PTSD-related research is performed on many levels, and many groups focus on fundamental aspects of the disorder. Using human patients to research human diseases is an effective way to learn. However, the acquisition of PTSD in humans is incidental thus rarely observed in real-time. Also the nature of the trauma is highly variable. Furthermore, inducing PTSD in healthy volunteers is not ethically viable. Because of these reasons using human subjects is less suitable to identify the factors that are related to brain mechanisms involved in (failure of) recovery after trauma exposure.

With the human hallmarks of PTSD in mind, multiple research groups set out to find more practical ways to learn about this complex disorder. With laboratory animals already in use within many branches of science, it did not take long before several PTSD models were being used. Now several animal models, usually involving rats or mice, are used ubiquitously and successfully instead. What makes animal models for psychological disorders like PTSD useful is disease symptoms and the underlying cause can be introduced - with individual differences - to animal populations large enough to grant statistical reliability. Relevant fundamental understanding can be generated in animals and be translated to human subjects for validation and implementation in treatment design. The consensus of what is known in humans has to be linked to animal studies continuously, in order to make sense of findings in animal models. Before animal models can be used for this, however, there must be convincing evidence for the model's validity.

Face, construct and predictive validity

As the high number of separate symptoms that PTSD

can cause indicates, the disorder is extremely variable among patients. Since it originates in the brain, arguably the most complex part of the (human) body, the diversity of aspects found in PTSD is far from easy to recreate in models. This is an important reason for many scientists to look for a select group of symptoms. All models are expected to display phenomenological resemblance, critical aspects of PTSD symptoms (face validity), causality or theoretical explanatory basis (construct validity) and a response to treatment similar to what is seen in humans (predictive validity). Since the human response to trauma is strongly dependent on a variety of risk factors and interpersonal variation, models that focus too much on exposure alone tend to miss an important part of the disorder. Good models should inherently display similar variation in response in a predictable way, not only depending on the strength of the inflicted stress. Determining the vital criteria and what is clinically relevant for a valid model is what makes this process so challenging.

Face validity is often tested using a variety of classical behavioural experiments. These include the plus maze, open field and startle response tests mainly for the assessment of anxiety. Construct and predictive validity are usually judged by following up on stress with measurements of hormone or drug responses, (endocrine) stress response, neurological changes and comorbidity^[22]. Several animal models have been developed to meet these requirements and mimic PTSD over the years, hoping to cover all the symptoms with face, construct and predictive validity. While it is practically impossible to recreate all features of a human psychiatric disorder in small animals with limited mental capacity, numerous models have been successful in reproducing key features. These validated models for PTSD are now being used to extrapolate knowledge to aid in finding a personalised treatment for humans.

Yehuda and Antelman's criteria for rationally evaluating PTSD animal models

Before the current availability of several valid animal models, there were no systematic approaches for evaluating stress models for their relevance to PTSD. Yehuda and Antelman^[23] devised a list for this purpose in 1993, which remains a useful way to compare different stressors. According to this list, at least 5 different criteria can be used to grade how comparable a model is to PTSD: (1) Even very brief stressors should induce biological or behavioural symptoms of PTSD; (2) The stressor should be capable of producing symptoms in a dose-dependent manner; (3) Produced biological alterations should persist or become more pronounced over time; (4) Alterations should have potential for bidirectional expression of biobehavioural changes; and (5) Interindividual variability in response is present as function of experience and/or genetics.

While this list was originally created to assess stress models for the use in PTSD research, it may now be equally useful for the comparison of existing models for

replicating specific aspects of PTSD.

STRESSORS IN ANIMAL MODELS

Several animal models have been developed over the years. Due to the variety of methods used in these models to mimic PTSD-inducing trauma, it is useful to divide them into physical, psychological and social stressors.

Physical stressors

Physical stressors are relatively basic strategies that use aversive stimuli to directly stress subjects, comparable to the near-death experiences or accidents such as those experienced by the soldiers that make up a large part of PTSD patients.

Single-prolonged stress: The single-prolonged stress (SPS) model is mainly rat-based, and set up around the development of PTSD resulting from one traumatic experience. The standard paradigm restrains rats for 2 h, subsequently subjecting them to 20 min forced swim and 15 min later to ether until unconsciousness. Failure to retain extinction memory, which is often observed in PTSD^[24] has been reproduced with the SPS model^[25]. The model also found increased fast negative feedback of the HPA-axis^[26,27], mimicking the neuroendocrine indicator of PTSD^[28]. SPS animals display reduced hippocampal synaptic plasticity which may be linked to decreased hippocampal function in PTSD, as well as increased acoustic startle^[29], which may signify the psychological hyperarousal that is considered to be an important attribute of PTSD as one of the DSM-5 criteria^[30]. Fear extinction was found to be linked to increased expression of glucocorticoid receptors in the hippocampus and prefrontal cortex^[31].

Restraint stress: Besides the restraint stress (RS) often used as part of the SPS procedure, restraint by itself is also used to generate PTSD-like anxiety in the RS model. Animals generally either have their head and limbs attached to a wooden board or are placed in a plastic restraint device, for a duration between 15 min and 2 h at a time^[32]. Afterwards immobility is often assessed using the forced swim test^[26], a combination that has shown sensitisation to the latter forced swim stressor following the time-dependent sensitisation or stress-restress model. Studies using this model demonstrated increased negative HPA feedback similar to that observed in PTSD^[23]. Acute and chronic restraint both generate significantly increased behavioural anxiety and nociception^[33], but the effects of chronic restraint stress can be protected against by stimulating alpha-2A adrenoceptors with guanfacine^[34].

Foot shock: Some groups use electrical shocks as a stressor. Although shocks can be given through the animal's tail, the most common choice in the footshock stress (FS) model is by the use of a floor of metal

rods^[35]. This shock-based strategy usually couples the aversive electrical stimulus to non-harmful factors, according to the classical fear conditioning procedure. Auditory cues are often used together with shocks in order to elicit post-shock fear recall using only sound^[36]. The environment in which the shocks are delivered also tends to get associated with a fear response, by using a contextual difference between this setup and a place considered safe such as the animal's home cage^[37]. Models based on this principle regularly include tests for fear extinction, which is impaired in PTSD^[38] and of a large part of non-pharmaceutical PTSD treatment such as exposure therapy^[39]. Rodents exposed to this procedure display reduced locomotion in new environments and reliable conditioned fear responses when confronted with cues associated with the shocks^[40]. Repeated footshock exposure increases anxiety-like behaviour in the elevated plus maze test^[41]. Returning the animals to the shock context weekly was found to increase their acoustic startle response, indicative of hyperarousal^[42]. Reduced baseline cortisol levels and enhanced negative HPA feedback are PTSD hallmarks^[43] not reflected reliably in inescapable shock models, where the expected HPA change was only found in female rats^[44]. The FS model remains useful in researching individual differences in recovery from traumatic fear, modelling the variation in human susceptibility to PTSD^[45]. Other risk factors such as variation in 5-HTTLPR in humans, that affects the prevalence of several anxiety disorders including PTSD, can be assessed in this model as well^[46-48]. 5-HTT knock-out rats, displaying increased freezing and impaired fear extinction^[49-51] or fear extinction recall^[52-54], have been used as model for the more PTSD-susceptible 5-HTTLPR genotype. The polymorphism results in differences in serotonin regulation that play an important role in anxiety disorders.

Stress-enhanced fear learning: Stress-enhanced fear learning (SEFL) relies on electrical shocks as well, utilising a single shock in a second environment (day 2) 24 h after unpredictable shocks on day 1, vs a control group that did not receive shocks on either day. Before any shocks are given in the second context on day 2, the animals' freezing is assessed as a measure of learned fear. On day 3 this is repeated once more in context 2 to evaluate fear memory^[55]. Subsequent shocks were shown to improve the resulting fear response lasting several months^[56]. Even mild stressors can be used to generate learned fear, and the strength of the sensitising shock affects the extent of sensitisation^[57]. Mice subjected to the SEFL model show several PTSD-like symptoms including hypervigilance, insomnia, impaired attention and risk assessment and attenuated corticosterone levels. This behaviour is mediated by CRF receptors in the stria terminalis, where upregulation of CRF receptor type 2 mRNA corresponded with PTSD-like behaviour, and lentiviral knockdown reduced susceptibility to the symptoms^[58]. Overexpression of

this receptor improves PTSD-like symptoms in rats as well^[59].

Underwater trauma: Underwater trauma (UT), not to be confused with the forced swim test, induces traumatic stress by placing animals in water that is too deep to stand, leading to 30 s of forced swimming before submerging the subjects for 30 s^[60]. The procedure has been proven to significantly increase anxiety-like behaviour in rats^[61], and reminders of UT trigger several memory-related changes in rats' dentate gyrus^[62] as well as the amygdala and hippocampus^[63].

Social stressors

Instead of relying on direct aversive stimuli, social stressors make use of the natural social behaviour of animals. Since humans are responsive to traumatic social experiences and have been known to develop PTSD in instances such as rape and (childhood) abuse, it makes sense that the same is true for other species.

Housing instability: The housing instability (HI) model pairs individual animals with different cage cohorts frequently, for instance each day^[64]. This model makes sense considering PTSD is affected by HI of patients^[65,66]. Animals subjected to this model are often first exposed to cats, following the predator-based psychosocial stress (PPS) model. After this combined procedure, mice displayed impaired acclimation to new environments^[67]. Effects found in rats are increased corticosterone suppression and lowered baseline levels (as assessed by dexamethasone suppression test) indicative of HPA dysfunction, as well as increased freezing to stressor context and heightened elevated plus maze anxiety^[68].

Social instability: Just like the random cage cohort HI model, PTSD-like symptoms can be created using social isolation (SI). Isolation for at least 1 d in adult mice leads to more contextual freezing and impaired fear extinction during FS-like fear conditioning^[69]. Overlap with the prior HI model was found in the form of increased anxiety and HPA changes, although the latter is formed by impaired suppression and higher baseline levels of corticosterone in the SI model^[70]. GAD65 haplodeficiency was found to grant stress resilience to mice, most likely through the maturation of GABAergic transmission^[71].

Early life stress: Early life stress (ELS) plays an important role in the development of PTSD during adulthood. Inducing social instability through maternal isolation of rats generates similar results as the SI model on adult animals^[72]. Traumatizing events experienced by children were found to influence the chance to develop PTSD-like symptoms later in life, as well as their complexity^[73]. Maternal separation of animals mimics childhood trauma by separating mother and pups for 1 or several hours, usually from postnatal day 2 to 14.

Studies using this strategy found sex dependency in acoustic startle response, anxiety-like behaviour and HPA function^[74]. Both male and female adults display increased anxiety^[75], but studies regarding hyperarousal find conflicting evidence, possibly due to the use of different ways to test arousal^[76]. When ELS is followed by other stress models once subjected animals are adult, it increases the response to another stressor. SPS after ELS through maternal separation leads to increased contextual freezing and anxiety-like behaviour^[72].

Social defeat: In the social defeat (SD) model, subjects are exposed to and suppressed by a single aggressor animal^[77,78]. Suppressed animals can be categorised as either susceptible or resilient, and while both express anxiety-like behaviour, only the susceptible population shows increased avoidance^[79]. Susceptible animals display blunted corticosterone levels, while the resilient group increased concentrations 39 d after the stressor^[80]. SD is regularly used for bidirectional behavioural symptoms, and suitable for examining the neurobiological mechanisms of PTSD^[76].

Psychological stressors

While both physical and social stressors generate PTSD-like responses by using potent stimuli, most of the involved models that rely on population averages do not take into account that humans display varied vulnerability to trauma, individuals being susceptible or resilient to the development of PTSD. This aspect is better reproduced with psychological stressors, which generally make use of the instinctual response to natural predators.

PPS: PPS model relies on a lack of control during threats, disruptive reminders of stressful experiences and limited social interaction that are also features of human PTSD^[81-83]. The PPS model periodically immobilises rodents, followed by confrontations with a predator they naturally fear, and chronic social instability over an extended period of time^[84]. This procedure causes increased anxiety, impaired cognition, cardiovascular reactivity and startle response, as well as an exaggerated response to yohimbine similar to that of human PTSD patients^[64]. The idea that epigenetic DNA modification plays a fundamental role in anxiety disorders such as PTSD has been around for a while, and long-term traumatic memory expression is considered to be important in this process^[85]. The brain-derived neurotrophic factor gene has been found to be selectively methylated in the hippocampus of rats that underwent the PPS paradigm, which supports the theory that traumatic stress causes (epigenetic) changes in brain regions regulating cognition and stress regulation. The PPS model also mimics the reduction of basal glucocorticoids found in humans^[68,86]. PPS models are also used to predict responsiveness to new drugs

Table 1 A list of posttraumatic stress disorder animal models and the separate criteria according to DSM-5 that each model has been reported to meet (according to PubMed literature search, individual references not listed)

Animal model for PTSD	DSM-5 criteria ¹
Single-prolonged stress	A, B, C, D, E, F, G, H
Restraint stress	A, B, C, D, E, F, G, H
Foot shock	A, B, C, E, F, G, H
Stress-enhanced fear learning	A, B, C, E, F, G, H
Underwater trauma	A, B, E, F, G, H
Predator-based psychosocial stress/predator scent stress	A, B, C, D, E, F, G, H
Housing instability	A, B, E, G, H
Social instability	A, B, E, F, G, H
Early life stress	A, B, C, D, E, F, G, H
Social defeat	A, B, C, E, F, G, H

¹The listed criteria are: Presence of a stressor (A), intrusive symptoms (B), avoidance (C), negative changes in cognition and mood (D), changes in arousal and reactivity (E), persistence of symptoms (F), functional significance (G) and exclusion of other factors that may cause the displayed symptoms (H). PTSD: Posttraumatic stress disorder.

Table 2 A comparison of animal models based on Yehuda and Antelman's criteria and available publications

Criterion	Most suitable models per criterion ¹
Even brief stressors induce biological/behavioural effects	All models are comparably suitable
Intensity-dependent responses	FS, SEFL, RS, PPS/PSS
Persistence of alterations over time	All except HI
Bi-directional expression of behavioural changes	SPS, SD
Reliable production of interindividual variability	FS, PPS/PSS, SD

¹The animal models listed here are: Foot shock (FS), stress-enhanced fear learning (SEFL), restraint stress (RS), predator-based psychosocial stress (PPS)/predator scent stress (PSS), housing instability (HI), single-prolonged stress (SPS) and social defeat (SD).

for PTSD. A study found that post-trauma treatment, with several therapeutics, prevented the development of PTSD-like symptoms in PPS rats^[87].

Predator scent stress: Predator scent stress (PSS) is a model suitable for recreating the variation that humans display in responding to trauma, inducing a stressor by confronting animals with the scent of one of their natural predators. It is more practical than the previously mentioned PPS in that it removes the need for actual predator exposure, and instead suffices with functional cues. For instance, rats can be brought into contact with used cat litter for 10 min, with the control group exposed to clean cat litter only^[88]. Just like the part of humans that are susceptible to permanent psychological trauma, rats in the PSS model can be grouped in ranks of sensitivity. Using elevated plus maze, acoustic startle and freezing to cues it was determined that only 25% of subjected animals developed PTSD-like behavioural changes, 25% responding minimally and 50% intermediately^[89]. The results found using the PSS model show a genotype dependency also seen in human PTSD^[90]. The involvement of cytoarchitectural changes in rats' amygdala and hippocampus has also been demonstrated on behavioural disruption following PSS^[91].

CONCLUSION

Animal models are a widely used method to research PTSD without the need for actual victims. Any finding in a model provides a prediction for humans, giving scientists a valuable idea of what to expect mechanistically and in treatment response. When looking at the validity of the listed animal models, one finds that they all display enough symptoms of PTSD to have face validity. Since all stressors work at least roughly *via* the same fear pathways as PTSD-inducing traumas, it is not hard for them to meet the construct validity criterion. Predictive validity, however, is best considered for each individual discovery, because the symptoms of PTSD and individual human responses are too diverse to be judged for each model as a whole. Accordingly, the DSM-5 criteria for PTSD can be used to list the (behavioural) effect of the symptoms that individual animal models reproduce (Table 1).

The fact that all of the listed models are currently being used already indicates they display a decent amount of validity, their relevance for PTSD determined by replication of symptoms *via* comparable stress mechanisms. A number of DSM-5 criteria for PTSD have to be met for any animal model in order to qualify, criterion A, B, G and H. The remaining criteria show that not all models have been proven to mimic all symptoms of

PTSD. However, since different animal models are not only used to experiment with all or the same symptoms, it remains useful to judge individual models based on what they excel at. While individual symptoms are effectively assessed using DSM-5 criteria, Yehuda and Antelman provide a more suitable way to compare different stressors (Table 2).

The amount of publications of each model is mainly a measure for its popularity among researchers but also implies reliability, offering further proof that the model grants viable results. This does not automatically mean that less ubiquitous ones are worse, and new models can still prove better than the current ones. A model not meeting one of the DSM-5 criteria for PTSD does not necessarily mean it cannot be met, but rather has not yet been proven sufficiently. It should not be forgotten that new experiments and knowledge may work best with new models instead of those that are known now, and obtaining the optimal reflection of the human disorder is only achieved when the findings of all models are combined. Consequently, translation of individual discoveries in animal models to human patients must be fulfilled in order to maximise the practical impact on the field.

REFERENCES

- American Psychiatric Association.** Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013
- O'Doherty DC,** Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Res* 2015; **232**: 1-33 [PMID: 25735885 DOI: 10.1016/j.psychres.2015.01.002]
- Wang Z,** Neylan TC, Mueller SG, Lenoci M, Truran D, Marmar CR, Weiner MW, Schuff N. Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. *Arch Gen Psychiatry* 2010; **67**: 296-303 [PMID: 20194830 DOI: 10.1001/archgenpsychiatry.2009.205]
- Lei D,** Li K, Li L, Chen F, Huang X, Lui S, Li J, Bi F, Gong Q. Disrupted Functional Brain Connectome in Patients with Posttraumatic Stress Disorder. *Radiology* 2015; **276**: 818-827 [PMID: 25848901 DOI: 10.1148/radiol.15141700]
- Simsek S,** Uysal C, Kaplan I, Yuksel T, Aktas H. BDNF and cortisol levels in children with or without post-traumatic stress disorder after sustaining sexual abuse. *Psychoneuroendocrinology* 2015; **56**: 45-51 [PMID: 25800148 DOI: 10.1016/j.psyneuen.2015.02.017]
- Bremner JD,** Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 1995; **152**: 973-981 [PMID: 7793467 DOI: 10.1176/ajp.152.7.973]
- Yehuda R,** Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. *Biol Psychiatry* 1996; **40**: 79-88 [PMID: 8793040 DOI: 10.1016/0006-3223(95)00451-3]
- Hall BS,** Moda RN, Liston C. Glucocorticoid Mechanisms of Functional Connectivity Changes in Stress-Related Neuropsychiatric Disorders. *Neurobiol Stress* 2015; **1**: 174-183 [PMID: 25729760 DOI: 10.1016/j.ynstr.2014.10.008]
- Hill MN,** Bierer LM, Makotkine I, Golier JA, Galea S, McEwen BS, Hillard CJ, Yehuda R. Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. *Psychoneuroendocrinology* 2013; **38**: 2952-2961 [PMID: 24035186 DOI: 10.1016/j.psyneuen.2013.08.004]
- Pizzimenti CL,** Lattal KM. Epigenetics and memory: causes, consequences and treatments for post-traumatic stress disorder and addiction. *Genes Brain Behav* 2015; **14**: 73-84 [PMID: 25560936 DOI: 10.1111/gbb.12187]
- Bremne JD,** Vermetten E. Stress and development: behavioral and biological consequences. *Dev Psychopathol* 2001; **13**: 473-489 [PMID: 11523844 DOI: 10.1017/S0954579401003042]
- Hoexter MQ,** Fadel G, Felicio AC, Calzavara MB, Batista IR, Reis MA, Shih MC, Pitman RK, Andreoli SB, Mello MF, Mari JJ, Bressan RA. Higher striatal dopamine transporter density in PTSD: an in vivo SPECT study with [(99m)Tc]TRODAT-1. *Psychopharmacology (Berl)* 2012; **224**: 337-345 [PMID: 22700036 DOI: 10.1007/s00213-012-2755-4]
- Gressier F,** Calati R, Balestri M, Marsano A, Alberti S, Antypa N, Serretti A. The 5-HTTLPR polymorphism and posttraumatic stress disorder: a meta-analysis. *J Trauma Stress* 2013; **26**: 645-653 [PMID: 24222274 DOI: 10.1002/jts.21855]
- Rosso IM,** Weiner MR, Crowley DJ, Silveri MM, Rauch SL, Jensen JE. Insula and anterior cingulate GABA levels in posttraumatic stress disorder: preliminary findings using magnetic resonance spectroscopy. *Depress Anxiety* 2014; **31**: 115-123 [PMID: 23861191 DOI: 10.1002/da.22155]
- Bergado-Acosta JR,** Sangha S, Narayanan RT, Obata K, Pape HC, Stork O. Critical role of the 65-kDa isoform of glutamic acid decarboxylase in consolidation and generalization of Pavlovian fear memory. *Learn Mem* 2008; **15**: 163-171 [PMID: 18323571 DOI: 10.1101/lm.705408]
- Liberzon I,** King AP, Ressler KJ, Almlı LM, Zhang P, Ma ST, Cohen GH, Tamburrino MB, Calabrese JR, Galea S. Interaction of the ADRB2 gene polymorphism with childhood trauma in predicting adult symptoms of posttraumatic stress disorder. *JAMA Psychiatry* 2014; **71**: 1174-1182 [PMID: 25162199 DOI: 10.1001/jamapsychiatry.2014.999]
- Zoladz PR,** Kalchik AE, Hoffman MM, Aufdenkampe RL, Lyle SM, Peters DM, Brown CM, Cadle CE, Scharf AR, Dailey AM, Wolters NE, Talbot JN, Rorabaugh BR. ADRA2B deletion variant selectively predicts stress-induced enhancement of long-term memory in females. *Psychoneuroendocrinology* 2014; **48**: 111-122 [PMID: 24997351 DOI: 10.1016/j.psyneuen.2014.06.012]
- Taylor FB,** Lowe K, Thompson C, McFall MM, Peskind ER, Kanter ED, Allison N, Williams J, Martin P, Raskind MA. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. *Biol Psychiatry* 2006; **59**: 577-581 [PMID: 16460691 DOI: 10.1016/j.biopsych.2005.09.023]
- Connor DF,** Grasso DJ, Slivinsky MD, Pearson GS, Banga A. An open-label study of guanfacine extended release for traumatic stress related symptoms in children and adolescents. *J Child Adolesc Psychopharmacol* 2013; **23**: 244-251 [PMID: 23683139 DOI: 10.1089/cap.2012.0119]
- Wangelin BC,** Powers MB, Smits JA, Tuerk PW. Enhancing exposure therapy for PTSD with yohimbine HCL: protocol for a double-blind, randomized controlled study implementing subjective and objective measures of treatment outcome. *Contemp Clin Trials* 2013; **36**: 319-326 [PMID: 23939512 DOI: 10.1016/j.cct.2013.08.003]
- Rampp C,** Binder EB, Provençal N. Epigenetics in posttraumatic stress disorder. *Prog Mol Biol Transl Sci* 2014; **128**: 29-50 [PMID: 25410540 DOI: 10.1016/B978-0-12-800977-2.00002-4]
- Siegmund A,** Wotjak CT. Toward an animal model of posttraumatic stress disorder. *Ann N Y Acad Sci* 2006; **1071**: 324-334 [PMID: 16891581 DOI: 10.1196/annals.1364.025]
- Yehuda R,** Antelman SM. Criteria for rationally evaluating animal models of posttraumatic stress disorder. *Biol Psychiatry* 1993; **33**: 479-486 [PMID: 8513032 DOI: 10.1016/0006-3223(93)90001-T]
- Milad MR,** Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerker K, Orr SP, Rauch SL. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol Psychiatry* 2009; **66**: 1075-1082 [PMID: 19748076]

- DOI: 10.1016/j.biopsych.2009.06.026]
- 25 **Knox D**, George SA, Fitzpatrick CJ, Rabinak CA, Maren S, Liberzon I. Single prolonged stress disrupts retention of extinguished fear in rats. *Learn Mem* 2012; **19**: 43-49 [PMID: 22240323 DOI: 10.1101/lm.024356.111]
 - 26 **Liberzon I**, Krstov M, Young EA. Stress-restress: effects on ACTH and fast feedback. *Psychoneuroendocrinology* 1997; **22**: 443-453 [PMID: 9364622 DOI: 10.1016/S0306-4530(97)00044-9]
 - 27 **Liberzon I**, López JF, Flagel SB, Vázquez DM, Young EA. Differential regulation of hippocampal glucocorticoid receptors mRNA and fast feedback: relevance to post-traumatic stress disorder. *J Neuroendocrinol* 1999; **11**: 11-17 [PMID: 9918224 DOI: 10.1046/j.1365-2826.1999.00288.x]
 - 28 **Yehuda R**, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW. Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. *Am J Psychiatry* 1993; **150**: 83-86 [PMID: 8417586 DOI: 10.1176/ajp.150.1.83]
 - 29 **Khan S**, Liberzon I. Topiramate attenuates exaggerated acoustic startle in an animal model of PTSD. *Psychopharmacology* (Berl) 2004; **172**: 225-229 [PMID: 14586539 DOI: 10.1007/s00213-003-1634-4]
 - 30 **Kohda K**, Harada K, Kato K, Hoshino A, Motohashi J, Yamaji T, Morinobu S, Matsuoka N, Kato N. Glucocorticoid receptor activation is involved in producing abnormal phenotypes of single-prolonged stress rats: a putative post-traumatic stress disorder model. *Neuroscience* 2007; **148**: 22-33 [PMID: 17644267 DOI: 10.1016/j.neuroscience.2007.05.041]
 - 31 **Knox D**, Nault T, Henderson C, Liberzon I. Glucocorticoid receptors and extinction retention deficits in the single prolonged stress model. *Neuroscience* 2012; **223**: 163-173 [PMID: 22863672 DOI: 10.1016/j.neuroscience.2012.07.047]
 - 32 **Vallès A**, Martí O, Armario A. Long-term effects of a single exposure to immobilization: a c-fos mRNA study of the response to the homotypic stressor in the rat brain. *J Neurobiol* 2006; **66**: 591-602 [PMID: 16555238 DOI: 10.1002/neu.20252]
 - 33 **Gameiro GH**, Gameiro PH, Andrade Ada S, Pereira LF, Arthuri MT, Marcondes FK, Veiga MC. Nociception- and anxiety-like behavior in rats submitted to different periods of restraint stress. *Physiol Behav* 2006; **87**: 643-649 [PMID: 16488452 DOI: 10.1016/j.physbeh.2005.12.007]
 - 34 **Hains AB**, Yabe Y, Arnsten AF. Chronic Stimulation of Alpha-2A-Adrenoceptors With Guanfacine Protects Rodent Prefrontal Cortex Dendritic Spines and Cognition From the Effects of Chronic Stress. *Neurobiol Stress* 2015; **2**: 1-9 [PMID: 25664335 DOI: 10.1016/j.ynstr.2015.01.001]
 - 35 **Van Dijken HH**, Van der Heyden JA, Mos J, Tilders FJ. Inescapable footshocks induce progressive and long-lasting behavioural changes in male rats. *Physiol Behav* 1992; **51**: 787-794 [PMID: 1594677 DOI: 10.1016/0031-9384(92)90117-K]
 - 36 **Dębiec J**, Bush DE, LeDoux JE. Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats—a possible mechanism for the persistence of traumatic memories in PTSD. *Depress Anxiety* 2011; **28**: 186-193 [PMID: 21394851 DOI: 10.1002/da.20803]
 - 37 **Eskandarian S**, Vafaei AA, Vaezi GH, Taherian F, Kashefi A, Rashidy-Pour A. Effects of systemic administration of oxytocin on contextual fear extinction in a rat model of post-traumatic stress disorder. *Basic Clin Neurosci* 2013; **4**: 315-322 [PMID: 25337363]
 - 38 **Marin MF**, Camprodon JA, Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: implications for PTSD treatment and beyond. *Depress Anxiety* 2014; **31**: 269-278 [PMID: 24634247 DOI: 10.1002/da.22252]
 - 39 **Powers MB**, Medina JL, Burns S, Kauffman BY, Monfils M, Asmundson GJ, Diamond A, McIntyre C, Smits JA. Exercise Augmentation of Exposure Therapy for PTSD: Rationale and Pilot Efficacy Data. *Cogn Behav Ther* 2015; **44**: 314-327 [PMID: 25706090 DOI: 10.1080/16506073.2015.1012740]
 - 40 **Pijlman FT**, Herremans AH, van de Kieft J, Kruse CG, van Ree JM. Behavioural changes after different stress paradigms: prepulse inhibition increased after physical, but not emotional stress. *Eur Neuropsychopharmacol* 2003; **13**: 369-380 [PMID: 12957336 DOI: 10.1016/S0924-977X(03)00040-3]
 - 41 **Belda X**, Rotllant D, Fuentes S, Delgado R, Nadal R, Armario A. Exposure to severe stressors causes long-lasting dysregulation of resting and stress-induced activation of the hypothalamic-pituitary-adrenal axis. *Ann N Y Acad Sci* 2008; **1148**: 165-173 [PMID: 19120106 DOI: 10.1196/annals.1410.038]
 - 42 **Pynoos RS**, Ritzmann RF, Steinberg AM, Goenjian A, Prisecaru I. A behavioral animal model of posttraumatic stress disorder featuring repeated exposure to situational reminders. *Biol Psychiatry* 1996; **39**: 129-134 [PMID: 8717611 DOI: 10.1016/0006-3223(95)00088-7]
 - 43 **Daskalakis NP**, Lehrner A, Yehuda R. Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. *Endocrinol Metab Clin North Am* 2013; **42**: 503-513 [PMID: 24011883 DOI: 10.1016/j.ecl.2013.05.004]
 - 44 **Louvar H**, Maccari S, Lesage J, Léonhardt M, Dickes-Coopman A, Darnaudéry M. 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**: 92-99 [PMID: 16081221 DOI: 10.1016/j.psyneuen.2005.05.014]
 - 45 **Holmes A**, Singewald N. Individual differences in recovery from traumatic fear. *Trends Neurosci* 2013; **36**: 23-31 [PMID: 23260015 DOI: 10.1016/j.tins.2012.11.003]
 - 46 **Xie P**, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, Weiss RD, Farrer L, Gelemtner J. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. *Arch Gen Psychiatry* 2009; **66**: 1201-1209 [PMID: 19884608 DOI: 10.1001/archgenpsychiatry.2009.153]
 - 47 **Grabe HJ**, Spitzer C, Schwahn C, Marcinek A, Frahnw A, Barnow S, Lucht M, Freyberger HJ, John U, Wallaschofski H, Völzke H, Roskopf D. Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population. *Am J Psychiatry* 2009; **166**: 926-933 [PMID: 19487392 DOI: 10.1176/appi.ajp.2009.08101542]
 - 48 **Thakur GA**, Joobar R, Brunet A. Development and persistence of posttraumatic stress disorder and the 5-HTTLPR polymorphism. *J Trauma Stress* 2009; **22**: 240-243 [PMID: 19444877 DOI: 10.1002/jts.20405]
 - 49 **Shan L**, Schipper P, Nonkes LJ, Homberg JR. Impaired fear extinction as displayed by serotonin transporter knockout rats housed in open cages is disrupted by IVC cage housing. *PLoS One* 2014; **9**: e91472 [PMID: 24658187 DOI: 10.1371/journal.pone.0091472]
 - 50 **Nonkes LJ**, de Pooter M, Homberg JR. Behavioural therapy based on distraction alleviates impaired fear extinction in male serotonin transporter knockout rats. *J Psychiatry Neurosci* 2012; **37**: 224-230 [PMID: 22353635 DOI: 10.1503/jpn.110116]
 - 51 **Narayanan V**, Heiming RS, Jansen F, Lesting J, Sachser N, Pape HC, Seidenbecher T. Social defeat: impact on fear extinction and amygdala-prefrontal cortical theta synchrony in 5-HTT deficient mice. *PLoS One* 2011; **6**: e22600 [PMID: 21818344 DOI: 10.1371/journal.pone.0022600]
 - 52 **Wellman CL**, Izquierdo A, Garrett JE, Martin KP, Carroll J, Millstein R, Lesch KP, Murphy DL, Holmes A. Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knock-out mice. *J Neurosci* 2007; **27**: 684-691 [PMID: 17234600 DOI: 10.1523/JNEUROSCI.4595-06.2007]
 - 53 **Hartley CA**, McKenna MC, Salman R, Holmes A, Casey BJ, Phelps EA, Glatt CE. Serotonin transporter polyadenylation polymorphism modulates the retention of fear extinction memory. *Proc Natl Acad Sci USA* 2012; **109**: 5493-5498 [PMID: 22431634 DOI: 10.1073/pnas.1202044109]
 - 54 **Pang RD**, Wang Z, Klosinski LP, Guo Y, Herman DH, Celikel T, Dong HW, Holschneider DP. Mapping functional brain activation using [¹⁴C]-iodoantipyrine in male serotonin transporter knockout mice. *PLoS One* 2011; **6**: e23869 [PMID: 21886833 DOI: 10.1371/

- journal.pone.0023869]
- 55 **Rau V**, DeCola JP, Fanselow MS. Stress-induced enhancement of fear learning: an animal model of posttraumatic stress disorder. *Neurosci Biobehav Rev* 2005; **29**: 1207-1223 [PMID: 16095698 DOI: 10.1016/j.neubiorev.2005.04.010]
 - 56 **Rau V**, Fanselow MS. Exposure to a stressor produces a long lasting enhancement of fear learning in rats. *Stress* 2009; **12**: 125-133 [PMID: 18609302 DOI: 10.1080/10253890802137320]
 - 57 **Poulos AM**, Zhuravka I, Long V, Gannam C, Fanselow M. Sensitization of fear learning to mild unconditional stimuli in male and female rats. *Behav Neurosci* 2015; **129**: 62-67 [PMID: 25621793 DOI: 10.1037/bne0000033]
 - 58 **Lebow M**, Neufeld-Cohen A, Kuperman Y, Tsoory M, Gil S, Chen A. Susceptibility to PTSD-like behavior is mediated by corticotropin-releasing factor receptor type 2 levels in the bed nucleus of the stria terminalis. *J Neurosci* 2012; **32**: 6906-6916 [PMID: 22593059 DOI: 10.1523/JNEUROSCI.4012-11.2012]
 - 59 **Elharrar E**, Warhaftig G, Issler O, Sztainberg Y, Dikstein Y, Zahut R, Redlus L, Chen A, Yadid G. Overexpression of corticotropin-releasing factor receptor type 2 in the bed nucleus of stria terminalis improves posttraumatic stress disorder-like symptoms in a model of incubation of fear. *Biol Psychiatry* 2013; **74**: 827-836 [PMID: 23871471 DOI: 10.1016/j.biopsych.2013.05.039]
 - 60 **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 [PMID: 9676829 DOI: 10.1016/S0165-1781(98)00030-4]
 - 61 **Moore NL**, Gauchan S, Genovese RF. Differential severity of anxiogenic effects resulting from a brief swim or underwater trauma in adolescent male rats. *Pharmacol Biochem Behav* 2012; **102**: 264-268 [PMID: 22584043 DOI: 10.1016/j.pbb.2012.05.002]
 - 62 **Ardi Z**, Ritov G, Lucas M, Richter-Levin G. The effects of a reminder of underwater trauma on behaviour and memory-related mechanisms in the rat dentate gyrus. *Int J Neuropsychopharmacol* 2014; **17**: 571-580 [PMID: 24565178 DOI: 10.1017/S14611457130101272]
 - 63 **Ritov G**, Ardi Z, Richter-Levin G. Differential activation of amygdala, dorsal and ventral hippocampus following an exposure to a reminder of underwater trauma. *Front Behav Neurosci* 2014; **8**: 18 [PMID: 24523683 DOI: 10.3389/fnbeh.2014.00018]
 - 64 **Zoladz PR**, Conrad CD, Fleshner M, Diamond DM. Acute episodes of predator exposure in conjunction with chronic social instability as an animal model of post-traumatic stress disorder. *Stress* 2008; **11**: 259-281 [PMID: 18574787 DOI: 10.1080/10253890701768613]
 - 65 **Kim HG**, Harrison PA, Godecker AL, Muzyka CN. Posttraumatic stress disorder among women receiving prenatal care at three federally qualified health care centers. *Matern Child Health J* 2014; **18**: 1056-1065 [PMID: 23912314 DOI: 10.1007/s10995-013-1333-7]
 - 66 **Rollins C**, Glass NE, Perrin NA, Billhardt KA, Clough A, Barnes J, Hanson GC, Bloom TL. Housing instability is as strong a predictor of poor health outcomes as level of danger in an abusive relationship: findings from the SHARE Study. *J Interpers Violence* 2012; **27**: 623-643 [PMID: 21987519 DOI: 10.1177/0886260511423241]
 - 67 **Saavedra-Rodríguez L**, Feig LA. Chronic social instability induces anxiety and defective social interactions across generations. *Biol Psychiatry* 2013; **73**: 44-53 [PMID: 22906514 DOI: 10.1016/j.biopsych.2012.06.035]
 - 68 **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**: 1531-1545 [PMID: 22421563 DOI: 10.1016/j.psyneuen.2012.02.007]
 - 69 **Pibiri F**, Nelson M, Guidotti A, Costa E, Pinna G. Decreased corticolicmbic allopregnanolone expression during social isolation enhances contextual fear: A model relevant for posttraumatic stress disorder. *Proc Natl Acad Sci USA* 2008; **105**: 5567-5572 [PMID: 18391192 DOI: 10.1073/pnas.0801853105]
 - 70 **Butler TR**, Ariwodola OJ, Weiner JL. The impact of social isolation on HPA axis function, anxiety-like behaviors, and ethanol drinking. *Front Integr Neurosci* 2014; **7**: 102 [PMID: 24427122 DOI: 10.3389/fnint.2013.00102]
 - 71 **Müller I**, Obata K, Richter-Levin G, Stork O. GAD65 haplo-deficiency conveys resilience in animal models of stress-induced psychopathology. *Front Behav Neurosci* 2014; **8**: 265 [PMID: 25147515 DOI: 10.3389/fnbeh.2014.00265]
 - 72 **Imanaka A**, Morinobu S, Toki S, Yamawaki S. Importance of early environment in the development of post-traumatic stress disorder-like behaviors. *Behav Brain Res* 2006; **173**: 129-137 [PMID: 16860405 DOI: 10.1016/j.bbr.2006.06.012]
 - 73 **Cloitre M**, Stolbach BC, Herman JL, van der Kolk B, Pynoos R, Wang J, Petkova E. A developmental approach to complex PTSD: childhood and adult cumulative trauma as predictors of symptom complexity. *J Trauma Stress* 2009; **22**: 399-408 [PMID: 19795402 DOI: 10.1002/jts.20444]
 - 74 **de Jongh R**, Geyer MA, Olivier B, Groenink L. The effects of sex and neonatal maternal separation on fear-potentiated and light-enhanced startle. *Behav Brain Res* 2005; **161**: 190-196 [PMID: 15878207 DOI: 10.1016/j.bbr.2005.02.004]
 - 75 **Kalinichev M**, Easterling KW, Plotsky PM, Holtzman SG. 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**: 131-140 [PMID: 12076732 DOI: 10.1016/S0091-3057(02)00781-5]
 - 76 **Whitaker AM**, Gilpin NW, Edwards S. Animal models of post-traumatic stress disorder and recent neurobiological insights. *Behav Pharmacol* 2014; **25**: 398-409 [PMID: 25083568 DOI: 10.1097/FBP.0000000000000069]
 - 77 **Yang R**, Daigle BJ, Muhie SY, Hammamieh R, Jett M, Petzold L, Doyle FJ. Core modular blood and brain biomarkers in social defeat mouse model for post traumatic stress disorder. *BMC Syst Biol* 2013; **7**: 80 [PMID: 23962043 DOI: 10.1186/1752-0509-7-80]
 - 78 **Pulliam JV**, Dawaghreh AM, Alema-Mensah E, Plotsky PM. Social defeat stress produces prolonged alterations in acoustic startle and body weight gain in male Long Evans rats. *J Psychiatr Res* 2010; **44**: 106-111 [PMID: 19573876 DOI: 10.1016/j.jpsychires.2009.05.005]
 - 79 **Russo SJ**, Murrough JW, Han MH, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci* 2012; **15**: 1475-1484 [PMID: 23064380 DOI: 10.1038/nn.3234]
 - 80 **Krishnan V**, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 2007; **131**: 391-404 [PMID: 17956738 DOI: 10.1016/j.cell.2007.09.018]
 - 81 **Kushner MG**, Riggs DS, Foa EB, Miller SM. Perceived controllability and the development of posttraumatic stress disorder (PTSD) in crime victims. *Behav Res Ther* 1993; **31**: 105-110 [PMID: 8417720 DOI: 10.1016/0005-7967(93)90048-Y]
 - 82 **Piotrkowski CS**, Brannen SJ. Exposure, threat appraisal, and lost confidence as predictors of PTSD symptoms following September 11, 2001. *Am J Orthopsychiatry* 2002; **72**: 476-485 [PMID: 15792033 DOI: 10.1037/0002-9432.72.4.476]
 - 83 **Tsai J**, Harpaz-Rotem I, Pietrzak RH, Southwick SM. The role of coping, resilience, and social support in mediating the relation between PTSD and social functioning in veterans returning from Iraq and Afghanistan. *Psychiatry* 2012; **75**: 135-149 [PMID: 22642433 DOI: 10.1521/psyc.2012.75.2.135]
 - 84 **Corley MJ**, Caruso MJ, Takahashi LK. Stress-induced enhancement of fear conditioning and sensitization facilitates extinction-resistant and habituation-resistant fear behaviors in a novel animal model of posttraumatic stress disorder. *Physiol Behav* 2012; **105**: 408-416 [PMID: 21925525 DOI: 10.1016/j.physbeh.2011.08.037]
 - 85 **Yehuda R**, Koenen KC, Galea S, Flory JD. The role of genes in defining a molecular biology of PTSD. *Dis Markers* 2011; **30**: 67-76 [PMID: 21508511 DOI: 10.1155/2011/185354]

- 86 **Yehuda R.** Status of glucocorticoid alterations in post-traumatic stress disorder. *Ann N Y Acad Sci* 2009; **1179**: 56-69 [PMID: 19906232 DOI: 10.1111/j.1749-6632.2009.04979.x]
- 87 **Zoladz PR,** Fleshner M, Diamond DM. Differential effectiveness of tianeptine, clonidine and amitriptyline in blocking traumatic memory expression, anxiety and hypertension in an animal model of PTSD. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; **44**: 1-16 [PMID: 23318688 DOI: 10.1016/j.pnpbp.2013.01.001]
- 88 **Cohen H,** Kaplan Z, Matar MA, Loewenthal U, Zohar J, Richter-Levin G. Long-lasting behavioral effects of juvenile trauma in an animal model of PTSD associated with a failure of the autonomic nervous system to recover. *Eur Neuropsychopharmacol* 2007; **17**: 464-477 [PMID: 17196373 DOI: 10.1016/j.euroneuro.2006.11.003]
- 89 **Cohen H,** Zohar J. An animal model of posttraumatic stress disorder: the use of cut-off behavioral criteria. *Ann N Y Acad Sci* 2004; **1032**: 167-178 [PMID: 15677404 DOI: 10.1196/annals.1314.014]
- 90 **Cohen H,** Geva AB, Matar MA, Zohar J, Kaplan Z. Post-traumatic stress behavioural responses in inbred mouse strains: can genetic predisposition explain phenotypic vulnerability? *Int J Neuropsychopharmacol* 2008; **11**: 331-349 [PMID: 17655807 DOI: 10.1017/S1461145707007912]
- 91 **Cohen H,** Kozlovsky N, Matar MA, Zohar J, Kaplan Z. Distinctive hippocampal and amygdalar cytoarchitectural changes underlie specific patterns of behavioral disruption following stress exposure in an animal model of PTSD. *Eur Neuropsychopharmacol* 2014; **24**: 1925-1944 [PMID: 25451698 DOI: 10.1016/j.euroneuro.2014.09.009]

P- Reviewer: Santarcangelo EL

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

