

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

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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

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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

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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.

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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.

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