Current Status of Animal Models of Posttraumatic Stress Disorder: Behavioral and Biological Phenotypes, and Future Challenges in Improving Translation

Supplemental Information

Supplemental Table S1: PTSD-related phenotypes in animal models of PTSD – Effects in males

Model	Hyperalgesia	General avoidance	Avoidance of trauma-specific cues	Increased fear learning	Reduced fear extinction	Arousal	Depression/ Anhedonia	Memory deficits (hippocampal function)
Inescapable foot shocks	Thermal hyperalgesia (hot-plate test) (1wk) (1)	**- avoidance** (EPM) (1-56 days) (1-3); ¯ social behavior (SIT) (1-56 days) (2; 4); - avoidance of conspecific or open spaces (10 days) (4)	**- freezing (situational reminder)** (1-56 days) (5; 6)	N/A	N/A	- startle (4 wks) (7)	**- immobility** (FST) (31 days) (8)	¯ **spatial learning** (MWM) (1 wk) (1); ¯ short-term memory (NORT) (9)
Predator scent/stress	- thermal nociception (Hargreaves) (5 days) (10)	**- avoidance (EPM, LD)** (1 wk-3 months) (11-16); ¯ social behaviors (SIT) (4 wks) (17)	**- avoidance in trauma reminder test** (9-14 days) (15; 18); - freezing (situational reminder) (1-4 wks) (17)	- freezing in contextual fear memory (3 months) (12; 13)	¯extinction (3 wks-3 months) (12; 13)	**- startle and startle habituation** (1 wk-3 months) (11; 12; 17); ¯ PPI (9 days) (19); NE in mice	N/A	¯ object recognition memory; ¯ spatial memory (RAWM) (3 wks-3 months) (13; 20)
Single prolonged stress	**- mechanical hyperalgesia** (von Frey test) (1 wk) (21)	**- avoidance** (OF, EPM, LD) (1-3 wks) (21-26)	N/A	**- context and cue fear recall** (1 wk) (26-31)	¯**extinction recall** (1-2wks) (23; 27; 32-34)	**- startle** (1-2 wks) (25; 28); ¯ PPI[m] (1-2 wks) (35)	- immobility (FST) (1 wk) (25); anhedonia (SP) (1-3 wks) (23; 24)	¯**spatial learning and memory** (MWM, RAWM) (1-2 wks) (24; 28; 36); ¯cognitive flexibility (1 wk) (37)
IMO/ restraint stress	N/A	- avoidance (EPM, LD) (10-14 days) (38-43)	N/A	**- cue fear recall** (1wk) (38; 44); - generalization (10 days) (41); ¯ context fear (10-35 days) (41; 45)	¯**extinction** (10 days) (41; 44)	- startle (7-12 days) (42; 46)	- immobility (FST) and anhedonia (SP) (5 wks) (45)	¯ spatial memory (MWM) (9-11 days) (38; 47)
UVS	- thermal hyperalgesia (hot plate test or acetone test); - licking behavior (formalin test) (5 wks) (48)	**- avoidance** (EPM, OF, novelty-suppressed feeding test, MB) (1-3 wks) (49-56); - avoidance (avoidance/escape task) (2 wks) (57); no changes in inhibitory avoidance task (1-7 days) (55)	N/A	- contextual freezing[m] (1 wk) (58)	¯extinction (1 wk) (58)	- startle (54; 55)	**- immobility** (FST, TST) (1-10 wks) (50; 54; 59; 60); **- anhedonia** (SP) (1-3 wks) (49; 50; 52; 59)	¯ **spatial memory** (EPM, NORT, MWM) (1-2 wks) (59; 61-63); ¯ working memory (T-maze) (1 wk) (64); ¯ memory in passive avoidance (65)
Social defeat	**- thermal analgesia (hot plate test)** (66)**; - hyperalgesia (mechanical)** (4-10 days) (67)	**- avoidance** (EPM, OF) (1d-4wk) (68; 69)	**- social avoidance** (SAAT, SIT) (4-10 days) (70)	Inconsistent data on cue and context fear (2-21 days) (71-74)	- extinction (2-5 days) (75-77)	**- startle** (1-4 days) (78-80)	**- anhedonia** (SP, ICSS, PRT) (3-21 days) (81-85)	¯**working memory** (T maze); ¯ spatial memory (MWM); ¯ recognition memory (NORT) (5-20 days) (68; 86-88)

[m]effect reported only in mice; EPM, elevated plus maze; FST, forced swim test; ICSS, intracranial self-stimulation; IMO, immobilization; LD, light-dark box; MWM, Morris water maze; MB, marble burying; NE, no effect; NORT, novel object recognition task; OF, open field; PPI, prepulse inhibition of acoustic startle; PRT, probabilistic reward task; RAWM, radial arm water maze; SAAT, social approach-avoidance test; SIT, social interaction test; SP, sucrose preference; TST, tail suspension test; UVS, unpredictable variable stress. **In bold**: most robust and reproduced findings. **N.B.: The studies describing several PTSD-like phenotypes are not exclusive to this table, most comprehensive and robust findings as well as recency were used to prioritize addition of citation to the table.**

Supplemental Table S2: PTSD-related phenotypes reproduced in animal models of PTSD – Effects in females

Model	Hyperalgesia	General avoidance	Avoidance of trauma-specific cues	Increased fear learning	Reduced fear extinction	Arousal	Depression/ Anhedonia	Memory deficits (hippocampal function)
Inescapable foot shocks	N/A	No changes in avoidance (OF) (10 days) (89)	- avoidance to open spaces (90); - freezing (situational reminder) (10 days) (89)	N/A	N/A	N/A	N/A	N/A
Predator scent/stress	N/A	- avoidance (EPM) (1 wk) (91); - avoidance (composite of OF/LD) (1 wk) (92)	- avoidance in trauma-reminder test (2 wks) (92)	N/A	N/A	- or - startle (1 wk) (91; 92)	N/A	No changes in spatial memory (MWM) (91)
Single prolonged stress	N/A	N/A	N/A	- context and cue fear recall (1 wk) (31)	N/A	N/A	N/A	N/A
IMO/restraint stress	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UVS	N/A	- avoidance (OF) (93)	N/A	N/A	N/A	N/A	- immobility (FST, TST) (60; 93)	N/A
Social defeat	N/A	N/A	- social avoidance (SAAT, SIT) (4-10 days) (94)	N/A	N/A	N/A	- anhedonia (SP) (3-21 days) (95)	N/A

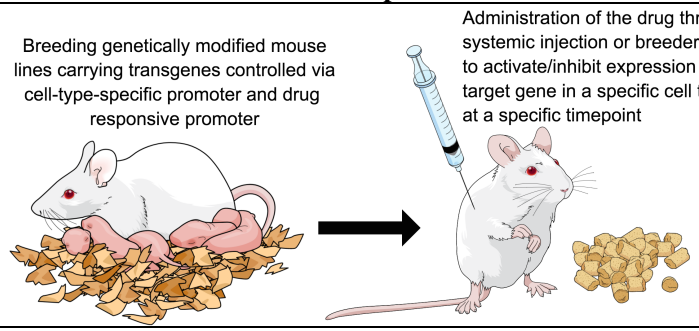
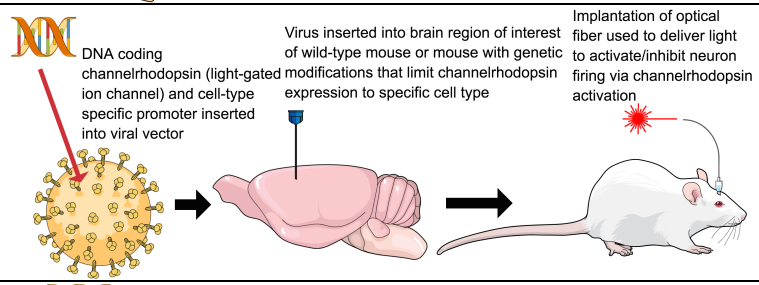
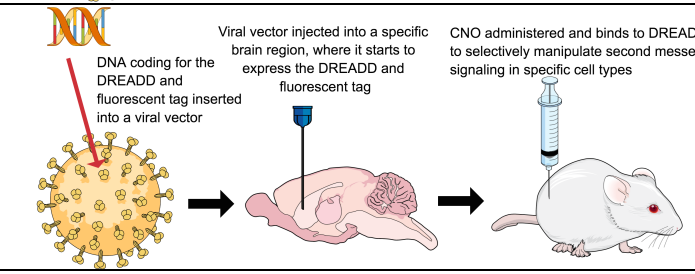
EPM, elevated plus maze; MWM, Morris water maze; OF, open field; REM, rapid eye movement; SAAT, social approach-avoidance test; SIT, social interaction test; SP, sucrose preference; TST, tail suspension test; UVS, unpredictable variable stress.

Supplemental Table S3: PTSD-related biological phenotypes reproduced in animal models of PTSD – Effects in females

Model	Fear circuit dysfunctions (PFC-Amygdala)	HPA axis function	Peripheral vs. Central inflammation	Hippocampal structure/morphology	Sleep disturbances	Reversed by SSRIs
Inescapable foot shocks	N/A	Plasma: No changes in basal CORT (10 days) (89) Brain: N/A	Plasma: N/A Brain: N/A	N/A	N/A	N/A
Predator scent/stress	N/A	Plasma: - basal CORT (1 wk) (91) Brain: N/A	Plasma: N/A Brain: N/A	N/A	N/A	N/A
Single prolonged stress	N/A	Plasma: N/A Brain: N/A	Plasma: N/A Brain: N/A	¯ LTP/LTD (1 wk) (31)	N/A	N/A
IMO/Restraint stress	N/A	Plasma: N/A Brain: N/A	Plasma: N/A Brain: N/A	Mild or no change compared to males (96; 97), but stronger decrease of neurogenesis (98)	Mild or no change in NREM & REM (1 day) (99; 100)	N/A
UVS	¯ cFos-positive cells (PFC) and - ¯ c-Fos-positive cells (Amy) (93)	Plasma: N/A Brain: N/A	Plasma: N/A Brain: N/A	N/A	N/A	N/A
Social defeat	N/A	Plasma: - basal CORT (12 days) (101) Brain: N/A	Plasma: N/A Brain: N/A	N/A	¯ REM; - NREM (1-28 days) (101)	N/A

Amy, amygdala; CORT, corticosterone; HPA, hypothalamic-pituitary-adrenal; LTP/LTD, long-term potentiation/depression; NREM, non-rapid eye movement; PFC, prefrontal cortex; REM, rapid eye movement; SSRIs, selective serotonin reuptake inhibitors; UVS, unpredictable variable stress.

Supplemental Table S4. Additional tools to probe gene pathways and circuits implicated in PTSD pathophysiology

Manipulation	Schematic representation	Description	References
Conditional, cell-type specific modulation of gene expression		Regulate gene expression in specific cell types to selectively manipulate PTSD-relevant signaling pathways in specific circuits at various time-points before and after stress manipulations	(92; 102-104)
Optogenetic approach		High resolution and dynamic control of excitability of neurons in PTSD-relevant circuits and cell types (via activation of light-gated ion channels)	(105-107)
Chemogenetic approach: DREADD		Express mutated GPCRs (Gi, Gs, Gq) selectively activated by otherwise inert drugs (e.g. CNO); enables acute and chronic modulation of cell function via activation of select second messenger cascades in specific cell types and circuits.	(108-110)

CNO, Clozapine-N-oxide; DREADD, Designer Receptors Exclusively Activated by Designer Drugs; GPCRs, G-protein coupled receptors. The figures presented in the table were created on the Mind the Graph platform www.mindthegraph.com.

Box S1. Model organisms for studying PTSD pathology and its treatment: future directions

Numerous well-established and robust paradigms that induce specific patterns of enduring PTSD-relevant behavioral and biological phenotypes are now available. The focus in future will be to refine these models as clinical studies of PTSD pathology and treatment response mature.

What is urgently needed to understand the validity of current PTSD models? Characterize (1) effects in females, (2) sensitivity of these paradigms to early-life stress, and (3) identify behavioral and biological risk factors that predict individual response variance across models.

How can we enhance translation of treatments to clinical trials? Incorporate biological measures that are homologous across-species (e.g. peripheral biomarkers, imaging, physiology) to (1) identify predictors of individual risk that also measurable in clinic and (2) provide biological outcome measures to complement behavioral measures of stress response. Clinical studies should also incorporate homologous biological measures to inform model validity.

What tools are on the horizon? Optogenetic and DREADD technologies support testing of complex circuit models of PTSD etiology. Once validated, they could provide circuit-based models of PTSD pathology that will complement current stress manipulation models.

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