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The advent of fear conditioning as an animal model of post-traumatic stress disorder: Learning from the past to shape the future of PTSD research

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► To cite this version:

Thomas C. M. Bienvenu, Cyril Dejean, Daniel Jercog, Bruno Aouizerate, Mael Lemoine, et al.. The advent of fear conditioning as an animal model of post-traumatic stress disorder: Learning from the past to shape the future of PTSD research. *Neuron*, 2021, 109 (15), pp.2380-2397. 10.1016/j.neuron.2021.05.017 . hal-03386102

HAL Id: hal-03386102

<https://hal.science/hal-03386102>

Submitted on 22 Aug 2023

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1 *The advent of fear conditioning as an animal model of post-traumatic stress disorder:*
2 *learning from the past to shape the future of PTSD research*
3
4

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21
22 **Abstract**

23 Translational research on post-traumatic stress disorder (PTSD) has produced limited improvements
24 in clinical practice. Fear conditioning (FC) is one of the dominant animal models of PTSD. In fact, FC
25 is used in many different ways to model PTSD. The variety of FC-based models is ill-defined,
26 creating confusion and conceptual vagueness, which in turn impedes translation to the clinic. This
27 article takes a historical and conceptual approach to provide a comprehensive picture of current
28 research and help re-orientate the research focus. This work historically reviews the variety of models
29 that have emerged from the initial association of PTSD with FC, highlighting conceptual pitfalls that
30 have limited translation of animal research into clinical advances. We then provide some guidance on
31 how future translational research could benefit from conceptual and technological improvements to
32 translate basic findings in patients. This objective will require transdisciplinary approaches and should
33 involve physician, engineers, philosophers and neuroscientists.
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Introduction

38 Post-traumatic stress disorder (PTSD) manifests itself after intense psychological distress (trauma
39 (including man-made disaster or accident), war, sexual assault, or natural disaster) by various post-
40 traumatic stress-related reactions, resulting in significant clinical impairment. Post-traumatic stress
41 disorder was first described in 1980, in the third edition of the Diagnostic and Statistical Manual of
42 Mental disorders (DSM; American Psychiatric Association, 1980). In DSM-5, PTSD is defined by
43 intrusive traumatic memories and their avoidance as well as alterations in mood and cognition, and
44 hyperarousal, following psychological trauma (American Psychiatric Association, 2013; **Box 1**).
45 Current therapeutic options include psychotherapy with trauma-focused exposure or desensitization
46 and pharmacotherapy, chiefly with antidepressants. However, many patients remain insufficiently
47 relieved, with modest clinical improvement observed with both medication and psychotherapy, and
48 high non-response rates (> 20% and > 40%, respectively; Bisson et al., 2013; Bradley et al., 2005;
49 Davidson et al., 2006; Stein et al., 2006). Translational research carries great hope to improve
50 conditions of patients with PTSD who suffer from severely impaired daily lives. However, despite
51 three decades of intensive investigation, limited clinical care improvement has resulted from PTSD
52 research. This apparent lack of efficacy questions the way translational research is conducted in the
53 field of PTSD.

54

55 Translational research largely relies on animal models to mimic and understand pathogenic processes
56 and, in turn, to design therapeutic interventions (Nestler and Hyman, 2010). The possibility to study
57 mental disorders with animal models is traditionally evaluated with three criteria: construct validity
58 (the conformity of the model to the hypothesized mechanism of the disorder), face validity (the
59 resemblance of the model with the observable features of the disorder) and predictive validity (the
60 way models respond similarly to patients upon various –e.g., pharmacological– challenges) (Nestler
61 and Hyman, 2010; Willner, 1984). Fear conditioning (FC) is one of the leading animal models used in
62 PTSD research (Johnson et al., 2012; Ross et al., 2017). According to a PubMed search, about 100
63 articles/year have been published on this topic during the last five years. Classical FC consists of

64 pairing a neutral stimulus (typically a sound) and a mild aversive cue (e.g., an electrical footshock).
65 Initially, the neutral stimulus is conditioned, i.e. its presentation becomes sufficient to elicit defensive
66 fear behaviors (e.g., *freezing* immobilization). Subsequent presentations of the conditioned cue lead to
67 a gradual reduction of defensive states, a phenomenon known as *fear extinction*.

68

69 To model PTSD, classical FC may be used alone (Ross et al., 2017) or integrated into more complex
70 models (Deslauriers et al., 2018). Various modified versions of FC have been developed in the past
71 decades, such as a classical FC model focusing on spontaneously reduced extinction to model
72 extinction deficits observed in patients with PTSD (e.g. Yehuda and LeDoux, 2007), modified
73 versions of the FC paradigm to model trauma more closely (e.g. conditioning to a predator instead of
74 a sound, e.g. Zoladz et al., 2012), or classical FC to demonstrate extinction deficit as a symptom *after*
75 a distinct trauma-inducing protocol (e.g., immobilization stress; (Andero et al., 2013).

76 Intriguingly, aversive conditioning was not originally designed to study the pathophysiology of
77 mental disorders. Instead, it has been used for more than 80 years, long before the definition of PTSD,
78 to study fundamental neurobiological processes such as memory, emotions or a combination of both
79 (emotional memory (Flandreau and Toth, 2017; LeDoux, 2000; Pavlov, 1927). Moreover, as a
80 pathophysiological model, FC is not specific to PTSD, as it is also used to model other anxiety-related
81 disorders, including specific phobia and obsessive-compulsive disorder (Berardi et al., 2014;
82 Dougherty et al., 2018). Finally, other issues related to the validity of FC as a model of PTSD are
83 related to its reductionist approach and its potentially adaptive (reaction to low-intensity stimuli)
84 rather than its potentially pathological nature (in response to life-threatening events) (Beckers et al.,
85 2013; Flandreau and Toth, 2017; Lisieski et al., 2018). These arguments question the specificity and
86 the validity of FC to study PTSD.

87

88 We argue that the diversity in FC-based models of PTSD marks a preference for experimental
89 tractability (i.e. the fact that those models are based on FC) over conceptual validity, therefore
90 creating conceptual confusion over what exactly is modeled. It is generally accepted that a model of a
91 human disease deviates from the initially suspected mechanisms as far as scientists judge this

92 deviation relevant to explain the disease. However, if the relationship between the mechanisms and
93 the human disease is unclear, this deviation cannot satisfactorily model this human disease. To
94 investigate these problems and move forward in the field, a historical and conceptual approach is
95 necessary. In other words, it is critical to understand how PTSD and fear conditioning constructs
96 intersect and how the arguments supporting the use of fear conditioning to model PTSD have evolved
97 during the progressive ramification of heterogeneous FC-based models.

98

99 This Perspective article aims at clarifying the current state of FC-based animal research on PTSD,
100 using a historical approach to elucidate the original and derivative meaning of FC-based animal
101 models. Sociological, political and scientific contexts of these developments were analyzed. Based on
102 this historical clarification, we identified conceptual issues and propose actionable guidance for
103 refining research in the field of PTSD.

104

105 **1. Linking fear conditioning to PTSD: a historical and conceptual perspective**

106 Soon after the recognition of PTSD as a distinct psychiatric disorder (DSM-III, 1980), FC in animals
107 was proposed by American clinician-scientists to recapitulate the main aspects of PTSD and as a
108 potential animal model to study its underlying neurobiology. Seminal work also pointed to limitations
109 of the FC model. This theoretical corpus appeared in the aftermath of the Vietnam war on the grounds
110 of experimental psychology and emerging theories of emotional memory. Collectively, this corpus
111 has had a lasting influence on translational research in the field of PTSD.

112

113 *A unique historical context: the combined legacy of the Vietnam war and experimental psychology*

114 Posttraumatic Stress Disorder emerged as a recognized clinical entity in a highly political context.
115 Indeed, it was created in 1980, following Vietnam veteran activism to recognize specific war-related
116 disorders in the late 1970s.

117 War-related mental disorders had indeed attracted the attention of psychiatrists since WWI for their
118 peculiar clinical presentation (Crocq and Crocq, 2000). However, the first publication describing a
119 condition akin to PTSD came during WWII with a seminal book on war neuroses (Kardiner, 1941),
120 and it is not until 1980 that post-traumatic disorder became a distinct entity. The DSM-III committee,
121 under activist pressure, deemed it sufficiently distinct from other mental conditions to create a novel
122 diagnosis.

123 With help from medical supporters, Vietnam veteran activists obtained the creation of a Committee
124 on Reactive Disorders to report to the DSM-III task force in 1975. The committee was composed of 3
125 DSM-III task force members, two psychiatrists, and Robert Spitzer, chair of the task force. Spitzer
126 instructed them to work with Robert Lifton, Chaim Shatan (psychiatrists and supporters of the
127 Vietnam veterans cause) and Jack Smith (a Vietnam veteran). Lifton, Shatan, and Smith defended and
128 obtained the integration of the “Post-traumatic stress disorder” into the American psychiatric
129 nomenclature as a formal diagnostic entity with the publication of DSM-III in 1980 (Scott, 1990).

130 It is important to note that theories of *stress* and behaviorism influenced the construction of the novel
131 disorder. At the time, the concept of stress, invented by Selye (Selye, 1956), was highly influential,
132 and behaviorism dominated American psychology (following experimental work on classical and

133 operant conditioning by Skinner and Rescorla, among others). During preparatory work for DSM-III,
134 the original proposal of the Vietnam Veterans Working group was “post-combat disorder”. Their
135 views were confronted with opinions from clinicians and researchers, among which researchers on
136 stress and anxiety, including Mardi J. Horowitz. Other causes of trauma were added, and the name
137 proposed by the committee for the new diagnosis entity was “catastrophic stress disorder”. Finally,
138 Spitzer set the disorder’s name as “post-traumatic stress disorder” (Scott, 1990). The name of the
139 disorder, centered on the notion of stress, carries its legacy, grounding PTSD in the field of
140 experimental psychology.

141 After the recognition of PTSD as a disorder, PTSD clinics were created and run throughout the USA
142 by the Veterans Affairs department. Scientific research on PTSD resonated in Veterans Affairs
143 centers, as it was stimulated by clinical cases encountered by healthcare professionals and enabled by
144 substantial financial funding from the federal government. Clinical research centers housed a
145 community of pioneering clinician-scientist investigators who had a lasting influence on the field,
146 including Dennis S. Charney, Lawrence Kolb, John Krystal and Roger Pitman (see below).

147

148 One can postulate that recognizing PTSD as an entity in the unique historical and political context of
149 the 1980s in the USA, while conditioning theories had gained importance in the scientific community,
150 stimulated the formulation of mechanistic accounts of PTSD with FC theories. In general, PTSD
151 appears to be what sociologists, historians, and philosophers of psychiatry call a ‘social construct’
152 (Hacking, 2000), that is, the fashioning of an object of investigation under the influence of social,
153 cultural, and historical forces. The emergence of PTSD is an answer to a social demand for the
154 medicalization of a condition. Philosopher J. Wakefield has insisted that insofar as the disease entity
155 is “conceptually valid” (i.e. allowing for a rigorous and relevant clinical difference between disorder
156 and non-disorder), it remains legitimate (Wakefield, 1992). This question was investigated by
157 Wakefield himself in the case of Major Depressive Disorder (Horwitz and Wakefield, 2007;
158 Wakefield et al., 2007). The consequences for neurobiological and experimental investigations are not
159 that social construction invalidates a disease entity from the beginning and forever, but that it
160 constitutes a sort of initial bias in the preliminary phases of investigation, that further needs to be

161 rectified. Philosopher M. Lemoine proposed the idea that scientific research tries to “naturalize”
162 mental disorders initially targeted through social construction, a process which sometimes, but not
163 always, meets success (Lemoine, 2014). The modeling of PTSD by fear conditioning, sensitization,
164 etc., that are reviewed in the first part of the present paper, must be thought of as so many attempts to
165 naturalize PTSD.

166

167 *The origins of fear conditioning as an explanatory model of PTSD*

168 Original accounts linking FC to PTSD did so by analogy, with conditioning mimicking trauma and
169 conditioned distress expression in the presence of trauma reminders mimicking reexperiencing.

170 The first explicit link between FC and *PTSD* was drawn in 1982 by Kolb and Mutalipassi, who
171 proposed persistent conditioned responses to reflect a “subclass of delayed and chronic PTSD” (Kolb
172 and Mutalipassi, 1982). This hypothesis was made based on the clinical observations of Vietnam
173 Veterans during experimental procedures in specialized Veterans Affairs clinics. In these
174 experiments, barbiturate narcosynthesis was used to elicit abreaction (phasic expression of PTSD
175 symptoms) in response to combat sounds (Kolb and Mutalipassi, 1982). These psychophysiological
176 observations were later published in Blanchard et al., 1982). The authors noted that behavioral and
177 physiological hyperreactivity in war veterans was similar to that observed in fear-conditioned animals
178 (Kolb, 1987; Kolb and Mutalipassi, 1982). Interestingly, they traced the FC theory back to seminal
179 work published before PTSD was recognized, after WWI- II, when *war neurosis* was a subject of
180 interest (Dobbs and Wilson, 1960; Gillespie, 1942; Kardiner, 1941). Kolb particularly refers to an
181 article published in 1960 (Dobbs and Wilson, 1960), which he thought was “overlooked” (Kolb, 1987,
182 1993).

183 Other research groups later adopted the FC-PTSD analogy (Brett, 1985; Keane et al., 1985; Pitman,
184 1989; Shalev and Rogel-Fuchs, 1993; Shalev et al., 1992). The FC theory was indeed supported by
185 their psychophysiological experiments performed in Vietnam veterans suffering from PTSD, who
186 displayed excessive autonomic and hormonal stress responses to trauma reminders (Blanchard et al.,
187 1982; Boudewyns and Hyer, 1990; Malloy et al., 1983; McFall et al., 1990; Pallmeyer et al., 1986;
188 Pitman, 1987).

189 It is worth emphasizing that the theoretical modeling of PTSD with FC appeared to recapitulate
190 cardinal features that distinguished PTSD from other disorders, namely an identified traumatic event
191 and the event-related distress response (including rage and arousal), making it particularly appealing
192 to study PTSD (Keane et al., 1985; Kolb and Mutalipassi, 1982; Pitman, 1989).

193

194 *Limitations of the classical fear conditioning model and alternative theories*

195 Some limitations of the FC model of PTSD were identified soon after its formulation. In particular,
196 FC fell short in explaining some aspects of PTSD (then defined by DSM-III-R (American Psychiatric
197 Association, 1980)), including symptoms not triggered by proximal reminders (increased arousal,
198 numbing, avoidance), and the chronic forms of PTSD.

199 Extensions of the FC model were then formulated to explain the generalization of fear responses and
200 avoidance (Keane et al., 1985). Second-order conditioning was proposed to mediate fear
201 generalization. In this extended paradigm, trauma re-experiencing in various contexts leads to novel
202 associative memories and stress responses not directly related to trauma reminders (Keane et al.,
203 1985). Negative reinforcement, i.e. the rewarding experience of avoidance of trauma reminders,
204 similar to Mowrer's two-factor learning, was proposed to explain avoidance (Keane et al., 1985).

205 Physician-scientists Charney, Krystal and colleagues proposed that *sensitization*, the enduring
206 increased reactivity of the arousal system by traumatization, could better account for the full PTSD
207 spectrum (Charney, 1993; van der Kolk, 1987; van der Kolk et al., 1985; Kosten and Krystal, 1988;
208 Krystal, 1990). They inferred that the inescapable shock paradigm (a paradigm then used to study
209 stress responses) would be a better model to study PTSD in animals than classical FC. Inescapable
210 shocks could better capture non-associative symptoms, such as increased arousal and numbing-
211 similar to *learned helplessness* (Charney, 1993; van der Kolk, 1987; van der Kolk et al., 1985; Kosten
212 and Krystal, 1988; Krystal, 1990), but also associative symptoms, as strong electrical shocks are
213 expected to induce at least some conditioning (Kosten and Krystal, 1988).

214 Of note, Kolb and Mutalipassi, the first defenders of the conditioning theory for PTSD, remained
215 cautious about the explanatory and operational power of FC, "the total phenomenology of post-
216 traumatic stress disorders of war are far beyond full explanation within the learning theory model",

217 and they also alluded to “hyperactivity” (Kolb and Mutalipassi, 1982). In the article “Once Bitten,
218 Twice Shy: Beyond the Conditioning Model of PTSD” published in 1993, Pitman, a defender of FC,
219 recognized that some symptoms of PTSD were “not conditional enough”, that is, could not be easily
220 explained by the FC model (Pitman et al., 1993).

221 Another limitation of the FC model, and more particularly related to the extinction of conditioned fear
222 behavior, was the apparent contradiction between the duration of PTSD, particularly in delayed and
223 chronic forms, and the susceptibility of FC to a rapid extinction process. Two complementary
224 explanations were advanced to further resolve this discrepancy: first, the strength of the initial
225 conditioned memory (Keane et al., 1985; Pitman, 1989; Shalev and Rogel-Fuchs, 1993) and second,
226 the weakness of fear extinction in PTSD (Charney, 1993; Keane et al., 1985; Kolb, 1987). In
227 particular, Pitman introduced the concept of “*superconditioning*”, whereby stress hormones released
228 in response to particularly traumatic events would strengthen memory consolidation, resulting in
229 “overconsolidation” and resistance to extinction (Pitman, 1989). Borrowing from epilepsy research,
230 traumatic memory consolidation by repeated trauma re-experiencing was proposed to occur by self-
231 perpetuating sensitization, in the form of *kindling*, and explain chronicity (van der Kolk, 1987).
232 Deficient extinction was early proposed to exist in PTSD and even to be a predisposing factor to
233 develop PTSD (Kolb, 1987). Interestingly, Charney, Krystal and their groups formulated the
234 hypothesis that the chronicity of PTSD symptoms results from the interaction between a deficient
235 extinction and indelible memory traces of the trauma (Charney, 1993; Shalev and Rogel-Fuchs,
236 1993). As we will argue, conditioned fear extinction has later played a crucial role in the evolution of
237 PTSD models and theories.

238 By the early 1990s, FC, and sensitization-based procedures (e.g., inescapable shock), were the main
239 proposals for modelling PTSD in animals (**Figure 1**).

240 This pioneering period for conceptual PTSD modeling culminated in the proposal of validity criteria
241 for animal models of PTSD by Yehuda and Antelman (Yehuda and Antelman, 1993). They proposed
242 five criteria that “were derived by paring down PTSD phenomenology to its most basic components

243 and identifying relevant counterparts for these clinical characteristics based on animal studies: 1-
244 Even brief stressors should be capable of inducing biological and behavioral sequelae of PTSD; The
245 stressor should 2- be capable of producing the PTSD-like sequelae in a dose-dependent manner; 3-
246 produce biological alterations that persist over time or become more pronounced with the passage of
247 time; 4- induce biobehavioral alterations that have the potential for bidirectional expression (e.g.,
248 arousal and numbing); and 5- interindividual variability in response to stressor should be present
249 either as a function of experience, genetics, or a combination of the two.”

250 After a decade of theoretical work and the proposal for animal models of PTSD, publications of
251 dedicated models started to appear in the literature. Below, we recapitulate the creation of the leading
252 animal models of PTSD, identify their creators, and analyze their links (or absence thereof) with FC.
253 Initial models were essentially sensitization-based (1990’s), while FC-based models appeared and
254 gained importance later (2000’s). Thereafter, we present how FC-based models of PTSD have
255 ramified during the last fifteen years by integrating FC in various ways and propose a historical and
256 conceptual framework to understand those gradual changes.

257

258 *Initial modeling of PTSD with sensitizing stressors*

259 The first articles presenting experimental data and *explicitly* claiming to model PTSD in animals were
260 published in the 1990s and used trauma-like stressors in rodents, based on sensitization theories. They
261 largely recycled existing behavioral paradigms applied to study neuroendocrine aspects of stress
262 responses.

263 In the first published PTSD model by Adamec and Shallow in 1993 (**the Predator stress model**), rats
264 directly exposed to cats displayed a long-lasting increase in anxiety behavior in an elevated plus maze
265 (Adamec and Shallow, 1993). This model was anchored in sensitization theories and was argued to
266 display good face validity compared to the FC model that lacked explanatory power in general arousal
267 and long-term manifestation (citing Keane et al., 1985; Kolb, 1987; Kolb and Mutalipassi, 1982).

268 Later on, two articles describing an *Inescapable shock* PTSD model were published. They identified
269 their experiments as sensitization processes (Pynoos et al., 1996; Servatius et al., 1995). In the first

270 study, electrical tailshocks in physically restrained rats led to increased auditory startle responses and
271 transient blood corticosterone elevation (Servatius et al., 1995). Validity was defended with similarity
272 in causes (construct validity) and behavioral and biological manifestations (face validity) (Servatius et
273 al., 1995). In the second study, Pynoos et al. specifically designed the model to study PTSD and
274 applied single bouts of footshocks to mice in a closed arena and subsequently exposed them to
275 situational reminders to prevent desensitization (Pynoos et al., 1996). Animals displayed a range of
276 anxiety-related behavior in the elevated plus maze and a gradual increase in auditory startle reflex in
277 the aversive context, which they referred to as a time-dependent sensitization. This nomenclature and
278 validity discussion were based on Yehuda's seminal article (Yehuda and Antelman, 1993).

279 Liberzon and colleagues proposed a *Single prolonged stress* model, which displays sensitized
280 neuroendocrine abnormalities similar to PTSD (Liberzon et al., 1997). In this model, rats were taken
281 through a "single session of prolonged stress" consisting of restraint, followed by forced swim, and
282 after recovery, by exposure to ether vapors until loss of consciousness. Feedback of the HPA axis
283 (decreased ACTH response following corticosterone administration) was increased in stress animals
284 after a delay period, a phenomenon the authors interpreted as (time-dependent) sensitization of the
285 HPA axis. The authors claimed inspiration from Yehuda and Antelman and criticized the inescapable
286 shock model for lacking validity in prolonged changes in the HPA axis "characteristic of PTSD",
287 despite good face validity (Liberzon et al., 1997; Yehuda and Antelman, 1993).

288 *Immobilization stress* was the last of the four sensitization-based PTSD models created in this initial
289 period (Marti et al., 2001). In this model, forced immobilization of rats on a wooden board led to the
290 gradual reduction of the HPA response upon re-exposure to the same stress or forced swim stress
291 (Marti et al., 2001). The authors referred to this phenomenon as time-dependent desensitization and
292 entirely based their model on Yehuda's criteria of validity (Yehuda and Antelman, 1993).

293

294 As detailed above, sensitization-based predatory stress, inescapable shock, single prolonged stress and
295 immobilization stress paradigms were the first explicit PTSD models, highly influenced by theoretical
296 work published in the 1980s and followed the seminal publication by Yehuda and Antelman (Yehuda
297 and Antelman, 1993). The latter oriented their focusing on non-associative aspects, i.e. sensitization

298 theories of PTSD. These sensitization-based models have had a lasting influence, as they still
299 represent some of the most frequently used animal models of PTSD (Deslauriers et al., 2018). We
300 found 667 articles on Pubmed of animal research from inception until 01/01/2020 that contained the
301 terms "model" and "PTSD". Terms related to the 4 sensitization-based models of PTSD were found
302 frequently: "single prolonged stress" (n= 184/667; 27,6%), "predator" or "predatory" (n= 96; 14,4%),
303 "inescapable" (n= 54; 8,1%), and "immobilization" (n= 15; 2,2%), suggesting links with these
304 paradigms. A quarter of all studies referring to animal models of PTSD (177/667; 26,5%) also
305 referred to FC ("fear conditioning", "conditioned fear", "cued fear", "contextual fear" or "pavlovian").
306 Thus, while FC was surprisingly absent in initial PTSD models, this finding demonstrates that FC is
307 often cited in PTSD research (and vice versa), indicating that FC plays a highly influential role in
308 PTSD research.

309

310

311 *Introduction of FC-based models*

312 Although initial theoretical work gave strong credit to FC theories, it is not until 2003 that
313 experimental paradigms used FC to model PTSD. Four articles were found to be the first evidence of
314 FC-based experimental models of PTSD (Balogh and Wehner, 2003; Dębiec and Ledoux, 2004;
315 Pawlyk et al., 2005; Rau et al., 2005). The need for their careful analysis is underlined by the fact that
316 they have been frequently cited in review articles (Berardi et al., 2014; Siegmund and Wotjak, 2006)
317 as seminal FC-based animal models of PTSD.

318 In the first article, mice were submitted to classical cued FC, and the authors observed a strong
319 heterogeneity of cued and contextual freezing responses across mouse strains. In particular, fear
320 responses of several strains increased after two weeks, irrespective of the context, indicative of fear
321 generalization. It is this dimension and not conditioned fear itself the authors proposed pertaining to
322 PTSD (Balogh and Wehner, 2003). They discussed the opposing arguments regarding the validity of
323 FC to study PTSD (Kolb, 1984; Pitman, 1989), retaining the validity of variable fear generalization
324 across strains, derived from Yehuda and Antelman's criteria (Yehuda and Antelman, 1993): 1) brief

325 stressor; 2) dose-dependency to the number of shocks, 3) delayed generalization, 4) diverse stress
326 behavior, 5) variability correlated with genetic traits.

327 The second article used cued fear conditioning in rats and showed that systemic and intra-amygdala
328 infusion of the beta-adrenergic receptor antagonist propranolol immediately after memory reactivation
329 impaired cued fear expression, while the same infusion immediately after conditioning had no effect.

330 The authors concluded that noradrenergic signaling plays a critical role in the reconsolidation of
331 retrieved memory and that propranolol may be useful for treating PTSD (Dębiec and LeDoux, 2004).

332 Surprisingly, they did not discuss predictive validity or the choice of the FC paradigm.

333 The third article used contextual fear conditioning to “provide insight into the neural substrates of
334 disturbed sleep in PTSD” (Pawlyk et al., 2005). The main result was that fear conditioning reduced
335 the number and duration of Rapid Eye Movement sleep epochs; a result they interpreted as the
336 potential effect of trauma reminder on sleep in PTSD (Pawlyk et al., 2005). The authors explicitly
337 defended their FC-based model for modelling psychological trauma with conditioning and displaying
338 a key feature of PTSD in disturbed sleep in the presence of trauma reminders.

339 The fourth article explicitly using FC to model PTSD was published in 2005 by Fanselow and
340 colleagues (Rau et al., 2005). Although it is frequently cited as a FC model, it reported a combination
341 of sensitization and FC, with sensitization playing the central pathogenic role. Prior to fear
342 conditioning, rats received strong electrical footshocks as a stressor over an extended period. This
343 stress enhanced the freezing response of rats one day after contextual fear conditioning elicited by one
344 shock in a novel context. The authors referred to this effect as “stress-induced enhancement of fear
345 learning”. The effect was resistant to extinction, and synaptic plasticity blockers (the NMDA
346 antagonist APV) injected before the first stressor, indicating that the observed effect reflected
347 sensitization, independent of conditional learning. Notably, in this article, Fanselow and colleagues
348 criticized the FC model as being insufficient alone to adequately model all of the complexities of
349 PTSD (Rau et al., 2005). As a result, the frequent citation of this article as an example of a FC model
350 of PTSD appears misleading.

351

352 Overall these four articles used diverse protocols (cued, contextual) and surprisingly defended various
353 standpoints regarding the links between PTSD and FC. Only one (Pawlyk et al., 2005) used classical
354 FC to explicitly model PTSD for its associative dimensions (as proposed by Kolb and Mutalipassi;
355 Kolb and Mutalipassi, 1982) while others emphasized non-associative fear generalization and
356 sensitization. The relative lack of conceptual discussions and references to previous theoretical work
357 in these articles is striking. We discuss below how the paucity of conceptual considerations has
358 continued to be detrimental for the field.

359

360 *Current use of fear conditioning-based models*

361 The vast majority of current animal models of PTSD integrate FC in some way, often using
362 heightened fear expression during extinction as a readout for PTSD-like phenotypes (Deslauriers et
363 al., 2018). Increased fear expression and/or impaired extinction may occur spontaneously by
364 individual variability or result from direct interventions, either biological (e.g., drug administration) or
365 behavioral (after stress protocols, i.e. *de novo* FC). In this section, the main categories of current FC-
366 based PTSD models are summarized, and their conceptual contents and validity are discussed.

367 Articles using FC in PTSD models can be divided into three categories: 1) classical FC with potential
368 biological interventions, 2) modified FC using stressors from sensitization-based models and, 3) *de*
369 *novo* FC in sensitization-based models.

370 *Classical FC* has mainly been used to model interindividual variability in extinction deficits.
371 Deficient extinction has been reported to occur spontaneously in some genetic mouse strains. For
372 instance, Holmes, Singewald and colleagues found cued fear extinction deficits in the 129S1/SvImJ
373 mouse strain (e.g., Hefner et al., 2008)). They argued that this mouse line was useful to model this
374 aspect of PTSD and interindividual variability, a model also defended by Yehuda and LeDoux
375 (Yehuda and LeDoux, 2007). We recently used a similar paradigm in C57/BL6 mice, where cued
376 conditioned fear behavior followed a bimodal distribution after extinction, indicating a subset of
377 animals displayed impaired recall of extinction memory. Mimicking Eye Movement Desensitization
378 and Reprocessing (EMDR) therapy with alternating electrical stimulation of the eyelids led to a
379 unimodal distribution of low freezing during extinction recall (Wurtz et al., 2016). Construct validity

380 was supported by conditioning reproducing trauma, face validity by impaired extinction recall, and
381 predictive validity by improvement following EMDR-like treatment. Related to this work, Baek *et al.*
382 used FC to study the biological underpinnings of EMDR therapy (Baek et al., 2019) without
383 discussing the model validity, however. An alternative example is given in an article reporting
384 alterations in conditioned context discrimination in mice following corticosterone injections in the
385 dorsal hippocampus (Kaouane et al., 2012). The authors interpreted these findings as representing
386 “PTSD-like memory impairments” in that mice showed a deficit in restricting fear reactions to
387 appropriate context (D1 criterion of PTSD in DSM-5) (Kaouane et al., 2012). Apart from this aspect
388 pertaining to a single sub-category of symptoms, the validity of the model, including its relevance to
389 other PTSD symptoms, was not discussed in the article. Overall, models using classical FC are
390 heterogeneous, and validity was found to be insufficiently discussed in most of the cases.

391 *Stressor/Sensitization-based models* described above have also been modified to reconcile FC and
392 sensitization theories. Predator stress using cat was merged with conditioning, either by exposing rats
393 to a soiled cat litter and testing conditioned fear by subsequent exposure to a clean litter (Cohen,
394 2006; Zohar et al., 2008), or by pairing cat exposure to a sound testing fear upon sound presentation
395 alone (Zoladz et al., 2012). The most complete model of PTSD derived from the inescapable shock
396 paradigm and was reported in a pivotal article by Siegmund and Wotjak in 2007 (Siegmund and
397 Wotjak, 2007). They submitted several mice of various genetic backgrounds to a single, intense
398 footshock. Part of the mice displayed conditioned -associative- responses to context, increasing with
399 shock intensity and persisting over time. Non-associative features were validated as well. Increased
400 startle reflex developed and remained present over time. Shocked mice also displayed reduced social
401 interactions, neophobia and immobility in the forced swim test. These alterations were variable
402 among genetic strains and revertible by chronic SSRI fluoxetine administration. Siegmund and
403 Wotjak defended the validity of their model based on Yehuda and Antelman’s proposal (Yehuda and
404 Antelman, 1993). In a review article, the same authors stated, “we extend[ed] Yehuda’s and
405 Antelman’s criteria by directing the focus of interest to the hypothesized involvement of two
406 important biological processes, conditioning and sensitization, in the development and maintenance of
407 PTSD” (Siegmund and Wotjak, 2006). They also referred to Balogh and Wehner (Balogh and

408 Wehner, 2003) and Pynoos and colleagues (Pynoos et al., 1996) to insist on the similarity of their
409 results with persistent conditioned fear and sensitized fear, respectively. Regardless of their validity,
410 these modified FC protocols pose a semantic problem with major implications. Indeed, modified and
411 classical conditioning are conceptually close, but the behavioral paradigms differ greatly, raising the
412 possibility that different underlying neural mechanisms are implicated. Moreover, it can be hard to
413 completely isolate sensitization from associative learning. For instance, in the Rau et al., 2005 paper,
414 placing back the animals in the training context for extinction could have reactivated sensitized
415 mechanisms that could have in turn interacted with extinction processes (Rau et al., 2005).

416

417 In the last class of models, FC is applied after stress induction, a procedure referred to as *FC de novo*
418 (Deslauriers et al., 2018). In a first example, single prolonged stress was applied before contextual
419 fear conditioning and induced impaired, reduced fear extinction (Yamamoto et al., 2008). Impaired
420 expression and extinction of fear were interpreted as a resemblance between the SPS model and
421 PTSD. In a second example, Ressler and colleagues have modeled psychological trauma with
422 immobilization stress and demonstrated that mice exposed to immobilization displayed significantly
423 delayed fear extinction (Andero et al., 2013).

424 Such *FC de novo* models are justified mainly by *face validity* arguments, based on laboratory
425 observations of increased conditioning and/or impaired extinction in subjects with PTSD (Pitman et
426 al., 2012) that can be replicated in animal models (Deslauriers et al., 2018). Impaired processing of
427 conditioned fear can be considered a symptom of PTSD, an interpretation proposed in the first study
428 of this kind by Grillon, Krystal's collaborator (Grillon and Morgan III, 1999). Delayed extinction
429 after "*de novo*" FC in PTSD patients lends support to these models. On the other hand, Ressler and
430 colleagues interpret impaired extinction, also found in PTSD patients, as part of the causal pathway
431 leading to PTSD (Andero et al., 2013). However, conditioning already-traumatized subjects to novel
432 cues is quite different from modeling trauma with conditioning cues (a problem we discuss below).

433 The way FC has been incorporated in PTSD modeling is summarized in **Figure 2**.

434

435 *Why fear conditioning has come back and evolved in PTSD modeling*

436 After theoretical proposals for the FC/PTSD analogy, the alternative sensitization theory has
437 dominated early experimentation in animals to model PTSD. This was followed by a reminiscence of
438 FC in various forms and by its combination with sensitization in current models (Deslauriers et al.,
439 2018).

440 We propose two tentative explanations based on the contextual study of the 2000-2010s period: the
441 first one consists of a regained interest for FC overall, whereas the second one presents a greater focus
442 on neural mechanisms underlying FC extinction and its alterations in PTSD. Both aspects of PTSD
443 research were driven by technical advances to study brain function: in the study of synaptic
444 physiology in animals and in functional brain imaging in human.

445

446 Concerning the first explanation, fear conditioning as an experimental paradigm has regained interest
447 in the 1990s as a simple and readily reproducible protocol to study neurobiological underpinning of
448 emotions, while intentionally leaving out their subjective components (LeDoux, 2000). This paradigm
449 shift has allowed the application of modern neuroscience tools to study the circuits of fear
450 conditioning in great details. Thus, intracellular recordings of synaptic events, *in vivo* recordings of
451 neural activity with electrical and optical tools, and manipulation of brain circuits activity with
452 pharmacology/optogenetics have together concentrated the research activities of tens of research
453 teams worldwide and become a leading topic in Neuroscience. The knowledge accumulated has likely
454 impregnated experimental work on PTSD, either by researchers directly studying PTSD or by
455 researchers keen to translate their fundamental work to psychiatric conditions such as PTSD. In
456 agreement with this hypothesis, Yehuda and LeDoux similarly wrote: “One idea that arose was that
457 PTSD might reflect strong associative learning akin to Pavlovian fear conditioning ...Part of the
458 attraction of fear conditioning was that much was concurrently being learned about the neurobiology
459 of this behavioral paradigm from animal studies” (Yehuda and LeDoux, 2007). Strikingly, we found
460 that links between FC neurobiology and PTSD were laid out from the beginning of PTSD research in
461 the 1990s. Theories of synaptic plasticity as a basis for FC memory and their implication in PTSD had
462 indeed been formulated by some of the pioneers identified in the first part of this article, referring in
463 their theoretical accounts of PTSD to the fear circuits and the work of Michael Davis and Joseph

464 LeDoux in their theoretical accounts of PTSD (e.g. Charney, 1993; Shalev and Rogel-Fuchs, 1993;
465 Shalev et al., 1992). Moreover, synaptic changes in the temporo-amygdaloid were proposed by Kolb
466 to be implicated in PTSD, citing Kandel (Kolb, 1987). The implication of long-term synaptic
467 potentiation in PTSD by FC was further proposed by Charney (Charney, 1993) after the
468 demonstration that the pharmacological blockade of NMDA receptors in the basolateral amygdala
469 prevents the acquisition of the fear-potentiated startle response (Miserendino et al., 1990). These
470 theories still occupy a leading position in PTSD pathophysiological accounts (Ross et al., 2017).
471 Thus, it is likely that the modeling of PTSD closely followed developments in the field of FC that
472 have allowed the direct study of FC induction, expression and extinction mechanisms.

473 Concerning the second explanation related to conditioned fear extinction, it appears that current
474 models of PTSD largely rely on conditioned fear extinction deficits. As such, interest in fear
475 extinction has most likely contributed *conceptually* to the development of FC-based models of PTSD,
476 complementing the conditioning/trauma analogy. Several translational concepts may be listed to
477 explain this trend.

478 First, deficient fear extinction can be ethiopathogenic, i.e. insufficient extinction of traumatizing
479 memories could underly the capability of symptoms to express remotely from the trauma (Pitman et
480 al., 2012; VanElzakker et al., 2014), relating to construct validity. Second, subjects with PTSD
481 typically display reduced extinction of novel aversive memories in the experimental setting (e.g.,
482 Garfinkel et al., 2014); thus, a model with reduced extinction would *resemble* PTSD, that is, would
483 have face validity. Third, and perhaps most importantly, extinction has been applied as a theoretical
484 framework to explain the working mechanisms and drawbacks of exposure-based therapy (Milad et
485 al., 2014; Ross et al., 2017; VanElzakker et al., 2014), relating to predictive validity. Understanding
486 the underlying mechanisms of extinction, would in turn allow the design of novel treatments and the
487 improvement of therapeutic outcomes in PTSD (VanElzakker et al., 2014). Moreover, experimental
488 FC extinction is a highly translatable model, allowing the application of brain imaging in healthy and
489 PTSD-suffering subjects. On the contrary, it is difficult to model other constructs such as sensitization
490 in Human, a bias that may have contributed to the greater focus on extinction. Overall, scientific and
491 medical trends have continued to shape the modelling of PTSD, have led to focus on FC-based

492 models, and have moved PTSD modeling from FC analogies toward more complex models that
493 comprise extinction deficits.

494

495 Moreover, the renewed interest in FC-based models of PTSD may have come with renewed interest in
496 PTSD itself. Indeed, this paradigm shift has occurred in the 2000s, after collectively traumatizing
497 events in the USA, including 9/11 and the subsequent Afghanistan war. In support of this hypothesis,
498 the number of publications mentioning “PTSD and fear conditioning” has grown sharply after 2001.
499 Impaired conditioned fear and extinction are at the intersection of animal models, brain imaging and
500 clinical sciences and have attracted phenomenal research effort in a particular historical and political
501 context. **Figure 3** recapitulates the history of PTSD models in relation to FC.

502

503 In summary, while initial animal models of PTSD left FC out and followed earlier work focusing on
504 sensitization-based theories, attention for FC to study PTSD came back in years 2000s and largely
505 focused on extinction, leading to the creation of various experimental paradigms integrating FC in
506 diverse animal models. We posit that this trend has been influenced by novel scientific and medical
507 developments in the fields of FC and PTSD and has been stimulated by the renewed interest in PTSD
508 in the USA after collective traumatic events. Current theories and models of PTSD derive from a
509 historical legacy and have favored experimental tractability. In this first part, some conceptual flaws
510 resulting from the diversity of FC-based models have been highlighted. In the second part of this
511 article, we expand this critical analysis on conceptual grounds and propose actionable perspectives to
512 improve translational research in the field of PTSD.

513

514 **2. Learning from the past to draw the future of PTSD research**

515 Reviewing the 30-year history of animal models that include FC to mimic PTSD has revealed an
516 evolution from a simple theoretical analogy (conditioning: trauma / cued fear response: re-
517 experiencing) to heterogeneous models that incorporate sensitizing stressors and/or rely on fear
518 extinction deficits. History reveals that translating basic research in PTSD to the clinic has been
519 hampered by the lack of a clear conceptual framework. The scientific community has largely focused
520 on FC, notably advancing our understanding of the mechanisms governing conditioned fear encoding,
521 expression and extinction. However, unclear conceptual boundaries of PTSD and its models and
522 excess emphasis on conditioning and extinction may have limited innovation. Moreover, the field has
523 still not developed fine knowledge of neurobiological processes in animal models of PTSD. Finally,
524 tools to precisely manipulate brain dynamics in humans are still lacking. In the next section, some
525 operational guidance for future PTSD research are provided, which, from our point of view, should
526 involve closer interactions between physicians, scientists and a broader methodological perspective
527 where philosophers of science can help (**Figure 4**).

528

529 *The rigorous application of criteria of validity to animal models of PTSD.*

530 *Expanding the traditional criteria of validity*

531 The conceptual vagueness surrounding PTSD stems in two correlated problems. The first one is
532 related to the *conceptual validity* of various theories or models of PTSD. The second problem
533 originates in the prominence and heterogeneity of FC as a theoretical model for PTSD.

534

535 For instance, philosopher Jerome Wakefield proposed the notion of “conceptual validity” to assess the
536 ability of a definition to discriminate disorder from non-disorder (Wakefield, 1992), and has
537 investigated it thoroughly in the case of Major Depressive Disorder (Horwitz and Wakefield, 2007;
538 Wakefield et al., 2007). The main idea behind the *conceptual validity* argument is that any model of a
539 particular disorder should target only one and the very same human disorder. Intuitively, it sounds
540 challenging to determine whether a particular mechanism engaged in a specific experimental design
541 corresponds to what really and exclusively happens in a specific human disorder. In other words, it is

542 complex to evaluate if this mechanism is never engaged in another disorder or under similar, non-
543 pathologic conditions. From a mechanistic standpoint, there is probably as much biological variety
544 underlying PTSD in a human population as in any other diseases.

545 Belzung and Lemoine went further into this problem with a decomposition of the three traditional
546 criteria of validity of animal models of mental disorders (face, construct and predictive validity) into
547 five main criteria and nine subcriteria (Belzung and Lemoine, 2011) see **Table 1**). Each of these
548 criteria should participate in assessing the validity of an animal model of PTSD and be scored
549 independently from the others. To illustrate the utility of this classification to refine the evaluation of
550 animal models, we have applied these refined criteria to the PTSD models reviewed in section 1
551 (**Figure 5**).

552

553

554

555 A visual analysis of **Figure 5** indicates that the field has primarily focused on ethological (behavioral
556 symptoms) and induction (tractable relationship between triggering factor and observable effects)
557 validity criteria, and only secondarily on triggering validity criterion (transformation into a
558 pathological organism). This can be interpreted as the result of a constant reference of the field to the
559 five criteria proposed by Yehuda and Antelman (see section 1). This focus has also led to discussions
560 about the multidimensionality of the disorder and whether it should be modelled. Strikingly, there is
561 little articulated discussion on the correct species or strain or initial developmental process that should
562 lead some species, strains or individual to higher vulnerability to PTSD than others.

563

564 A specific assessment could be proposed to go further with regard to mechanistic validity. The main
565 assumption of this criterion is that understanding the neurobiological mechanism engaged in a
566 specific animal model is necessary for translation to occur. The knowledge of mechanisms engaged
567 thereby justify the direct application of the findings to the targeted disease simply by analogy. This is
568 classically referred to as the problem of extrapolation. The philosopher of Science Daniel Steel
569 pointed out that such a simple mechanistic solution is likely to fail due to the “extrapolator’s circle”,
570 which can be resumed as follows. If we did not know anything about the mechanisms involved in the
571 targeted disease, using an animal model would be unjustifiable. However, if we already knew that the
572 animal model and the target disease are similar in causally relevant aspects, using an animal model
573 would be useless (Steel, 2008). Steel proposed a strategy to improve the extrapolation (summarized in
574 **Table 2**).

575 Steel’s conceptual framework indicates that the validity of a model should instead concentrate on the
576 fact that it targets a population rather than a potential and unlikely unique mechanism in this
577 population. His analysis takes into account the facts that *(i)* there are always confounding effects of
578 the experimental intervention, that *(ii)* many potential mechanisms could link the same cause to the
579 same effect in various individuals, and that *(iii)* in a population, many individuals present different

580 combinations of these causal pathways. In these conditions, the inference cannot hold at the individual
581 level but will consist in projecting a probability distribution in a population. The inference justifies
582 claims on the direction of the causal influence (excitatory or inhibitory), more rarely about the
583 monotonicity (shape of the dose-effect curve) or on the quantity of the effect. **Table 2** presents a list
584 of conditions that strengthen the validity of the extrapolation and offers examples in PTSD modeling.
585 Based on that proposal, we provide examples illustrating its applicability to PTSD (**Table 2**).

586

587 Besides the limited use of conceptual assessment of PTSD models, the second problem stems in the
588 prominence and heterogeneity of FC as a theoretical model for PTSD. It has become so natural to
589 assimilate one concept with the other that the field concentrated on improving FC-based models rather
590 than examining whether they are the most relevant to PTSD in the first place and whether good
591 alternatives exist. The problem is even more complex if we consider that the conceptualization of
592 PTSD itself has been strongly influenced by experimental stress and conditioning theories.

593 Integration of FC in PTSD models, we have seen, has evolved from initial proposals in many
594 divergent directions, from classical FC to modified FC in the form of biological alterations and
595 conditioning to sensitizing stressors and to FC induced after sensitization (*de novo* FC). Referring to
596 “fear conditioning” models in so many different, heterogeneous cases represents a major semantic
597 confusion. Examination of concepts at stake with *de novo* FC is daunting: is FC the trauma? Impaired
598 extinction a symptom? The cause of PTSD? An epiphenomenon? Is it acquired in response to trauma
599 or a vulnerability factor?

600 In turn, semantic and conceptual approximations are responsible for theoretical assimilation and
601 oversimplification. As a result, the dominant, wide audience narrative for PTSD pathophysiology at
602 the scale of neural circuits comprises conclusions drawn from classical FC and extinction in normal
603 conditions (see (Wikipedia, 2020)). This overlooks the complexity of PTSD and its most recent animal
604 models. Overall, the field suffers from conceptual confusion, and we argue that medical progress has
605 been impeded by fragile, simplified theories resting on undifferentiated use of distinct models. This

606 situation is perpetuated by the paucity of conceptual discussion addressing what aspects of PTSD are
607 modeled in most of the recent experimental literature.

608

609 *Implementing the systematic evaluation of model validity*

610 We propose endorsing guidelines for a clarified PTSD model nomenclature and validity assessment.

611 Validity criteria should be explicitly stated and discussed in each research article related to models of

612 PTSD. Models of PTSD using FC are heterogeneous. Based on the historical and conceptual review

613 of the models, they could be classified as “classical”, “modified” (e.g., injecting corticosterone in the

614 hippocampus following FC; Kaouane et al., 2012), “stressor-based” (e.g., using a cat as an

615 unconditioned stimulus; Zoladz et al., 2012) and “*de novo/sensitized*” (after sensitizing stress;

616 Deslauriers et al., 2018) FC models. Model category needs to be stated in research articles to allow

617 conceptual debate. In line with this, validity criteria used by the authors to defend their model should

618 be explained, and when necessary, discussed. Leading scientific journals, which require

619 supplementary material to report on statistical and methodological aspects of experimental

620 neuroscience (e.g., STAR Methods in Neuron; <https://www.cell.com/star-authors-guide>) offer a great

621 opportunity to improve reproducibility and transferability of basic research. We believe validity

622 criteria of animal models should be included in this effort. Validity criteria need to be defined *a*

623 *priori*. Large, consensual categories could be used systematically, for instance, construct, face, and

624 predictive validity (Nestler and Hyman, 2010; Willner, 1984). On the other hand, room should be left

625 for authors to offer precisions regarding the nature of validity criteria, using refined criteria such as

626 those of Lemoine and Belzung (Belzung and Lemoine, 2011). For instance, whether a particular

627 footshock shows construct validity could be discussed regarding its parameters (intensity, duration

628 etc.) and whether those are sufficiently noxious to model a psychological trauma. To remain

629 operational, the definition of validity criteria should involve both scientists and philosophers of

630 science. The latter are most proficient with the history of science and the conceptual interpretation of

631 experimental data, in order to clarify validity criteria and conceptual limitations. They also have a

632 habit of collaborating with scientists to help clarify and solve scientific questions (for an example of

633 such collaborative effort in the field of major depression, see Belzung and Lemoine, 2011).

634 Systematic application and detailed reporting of validity criteria may seem trivial at first. However, it
635 is currently largely missing (including in high-impact articles). Likewise, complete methodological
636 descriptions may have seemed obvious, but only recently, with mandatory reporting, was
637 neuroscience able to move forward in enabling reproducibility of experimental work.

638 Because of the unique features of PTSD (its identified causal factor and reminder-evoked distress),
639 we believe researchers should favor PTSD models that mimic pathological processes including
640 intense, traumatic stress (construct/pathogenic validity). In categorical terms, a model should also
641 display face validity with a phenotype similar to several, ideally all, DSM-5 criteria, including fear
642 responses to trauma reminders (see excellent previous reviews: (Deslauriers et al., 2018; Goswami et
643 al., 2013; Richter-Levin et al., 2019). Predictive validity is more difficult to implement, as no gold-
644 standard, efficient treatment is available to benchmark animal models. To date, contextual FC with a
645 single intense shock, such as developed and tested by Siegmund and Wotjak (Siegmund and Wotjak,
646 2007), appears to show the greatest level of construct, face and predictive validity (**Figure 5**).

647 Interindividual variability and susceptibility should also be studied to delineate normal and
648 pathological states (Richter-Levin et al., 2019; Siegmund and Wotjak, 2006; Yehuda and Antelman,
649 1993; Yehuda and LeDoux, 2007). An illustrative example of an animal model based on
650 interindividual variability is derived from addiction pathology for which it is well known in the target
651 clinical population that only a fraction of, e.g. cocaine users, will develop true addiction mainly
652 characterized by a loss of control over compulsive behavior (American Psychiatric Association,
653 2013). A multi-symptomatic behavioral model was developed in rodent that incorporated two critical
654 features of clinical addiction (Deroche-Gamonet et al., 2004); the maladaptive nature of drug use and
655 variations in individual risk. This animal model of cocaine addiction was developed by testing the
656 main three dimensions contribution to the nine DSM-5 behavioral criteria for severe Cocaine Use
657 Disorder (CUD): (i) the motivation for the drug, (ii) the capacity to limit drug-seeking, and (iii) drug
658 seeking despite negative consequences. Similarly, whereas only a fraction of trauma-exposed patients
659 will develop PTSD (Kessler et al., 2005), the integration of individual variability in the development
660 of animal models for PTSD remains anecdotal, although some recent models have attempted to model
661 this particular aspect (Wurtz et al., 2016) for a recent review, see (Richter-Levin et al., 2019).

662 The conceptual span of each model and tested dimensions will need particular attention. Ideally,
663 several animal models with different conceptual characteristic should be used before reliable
664 conclusions may be drawn. In animal models of depression, it has been shown that none of the
665 available models fully recapitulates epigenetics of human depression, but that all the models somehow
666 overlap with different domains of the disorder (Peña and Nestler, 2018). As an analogy, various PTSD
667 models may be complementary in modeling different aspects of the disease and should be combined
668 to generate solid hypotheses. This may seem ambitious and the task intimidating, but worth the
669 investment and the outcome hoped for by researchers, clinicians and patients. Thus, despite
670 conceptual setbacks, FC integrated into pathological models and with clear conceptual boundaries
671 may remain a helpful tool to model associative dimensions of PTSD. On top of a careful, refined
672 examination of validity (including conceptual validity) and extrapolability, we propose to
673 systematically assess the latter directly with hypothesis-testing Human research in healthy subjects
674 and patients with PTSD to accelerate clinically meaningful discovery.

675

676 ***The necessity for more research on human subjects***

677

678 *Fundamental research in human subjects*

679 There has been acknowledgeable progress in human research using FC modelling. For instance, over
680 the past years, it has become clear that dedicated extinction protocols performed at specific timepoints
681 related to the retrieval of aversive memories may strengthen the erasure of fear memories in both
682 animals and humans (Quirk et al., 2010). Following the seminal work of Susan Sara and Joseph
683 Ledoux related to the reconsolidation of associative memories (Nader et al., 2000; Przybylski and
684 Sara, 1997), extinction learning performed within the reconsolidation window following fear retrieval
685 led to the erasure of fear memories in rodents (Monfils et al., 2009). Interestingly, the translatability
686 of the findings was demonstrated a year later in healthy humans (Agren et al., 2012; Schiller et al.,
687 2010), but see (Golkar et al., 2012)) although the approach tested in patients with PTSD demonstrated
688 partial efficacy, mainly on physiological outcomes (Vermees et al., 2020). The efficiency of such
689 approaches has been evaluated in other disease as well, such as addictive behavior (for a recent

690 review, see Lee et al., 2017). In a reverse translational approach, the Eye Movement Desensitization
691 and Reprocessing protocol (EMDR), a procedure used to treat PTSD, was first identified fortuitously
692 in humans (Shapiro, 1989) and subsequently implemented in FC and extinction-based animal models
693 to evaluate the underlying mechanisms (Baek et al., 2019; Wurtz et al., 2016). Likewise, it is
694 important to mention that the development of specific FC and extinction -related animal models were
695 key in providing the conceptual roots for some of the historical therapeutic advances for PTSD (i.e.
696 exposure based-therapies). Thus, fundamental research on human subjects appears to be an interesting
697 approach to strengthen the development of novel therapeutic approaches for PTSD patients and
698 identify the underlying mechanisms.

699

700 *Clinical research in pathological population*

701 In addition to research on healthy human subjects, research in subjects with PTSD remains essential
702 in refining clinically relevant dimensions and in testing and generating mechanistic hypotheses.

703 Constantly re-evaluating the definition of trauma-related disorders and the concepts at stake is a key
704 challenge to be met. In the last version of the Diagnostic and Statistical Manual of mental disorders,
705 PTSD has been separated from anxiety disorders, and more emphasis has been placed on avoidance to
706 better conceptualize the disorder. However, these modifications do not make a clear paradigm shift in
707 clinical care or modelling of PTSD. The recognition of PTSD in the psychiatric nosography appears
708 heavily impregnated by behaviorism and theories of stress (see above and Scott, 1990; Young, 1997).

709 As such, the concept of PTSD is tightly linked to experimental psychology constructs such as stress
710 and conditioning. The name of the disorder itself is reflective of its theoretical influence. Conditions
711 related to intense psychological trauma has been conceptualized as a post-stressor (di)stress disorder.

712 We reason that, as a result, the definition of PTSD itself may have constrained the disorder to circular
713 reasoning (modeling stress to understand stress). Intriguingly, it is unclear whether the FC model
714 pertains to the conscious experience of emotions or to recently evolved feelings central in PTSD
715 (guilt, shame etc.; for a discussion of this, we refer to the exchange between (LeDoux, 2014; LeDoux
716 and Pine, 2016), and Fanselow and Pennington, 2017). In a panel discussion led in 2015 by Yehuda,
717 PTSD specialists have expressed skepticism toward the FC model, including Krystal and Neylan.

718 Krystal said, “The fear-based model that has advanced the field is beginning to look a bit outdated.
719 We need to think in other ways and test them out” (Yehuda, 2006).

720 The boundaries of “PTSD” are subject to caution regarding specificity, sensibility and homogeneity of
721 the diagnostic category, and alternative definitions of this mental disorder are sought to improve
722 translational research. Indeed, PTSD significantly overlaps with mood and anxiety disorders.
723 Moreover, the current descriptions of “post-traumatic stress disorder” do not consider some cases,
724 e.g., somatic expression of intense stress, such as psychogenic paralysis, observed in many
725 traumatized WWI soldiers (Crocq and Crocq, 2000). In addition, PTSD encompasses a heterogeneous
726 set of clinical presentations; for instance, patients with PTSD may display opposite emotional
727 reactivity (excessive or numbed). Clinical dimensions and their variations may be relevant to one
728 group of subjects but not others.

729 Several interesting alternatives to the recognition of monolithic categories of patients defined by a
730 group of subjective symptoms have been proposed. The Research Domain Criteria system (RDoC)
731 embraces a definition of mental disorders by a matrix of constructs, consisting of neurobiological
732 modules. The RDoC matrix is organized in six domains : negative valence systems, positive valence
733 systems, cognitive systems, systems for social processing, arousal/regulatory systems and
734 sensorimotor systems. For instance, the negative valence system includes acute threat (*fear*) as a
735 construct. Constructs are meant to be explainable at various scales (e.g. molecular, genetic,
736 neurocircuitry and behavior), each containing measurable variables (NIMH site, (Insel, 2014; Insel et
737 al., 2010). Group of patients may thus be identified based on objective measurements, unified by
738 pathophysiological-relevant alterations in brain systems. Post-traumatic conditions may instance
739 involve the negative valence system of fear, which can be studied using fear conditioning.

740 Dimensional definitions of mental disorders based on high dimensionality biological variables offer
741 another promising avenue. In this framework, computational strategies, e.g. classifiers using machine
742 learning, represent a necessary tool if a dimensional strategy is to succeed in translational psychiatry.
743 A review of computational psychiatry is beyond the scope of this article, and we refer to previous
744 reviews (Huys et al., 2016; Montague et al., 2012). Interestingly, it has been proposed that analytic

745 models oriented by some pathophysiological theory may help reduce dimensionality and improve
746 classification strategies (Huys et al., 2016).

747

748 Animal models can inform the selection of biological parameters to be measured in clinical
749 populations. Nonetheless, biology-based strategies using computational and modular approaches are
750 not devoid of conceptual questions that pertain to animal modeling. First, studying mental dimensions
751 at various biological scales imply conceptual jumps from one level to the next. For instance,
752 approximating negative valence with fear and modeling the latter with fear conditioning is a matter of
753 debate for how well fear conditioning in rodents represents the human experience of fear (Fanselow
754 and Pennington, 2017; LeDoux 2014; LeDoux and Pine, 2016). Second, the RDoC matrix is
755 constructed on the basis of physiological models. Differences between normal and pathological
756 conditions may not only be quantitative but also qualitative, and there is no guarantee as to whether
757 understanding normal functioning in animals will help capture pathological alterations in patients.
758 The RDoC project aims to continuously incorporate refinements (Insel, 2014). The inclusion of
759 “pathological” animal models in the matrix may increase its clinical usefulness. Third, studying
760 modules independently might miss important interactions between highly interconnected
761 neurobiological systems. Finally, if RDoC and computational approaches reach their goal to redefine
762 clusters of patients, animal models will remain important in identifying and testing therapeutic targets.
763 In this scenario, it is tempting to think that “best” animal models should recapitulate all the observed
764 alterations (a situation close to the current categorial approach) and validate extrapolation criteria as
765 proposed by Steel. Overall, we argue that conceptual issues are not smaller in neurobiology-based vs.
766 categorial symptom-based approaches. The careful evaluation of animal models using extended
767 criteria and conceptual analysis applies equally to these strategies.

768

769 In mirror of the patient to animal translation, translation can be attempted, for instance, by applying
770 functional brain imaging in subjects with PTSD to examine if brain networks and their interactions
771 observed in animals hold true at the scale of brain regions. For instance, the implication of the
772 prefrontal-amygdala pathway has been evaluated using PET or fMRI during recollection of traumatic

773 events in PTSD patients, revealing decreased activity in the ventromedial prefrontal cortex (vmPFC)
774 and increased activity in the amygdala (Bremner, 1999; Bremner et al., 1999; Lanius et al., 2001;
775 Liberzon et al., 1999; Lindauer et al., 2004; Pissiota et al.; Rauch et al., 2006; Shin et al., 1997, 2004;
776 but see Shin et al. 2005)

777 Moreover, clinical research has recently generated interesting hypotheses related to potential
778 mechanisms that could modulate memory reconsolidation, the link between generalization and
779 anxiety disorders, the impact on personality traits on reconsolidation processes or the role of
780 individual variability to the development of maladaptive fear behavior, some of which are not always
781 testable in animal models ((Dunsmoor and Paz, 2015; Kindt and van Emmerik, 2016; Sevenster et al.,
782 2012; Soeter and Kindt, 2013). Where possible, however, mechanistic accounts should be integrated
783 to improve animal models and translation.

784 If basic research should integrate clinical knowledge into more relevant animal models, clinical
785 research should continue to interrogate, refine and integrate explanatory models of PTSD. These
786 findings could, in turn be applied to assess and refine animal models in a virtuous translational circle.
787 Ultimately, physicians and patients themselves will play a key role and determining the efficacy of
788 biological interventions on symptoms that are meaningful for the subjects.

789

790 ***Reversing pathogenic mechanisms by targeting brain circuits***

791 *Going further into mechanistic studies in Animal models.*

792 Besides conceptual issues, available animal models may be sufficiently valid but have been
793 insufficiently exploited to conclude on their usefulness. In contrast with research on classical FC and
794 recent progress of the underlying circuits using advanced technologies widely used to record (*in vivo*
795 electrophysiology, population-based photometry, single-cell calcium imaging) and manipulate (with
796 optogenetics or chemogenetics) brain activities in behaving rodents (e.g., Burgos-Robles et al., 2017;
797 Courtin et al., 2014; Grewe et al., 2017; Vetere et al., 2017; Yamamoto et al., 2018), research using
798 dedicated models of PTSD have lagged behind. We argue that there is a chance to accelerate the
799 discovery of pathogenic circuit mechanisms at stake in PTSD by applying modern tools to animal
800 models of PTSD.

801 Translational research should focus on PTSD-like paradigms that are simple and reproducible while
802 retaining a high level of validity. By performing simultaneous recordings and manipulations of brain
803 circuits in PTSD models, scientists may be able to causally interrogate pathological mechanisms and
804 identify biomarkers as well as therapeutic strategies. In a classical FC paradigm, the emergence of
805 slow oscillations in the prefrontal cortex has been shown to entrain neuron assemblies controlling fear
806 and directly mediate freezing behavior (Dejean et al., 2016; Karalis et al., 2016). Optogenetic
807 inhibition of these neuron ensembles during slow prefrontal oscillations drastically reduced fear
808 expression (Dejean et al., 2016), suggesting it might represent a therapeutic target in anxiety and fear-
809 related disorders. However, whether this and other types of biomarkers observed with FC hold true in
810 actual animal models of psychiatric disorders and represent modifiable therapeutic targets remains
811 untested.

812

813 *Manipulating brain circuits in Human.*

814 Developing therapeutic strategies to restore normal circuit functioning could provide tremendous
815 clinical progress in a near future (Gordon *on being a circuit psychiatrist*). Targeted manipulations of
816 brain activity would offer specificity to biological interventions, a major problem with
817 pharmacotherapy. This is one of the main examples of animal and human research being integrated to
818 identify brain circuits and dynamic mechanisms implicated in PTSD. For instance, transcranial
819 magnetic stimulation of the ventromedial prefrontal cortex in an animal model combining FC and
820 sensitization (as described by (Siegmund and Wotjak, 2007) was sufficient to counteract contextual
821 fear conditioning and neophobia, offering the basis for potential therapeutic protocols (Legrand et al.,
822 2019).

823 However, even in the ideal case scenario of fully valid animal models leading to the identification of
824 biomarkers and brain sub-circuits implicated in PTSD, manipulating the Human precisely enough
825 remains a major challenge. Current technologies (such as transcranial magnetic stimulation) have a
826 specificity limited to a brain subregion, at best, and their stimulation patterns are independent of
827 ongoing brain activities. Future technologies may bring considerable progress with closed-loop
828 neuromodulation strategies, i.e. restoring online physiological states in dysfunctional networks

829 (Bouthour et al., 2019; Krook-Magnuson et al., 2015). Local neuromodulation currently requires
830 intracerebral electrical stimulation. Strategies to obtain non-invasive deep brain stimulation have been
831 proposed, but their actual efficacy, transferability to Human and portability remain to be demonstrated
832 (Cagnan et al., 2019; Grossman et al., 2017). Moreover, electrical stimulation, be it invasive or non-
833 invasive, will not allow manipulation of precise, intermingled neuron populations. Optogenetic
834 manipulation of the Human brain is a promising but far-fetched research avenue (Krook-Magnuson et
835 al., 2015). One of many problems facing optogenetic manipulation of human brain circuits is the low
836 penetration of visible light in brain tissue. An elegant technological solution is being developed that
837 uses the conversion of highly penetrative infrared light into visible light within the brain, using
838 upconversion nanoparticles (Chen et al., 2018). Clinical grade developments of such strategies might
839 transform precision medicine in the field of neurological and mental disorders.

840 Without tools that allow translational testing in patients of preclinical findings, one cannot simply
841 blame animal models for insufficient validity. As philosophers are pivotal in discussing the validity of
842 animal models, expert engineering will be required to advance neuromodulation treatments in
843 psychiatric disorders.

844 Proposed lines of guidance for refining PTSD research identified through historical and conceptual
845 analyses are summarized in **Figure 4**.

846

847 **Conclusion**

848 By providing material to understand the history of conceptual links between PTSD and fear
849 conditioning, this work places current research on the neurobiology of PTSD in a clearer conceptual
850 framework. Fear conditioning-based models of PTSD might be useful to advance fundamental and
851 translational PTSD research, provided concepts are clarified and models critically evaluated.
852 Classifications of mental disorders are a moving target for animal research (Flandreau and Toth,
853 2017), but one cannot bring progress without the other. Translation to medical applications will also
854 require novel therapeutic tools to manipulate precise neural circuits in the central nervous system.
855 Overall, future innovation in PTSD research will need fostering interactions between physician,
856 scientists, engineers, philosophers of sciences and training physician-scientists with diverse
857 theoretical and experimental background. Translating neurobiological research to PTSD treatments
858 thus calls for patience and modesty. We hope that a better grasp of PTSD models history will help
859 select relevant information, refine and create novel experiments to study PTSD.

860

861 **LEGENDS**
862

863 **Figure 1: Summary of the conceptual models for PTSD identified in the 1980's -early 1990's**
864 **literature.**

865 Traumatic events lead to fear conditioning and sensitization that respectively underly PTSD
866 symptoms of reexperiencing and avoidance, and hyperarousal and numbing. Distinct animal models
867 were initially proposed accordingly.

868 **Figure 2: Conceptual summary of current PTSD models.** Trauma induction may be obtained with
869 classical fear conditioning or stressor-based protocols (e.g. single prolonged stress). The latter may be
870 followed by fear conditioning (*de novo*), which can be interpreted as the trauma itself, or as a
871 manifestation of PTSD in reduced fear extinction (“trauma?” in the figure). Interindividual variability
872 results in various degrees of resilient and pathological phenotypes.

873 **Figure 3: Historical links between PTSD and animal modeling using fear conditioning.**
874 Sociological and political contexts are highlighted, as well as clinical nosography.

875 **Figure 4: Shaping the future of PTSD research.** Improving PTSD research will require conceptual
876 clarifications in both animal and clinical research domains that are currently vague and ill-defined, as
877 well as developments in integrating basic, clinical and engineering research.

878

879 **Figure 5. Assessment of the validity of major models of PTSD using refined criteria.** blank =
880 met criteria (3 points); dark grey = unmet criteria (1 point); light grey = partially met criteria (2
881 points). Note: only specific contents of the selected articles were analyzed to illustrate the strategy.
882 Complementary information compiling literature on these models can be found in (Deslauriers et al.,
883 2018). * if the initial stress is considered as the trauma.

884

885 **Table 1. Refined Criteria of validity for animal models of mental disorders.** Adapted from
886 Belzung and Lemoine (2011).

887 **Table 2. Conditions reinforcing the validity of an extrapolation (after Steel 2008) and examples**
888 **in PTSD.** In this table, Steel's nomenclature was reformulated to be translatable to the neurobiology
889 of PTSD.
890

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1224 **Acknowledgements**

1225 The authors thank reviewers and Pierre Burbaud, Olivier Doumy, Wissam El Hage, H  l  ne Verdoux

1226 and the members of the Herry lab for their critical comments on previous versions of this manuscript.

1227 Ekaterina Escoffier Centre Hospitalier Charles Perrens, Bordeaux is acknowledged for finding

1228 historical manuscripts.

1229 Funding: Thomas CM Bienvenu is the recipient of a clinical-scientist fellowship CCA-Inserm

1230 Bettencourt.

1231

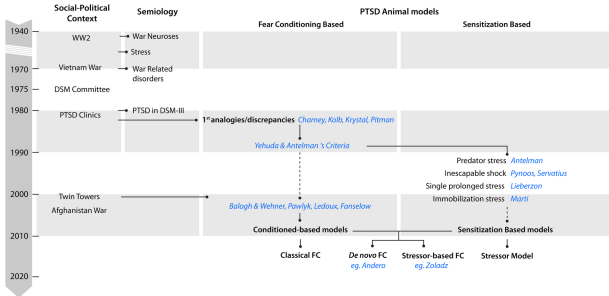
1232 **Declaration of Interests**

1233

1234 Bruno Aouizerate received speaker's honoraria and/or a travel allowance from Lundbeck,

1235 Janssen-Cilag, Sanofi and Eli Lilly. He has served on the advisory board of Janssen-Cilag.

1236





Conditioning



PTSD (DSM-III)

Re-experiencing

Avoidance

Sensitization



Hyperarousal

Numbing

Model

Fear conditioning

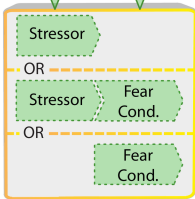
Inescapable Shocks

Initial Population



Induction

Trauma? Trauma?



Phenotype Variability



CURRENT STATE

Animal Research

Fear cond
Fear cond. de novo
Stressor based

Limited
Translation

Human Research

PTSD

PERSPECTIVES

- Conceptual
Validity

- Phenotyping
(multidimension)
- Circuits

Refine

Integration

Fundamental

Clinical

- Mechanisms
- Theories

- Categories
- Dimensions
- Therapy

Engineering

Circuit
Modulation

	Homological validity		Pathogenic validity		Mechanistic validity	Face validity		Predictive validity		Overall score Orange = 20 to 27 Yellow = 14 to 19 Grey = 9 to 13	
	Species validity	Strain validity	Ontopathogenic validity	Triggering validity		Ethological validity	Biomarker validity	Induction validity	Remission validity		
Classical FC model	(Balogh & Wehner, 2003)	Mouse	Strong variability among strains	No intervention to induce vulnerability	Identified event but no life threat	Not specifically studied	Fear generalization in some strains	Not specifically tested	Response to trauma reminders	Not tested	17 / 27
	(Debiec & Ledoux, 2004)	Rat	No choice of a specific strain	No intervention to induce vulnerability	Identified event but no life threat	Propranolol after memory reactivation (implication of the noradrenergic system in memory reconsolidation)	Cued fear responses	Not specifically tested	Response to trauma reminders	Reduction of cued fear by propranolol (but no clear equivalent in PTSD (e.g., Rouillet et al., 2021))	16 / 27
	(Pawlyk et al., 2005)	Rat	No specific strain	No intervention to induce vulnerability	Identified event but no life threat	Not specifically studied	Sleep disturbance	Reduces REM sleep duration	Identified stressor but no immediate temporal relationship between trauma & effect	Not tested	13 / 27
	(Kacouane et al., 2012)	Mouse	No specific strain	Corticosterone injections in dorsal hippocampus	Identified event but no life threat	Partial implication of glucocorticoids in PTSD but no evidence for increased hippocampal levels in PTSD	Impairment in contextual fear but cued fear enhancement & generalization	Decreased hippocampal activation, increased amygdala activity	Response to trauma reminder	No tested	19 / 27
	(Wurtz et al., 2016)	Mouse	No specific strain	No intervention to induce vulnerability	Identified event but no life threat	Not specifically tested	Cued fear & impaired extinction in some subjects (interindividual variability)	Not tested	Response to trauma reminder	EMDR simulated by alternate electrical stimulation enhanced extinction of fear	16 / 27
Stressor based	<u>Predator stress</u> (Adamec & Shallow, 1993)	Rat	No specific strain	No intervention to induce vulnerability	Identified intense traumatic event	Not specifically tested	Increased, long lasting anxiety behavior	Not tested	Identified stressor but no immediate temporal relationship between trauma & effect	Not tested	14 / 27
	<u>Inescapable shock</u> (Pynoos et al., 1996)	Mouse	No specific strain	No intervention to induce vulnerability	Identified intense traumatic event	Not specifically tested	Enhanced anxiety & cued-evoked fear behavior	Not tested	Identified stressor & enhanced effects with reminders of the trauma	Not tested	15 / 27
	<u>Inescapable shock</u> (Servatius et al., 1995)	Rat	No specific strain	No intervention to induce vulnerability	Identified traumatic event but lower noxious level & repeated	Not specifically tested	Increased, long lasting reminder-evoked fear behavior	Transient blood corticosterone elevation, but no prolonged changes of the HPA axis reactivity	Identified stressor but no immediate temporal relationship between trauma & effect	Not tested	14 / 27
	<u>Single prolonged stress</u> (Liberzon et al., 1997)	Rat	No specific strain	No intervention to induce vulnerability	Identified traumatic events but the combination of various stressors	Sensitization of negative feedback to the corticotropin HPA axis	Not tested	Sensitization of negative feedback to the corticotropin HPA axis	Identified stressor but no immediate temporal relationship between trauma & effect	Not tested	15 / 27
	<u>Immobilization stress</u> (Marti et al., 2001)	Rat	No specific strain	No intervention to induce vulnerability	Identified intense traumatic event	Sensitization of negative feedback to the corticotropin HPA axis	Not tested	Reduction of the HPA response to restress	Identified stressor & biological responses to trauma reminder	Not tested	17 / 27
Stressor-based FC	<u>Inescapable shock</u> (Sigmund&Wotjak, 2007)	Mouse	Strong variability among strains	No intervention to induce vulnerability	Identified intense traumatic event	Not specifically tested	Increased, long lasting anxiety behavior	Not tested	Identified stressor & responses to trauma reminder	Normalized fear responses upon chronic Fluoxetine administration	20 / 27
	<u>Predator stress</u> (Zohar et al., 2008)	Rat	No specific strain	No intervention to induce vulnerability	Identified traumatic event but moderate intensity (cat odor)	Not specifically tested	Increased, long lasting anxiety & conditioned fear behavior	Not tested	Identified stressor & behavioral responses to trauma reminder	Reduction in acute responses by pregabalin administration (limited evidence in human)	15 / 27
	<u>Predator stress</u> (Zoladz et al., 2012)	Rat	No specific strain	Social instability but intermingled with cued cat exposure	Identified intense traumatic event	Sensitization of negative feedback to the corticotropin HPA axis	Increased, long lasting anxiety & conditioned fear behavior	reduction of the HPA response to restress	Identified stressor and behavioral responses to trauma reminder	Not tested	20 / 27
De novo FC	<u>Single prolonged stress</u> (Yamamoto et al., 2008)	Rat	No specific strain	No intervention to induce vulnerability*	Identified traumatic events but the combination of various stressors	Plasticity of glutamatergic transmission via NMDA receptors	Reduced conditioned fear extinction to context	Increased NMDA receptor transcription (mRNA)	Identified stressor but no immediate temporal relationship between trauma & effect	Reduction in extinction deficit by D-Cycloserine (limited evidence in Human, Baker et al., 2007)	18 / 27
	<u>Immobilization stress</u> (Andero et al., 2013)	Mouse	No specific strain	No intervention to induce vulnerability*	Identified intense traumatic event	Dysregulation of nociception signaling	Reduced conditioned fear extinction to cue	Altered amygdala expression of the nociceptin / orphanin	Identified stressor but no immediate temporal relationship	Fear conditioning impairment by nociception agonist	19 / 27
Overall score (Orange= 39 to 45, Yellow= 24 to 38, Grey= 15 to 23)	17 / 45	19 / 45	18 / 45	36 / 45	28 / 45	40 / 45	23 / 45	39 / 45	23 / 45		

Kind of validity	Homological validity		Pathogenic validity		Mechanistic validity	Face validity		Predictive validity	
Aspect of validity	<i>Species validity</i>	<i>Strain validity</i>	<i>Ontho-pathogenic validity</i>	<i>Triggering validity</i>		<i>Ethological validity</i>	<i>Biomarker validity</i>	<i>Induction validity</i>	<i>Remission validity</i>
Object of validity	Species	Strain	Interaction transforming an organism into a vulnerable organism	Interaction transforming an initial or vulnerable organism into a pathological organism	Theoretical cognitive or neurobiological mechanism producing the observable effect of the disease	Behavioral symptoms of the disease	Biomarkers associated with the disease	Relation between the triggering factor and the observable effects of the disease	Relation between the therapeutic agent and the observable effects of the disease

Condition	The extrapolation is sounder if...	Example in PTSD
Modularity	...the mechanism of interest is causally more isolated from other mechanisms.	Conditioning involves fewer processes than sensitization
Mechanistic homogeneity in the target clinical population	...the effect observed is not the result of several mechanisms	At least two mechanisms in PTSD: Prefrontal hypoactivation and/or amygdala hyperactivity
The purity of experimental intervention	... the mechanism is precisely targeted	Direct biological interventions (e.g., hippocampal corticosterone injection (Kaouane et al., 2012) are better targeted than, e.g. classical fear conditioning
No neutralizing effect in the model	...conflicting effects of the intervention do not exactly counterbalance each other.	Classical fear conditioning has confounding endocrine effects with no negative feedback on HPA axis and compensatory corticosterone increase upon fear reactivation (e.g. (Albrecht et al., 2013); whereas sensitization stress with negative HPA feedback (e.g., (Zoladz et al., 2012)
No neutralizing effect in the clinical population	... conflicting effects of the mechanisms triggered by ethiopathogenic factors do not exactly counterbalance each other.	HPA activation following trauma is not sufficient to relieve stress, or could even be pathogenic, in PTSD patients
Comparative process tracing	...significant differences between the model and the clinical population are known	Conditioned fear extinction is slower in rodents than in humans (LaBar et al., 1998; Phelps et al., 2004)