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A return to the psychiatric dark ages with a two-system framework for fear

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ABSTRACT

The past several decades has seen considerable progress in our understanding of the neurobiology of fear and anxiety. These advancements were spurred on by envisioning fear as emerging from the coordinated activation of brain and behavioral systems that evolved for the purpose of defense from environmental dangers. Recently, Joseph LeDoux, a previous proponent of this view, published a series of papers in which he challenges the value of this approach. As an alternative, he and colleagues propose that a 'two-system' framework for the study of responses to threat will expedite the advancement of medical treatments for fear disorders. This view suggests one system for autonomic and behavioral responses and a second for the subjective feeling of fear. They argue that these two systems operate orthogonally and thus inferences concerning the emotion of fear cannot be gleaned from physiological and behavioral measures; confounding these systems has impeded the mechanistic understanding and treatment of fear disorders. Counter to the claim that this view will advance scientific progress, it carries the frightening implication that we ought to reduce the study of fear to subjective report. Here, we outline why we believe that fear is best considered an integrated autonomic, behavioral, and cognitive-emotional response to danger emerging from a central fear generator whose evolutionarily conserved function is that of defense. Furthermore, we argue that although components of the fear response can be independently modulated and studied, common upstream brain regions dictate their genesis, and therefore inferences about a central fear state can be garnered from measures of each.

1. Introduction

Across phylogeny, organisms display characteristic responses to danger, allowing them to avoid predation and other dangers in their environment (Bolles, 1970; Fanselow & Lester, 1988). These responses entail both internal physiological changes including increased heart rate and respiration, and external behaviors such as fight and flight responses (Davis, 1992; Fendt & Fanselow, 1999; Perusini & Fanselow, 2015).

The mental health field has placed great interest in responses to danger (also referred to as defensive behavior) in an effort to understand fear and anxiety disorders, often conceptualized as the body's defensive response exceeding its adaptive function. Owing largely to the relative ease with which behavioral and physiological responses to threat can be evoked in model organisms, as well as the quantitative manner in which they can be measured, we now know a great deal about defensive circuits in the brain (Davis, 1992; Duvarci & Pare, 2014; Fanselow & LeDoux, 1999; Johansen, Cain, Ostroff, & LeDoux, 2011; Paré, Quirk, & Ledoux, 2004). This research has already provided us with the ability to predict the efficacy of therapeutic drugs, from benzodiazepines for the reduction of fear and anxiety (Fanselow & Helmstetter, 1988; File & Pellow, 1985; Hart, Sarter, & Berntson, 1998) to D-cycloserine for the augmentation of exposure therapy (Bouton, Vurbic, & Woods, 2008; Bowers & Ressler, 2015; Mataix-Cols et al., 2017; Woods & Bouton, 2006). In addition, studies of the ontology of defensive responses have provided us with information relevant to behavioral therapies; for example, understanding why exposure therapy is liable not to transfer beyond the therapist's office (Bouton, 2002, 2004; Bouton, Westbrook, Corcoran, & Maren, 2006).

In several recent and widely publicized papers, LeDoux and colleagues call into question the utility of using autonomic and behavioral responses to danger to make inferences about the associated subjective emotional states of fear and anxiety (LeDoux & Pine, 2016). They argue that autonomic and behavioral responses to threat are orthogonal to the subjective experience of fear (Fig. 1A). Therefore, the terms fear and anxiety should only be used in reference to subjective mental experience, and should be studied accordingly. They propose that the failure to distinguish the systems supporting fear and anxiety from those giving rise to the autonomic and behavioral responses to threat – their 'two-system framework' – is one of the reasons that 'progress has stalled in

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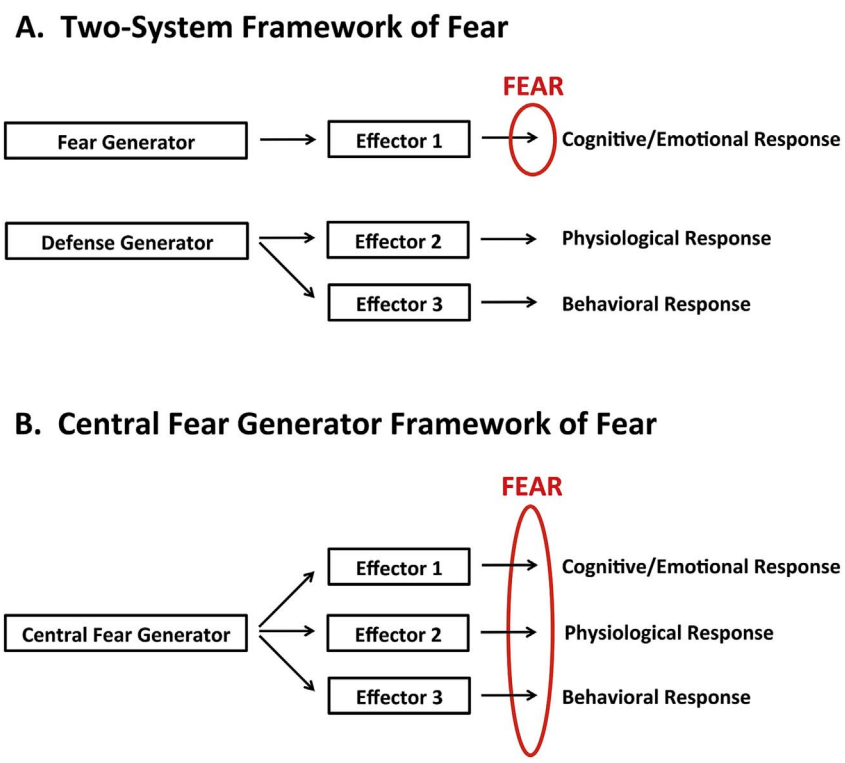

Fig. 1. Two opposing models for fear. A) The two-system framework proposed by LeDoux and Pine posits that the emotional experience of fear emerges from a distinct neuronal circuit than that which is responsible for the physiological and behavioral responses to threat. The term fear only refers to the subjective, cognitive/emotional experience in response to threat. B) The central fear generator framework advances that the various responses to threat (cognitive/emotional, physiological, and behavioral) emerge from a central neuronal circuit. Here, the term fear represents an integrated response.

treatment development for mental disorders' (LeDoux & Brown, 2017; LeDoux & Pine, 2016; LeDoux, 2017).

Here we contend with this view, and argue that the autonomic, behavioral, and cognitive-emotional responses to danger are best conceptualized as the unitary result of activation of a central fear generator (i.e. one-system).

2. The damage of a two-system framework

Before beginning, it is paramount to state that we are not writing this response only because we believe the two-system framework is theoretically troubled. Rather, we were compelled to do so because such a view has the potential to wreak havoc on progress in the field of mental health. Already the National Institute of Mental Health has broadcast one of these papers (NIMH., 2016), suggesting it has the potential to influence policy. Here are some notable problems:

First, if the subjective emotion of fear is orthogonal to its autonomic and behavioral counterparts, then all use of non-human animals to advance translation to the clinic in the study of fear can essentially be thrown out the window. Animals cannot tell us of their subjective emotional responses, and therefore they should not be used to study fear as an emotional experience. Sure, they can be used to study the physiological and behavioral responses to danger, but according to the two-system framework, this is moot, as an understanding of these responses would do little to lessen the subjective distress of patients. Any insights gained by the ability to probe specific neural circuits and test the efficacy of medications, as well as the environmental control that animal studies provide us with, would be gone.

Second, the inability to use physiological and behavioral measures to study fear does not merely apply to non-human animals. This must also hold true in humans, because across species the two-system framework holds that these measures do not predict the subjective experience of fear. Thus, experimental work examining behavioral and physiological responses in humans to assess fear would similarly need to be discarded.

Without physiological and behavioral indices of fear in human and non-human animals, we are left to study subjective responses. Of course, the reason the field moved away from subjective report is no mystery: they are often difficult to reliably quantify and subject to diverse response biases that can variably over-/under-estimate the subjective experience of fear. The demand characteristics of the situation may also influence self-report: for example, fear may be under-reported by a dedicated soldier and over-reported by someone wishing to persuade a physician to prescribe medications. Moreover, subjective report can only be captured from individuals capable of using language to communicate their subjective experience (because again, behavioral indicators are not reliable). This poses serious issues, as the study of emotional experience in young children, or adults with language disabilities, would be beyond scientific reach.

However inconvenient, if the two-system framework were correct, these would be the ramifications. Thankfully, we believe that there is little evidence that supports the two-system framework. Indeed, the vast preponderance of the literature, even that reviewed by LeDoux and and colleagues, clearly favors the central state view. In addition, upon scrutiny of the two-process framework we believe that it actually suggests that the subcortical circuits supporting defense are the unique and paramount circuits in driving fear.

3. The argument for a central fear generator

Not unlike previous models (Davis, 1992; Fendt & Fanselow, 1999; Johansen et al., 2011), we propose that fear is a coordinated reaction to danger involving autonomic, behavioral and cognitive responses emerging from a central fear generator. This central fear generator then recruits downstream effectors that control a restricted range of the response (Fig. 1B).

Traditionally, it has been assumed that the central generator of fear is the amygdala, because damage to the amygdala is able to gravely impact a multitude of defensive behaviors, and because plasticity within the amygdala is essential for fear learning to occur (Davis, 1992; Fanselow & LeDoux, 1999; Fendt & Fanselow, 1999; Maren, 2003, 2005; Rumpel, LeDoux, Zador, & Malinow, 2005). We largely agree with this assumption and the following discussion will focus heavily on evidence concerning the amygdala. Nevertheless, it is important to

distinguish the argument that we are making, 1) that there is a central fear generator; from an argument that we are not making, 2) that the amygdala is the sole constituent of this generator.

LeDoux and colleagues (LeDoux & Brown, 2017; LeDoux & Pine, 2016; LeDoux, 2017) state several reasons why they believe that a single-system, amygdalocentric framework, is incorrect. Because we found their review to ignore evidence that is counter to their position, in addition to seminal work in the field of emotion, we address each of their major arguments in turn. In so doing, we hope to convince the reader that the single-system framework is the most parsimonious with the extant fear literature.

Argument # 1: "Patients with amygdala damage can still feel fear, panic, and pain"

If the amygdala was assumed to be the common generator responsible for the autonomic, behavioral, and cognitive-emotional responses to danger, then damage to the amygdala should severely impact all three responses. In contrast, if the two-system theory is correct, then destruction of the generator for one defensive response should leave responses generated by the second generator largely unaffected (Fig. 1A).

LeDoux and colleagues point to a subset of cases in which the conscious feeling of fear is preserved despite damage to the amygdala in human patients (Anderson & Phelps, 2002; Feinstein et al., 2013, 2016). This stands in contrast to extensive work in humans and non-human animals showing that bilateral amygdala perturbations are able to produce lasting impairments in the behavioral and physiological responses to danger (Bechara et al., 1995; Blanchard & Blanchard, 1972; Davis, 1992; Fendt & Fanselow, 1999; Gale et al., 2004; Gentile, Jarrell, Teich, McCabe, & Schneiderman, 1986; Klumpers, Morgan, Terburg, Stein, & van Honk, 2015; LaBar, LeDoux, Spencer, & Phelps, 1995; Maren, Aharonov, & Fanselow, 1996; Zhang, Harper, & Ni, 1986). Thus, they argue that the amygdala is likely to be responsible for defensive responses (autonomic and behavioral) but not conscious fear.

However, the findings they highlight are at odds with an equivalent number of studies showing that humans with bilateral damage to the amygdala – notably, one of three studies LeDoux and Pine cite is predominantly unilateral (Anderson & Phelps, 2002) – show reductions in their subjective reports of fear and subjective ratings of the approachability of fearful stimuli (Adolphs, Tranel, & Damasio, 1998; Feinstein, Adolphs, Damasio, & Tranel, 2011; Sprengelmeyer et al., 1999). Moreover, in the seminal studies of patient S.M., perhaps the most complete and extensively studied case of bilateral amygdala damage to date, a profound loss of all fear responses has been observed:

> "To provoke fear in SM, we exposed her to live snakes and spiders, took her on a tour of a haunted house, and showed her emotionally evocative films. On no occasion did SM exhibit fear, and she never endorsed feeling more than minimal levels of fear. Likewise, across a large battery of self-report questionnaires, 3 months of real-life experience sampling, and a life history replete with traumatic events, SM repeatedly demonstrated an absence of overt fear manifestations and an overall impoverished experience of fear. Despite her lack of fear, SM is able to exhibit other basic emotions and experience the respective feelings." (Feinstein et al., 2011)

It is important to note that SM's lesion has two very important features: 1) It is bilateral. 2) It is restricted to the amygdala; other structures are intact. Thus, it seems that the amygdala is central to both the autonomic/behavioral and cognitive-emotional responses of fear, consistent with the amygdala being a part of a central fear generator.

However, even if we were to concede that in some cases amygdala damage fails to affect subjective fear responses, in accordance with the two-system framework, it must also be the case that while subjective emotional responses are preserved, autonomic and behavioral responses are impoverished (as these responses are proposed to be dependent upon the amygdala). This is because these responses are proposed to be orthogonal and independently generated. However, in the same papers LeDoux and colleagues cite, both autonomic/behavioral and cognitive-emotional components of fear are preserved (Feinstein et al., 2013, 2016). Consequently, these findings are not in line with a two-system model either.

How then, does one account for the perseverance of fear in the absence of the so-called generator? Although damage to the amygdala of animals produces substantial deficits in fear responses, it is possible to overcome these deficits with extensive fear training (Maren et al., 1996; Poulos, Ponnusamy, Dong, & Fanselow, 2010; Zimmerman & Maren, 2011). We have previously shown that other subcortical brain regions are able compensate for amygdala damage (Poulos et al., 2010). Perhaps there are other components of a central fear generator that work in concert with the amygdala to produce fear responses, whose contributions are only revealed under the utmost of circumstances. Nevertheless, the predominance of data suggests that the amygdala is a major contributor to what appears to be a central fear generator.

It is also important to recognize that responses to danger are heterogeneous because threat itself is heterogeneous. Defensive behavior is organized around separable stages corresponding to the immediacy and/or proximity of the threat (Fanselow & Lester, 1988) and these stages correspond to the clinical states of anxiety versus fear versus panic (Perusini & Fanselow, 2015). This distinction is also represented in the NIMH RDoC separation of acute and potential threat and its relationship to fear and anxiety. These stages contain very different responses and importantly differing neuroanatomy (Fanselow, 1994). Only the intermediate stage (fear) is strongly tied to the amygdala. On the other hand, very high imminence threats are thought to depend more on the periaqueductal gray. Therefore, it is not that surprising that a patient with a damaged amygdala, but intact periaqueductal gray, shows normal panic reactions to CO_2 inhalation (Feinstein et al., 2013). LeDoux and colleagues' arguments are really directed at a simplistic straw man view that fear/defense is a singular entity solely supported by a single brain structure, the amygdala, and does not consider the richness of defensive behavior and the full neuroanatomy that supports it.

Argument # 2: "It has long been known that subjective experiences of fear and anxiety do not correlate well with measures of behavioral and physiological responses"

If a central fear generator exists, one would also assume that the autonomic, behavioral and cognitive-emotional responses to threat would be correlated with one another (i.e. when one is activated the others are activated, and to a similar degree). In an effort to support the two-system framework, LeDoux and colleagues point to cases where these responses to threat appear to be dissociable, and therefore at odds with the former assumption. In both blind-sight patients and when threat cues are subliminally presented to healthy individuals, there are reports of behavioral/autonomic responses to threat without cognitive-emotional responses (Bertini, Cecere, & Làdavas, 2013; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Lapate et al., 2016; Lissek et al., 2008; Luo et al., 2010; Mineka & Ohman, 2002; Morris, DeGelder, Weiskrantz, & Dolan, 2001; Tamietto & de Gelder, 2010; Vuilleumier & Pourtois, 2007; Vuilleumier, Armony, Driver, & Dolan, 2001; Whalen et al., 2004). However, a single-system model can actually easily account for such discrepancies. Autonomic, behavioral and cognitive-emotional responses to threat increase in proportion to the level of threat in the environment (Baldi, Lorenzini, & Bucherelli, 2004; Bevins, McPhee, Rauhut, & Ayres, 1997; Bitterman & Holtzman, 1952; Fanselow & Bolles, 1979; Fanselow & Kim, 1992; Hermans, Craske, Mineka, & Lovibond, 2006; Wiltgen, Sanders, Behne, & Fanselow, 2001). Nonetheless, these responses are likely to emerge at different time points, as the strength with which the central fear generator targets the downstream effectors giving rise to these responses is not

necessarily equal. The idea that physiological responses to stimuli emerge before conscious awareness of those stimuli is longstanding (Kouider & Dehaene, 2007; Morris, Ohman, & Dolan, 1998). Therefore, it is not biologically implausible that cognitive-emotional responses require greater input from the central fear generator to elicit a response than do autonomic/behavioral responses. Furthermore, if the cognitive-emotional and autonomic/behavioral responses are truly dissociable, both should be possible without the occurrence of the other. However, we know of no data to suggest that subjectve fear responses can occur without a concomitant autonomic/behavioral response.

Moreover, there are several reasons to believe that autonomic, behavioral and subjective fear responses are actually correlated quite well. First, it is generally accepted that autonomic, behavioral, and cognitive responses to danger all increase in proportion to the level of threat experienced (Baldi et al., 2004; Bevins et al., 1997; Bitterman & Holtzman, 1952; Fanselow & Bolles, 1979; Fanselow & Kim, 1992; Hermans et al., 2006; Wiltgen et al., 2001). Second, there is evidence that the different responses to threat are concordant within individuals, such that an individual endorsing high subjective fear is likely to also experience high autonomic/behavioral indices of fear (Hermans et al., 2006; Ollendick, Allen, Benoit, & Cowart, 2011; Thyer, Papsdorf, Davis, & Vallecorsa, 1984). While these correlations are admittedly not perfect, it must be considered that measurement error is likely to impact these correlations to some degree. Third, galvanic skin responses and heart rate changes covary with subjective responses to threat across the acquisition, extinction, and spontaneous recovery of learned fear responses (Lovibond, Davis, & O'Flaherty, 2000; Rodriguez, Craske, Mineka, & Hladek, 1999). Fourth, nearly all anxiety disorders are characterized by both exaggerated behavioral and subjective responses to threat (American Psychiatric Association, 2013), demonstrating that these phenotypes coalesce across the range of health and disease. Lastly, drug-induced reductions in autonomic and behavioral reactions to threat in animals have been used extensively to predict reductions in human fear (Bowers & Ressler, 2015). All of these findings suggest that autonomic/behavioral and cognitive-emotional reactions to threat are predictive of one another, and thus support the existence of a central fear generator.

4. A central fear generator with independent effectors

Above, we have outlined the evidence that the varied responses to threat are likely to arise from the activity of a central fear generator (see Fig. 1). This is not to suggest that the central fear generator is the end all and be all. This would be analogous to suggesting that movement begins and ends in the motor cortex and all disorders effecting movement must involve the motor cortex. Despite emanating from a central generator, components of the fear response are undoubtedly born of distinct effectors, capable of being independently modulated. For instance, lesions of the hypothalamus can disrupt autonomic responses to threat without impairing freezing responses, whereas lesions of the periaqueductal gray can produce a converse effect (Helmstetter & Tershner, 1994; LeDoux, Iwata, Cicchetti, & Reis, 1988). In light of this, biological variance within these effectors could potentially contribute to mental health in meaningful and predictable ways. If a particular disorder shows more marked autonomic responses, then sources of variation giving rise to these symptoms and their corresponding effectors should be targeted. One merit of the two-systems framework is that it tries to shift focus beyond the amygdala.

In addition, because components of the fear response are capable of being independently modulated, we must take caution in using any one measure to predict fear. Although these responses are generally well correlated, many things other than threat cause sympathetic activation, or inactivity (in the case of freezing), for that matter. When off target effects are possible, it is important to consider utilizing multiple responses to more reliably assess fear.

5. A logical inconsistency within the two-system framework

The two-system framework formally states that fear as a subjective experience arises from the neural circuitry that gives rise to working memory and conscious recollection, and more specifically, to episodic memory (LeDoux & Brown, 2017; LeDoux, 2017). As an example of an episodic memory, I can recall the what, where and when of yesterday's breakfast. This includes my memory for the flavors I experienced. I can use this memory to flexibly guide today's choices—yesterday I had bacon, better stick to oatmeal today. The neural circuits that support such episodic memories are also the neural systems that allow animals to take alternate paths when the one normally used is blocked. And in the two-systems framework, they support the subjective emotion of fear. The question then becomes what is unique about fear that differentiates it from other cognitions? The answer to this question is immediately apparent if one looks at LeDoux and colleagues' schematics [Figure 1b (LeDoux & Pine, 2016), Figure 2a (LeDoux, 2017) and Figure 5 (LeDoux & Brown, 2017)]: it is the input from the subcortical defensive system, and in the case of LeDoux and Brown, feedback from the behavioral responses generated by the subcortical defensive circuits. In other words, the unique qualities of subjective fear in the two-system framework reduce to the more parsimonious single generator model, where conscious fear reflects one component of an integrated response. Indeed, the additional machinery needed to generate subjective report probably adds additional noise, rendering it, as many previous to us have suggested, a less pure and objective measure of fear.

Flexibility of the cognitive systems that support fear is another feature of LeDoux and colleagues' model that has important clinical ramifications. Flexible cognition and memory lead to situationally adaptive changes in behavior, like navigating an alternate route. One reason that anxiety disorders are problematic however is that responses to fear are relatively inflexible. You cannot cure PTSD simply by telling the patient that their fear is now irrational and inappropriate because they are in a safe environment. This inflexibility of fear-related behavior is exactly what led Bolles to identify fear as the activation of defensive circuits (Bolles, 1970). While rats readily press a lever for all sorts of things the frightened rat finds it nearly impossible. Bolles' ideas pushed the study of fear away from an earlier two-factor theory where animals were thought capable of flexibly associating any response with fear reduction toward the idea that fear limits the behavioral repertoire to a restricted set of defensive responses. It is this recognition that allowed the amazing advances we now enjoy in understanding the mechanisms behind fear.

6. What then, is fear?

We have argued that there is a central fear generator that gives rise to the autonomic, behavioral, and cognitive-emotional responses to threat. One implication of such a view is that fear must be considered a multidimensional response to danger. Activation of the sympathetic nervous system alone is not fear, for many things cause sympathetic activation other than threat. Neither is the cognitive appraisal of danger in the environment, as this does not necessarily entail subjective distress or physiological changes. It is the coordinated activation of these responses that we should call fear. This view fits best with fear being an asset bestowed upon us by evolution, rather than being a uniquely human phenomenon as the two-system framework might suggest.

Moreover, because of the degree to which autonomic, behavioral, and cognitive-emotional responses covary in response to threat, it is viable to make assumptions about an organism's level of fear when assessing how these measures individually change in response to danger. It is important to emphasize that the relationship between these parameters and fear will be strongest when examining how they change in response to a threatening stimulus, as only under these circumstances can one be certain that the magnitude of the response will provide an estimate of fear (because by definition one can say that this is a

defensive response). To give an example, baseline levels of respiration will less accurately index fear than assessing the extent to which respiration changes in response to a threatening stimulus.

7. Implications for treatment

LeDoux and colleagues argue that the translation from the preclinical lab to the clinic has had limited success because, in the clinic, evaluation is based on subjective reports of fear and anxiety, while preclinical work has focused on behavioral measures that are irrelevant to subjective report. It is interesting then, that the one clinical approach they are optimistic for (D-cycloserine) was entirely based on behavioral research in rats (Walker, Ressler, Lu, & Davis, 2002). LeDoux and colleagues point out that clinical trials with D-cycloserine (DCS) have met with, at best, mixed success. However, anything more than a superficial look at the preclinical data immediately suggests that such mixed results should have been anticipated. The rationale behind DCS is that it facilitates activity at NMDA receptors, which were strongly implicated as necessary for fear extinction in rats (Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007; Falls, Miserendino, & Davis, 1992; Santini, Muller, & Quirk, 2001; Zimmerman & Maren, 2010). However, the choice of DCS was based on the fact that it was approved for use in humans for other conditions; not because it was particularly efficacious at the NMDA receptor (for several reasons DCS is not a particularly potent modulator of NMDA receptor function). Additionally, as a cognitive enhancer, DCS would be expected to enhance the rate of extinction, the result found by Davis and colleagues in rats (Davis, Walker, & Myers, 2003; Walker et al., 2002). However, the pioneering and programmatic rodent research of Mark Bouton indicates the problem with the effectiveness of extinction is not the rate at which it is learned but rather the fact that following extinction many conditions lead to recovery of the original fear memory (Bouton & Bolles, 1979; Bouton, 1993, 2004). In fact, Bouton showed that in rats when DCS enhances the rate of extinction, fear recovery remains an issue (Woods & Bouton, 2006). Additionally, and therefore not surprisingly, several animal studies indicated that DCS had at best mixed results in the lab—exactly what was found in clinical trials (Bowers & Ressler, 2015). The preclinical behavioral results clearly predict the clinical outcome when that literature is carefully considered.

8. Closing remarks

The two-process view would have us focus on subjective reports of fear and anxiety and abandon behavioral measures in both human and nonhuman animals. Even Freud, as long ago as 1885 recognized that patients' subjective reports of their psychiatric conditions were often misleading and inaccurate (Freud & Breuer, 1885). He also held the hope that in the future, psychiatric conditions would be best approached via mechanistic biology. Perhaps the greatest leap forward in the treatment of anxiety disorders was Wolpe's extinction/exposure oriented approach (Wolpe, 1958), which provided the basis for modern cognitive/behavioral therapy. It is worth remembering that Wolpe based his treatment regimen entirely on Ivan Pavlov's and Clark Hull's behavioral observations of dogs and rats, a testament to the clinical utility of bio-behavioral metrics in the treatment of fear (Hull, 1943; Pavlov, 1927). We fully appreciate that translation of laboratory neuroscience to the clinic has been, and will continue to be, a long hard road. However, adoption of LeDoux and colleagues' two-system model would push us back well over a century to what was truly the dark ages of psychiatry.

Conflict of interest statement

The authors declare no competing financial interests.

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