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Threat-related disorders as persistent motivational states of defense

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Abstract

Defensive motivation, broadly defined as the orchestrated optimization of defensive functions, encapsulates core components of threat-related psychopathology. The exact relationship between defensive functions and stress-induced symptoms, however, is not entirely clear. Here we review how some of the most important behavioral and neurological findings related to threat-related disorders -- lowering response threshold to threats, facilitated learning and generalization to new threatening cues, reduced appetitive sensitivity, and resistance to extinction of the defensive state -- map onto defensive motivational states, highlighting evidence that supports conjecturing threat-related disorders as persistent motivational states. We propose a mechanism for the perpetuation of the motivational state, progressively converting temporary defensive functions into persistent defensive states associated with distress and impairment.

The concept of Defensive Motivational State (DMS)[1,2]** refers to the orchestrated mobilization of organisms' resources to optimize defense in threatening occasions, changing how the organism will be affected by subsequent stimuli. Several potential defensive functions may have been hastily assumed to be "abnormal" given their occurrence in psychiatric disorders, and, thus, their natural and adaptive function in defense may have been overlooked. Here, we explore the defensive function of five sets of findings -- increased sensitivity to threats, facilitated threat conditioning, decreased appetitive sensitivity, increased resistance to extinction of defensive responses, and facilitated threat generalization -- and propose that they can be seen as interactive components of a unified defensive process. We first propose an extension of the DMS concept, incorporating these five components (Table 1), in light of the strong body of evidence for their occurrence in both laboratory-induced threat and real-life psychopathology. We then conjecture a mechanism through which normal time-limited DMS may perpetuate into intense and prolonged psychopathological conditions, necessitating interactions between these five defensive processes (Fig. 1).

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An extended concept of defensive motivational state

Increased threat sensitivity has been recognized as an important part of DMS and related psychopathologies [1,3,4]*. “Threats activate defensive survival circuits, and this lowers the threshold for the expression of each of the defensive responses” [1], biasing behavioral and cognitive processes towards defense. Evidence suggests that cumulative experiences with threats progressively lower this threshold and, of particular importance, early experiences with severe stress may cause long term sensitization in preparation to a potentially dangerous life ahead [5]**. From this perspective, the hyper-functional brain structures involved in defensive responses, such as the amygdala (Fig. 2), observed across anxiety and stress-related disorders, as well as in child maltreatment [6] and in hyper-sensitized states [4], could be seen as part of the constitution of an organism prepared to a hazardous world.

In addition to the non-associative learning process described above [4], *facilitated associative threat learning* can also be seen as a component of DMS as it may facilitate threat anticipation by rapidly responding to stimuli previously paired with threat without requiring many such pairings. Stress [7]*, especially inescapable [8]*, facilitates threat conditioning; and despite some dispute [9], this phenomenon appears to be observed also in threat-related disorders [9].

Whereas the processes above enhance defense, they also drive the organism’s resources away from other survival needs. To facilitate concentration of resources in defense, *reduced appetitive sensitivity* observed under stress [10]** has been proposed to be a component of DMS [1,5]. In an elegant demonstration, conditioned threats reduced responding to positive reinforcement, even when freezing was eliminated by dorsal periaqueductal gray lesion [11]. In the brain, stress was shown to cause physiological and structural changes related to decreased appetitive sensitivity and decreased positive affect (Fig. 2), characteristics also seen in some psychiatric disorders involving symptoms such as anhedonia and decreased motivation [5,10]. Nevertheless, responding to appetitive stimuli is in itself a survival need. The tradeoff between responding defensively and responding to other needs depends on variables such as the level of deprivation for specific appetitive stimuli (such as food and water), and threat risk.

It makes sense that, the greater the risk of threats, the stronger the resistance to abandon the defensive state. In this sense, increased *resistance to extinction of defensive responses* as well as facilitated recovery of threat memory can themselves act as components of DMS. Accordingly, extinction of defensive responses appears to be weakened by stress [7,12], especially unpredictable [8,13]. Upon reexposure, stress also facilitates the recovery of extinguished threat memory [7]. Similarly, childhood stress slows down extinction and facilitates recovery of defensive responses [12]. Despite some dispute regarding the phase of extinction and disorders affected, a general tendency towards enhanced resistance to extinction is seen in threat-related disorders [14], particularly in a complex interaction between early trauma, genetic predisposition and presence of diagnosis [15]. On the other hand, threat extinction was shown to be facilitated by food deprivation [16], which may represent a shift in the other direction, i.e., from defensive to appetitive motivation as food deprivation increases. According to this perspective, hypoactive Prefrontal Cortex (PFC; Fig.

2), whose activation is required for extinction retrieval [17,18], can be seen as a process that adaptively maintains the defensive state, rather than simply a toxic effect of stress.

The same logic can be applied to *facilitated generalization to new threatening cues* and related decreases in hippocampal function, since this may ensure responses to a wider range of variations of the original stimuli associated with threat. Indeed, stress enhances threat generalization of stimuli conditioned 24 hours earlier (but not on the same day) [19], and generalization is typically wider for aversive compared to appetitive or neutral stimuli [20]. Also, children exposed to severe stress [21] and people with anxiety disorders [9] show poor threat-safety discrimination, which might underlie threat generalization and its facilitation in anxiety disorders [22]. Decreased hippocampal discriminative function (Fig. 2) seen in people exposed to early stress [5,23] and in psychiatric disorders [5] may thus related to an organismic state less reliant on safety stimuli .

The transition to persistent motivational states of defense

There is a general acknowledgement that DMS relates to psychopathologies and, as mentioned above, there is in fact a remarkable coincidence between clinical phenomenon and data produced by basic and translational research. Understanding the transition from temporary defensive phenomena to persistent and impairing psychiatric conditions, however, is challenging. In the following section we propose a mechanism by which synergy between the five DMS components promotes perpetuation, leading to functional impairment and major psychological distress.

As noted above, increased sensitivity to threat is a major and probably the core component of psychopathologies such as post-traumatic stress and other anxiety disorders [1,3,4]. DMS activation threshold is lowered and more easily retriggered [4]. This process alone may explain some specific cases in which multiple intense stressors take place in a short period of time up to the point where the threshold is so low that quotidian smaller stressors can retrigger the state and perpetuate it (Fig. 1a).

However, it is only when a large part of the individual's world becomes aversive through facilitated generalization and conditionability that many previously neutral stimuli will keep on retriggering DMS (Fig. 1b), explaining both the occurrence of symptoms in apparently safe contexts and why the state is retriggered persistently even after a long time in a stress-controlled environment. The enhanced availability of threatening cues also adds extra intermittence to the reinforcement schedule and, thus, momentum to the mechanism [24].

Similarly, resistance to extinction, also proposed in isolation as an explanation for more persistent states [25], is unlikely to explain the phenomena alone in real life. Studies demonstrating slower extinction or failure to recall extinction memory under various conditions typically do so in the order of few learning trials. That is, the levels of responding would equalize by adding a few extra stimulus presentations or extinction sessions [7,8,12-18]. This model alone, although informative for elucidating learning mechanisms and their underlying neural substrates, can hardly account for months or even years of symptoms seen in clinical cases. According to our synergistic model, however, the longer

the threshold is lowered, the longer the opportunity for the encounter with a threat that is strong enough to retrigger DMS (Fig. 1b). Resistance to extinction can therefore lead to perpetuation if combined with other DMS components, particularly during the initial phases when the organism is not yet too sensitized.

Lastly, appetitive hyposensitivity contributes to DMS perpetuation by disengaging the organism from foraging activities. Deprivation of appetitive stimuli [26], mainly social [27], is highly stressful in itself and, in fact, frequently used to induce DMS in the laboratory. Appetitive hyposensitivity also reduces exposure to conditioned threats and, thus, hinders opportunities for extinction and discriminative training. Decreased appetitive sensitivity therefore appears to interact with the other DSM components to further perpetuates the process.

All in all, we argue that each component of the DMS alone could only explain a narrow range of real-life behaviors under very specific situations (Fig. 1a). Each component alone could not account for the lingering intensity observed in psychopathology and may be too atypical to account for the relatively high prevalence of threat-related disorders observed in the population. We propose that an interactive model can explain DMS perpetuation: reduced threat sensitivity retriggers DMS more easily and enhances response intensity; resistance to extinction maintains the enhanced response magnitude for longer periods; stimuli availability becomes more frequent through enhanced conditionability and generalization, providing more opportunities for retriggering; and the additional stress of appetitive deprivation further minimizes opportunities for extinction, avoidance and reward, prolonging DMS (Table 1; Fig. 1b).

Once achieved, this lingering DMS, which is so sensitized, persistent, and generalized, is unlikely to be interrupted spontaneously under normal circumstances. We conjecture that this is the point in which a disorder sets in and artificial interventions may be necessary to break the cycle. There is evidence to suggest that different treatments act on different DMS components to interrupt this cycle. Serotonergic antidepressants, for instance, appear to decrease sensitivity to threats [28], threat conditionability [29], and, despite data to the contrary [30], facilitate threat extinction [31]. Indirect evidence point to a modulatory role of the serotonergic system in threat generalization as well [32].

Appetitive hyposensitivity in acute threatening situations [11] may be consistent with the brief occurrence of these symptoms in exacerbations of anxiety disorders, but the pattern becomes chronic and stimulus-independent after persistent exposure to inescapable threats [10], a condition closer to what is seen in depression. Increased threat sensitivity seems to be a shared characteristic of depression and anxiety disorders, while decreased appetitive sensitivity and mesolimbic hypo-reactivity to appetitive stimuli appear to be more specifically related to depression [10,33]. In addition, depression is a common progression of anxiety disorders [34], further suggesting a progressive involvement of the mesolimbic system in DMS. In these cases, serotonergic antidepressants seem to work indirectly [35] and direct intervention over the appetitive system with a dopaminergic drug [36] or behavioral activation therapy [37] should be considered.

As reactivity to threats grows stronger, the transition to a more persistent state may progress to altered resting state activity and, eventually, structural changes, as seen, for instance, in hippocampus [38] and amygdala [39], solidifying a more persistent defensive way of interacting with the world. While antidepressants may reverse some of these structural changes [40], combined forms of behavioral and somatic interventions, operating on the separate DSM components in parallel may be required, considering the interactive engagement of DSM components. For instance, some people with early onset threat-related disorders may have developed important parts of their behavioral repertoire under DMS and, thus, incur high defensive and low appetitive motivation. Eventual treatments for that condition, usually in adulthood and with a serotonergic drug, will decrease anxiety, but also defensive motivation back to normal, which the patient sometimes perceive as insufficient. Complementary motivation based on appetitive components of life, such as personal growth and acknowledgement at work, are typically lacking in these patients, who may need behavioral interventions in this direction.

Conclusions

Cumulative effects of one's ontogeny [5], genetic [41]* and epigenetic [42]* dispositions, determined by the history of adaptation to a threatening world, may lead to a point in which perpetual DMS may have paid off from an evolutionary perspective. For example, a recent study showed that generalized anxiety disorder was associated with faster arrival to the emergency room and less complications after a heart attack [43]*. Thus, despite the burden involved, the potential of getting into permanent DMS may have been selected in "wilder" environments. In our current reality, though, this may not pay off, given our much longer life expectancy and technological resources.

The model proposed here is based on an inductive reasoning. Pursuing its validation with experiments specifically designed to test derived hypotheses is a necessary step. For instance, computational simulations could clarify the extent to which multiple (versus a single) DMS components contributes to the state's perpetuation. Furthermore, the processes and related structures discussed here are a first step towards the development of an integrative approach. The participation of additional processes and structures, such as the bed nucleus of the stria terminalis in sustained threats [2,3], should be incorporated to the model in order to increase its predictive power.

Exploring new components is also necessary for this agenda. Exposure to threatening contingencies can affect many different processes and, sometimes, in different or even opposite directions for unknown reasons. Both sensitization [44] and habituation [45], for instance, can result from repeated exposure to stress, but what determines the outcome direction is not completely understood [44]. Similarly, stress can increase appetitive sensitivity [46,47], as opposed to the appetitive hyposensitivity described above. Furthermore, manic states, known to involve appetitive hypersensitivity and threat hyposensitivity [48], are frequently influenced by stressful life events [49], and both depression and bipolar disorder are related to childhood stress [50]. Overall, an integrated approach of biobehavioral characteristics of related disorders, such as the one proposed here,

may improve our mechanistic understanding of the often complex and multifaceted psychopathology.

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*Special interest

**Outstanding interest

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HIGHLIGHTS

- Components of a defensive motivational state (DMS), such as enhanced threat sensitivity, are presumed to participate in threat-related psychiatric disorders.
- A major difference between common DMS and related disorders is the lingering intensity observed in the latter.
- Each DMS component alone could only explain a narrow range of real-life behaviors under very specific situations
- We propose a mechanism by which synergy between five DMS components promotes perpetuation, leading to major psychological distress

Figure 1. Schematic representation of the DMS perpetuation process.

Top panel: each DMS component acting alone would require very strong and frequent aversive conditioned and unconditioned stimuli to cause DMSs to overlap and perpetuate, and as such, cannot explain lingering and intense states of psychopathology. Bottom panel: a synergistic model can explain DMS perpetuation – defensive responses are progressively stronger and more easily triggered through sensitization; resistance to extinction maintains the enhanced response magnitude for longer periods and enhances the chances for retriggering while in a high DMS; triggering cues availability becomes more frequent through enhanced conditionability and generalization; and the additional stress of appetitive deprivation produces more aversive stimuli and further minimizes opportunities for

extinction, avoidance and reward. The synergy between DMSs components thus results in DMS perpetuation, as seen in pathological states. avUS, aversive unconditioned stimulus; avCS, aversive conditioned stimulus; DMS, defensive motivational state

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Figure 2. Schematic representation of the main structures involved in DMS and its perpetuation. Each change in the region's neural response (indicated by the arrows) would be a piece of an orchestrated organismic adaptation to a dangerous world.

Table 1.

Synthesis of the components of defensive motivational states, their adaptive function, and contribution to the synergistic process of perpetuation

DMS Component	Adaptive function	Perpetuation contribution
Increased threat sensitivity	Early detection of threats and stronger defensive responses	Lower threshold to trigger DMS making it more likely to be retriggered
Facilitated threat conditioning	Even earlier defense measures by contact with stimuli that usually precede the threat	Progressively more stimuli are capable of retriggering DMS through first or higher order Pavlovian conditioning
Weaker threat extinction	More conservative strategy to leave DMS may be favorable in risky environments	Longer periods of lowered threshold to have DMS retriggered
Facilitated threat generalization	Defense against a broader range of unknown stimuli and contexts (better safe than sorry strategy)	Broader range of contexts keep DMS threshold lower and increase the number of stimuli capable of retriggering DMS
Decreased appetitive sensitivity	Concentrate biobehavioral resources on defense	Lower foraging activity leading to extra stress (deprivation) and lower exposure to new learning about extinction and stimulus avoidance or controllability

DMS, defensive motivational state