Threat, its impacts over survival systems, and related behavioral disorders

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Abstract: Defensive and appetitive motivation systems have evolved to propitiate more sophisticated interactions with environment threats and needs, such as nutrients, water, reproduction, and temperature regulation. In contact with survival-relevant environmental stimuli, organisms change as a whole to maximize fitness to that occasion. In this paper, an overview on defensive systems is described, as well as some relevant aspects of defensive states, including their impacts over appetitive functions. A parallel between these characteristics and what is called threat-related disorders in the present paper is drawn and, finally, these similarities are used as basis for a theoretical proposition that at least part of these disorders can be seen as persistent states of defense.

Keywords: Survival/psychology; Mental disorders/psychology.

INTRODUCTION

Basic survival functions, such as defense, energy and water maintenance, reproduction, and temperature regulation, as well as the brain circuits involved in these functions, have been strongly implicated in the behavioral problems approached by psychiatry1-3. Despite having a long history in scientific psychology and neuroscience, approaching psychiatric disorders in these terms is a considerably new enterprise4. In the present paper, some important organismic changes observed in response to threats, as well as their relationships with psychiatric conditions will be discussed. As the organism react as a whole to these survival contingencies, rather than having compartmentalized responses and systems that operate independently for each of these functions, the impact of threatening contingencies over the other basic survival functions will also be discussed in the present paper in order to draw a more adequate picture of the actual phenomena. To that end, survival functions and related systems will be organized into two main groups, namely the defensive function, the main object of the paper, and the appetitive functions, which encompasses consummatory behavior, usually requiring approach and reward or positive reinforcement, such as food, water, and sex. It can be assumed that they form the basis for the negative and positive valence systems, respectively, of the Research Domain Criteria (RDoC) initiative, organized by the United States National Institute of Mental Health (NIMH), the most important initiative for the reorganization of psychiatric classification4.
Defensive systems

The organismic changes described above to optimize performance in the interaction with survival contingencies in general has been called global organismic states\(^1,3\), to emphasize the systemic and temporary nature of the process. The term Defensive Motivational States (DMSs) has been used by some authors to describe the organismic changes observed in threatened organisms\(^1-3\). In this section of the paper, we briefly describe how it works and draw a parallel with biobehavioral characteristics of related psychiatric disorders. This similarity, between DMSs and related disorders, is the basis for the theoretical proposal of threat-related disorders as persistent DMSs described at the end of this paper. Among the many defensive processes known to date, the present paper will focus on those with the most illustrative characteristics to describe their relationships with related psychiatric disorders.

A core feature of DMSs is an increased sensitivity to subsequent threats\(^5\), which is supposed to facilitate early and strong defensive responses. This process is thought to happen in response to both unconditioned threatening stimuli (Unconditioned Stimulus; US), such as a natural predator or painful stimuli, and to learned threats (Conditioned Stimulus; CS). One can learn about threats in the world by many means, but one of the most basic and essential ways is a process known as Pavlovian conditioning, in homage to the Russian physiologist Ivan Pavlov who first described the phenomenon\(^6\). The process, frequently used as a model of threat learning, occur through paired presentations of a neutral stimulus with the threatening US such that the organism learns that this stimulus predicts the US, so they learn to respond defensively to the (now) CS\(^7\).

This process involves neuroplasticity in many brain regions, but the amygdala has been the most extensively studied. Information regarding the CS and the US converge in the amygdala at the basolateral nucleus, where plasticity appears to occur\(^1\). More recently, synaptic plasticity was shown to occur in specific central amygdala circuits as well\(^8\), an area that receives outputs from the basolateral amygdala and connects with the brain stem, bringing about physiological changes. Outputs from the basolateral amygdala to the central nucleus and, from there, to the periaqueductal grey matter (PAG), in the brain stem, has been related to more species-specific and reflexive defensive reactions, such as freezing\(^3\). More recently, it was observed that outputs from the basal nuclei of the amygdala to the shell of the nucleus accumbens (NAcc) are involved in learned and sophisticated defensive responses, usually a form of conditioned active avoidance\(^9\). See Figure 1 for a schematic representation.

![Figure 1: CS – conditioned stimulus; US – unconditioned stimulus; LA – lateral amygdala; BA – basal amygdala, vmPFC – ventral medial pre-frontal cortex; ITC – intercalated cells; CEL – lateral nucleus of central amygdala; CEM – medial nucleus of central amygdala; PVN – paraventricular nucleus (hypothalamus); LH- lateral hypothalamus. During threat conditioning, the CS and the US converge in the amygdala. After several pairings, the CS alone will evoke an answer. Reaction like freezing are set through connections with the periaqueductual gray matter (PAG), whereas learned active avoidances depend on the connections of the Basal and Lateral nuclei of the amygdala with de Nucleus Accumbens (NAcc) Shell. On the other hand, different areas of the brain have regulatory function over the amygdala and other subcortical regions involved in the expression of defense. Each specific area and its participation in the final defensive outcome vary depending on many variables such as the specific function and imminence of the threat. When threat imminence is low, more sophisticated defenses that prevent the reduction of the imminence are predominant\(^10,11\). Cortical structures, especially the ventromedial portion of the prefrontal cortex (vmPFC), inhibit subcortical structures, like the amygdala\(^12\), which would be related to more reflexive defenses, as freezing and flight, allowing

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the occurrence of learned defenses through the involvement of the NAcc. Therefore, in these situations, the cortical regulatory structures will be strongly activated, whereas the subcortical structures involved in the expression of defensive reactions will have their activation inhibited. As the threat becomes more imminent, such an inhibition loosens up, allowing subcortical structures to activate and more reflexive and species-specific responses to occur.

Very similar top-down regulation of the amygdala by cortical structures such as the vmPFC occur in other regulatory processes, such as the extinction of defensive responses. Extinction of defensive responses occurs when unpaired presentations of the CS occur repeatedly such that the organism learns that the CS no longer predicts the US in that context and occasion. During the initial phases of extinction, sometimes referred to as extinction training, changes similar to long term potentiation, a strengthening of the synapsis connections, appear in those pathways.

Then, projections to the amygdala activate glutamatergic intercalated cells, which, in its turn, inhibits de central amygdala, competing with the activation of the basolateral nucleus. Even after extinction is learned, if some time passes without contact with the CS, new presentations of this stimulus may elicit defensive responses again. This phenomenon is known as spontaneous recovery and its occurrence is regulated by the vmPFC, which inhibit amygdala activity through connections between these two structures.

Figure 2. After threat conditioning, extinction training starts with the unpaired presentation of the CS. Extinction retrieval is necessary when the CS reappears after a period of absence (spontaneous recovery) or in a presentation in a different context (renewal). In some disorders, failure to retrieve extinction is a core characteristic of the condition, probably related to hypo-functional vmPFC and hippocampus. Figure adapted from.

The hippocampus takes part in this balance between responding defensively or not to a CS as a function of the context. When an organism learns threat extinction in a specific context, it tends to respond to the CS again if it is presented in a different context. This recovery of previously extinguished responses is known as renewal. Both spontaneous recovery and renewal are processes supposed to have a “better safe than sorry” strategy as nothing is known about the US predictive property of the CS in contexts and occasions that are not those when and where extinction took place. Whereas the vmPFC is known to modulate the amygdala activity in both situations, the hippocampus was shown to regulate the balance between these two structures as a function of the context. Similarly, through generalization and discrimination of the CS and other stimuli that were present in the context where threat conditioning took place, the hippocampus work by weighting the best tradeoff between responding defensively or not to a broader range of variation of the original stimuli, a process known as generalization.

Finally, the bed nucleus of stria terminalis (BNST) is thought to play a role in an unpredictability context, sustaining our defense response in a threat persistence. Studies with functional magnetic resonance found a signal of BNST with increased activation across conditions as a function of anxiety, growing with the unpredictability of the stimuli.
Defense system in psychiatric disorders

Fundamentally, all the structures and systems described above have their idiosyncrasies in psychiatric disorders related to threats and defense*. An increased sensitivity to threats observed in these cases is probably behind the marked rise in threat vigilance and cognitive bias toward threats observed in disorders such as anxiety, depression, and trauma-related disorders, as well as the corresponding biological characteristic, chiefly the hyper-(re)activity of the amygdala also observed in these disorders.

Moreover, patients with Post-traumatic Stress Disorder (PTSD) also show hypo-(re)activity of the vmPFC. As mentioned above, the vmPFC participates in the inhibition structures involved in the expression of defense, like the amygdala, in many processes in which these responses should be regulated, as in the case of extinction. Therefore, in conditions in which this mechanism is hypo-(re)active, such as in PTSD, depressive responses, which are already hyperintense, will also be poorly regulated.

Finally, subjects with these disorders have abnormal hippocampal function, poor threat contextualization, and facilitated threat generalization and, therefore, are always responding defensively to CSs that are only really threatening in specific contexts and to stimuli that only weakly resemble the original CS.

The appetitive system under threat

As mentioned above, when an organism faces a survival-relevant contingency, the organism changes as a whole to maximize performance in that interaction rather than having a biobehavioral system that works independently to that function. Therefore, even though the focus of the present paper is threat and defense, the impact of threats over other the other survival functions, as well as related organismic systems, need to be approached in order to have a better description of the complete phenomenon.

Roughly, appetitive motivation concerns behavior directed towards goals which are usually associated with rewards, such as food, water, and sex. These stimuli usually involve approach towards them usually work as positive reinforcers, i.e., their obtainment usually reinforces the responses that produced them.

In 1954, James Olds and Peter Milner reported a study in which rats would press a lever to obtain brief stimulations in specific brain regions. Not only this region was shown to have properties that were similar to those observed when different forms of appetitive stimuli were given as a consequence of an operant response, such as food, water, and sex, but it was, actually, even more reinforcing than those traditional and natural reinforcers. Although it is known today that different regions of the brain interact in specific manners to each sort of reinforcer, these findings suggested the existence of a common system that would be operate in, essentially, any positive reinforcement process.

After extensive research in the area, it was observed that the areas initially found to have reinforcing properties if stimulated were actually part of broader system, involving multiple neural elements involved. In general terms, reward and positive reinforcement, in the case of operant behavior, involves activity in the mesocorticolimbic system, which is constituted by dopaminergic projections from the ventral tegmental area (VTA) and their projections to nucleus NAcc, amygdala, PFC, and other forebrain regions. Dopaminergic stimulation of the NAcc by inputs from the VTA, sometimes referred to as the mesolimbic system, is a key occurrence related to reward and reinforcement processes, as well as motivation towards rewards. Interestingly, the participation of the system in the subjective pleasure experienced in these processes has been a matter of debate.

Recent findings have suggested that reward processing is different in some psychiatric conditions. The fact that these particularities strongly resemble those observed in organisms under threat (see below) led some author to propose that at least part of these disorders could also be seen as forms of threat-related disorders. Among the most important findings observed in appetitive-related functions and systems of disorders that are supposedly to be more directly related to threats are the blunted anticipatory experience of pleasure, overly conservative calculation of cost/benefit ratios, and deficits in reinforcement learning observed in depression. Furthermore, neuroimaging studies have been shown that depressed patients have reduced NAcc activity, mostly associated with impaired pleasure, as well as reduced activation of the caudate nuclei and the putamen, mainly associated with reward learning and reward prediction, respectively. Taken together, these findings suggest a general state of hyposensitivity to rewards observed in depression, a characteristic that has been shown by different measurement approaches.

*Most disorders currently categorized as anxiety disorders, obsessive compulsive disorder, threat- and stress-related disorders, and depression are thought to be threat-related disorders, but it is not possible to affirm that all cases that currently fulfill criteria for these disorders have are, indeed, threat-related disorders neither is possible to rule out the involvement of this survival function in other disorders, as threatening experiences are strongly related to virtually all types of psychiatric disorders. Future studies on the reclassification of psychiatric disorders may shed light on this issue.
Effects of threat over the defensive and the appetitive systems

In this paper, we described that a progressive sensitization to threats, facilitation of threat conditioning and generalization, and weaker extinction of defensive responses as some of the characteristic of DMSs. These are, therefore, some of the effects of threats over the defensive system itself.

We have also discussed that threat exposure can also affect other survival systems, such as the appetitive functions, in an orchestrated adaptation that optimizes defense. In general terms, appetitive engagements are suppressed not to compete with defense when this is a priority and many of the organismic resources usually involved in appetitive functions are recruited to work for defense. A good example of this reasoning is the NAcc, usually known to be involved in appetitive-related survival functions that, more recently, was shown to be a crucial part of learned active avoidance as well.

Possibly for these reasons, stress impairs appetitive sensitivity, decreasing behavior based on positive reinforcement and producing an effect very similar to what is observed in depression. It has been shown that, under threat, dopamine activity in the mesolimbic pathway is reduced, decreasing reward-oriented activity, motivation and behavior and motivation, as well as the pleasure experienced in these situations. If that situation persists long enough, though, the deprived appetitive need, such as food, grows in priority and the subject will eventually respond for it. After some water and food consumption, these needs fall below defense as priorities again, and the consummatory behaviors cease. This balance between survival priorities will fluctuate as described for as long as this environmental contingency persists.

Finally, even though it seems to exist a remarkable coincidence of the effects of threat over defensive and appetitive functions and systems and the vicissitudes of these systems in threat-related disorders, it is important to note, whereas the former is temporary, the latter is persistent. A few theoretical approaches to bridge this gap has been arisen (e.g. 2), but this area is still very poorly explored.

CONCLUSION

Current classifications of psychiatric disorders based on clinical consensus has shown to be fragile, with poor outcome prediction and inconsistent etiopathogenic findings. Initiatives like the RDoC aims to develop bottom-up constructs, based solid biobehavioral constructs like those proposed herein. Modern research tolls have been making it possible to improve the knowledge regarding our defense and appetitive systems and how they are altered in many psychological states, including those considered a disorder. These findings propitiate a neurobiological understanding of the heightened sensitivity, conditionability, and generalizability of threats, the weakened defensive regulation, and the reduced appetitive functions observed in these individuals. This view could point related sciences towards the right variables that need to be studied in order to improved prediction and control of these problems in strategies like prevention and treatment, as well as a better clinical management of individual cases in the clinical setting.

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