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International Journal of Psychophysiology 57 (2005) 5 – 14

INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY

www.elsevier.com/locate/ijpsycho

The neuropsychology of fear learning and fear regulation

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Received 19 November 2004; received in revised form 13 January 2005; accepted 21 January 2005
Available online 21 April 2005

Abstract

In the current review article it is suggested that fear is a central emotional state that can be activated by external threat cues. The subcortical defensive system cannot only be activated by intrinsically aversive events but shows also strong plasticity enabling previously innocuous stimuli to get access to the fear system after they were paired with painful outcomes. On the other hand, aversive conditioning does not only result in the acquisition of a defensive disposition, the organism also learns on a pure cognitive level that one stimulus predicts the occurrence of another stimulus. It is suggested here that potentiation of the acoustic startle reflex is a rather specific measure for fear acquisition, while skin conductance discrimination indexes contingency learning. It is shown that the acquisition of fear-potentiated startle does not require cortical processing of the conditioned stimulus. Moreover, data indicate that conditioned startle potentiation is abolished in patients with unilateral lesions of the amygdala. Finally, conditioned startle potentiation can be obtained without contingency awareness, which on the other hand is necessary for skin conductance conditioning to occur. It is suggested that the learning of stimulus relations is mediated by the hippocampus and that conditioned startle potentiation is also mediated by the hippocampus in trace conditioning.

Keywords: Fear conditioning; Startle potentiation; Amygdala; Awareness; Cortical blindness; Temporal lobectomy

1. Fear and fear learning

Fear is an aversive emotional state elicited by external threatening cues that activate the defensive fear system of an organism. This fear system then organizes a behavioral pattern to adjust to the threat. Therefore, fear is important for survival because it prepares the organism for effective escape and motivates avoidance. Escape and avoidance, however, are often at the endpoint of a dynamic defense response cascade as elaborated in the predator imminence model (see Fanselow, 1994; Lang et al., 1997 for a fuller description of this model). According to this model activation of the fear system increases with increasing proximity of the threatening or painful stimulus. As soon as the organism detects the threat, it often freezes and engages in higher vigilance towards the threat ("Where is it?," "Where does it move?"). With increasing proximity of the threat cue, the intensity of the fear response increases as the organism mobilizes energetic resources for escape. At a certain stage of proximity (the so-called circa-strike period) the organism escapes or (if escape is not possible) starts to fight or (if attack is no option) completely immobilizes (tonic immobilization; see Marks, 1987). As soon as the threatening cue disappears, the intensity of the fear response is reduced.

It is suggested here, that this fear system serves biologically useful functions since it enables the organism to effectively detect the threat and to automatically activate defensive behavior in order to adjust to it. Thus, following theoretical considerations by Öhman and Mineka (2001) the premise here is that the fear system has been shaped by evolutionary contingencies and can be characterized by four central features: *selectivity* with regard to input, *automaticity*, *encapsulation*, and a *specialized neural circuitry* (for a more extensive discussion see Öhman and Mineka, 2001). *Selectivity* means, that the fear system can easily be activated by stimuli that have been correlated with threatening encounters in the evolutionary past. Actually, fear of

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doi:10.1016/j.ijpsycho.2005.01.006

small animals (like snakes and spiders) or heights are much more frequent (see Costello, 1982) than fear of tools or motorcycles although the negative experiences with these objects of civilization are much more frequent than those with spiders or snakes. On the other hand, the fear system also shows strong plasticity enabling previously innocuous stimuli that were associated with threatening or painful outcomes to activate the fear system by themselves. Through these learning processes the range of stimuli that can activate the fear system can be expanded. Interestingly and in support of the proposed selectivity of the fear system, the organism is biologically prepared to form and to restore some associations more easily than others (see Garcia and Koelling, 1966; Hamm et al., 1989; Öhman, 1986). Moreover, evolution has shaped the fear system in a way that it can be initiated rather automatically (*automaticity* of fear activation). This means that stimuli can get access to the fear system even by only rapid and preliminary perceptual analyses of the stimulus. It will be demonstrated below, that conditioned fear responses can be conditioned to and later on elicited by stimuli that do not need do be processed in the primary visual cortex. LeDoux named this automatic route of fear activation the "low road" (see LeDoux, 2002). Third, the fear system is characterized by *encapsulation*, which means that once the system is activated it is difficult to influence the fear response by verbal instructions or stimulus awareness. It is indeed one of the defining features of phobias that the patient recognizes her/his fear to be excessive and unreasonable but has also no voluntary control over the intensity of the phobic response. Finally, the fear system is controlled by a *specific neural circuitry*.

In recent years much progress has been made to better understand the neural circuitry involved in the regulation of the fear system. Most of the evidence stems from neuroscience research with animals, but human work has supported these animal models to a great extent in recent years. In the following sections we will first elaborate the neural circuitry of fear and fear learning and will then report some human data that support these animal models.

2. The neural circuitry of fear learning and fear regulation

Accumulating evidence suggests that the *amygdala*, a limbic structure located in the anterior medial temporal lobe, is critically involved in fear regulation, fear learning, and fear memory formation. One line of evidence stems from animal research using fear-conditioning paradigms in which previously innocuous lights or tones are paired with nociceptive events (e.g., electric shock). A large body of evidence has demonstrated that lesions of the amygdala block many measures of conditioned and unconditioned fear, such as freezing, blood pressure elevation, heart rate changes, or fear-potentiated startle (Davis, 2000; Fanselow, 1994; Kapp et al., 1992; LeDoux, 1996). Fear-potentiated startle refers to the phenomenon, that the startle reflex – a cranial-to-caudal spreading wave of flexor movements along the neural axis that is elicited by an abruptly occurring sensory event – is augmented during fear conditioning. This indicates that the amygdala can modulate the output of the primary acoustic startle pathway that consists of three synapses in rodents (Davis, 1998). This modulatory influence of the amygdala is transmitted to the primary reflex pathway via the nucleus reticularis pontis caudalis (for more information see Hamm et al., 2003a). Furthermore, electrical stimulation of the amygdala elicits several fear-typical behaviors in many animals, including humans (Gloor, 1992), and also induces fear-potentiated startle.

Recent evidence suggests that individual subnuclei of the amygdala play different functional roles. The basolateral nucleus serves as the input region that receives information from the thalamus, hippocampus, and cerebral cortex (for a review see McDonald, 1998). Fully processed visual information is conveyed via the inferotemporal cortex primarily to the lateral nucleus of the amygdala (Amaral et al., 1992; Shi and Davis, 2001). The perirhinal cortex seems to be an important structure in relaying this cortical information to the amygdala because lesions of this area block conditioned startle potentiation to visual stimuli (Davis and Lee, 1998). Besides these cortical projections to the amygdala there is also a direct projection from the thalamus to the amygdala. Extensive work from LeDoux and coworkers (see LeDoux, 2002) has demonstrated that fear conditioning can be obtained without any cortical processing of the conditioned stimulus (CS) and that direct projections between the medial geniculate body of the thalamus and the amygdala exist that are probably involved in transmitting the information about the (acoustic) CS to the amygdala (see LeDoux et al., 1990). Recent data by Davis and coworkers have shown that there is also a direct connection between the lateral posterior nucleus of the thalamus and the basolateral complex of the amygdala that conveys visual CS information to the amygdala (Walker and Davis, 2002).

The basolateral nucleus projects to several target areas including the central nucleus of the amygdala that then projects via the stria terminalis and the ventral amygdalofugal pathways to several output regions in the diencephalon and brain stem that mediate the autonomic and somatic signs of fear (see Davis and Lang, 2003). Lesions of the central nucleus of the amygdala block the expression of fear-potentiated startle and blockade of the glutamate receptors in the central nucleus of the amygdala via local infusion of a non-NMDA receptor antagonist have the same effect. Fig. 1 gives a schematic description of the neural circuitry involved in fear learning and fear regulation.

While animal experimentation is necessary to understand the neural underpinnings of fear regulation and fear