

Extending animal models of fear conditioning to humans

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Accepted 25 April 2005

Available online 10 February 2006

Abstract

A goal of fear and anxiety research is to understand how to treat the potentially devastating effects of anxiety disorders in humans. Much of this research utilizes classical fear conditioning, a simple paradigm that has been extensively investigated in animals, helping outline a brain circuitry thought to be responsible for the acquisition, expression and extinction of fear. The findings from non-human animal research have more recently been substantiated and extended in humans, using neuropsychological and neuroimaging methodologies. Research across species concur that the neural correlates of fear conditioning include involvement of the amygdala during all stages of fear learning, and prefrontal areas during the extinction phase. This manuscript reviews how animal models of fear are translated to human behavior, and how some fears are more easily acquired in humans (i.e., social-cultural). Finally, using the knowledge provided by a rich animal literature, we attempt to extend these findings to human models targeted to helping facilitate extinction or abolishment of fears, a trademark of anxiety disorders, by discussing efficacy in modulating the brain circuitry involved in fear conditioning via pharmacological treatments or emotion regulation cognitive strategies.

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Keywords: Emotion; Learning; Amygdala; Prefrontal cortex; Infralimbic; Prelimbic; Acquisition; Extinction; Anxiety disorders; Emotion regulation

1. Introduction

Fear can be characterized by anxiety and agitation due to the expectation of impending danger. Fears can be acquired and expressed in a variety of ways. For example, one can develop a fear of dogs because of previous experiences (i.e., person was earlier bitten by a dog), verbal instructions (i.e., person is told that a dog bites) or mere observation (i.e., person observes a dog biting someone else). Regardless of how the fear was acquired, the person may express similar responses to the presentation of the dog, such as sweating, changes in heart rate, blood pressure and respiration. Fear can serve as an adaptive alert mechanism for the organism. However, fear can also be a detriment as feelings of anxiety persist and have a negative effect on day to day behavior. Therefore, it is important to also understand how fears are diminished, for example, how one stops expressing conditioned responses to the dog by relearning that the dog does not impose any danger. One focus of studies utilizing fear conditioning paradigms is to understand the neural mechanisms that enable acquisition of fear, and perhaps more importantly,

the mechanisms that lead to the extinction of fear and decreases in anxiety symptoms.

Much of our knowledge regarding fear and emotion comes from an extensive and elegant animal literature, results that are now being tested and applied in humans using neuropsychological and neuroimaging techniques. The following review briefly discusses fear conditioning as a model paradigm, concentrating on key findings regarding the neural circuitry of both acquisition and extinction in non-human animals, and how we can extend such findings to humans.

2. Acquisition and expression of fear learning

One of the simplest experimental tools for studying fear and anxiety is Pavlovian or classical fear conditioning, based on Ivan Pavlov's findings that a neutral stimulus can acquire affective properties due to an association with a biologically relevant stimulus (Pavlov and Anrep, 1927). Although there are other forms of aversive learning involving more complex operant or instrumental paradigms (Everitt et al., 2003; Killcross et al., 1997), for purposes of this review, classical conditioning paradigms will primarily be discussed. As described by Rescorla (1988, p. 158) "Pavlovian conditioning

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refers to the learning of relation among events that are complexly represented". This can be illustrated by a typical fear conditioning paradigm, which generally involves presentation of a neutral stimulus such as a tone. Initially, the tone will have little effect on an animal such as a rat. Conditioning occurs when the tone is associated with an aversive stimulus such as a mild foot shock, the unconditioned stimulus (US), which by itself elicits a fear response such as autonomic (i.e., changes in heart rate) and behavioral (i.e., freezing) responses. Through repeated associations, the rat learns that the tone predicts shock and presentation of the tone by itself, a conditioned stimulus (CS), is able to elicit a fear conditioned response (CR). Although most experimental paradigms of fear conditioning make use of repeated pairings between CS and US to achieve conditioning, it is important to note that the CS–US pairing is not essential or sufficient at times for conditioning to occur. Rather what is emphasized is the information that the CS provides about the occurrence of the US (Rescorla, 1988).

Fear conditioning occurs in different species, and similar neural underpinnings are also shared across species (LeDoux, 1996). One common brain region is the amygdala, an almond-shaped structure in the medial temporal lobe that has been previously implicated in processing emotional information such as fear (Aggleton, 2000; Kluver and Bucy, 1937; Weiskrantz, 1956). A potential fear circuitry in the brain has been elaborated primarily in rats, suggesting that the amygdala and its projections may be involved in both the acquisition and expression of conditioned fear (Davis, 1992; LeDoux, 1996; Rosen, 2004; Sarter and Markowitsch, 1985). In simple terms, sensory information from the cortex and thalamus is received by the amygdala which then projects to hypothalamic and brainstem targets that mediate conditioned responses (Amaral, 1986; McDonald, 1998; McDonald et al., 1996; Price, 2003; Swanson and Petrovich, 1998). The lateral nucleus of the amygdala, part of the basolateral complex, is the site of cortical and thalamic inputs (Amaral, 1986; LeDoux et al., 1990; McDonald et al., 1996) and lesions in this region lead to deficits in the acquisition of contingencies that predict aversive outcomes which are capable of causing fear in conditioning paradigms (Campeau and Davis, 1995; Goosens and Maren, 2001; Tazumi and Okaichi, 2002; Wilensky et al., 1999). Further, neuronal cell firing in the lateral nucleus is modulated by nociceptive stimulation and auditory inputs (Romanski et al., 1993) and firing properties are modified during fear conditioning (Quirk et al., 1997, 1995), suggesting a possible integration of CS and US information, although plasticity has been observed in other amygdala subnuclei as well during aversive conditioning (Pascoe and Kapp, 1985a,b). Thus, research suggests that convergence of CS–US information occurs in the lateral nucleus of the amygdala, relayed from cortical inputs that may regulate the learning and expression of affective behaviors (Rosenkranz et al., 2003).

Information processed in the lateral nucleus is further relayed to a different subnucleus of the amygdala, the central nucleus, an output unit of the amygdala (Price and Amaral, 1981; Smith and Pare, 1994). The central nucleus in turn projects to an array of areas responsible for mediating the

expression of fear and anxiety (Davis, 1992). Projections to the hypothalamus (Price and Amaral, 1981), for example, may be important for mediating autonomic responses such as skin conductance responses, blood pressure elevation and pupil dilation (see Davis, 2000 for review). Similarly, projections to midbrain nuclei such as the central grey (Hopkins and Holstege, 1978) or ventral tegmental area (Simon et al., 1979) may mediate some behavioral responses such as freezing and attention/vigilance, respectively.

Electrical stimulation of the central nucleus of the amygdala can lead to autonomic and behavioral changes associated with the expression of fear. Increases in blood pressure, for instance, are observed by stimulation of the central nucleus of unanesthetized rats (Tellioglu et al., 1997). In addition, such stimulation leads to increased arousal and vigilance as measured by cortical electroencephalographic (EEG) activity in rabbits (Kapp et al., 1994) and rats (Dringenberg and Vanderwolf, 1996). Certain conditioned responses expressed following fear conditioning can also be blocked with lesions of the central nucleus. Changes in the cardiovascular system of rabbits, for example, are no longer observed following specific lesions in the central nucleus of the amygdala (Kapp et al., 1979; McCabe et al., 1992). Decreased freezing is observed in rats that have lesions in the central nucleus pre and post conditioning (Davis, 2000). Lesions of the central nucleus in non-human primates can also lead to reduced expression of fear responses (Kalin et al., 2004). Further, it has been postulated that fear acquisition occurs due to increased activity in the lateral nucleus (in response to CS presentation) which leads to disinhibition of neurons in the central nucleus that then project to brainstem nuclei (Pare et al., 2004). This evidence suggests that the central nucleus of the amygdala is an essential part of a circuitry mediating fear conditioning.

The human amygdala has also been implicated in acquisition and expression of fear conditioning. Participants submitted to conditioning procedures, for example, show increased skin conductance responses (SCRs), a measure of arousal that serves as the expressed conditioned response, in the presence of a conditioned stimulus (Hygge and Ohman, 1978; LaBar et al., 1995). Interestingly, this effect has been observed even when the CS+ (stimulus that predicts the occurrence of an aversive US) is masked to prevent conscious awareness (Esteves et al., 1994). Increased SCRs in fear conditioning paradigms are also displayed by amnesic patients, who have an intact amygdala but damage to the hippocampus, even though they are unable to explicitly report which CS was associated with an US (Fried et al., 1997). Patients with unilateral (LaBar et al., 1995) and bilateral lesions of the amygdala (Bechara et al., 1995), however, show the reverse pattern as they fail to exhibit increases in SCR to a CS+ in a fear conditioning paradigm, despite showing explicit knowledge of the contingencies.

The psychophysiological and neuropsychological work is substantiated by recent neuroimaging studies. Functional magnetic resonance imaging methodology (fMRI), for example, allows researchers to investigate the human amygdala's role in fear learning. Early imaging studies were suggestive of a role for the human amygdala in processing fear-related stimuli,

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