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The role of the human amygdala in the production of conditioned fear responses

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The amygdala plays a central role in the acquisition and expression of fear memories. Laboratory animal studies indicate that the amygdala both receives sensory information and produces learned behavioral and autonomic fear responses. However, prior functional imaging research in humans has largely focused on amygdala activity elicited by fearful stimuli, giving less attention to this region's role in the production of fear responses. In contrast, the present study used functional magnetic resonance imaging to investigate the amygdala's influence on the generation of conditional fear responses. Significant increases in amygdala activity were observed during the production of conditioned (learning-related), but not orienting, nonspecific, and unconditioned (nonlearning-related) skin conductance responses. Further, greater amygdala activity was demonstrated during conditioned response production than during conditioned stimulus presentation. These results suggest the amygdala not only responds to fearful stimuli, but also generates learning-related changes in human autonomic fear expression. Published by Elsevier Inc.

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Autonomic responses are a basic component of our emotional reactions to fearful events. Skin conductance response (SCR), an index of electrodermal activity, is one popular psychophysiological measure of autonomic arousal that is often used to monitor emotional expression and fear learning in humans. Insights from lesion, electrical stimulation, and functional imaging studies have identified a core network of brain regions that mediate SCR (Boucsein, 1992; Critchley, 2002; Critchley et al., 2000; Patterson et al., 2002; Williams et al., 2000). A key component of this network is the hypothalamus, which receives cortical input from the ventromedial prefrontal cortex and subcortical projections from the amygdala (Critchley, 2002; Davis, 2000; Öngür and Price, 2000; Patterson et al., 2002). In turn, the hypothalamus projects to brain stem targets that control SCR. A number of other brain regions also influence SCR production. Electrical stimulation of the hippocampus, amygdala, cingulate, and frontal convexities elicit electrodermal changes (Mangina and Beuzeron-Mangina, 1996), while deficits in SCR production have been observed in patients with ventromedial prefrontal, right inferior parietal, and anterior cingulate cortex lesions (Tranel and Damasio, 1994). Further, human functional imaging studies have demonstrated activations within the thalamus, insula, cerebellum, cingulate, ventromedial prefrontal, orbital frontal, and inferior parietal cortices that are correlated with SCR (Critchley et al., 2000; Fredrikson et al., 1998; Nagai et al., 2004; Patterson et al., 2002; Williams et al., 2000). Together, these studies suggest that a core network of brain regions modulates SCR production across a wide variety of cognitive tasks.

Although the amygdala is considered an important component of the neural circuit for emotional expression (Davis 2000; LeDoux, 2000), this region may not be essential for general SCR production. For example, individuals with bilateral amygdala damage produce normal SCRs to a variety of visual and auditory stimuli, and fMRI studies exploring the neuroanatomical mechanisms of SCR production have not observed significant correlations between skin conductance and amygdala activity (Critchley et al., 2000; Patterson et al., 2002; Tranel, 2000; Tranel and Damasio, 1989; Williams et al., 2000). Although the amygdala does not appear necessary for general, nonlearning-related SCR production, this region may be involved in the generation of SCRs specific to certain learning-related processes. Specifically, the amygdala may modulate SCR production during Pavlovian fear conditioning (Bechara et al., 1995; Cheng et al., 2003; Critchley, 2002). In fear conditioning, a conditioned stimulus (CS) predicts an aversive event (unconditioned stimulus: UCS) such as shock or loud noise. Expression of a conditioned response (CR) to the CS is taken as evidence that a CS–UCS association has been learned.

Abbreviations: CS, conditioned stimulus; UCS, unconditioned stimulus; CS+, CS paired with the UCS; CS−, CS presented alone; CR, conditioned response; OR, orienting response; NSR, nonspecific response; UCR, unconditioned response; SCR, skin conductance response.

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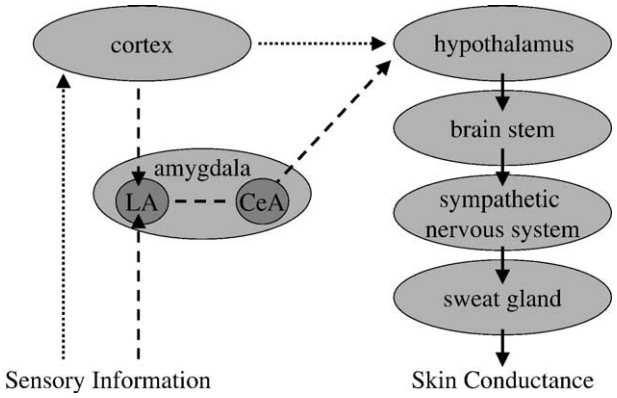

Fig. 1. Pathways believed to mediate general SCR production (dotted lines) and conditioned (learning-related) SCR production (dashed lines). Sensory information is transmitted to the cortex and lateral nucleus of the amygdala (LA). Projections from cortical regions to the hypothalamus appear to play a role in the generation of SCRs across a wide variety of cognitive processes. The LA projects to the central amygdala (CeA) which controls the expression of learned (conditioned fear) SCRs by way of projections to hypothalamus. Solid lines reflect the pathway that is common to both general and conditioned SCR production.

Fear conditioning studies with laboratory animals indicate that sensory information is projected to the lateral amygdala where critical synaptic plasticity takes place, and that projections from the amygdala's central nucleus to brain stem targets control learned behavioral and autonomic fear responses (Davis, 2000; LeDoux, 2000). Thus, the amygdala appears to be crucial for both the acquisition and expression of conditional fear. Therefore, the amygdala may be required for the generation of conditioned SCRs even though it is not necessary for SCRs elicited by other cognitive processes (see Fig. 1). Although most of the research exploring the amygdala's contribution to conditional fear has been conducted with laboratory animals, functional brain imaging studies have also demonstrated this region's involvement in human fear conditioning (Büchel et al., 1998; Cheng et al., 2003; Knight et al., 2004; LaBar et al., 1998). These imaging studies have typically explored amygdala activity elicited by stimulus presentations, and have given less attention to this region's role in the generation of behavioral and autonomic fear responses. Although a few imaging studies have demonstrated a relationship between fear expression and amygdala activity, their ability to differentiate amygdala activation elicited by stimulus presentations from activity associated with fear response production was limited (Büchel et al., 1998; LaBar et al., 1998; Phelps et al., 2001). Further, previous studies have not examined the amygdala's role in the generation of distinct types of SCRs.

The present study investigated the amygdala's role in the production of learning-related changes in SCR by exposing participants to a Pavlovian fear conditioning procedure in which learning-related (conditioned) and nonlearning-related (unconditioned, orienting, and nonspecific) SCRs were evoked (see Fig. 2). One tone (CS+) was repeatedly paired with a loud white-noise UCS, while a second tone (CS−) was presented alone. In addition, a series of novel, non-repeating sounds (Novel) were presented to elicit orienting responses because SCRs to CS− presentations tend to habituate within a few trials. Functional magnetic resonance imaging (fMRI) was used to determine the relationship between

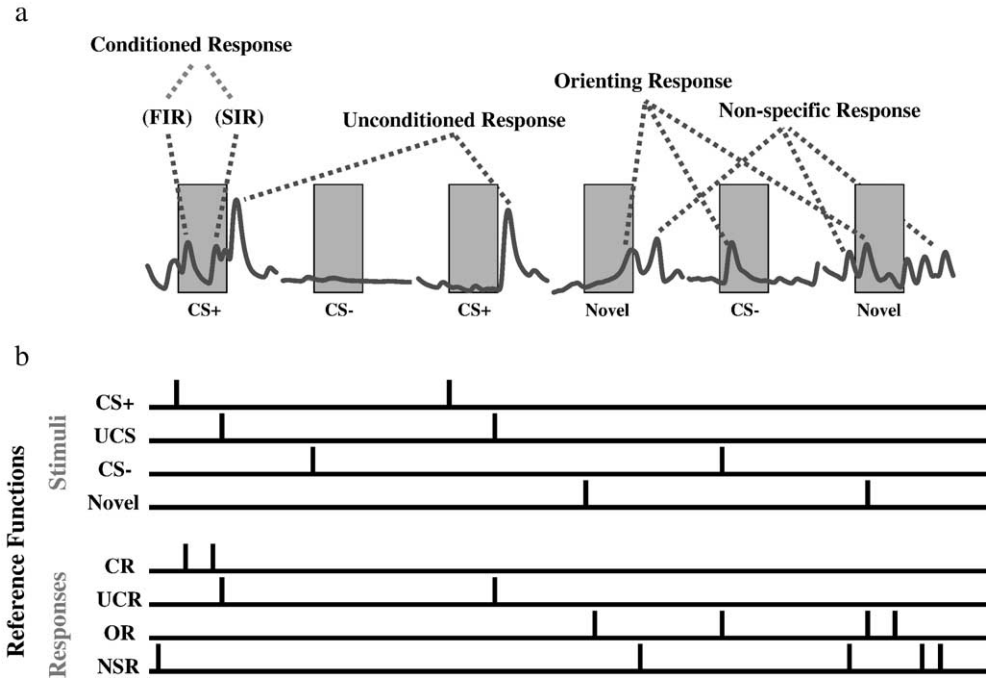

Fig. 2. Examples of skin conductance response (SCR) categorization and corresponding reference waveforms. (a) SCRs that occurred during the 10-s period following onset of the CS+, UCS, and CS−/CSu stimuli were classified as conditioned (CR), unconditioned (UCR), and orienting (OR) responses, respectively. SCRs produced during the inter-trial interval that were not elicited by these stimuli were classified as nonspecific responses (NSR). CRs were further separated into first (FIR) and second (SIR) interval responses. (b) Corresponding reference functions for all stimuli presented and responses evoked. Differences in the timing and occurrence of responses relative to the stimuli that evoke them permit the deconvolution of fMRI time-course data associated with stimulus presentations versus response production.