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Review article

Fear conditioning and extinction across development: Evidence from human studies and animal models☆

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ABSTRACT

The ability to differentiate danger and safety through associative processes emerges early in life. Understanding the mechanisms underlying associative learning of threat and safety can clarify the processes that shape development of normative fears and pathological anxiety. Considerable research has used fear conditioning and extinction paradigms to delineate underlying mechanisms in animals and human adults; however, little is known about these mechanisms in children and adolescents. The current paper summarizes the empirical data on the development of fear conditioning and extinction. It reviews methodological considerations and future directions for research on fear conditioning and extinction in pediatric populations.

Contents

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1. Introduction

The ability to identify danger emerges early in life and develops in a similar way across cultures. Young children tend to fear strangers or separation. When these fears diminish during schoolage, they typically are replaced by fears of animals or other natural dangers. In adolescence, fears arise of social circumstances and abstract dangers, such as the fear of humiliation. While extensive research charts developmental patterns of human fear in response to such intrinsically threatening events, far less research examines developmental aspects of learned fears. Because considerable basic research examines fear conditioning and extinction, particular interest has arisen in the development of these forms of learning.

This paper summarizes findings from developmental research on fear conditioning and extinction. It unfolds in four stages. Section 2 defines major concepts relevant to fear conditioning and extinction. Because few studies examine fear conditioning and extinction in children, Section 3 attempts to extrapolate to children and adolescents from data in animals and human adults. Section 4 details findings from the few available conditioning and extinction studies in children and adolescents, emphasizing the unique ethical and methodological considerations that complicate such work. The paper concludes by summarizing directions for future studies.

2. Studying fear conditioning and extinction developmentally

Fear conditioning, a form of associative learning, is a widely used experimental paradigm for investigating the psychophysiological processes and neural mechanisms sub-serving learning about danger cues in a range of mammalian species. In classical fear conditioning, a neutral conditioned stimulus (CS, e.g., tone) is repeatedly paired with an aversive stimulus (UCS, e.g., shock), yielding a CS-UCS association. Discrimination conditioning uses two CSs, one that is paired with the UCS (CS+) and another that is not (CS−). A conditioned response (CR, e.g., freezing behavior) is produced in response to the CS+, thus enhancing the organism's ability to respond to similar events in the future. This paradigm allows for the rapid induction of a learned fear state and the expression of learned fear-related behaviors. Conditioned fear responses have been found across multiple species and include various responses such as changes in autonomic activity (e.g., heart rate, blood pressure, skin conductance), defensive behaviors (e.g., freezing), endocrine response (e.g., hormone release), pain sensitivity (e.g., analgesia), and modulation of reflex expressions, like fear potentiated startle and eye blink response (LeDoux, 2000).

Extinction is a process during which the CS+ is presented in the absence of the UCS, leading the conditioned response (CR) to decline across repeated presentations. Based on numerous studies, extinction does not eradicate the initial CS+-UCS association but rather creates new learning, where the CS+ is associated with the absence of the UCS (for review see Bouton, 2002, 2004; Quirk & Mueller, 2008). Following successful extinction, the initial CS+-UCS association competes with the newer CS+-no-UCS association. When presentation of the extinguished CS triggers the no-UCS memory, it inhibits the original CR. Retrieval of extinction, also known as extinction recall, occurs when the extinguished CS+ is re-presented at a later time. Low levels of the fear expression (i.e., CR) indicate successful extinction recall, whereas high levels of fear expression indicate poor extinction recall (Quirk & Mueller, 2008). Fear responses may also reappear spontaneously with passage of time (i.e., spontaneous recovery), following contextual manipulations (i.e., renewal) or presentation of the UCS even in the absence of the CS+ (i.e., reinstatement) (Bouton, 2002).

Interactions between fear conditioning and extinction shape behavior, mainly during development, when the effects of learning can be particularly profound. Hence, understanding the developmental changes of these processes and the underlying neural correlates that support them informs a mechanistic understanding of fear and safety learning. In rodents, fear conditioning emerges early in life and involves subcortical areas, predominantly the amygdala; whereas the maintenance of extinction, as expressed in extinction recall, appears to emerge later in development and involves the prefrontal cortex and hippocampus (Kim & Richardson, 2010). Thus, when studying these learning-related processes, a developmental perspective examining maturation of brain regions supporting fear conditioning and fear extinction may explain the emergence of individual differences in fear and anxiety.

3. The neural circuitry underpinning fear conditioning and extinction

Most neuroscience research on fear conditioning uses animal models. Nonetheless, translating these findings to human studies is feasible due to the strong cross-species similarities in the physiology of fear (LeDoux, 2000). Animal models are particularly important for studying the emergence of fear conditioning across development as some of the procedures are less feasible in humans and particularly in children and adolescents. Therefore, findings from animal models can be translated to research in human adults, which in turn can be applied to pediatric populations.

3.1. Animal models

3.1.1. Fear conditioning

Fear conditioning involves processing sensory information about the CS and the UCS. Typically, the CS and UCS are presented in different sensory modalities (e.g., auditory tone and tactile shock) and thereby activate different sensory cortices as well as the thalamus and hypothalamus and the brainstem periaqueductal gray region. Ultimately, information about the CS and the paired UCS is thought to first converge in the basolateral nucleus of the amygdala. Initially, the neutral CS will produce weaker amygdala stimulation than produced by the UCS. Following CS-UCS pairings, the initially weak amygdala stimulation produced by the CS becomes stronger, reflecting a CS-UCS association. After this association is formed, the weak stimulus, presented on its own without the UCS, has the capacity to elicit a stronger amygdala response, thus influencing behavior and physiology through efferent projections from the central nucleus of the amygdala. This region of the amygdala sends projections to brainstem and motor areas that control the expression of fear responses across a variety of domains expressed via behavioral, autonomic nervous system, and endocrine responses (LeDoux, 2000).

The amygdala appears to mediate learning by influencing cortical plasticity via changes in synaptic connection. Once a CS-UCS association has been acquired, a decline in amygdala activation may occur (Buchel & Dolan, 2000), unless later-appearing changes in the CS-UCS association take place. For example, mounting evidence implicates a portion of the medial prefrontal region (mPFC), the so-called "pre-limbic" cortex, in enhancement of amygdala activity and its importance for expression of conditioned fear. Specifically, it is proposed that this region integrates input from other brain structures to enhance the expression of fear conditioning via excitatory projections to the amygdala (Corcoran & Quirk, 2007; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011; Sotres-Bayon & Quirk, 2010).

Relative to the considerable work on fear conditioning in mature rodents and primates, far less work examines developmental