Neurobiology of Learning and Memory 97 (2012) 301–312

Contents lists available at SciVerse ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Brain activity associated with omission of an aversive event reveals the effects of fear learning and generalization

Joseph E. Dunsmoor, Kevin S. LaBar *

Department of Psychology and Neuroscience, Center for Cognitive Neuroscience, Duke University, Durham, NC 27708, USA

ARTICLE INFO

Article history:
Received 2 December 2011
Revised 27 January 2012
Accepted 6 February 2012
Available online 26 February 2012

Keywords:
Pavlovian conditioning
Fear generalization
Electrodermal activity
Orienting response
Prediction error
Functional magnetic resonance imaging

ABSTRACT

During fear learning, anticipation of an impending aversive stimulus increases defensive behaviors. Interestingly, omission of the aversive stimulus often produces another response around the time the event was expected. This omission response suggests that the subject detected a mismatch between what was predicted and what actually occurred, thereby providing an indirect measure of cognitive expectancy. Here, we used functional magnetic resonance imaging to investigate whether omission-related brain activity reflects fear expectancy during learning and generalization of conditioned fear. During conditioning, a face expressing a moderate amount of fear (conditioned stimulus, CS+) signaled delivery of an aversive shock unconditioned stimulus (US), whereas the same face with a neutral expression was unreinforced. In a subsequent generalization test, subjects were presented with faces expressing more or less fear intensity than the CS+. Psychophysiological results revealed an increase in the skin conductance response (SCR) during learning when the US was omitted. Omission-related SCRs were also observed during the generalization test following the offset of high- but not low-intensity face expressions. Neuroimaging results revealed omission-related neural activity during learning in the anterior cingulate cortex, parietal cortex, insula, and striatum. These same regions also showed omission-related responses during the generalization test following highly expressive fearful faces. Finally, regression analysis on omission responses during the generalization test revealed correlations in offset-related SCRs and neural activity in the dorsomedial prefrontal cortex and posterior parietal cortex. Thus, converging psychophysiological and neural activity upon omission of aversive stimulation provides a novel metric of US expectancy, even to generalized cues that had no prior history of reinforcement.

1. Introduction

Anticipating an aversive event frequently results in an increase in sympathetic arousal. In the laboratory study of fear learning, this anticipatory conditioned response (CR) is taken as evidence that a subject has learned the relationship between a neutral conditioned stimulus (CS) and delivery of an aversive unconditioned stimulus (US). But what happens when the US is omitted? The effects of US omission have been examined primarily for its role in extinction learning (Pavlov, 1927). Interestingly, an orienting response (OR) is generated at the time an anticipated US is typically delivered but unexpectedly absent, revealing that the subject detects a mismatch between the predicted and actual outcome (Sokolov, 1963). In this way, the omission-related OR provides an indirect measure of subjective processes like cognitive expectancy (Siddle & Lipp, 1997). The omission-related response has received little attention in neuroimaging studies of human fear learning. Here, we examined whether psychophysiological and neural activity associated with omission of an aversive US provides an index of expectancy during the acquisition and generalization of fear.

A motivation for examining activity associated with stimulus omission is that, unlike stimulus-specific responses, the omission response occurs in the absence of sensory stimulation (O'Gorman, 1973; Siddle, Remington, Kuiack, & Haines, 1983). Therefore, omission-responses are not constrained by arousal induced by processing the CS itself and may simply reflect cognitive states related to a perceived violation in outcome expectancy. This feature of the omission response may be of particular value in the study of fear generalization, wherein a number of physically different stimuli that have never directly predicted the US nonetheless evoke a fear response after acquisition training. Previous research has uncovered several factors influencing the generalized CR, including perceptual (Guttman & Kalish, 1956; Pavlov, 1927) or conceptual (Dunsmoor, Martin, & Labar, 2011; Dunsmoor, White, & Labar, 2011; Razran, 1949) similarity to the CS, the physical intensity of the stimulus (Ghirlanda & Enquist, 2003), its emotional intensity (Dunsmoor, Mitroff, & LaBar, 2009) or learned equivalences through association with a common stimulus (Honey & Hall, 1989). Whether omission

* Corresponding author. Address: Duke University, Center for Cognitive Neuroscience, Box 90999, B203 LSRC Building, Research Drive, Durham, NC 27708, USA.
E-mail address: klabar@duke.edu (K.S. LaBar).

1074-7427/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2012.02.003

responses are concomitant with stimulus generalization, and are influenced by similar factors that affect the generalized CR, is unknown.

Omission related responses may provide an additional and complementary measure of learning and generalization that is not confounded by the myriad factors influencing cue-evoked anticipatory responses (e.g., the inherent fear-relevance of a CS that may determine conditioned responding (Öhman & Mineka, 2001) or variations in stimulus appearance, shape, or intensity that drive generalized responding). In this way, omission related activity may provide an unconfounded metric of cognitive expectancy, insofar as the magnitude of an omission response can be taken to reflect how strongly the subject had expected the US (Sokolov, 1963). We therefore hypothesized that omitting an aversive US would evoke an increase in psychophysiological and neural activity during learning and generalization testing when the US was expected relative to analogous time periods when the US was not expected. During functional magnetic resonance imaging (fMRI), subjects were presented with a range of faces of the same actor morphed between neutral and fearful endpoints before and after fear learning (see Fig. 1). During fear learning, the middle face value along the neutral-to-fearful continuum (CS+) intermittently coterminated with an electric shock US, whereas the most neutral face (CS−) was explicitly unreinforced.

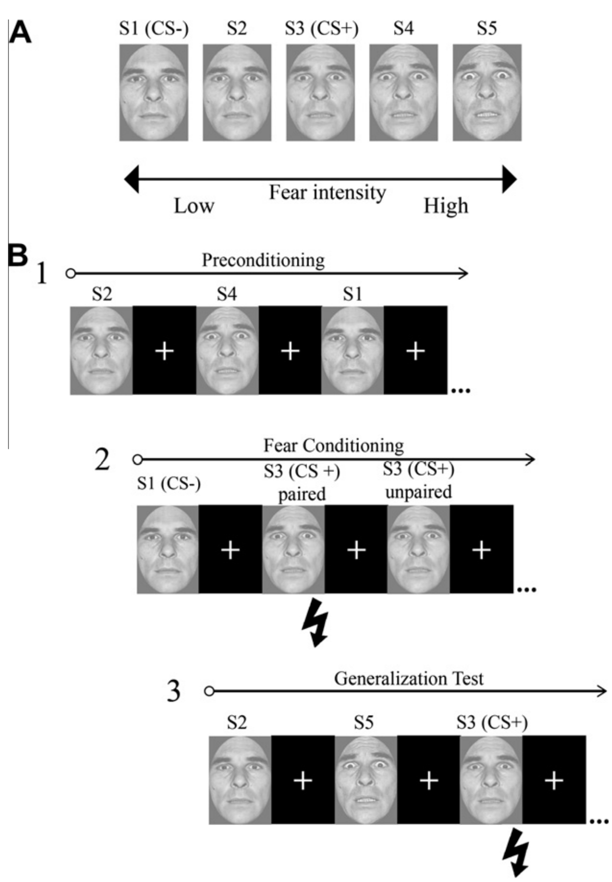

Fig. 1. Experimental paradigm. (A) The conditioned and non-conditioned stimuli (S1–S5) consisted of a single identity morphed between neutral and fearful endpoints. The S1 and S2 were considered "low intensity" fearful faces and the S4 and S5 were considered "high intensity" fearful faces for the purpose of analysis. (B) The experimental session included three phases: preconditioning, fear learning, and the generalization test. During fear learning, the US (pictured as a lightning bolt) followed the offset of $CS+_{paired}$ trials and was omitted on $CS+_{unpaired}$ trials. The US never followed the CS−. The CS+ was intermittently reinforced throughout the generalization test but never occurred following any of the other faces.

We first sought to identify psychophysiological and neural activity associated with the omission of the US during acquisition of conditioned fear when the US occurred with regularity following the CS+. We predicted increased skin conductance responses (SCRs) to the omission of the US following CS+ trials versus CS− trials for which the US had never occurred. This SCR finding would be in line with previous human electrodermal studies using non-aversive stimulus–stimulus associative learning procedures (Siddle, 1985; Siddle & Packer, 1987). We also predicted enhanced omission-related neural activity in regions important for detecting errors and signaling expectancy violations, including the dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), and striatum (Botvinick, Cohen, & Carter, 2004; Schultz & Dickinson, 2000). Such findings would replicate the limited number of recent fMRI studies reporting brain activity indexing US omission following CS+ trials (Linnman, Rougemont-Bucking, Beucke, Zeffiro, & Milad, 2011; Spoormaker, Andrade, et al., 2011; Spoormaker, Schroter, et al., 2011).

Our second goal was to investigate for the first time whether learning-induced omission responses extend to generalization trials for which the US had never actually been paired with the stimulus but may be expected nonetheless. Subsequent to acquisition training, subjects were presented with faces of the same actor containing more or less fear intensity than the CS+ during a test of stimulus generalization. We predicted increased SCRs following the offset of highly fearful expressions (but not low-intensity expressions), reflecting a violation in US expectancy to generalized threats as a function of emotional intensity (Dunsmoor et al., 2009). We also predicted that neural activity upon the offset of highly fearful expressions during the generalization test would overlap with US omission-related activity observed during learning, indicating that similar regions signal expectancy violations despite physical differences in the antecedent cue and reinforcement history. Finally, we examined whether offset-related neural activity correlates with offset-related SCRs during the generalization test, extending neuroimaging evidence for functional coupling between central and peripheral indices of fear learning (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Knight, Nguyen, & Bandettini, 2005).

2. Materials and methods

2.1. Subjects

Twenty-five healthy-right handed young adults participated in this study. Two subjects were not included in the final analysis due to excessive head motion (>3 mm in any direction) and nine subjects were not included due to a lack of SCR data (five subjects lacked SCR data due to technical issues, and four subjects showed no measurable responses). Fourteen healthy right-handed subjects (seven females; age range = 19–30; median age = 22 yrs) were included in the final analysis. All participants provided written informed consent in accordance with the Duke University Institutional Review Board guidelines.

2.2. Stimulus material

Stimuli consisted of a male face morphed along a gradient from neutral-to-fearful taken from the Ekman pictures of facial affect (Ekman & Friesen, 1976) positioned in a full-frontal orientation and cropped to remove hair, ears, and neckline. Five morphs were created along the continuum using Morph-Man 2000 software (STOIK): 11.11% fear/88.88% neutral, 33.33% fear/66.66% neutral, 55.55% fear/44.44% neutral, 77.77% fear/22.22% neutral, and 100% fear (see also Graham, Devinsky, & LaBar, 2007; Thomas, De Bellis,