Behavioural Brain Research 287 (2015) 34–41

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Neural correlates of individual differences in fear learning

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HIGHLIGHTS

- We recorded fMRI BOLD response and skin conductance response (SCR) to CS+ and CS−.
- The insula activated in response to CS+ versus CS− trials across participants.
- Amygdala reactivity to CS+ versus CS− was not observed across participants.
- Individual differences in CS+ > CS− SCR covaried with activity in right amygdala.
- Results suggest brain mechanism for individual differences in fear conditionability.

ARTICLE INFO

Article history:
Received 23 December 2014
Received in revised form 15 March 2015
Accepted 17 March 2015
Available online 24 March 2015

Keywords:
Fear conditioning
Amygdala
fMRI
Skin conductance response
SCR
Individual differences

ABSTRACT

Variability in fear conditionability is common, and clarity regarding the neural regions responsible for individual differences in fear conditionability could uncover brain-based biomarkers of resilience or vulnerability to trauma-based psychopathologies (e.g., post-traumatic stress disorder). In recent years, neuroimaging work has yielded a detailed understanding of the neural mechanisms underlying fear conditioning common across participants, however only a minority of studies have investigated the brain basis of inter-individual variation in fear learning. Moreover, the majority of these studies have employed small sample sizes (mean $n = 17$; range $n = 5$–27) and all have failed to meet the minimum recommended sample size for functional magnetic resonance imaging (fMRI) studies of individual differences. Here, using fMRI, we analyzed blood-oxygenation level dependent (BOLD) response recorded simultaneously with skin conductance response (SCR) and ratings of unconditioned stimulus (US) expectancy in 49 participants undergoing Pavlovian fear conditioning. On average, participants became conditioned to the conditioned stimulus (CS+; higher US expectancy ratings and SCR for the CS+ compared to the unpaired conditioned stimulus, CS−); the CS+ also robustly increased activation in the bilateral insula. Amygdala activation was revealed from a regression analysis that incorporated individual differences in fear conditionability (i.e., a between-subjects regressor of mean CS+ > CS− SCR). By replicating results observed using much smaller sample sizes, the results confirm that variation in amygdala reactivity covaries with individual differences in fear conditionability. The link between behavior (SCR) and brain (amygdala reactivity) may be a putative endophenotype for the acquisition of fear memories.

1. Introduction

In the domain of fear conditioning, inter-individual differences are the rule rather than the exception; for a given conditioned stimulus, some individuals display robust fear responding, while others

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http://dx.doi.org/10.1016/j.bbr.2015.03.035
0166-4328/

display little or no fear response. Evidence suggests that individual differences in fear responding are stable [1] and heritable [2], suggesting that they may reflect key neural differences. Importantly, such differences could be associated with resistance or vulnerability to anxiety disorders [3]. That is, individuals whose neural circuity predisposes them to remember fear more readily might be more likely to develop trauma-related psychopathology if exposed to a traumatic event [4]. In the past two decades, neuroimaging work has generated a detailed understanding of how fear responses are acquired in the human brain [5–7]. However, the majority of this work has focused on commonalities across participants, seeking to identify the neural regions involved in "typical" fear responding, while considering inter-individual variation in conditionability to be a source of statistical noise (e.g., necessitating the exclusion of "non-responders").

In a typical Pavlovian fear conditioning paradigm, participants are presented with a neutral stimulus, such as a colored light (conditioned stimulus, CS+) that is paired repeatedly with an aversive stimulus, such as mild electric shock (unconditioned stimulus, US). After multiple pairings, the CS+ comes to elicit a fear response (conditioned response, CR), which can be observed in contrast to the response elicited by an unpaired neutral stimulus (CS−). Animal studies of fear conditioning have consistently implicated the amygdala in learning this association and in the production of conditioned fear responses [8,9]. In humans, neuroimaging studies have revealed activation of the amygdala, the insula and the anterior cingulate cortex (ACC) during fear conditioning [10,11], using measures such as blood-oxygenated level dependent (BOLD) response, assessed via functional magnetic resonance imaging (fMRI).

Peripheral measures of fear learning such as skin conductance response (SCR), a measure of autonomic arousal, can be used to index fear conditioning success. SCR is represented in the brain by a number of regions overlapping with those involved in emotion [12,13]. While the amygdala does not appear to be essential for the production of SCRs (e.g., patients with bilateral amygdala damage produce normal SCRs to a number of visual and auditory stimuli [14]), trials that elicit larger conditioned SCRs are associated with increased amygdala reactivity to the CS, suggesting that the amygdala may be central to the expression of conditioned fear [15–17].

Prior neuroimaging work has elucidated commonalities in fear learning across individuals, and has begun to shed light on the neural correlates of trial-to-trial (i.e., within-subject) variability in conditioned SCR responding. However, examination of the neural generator(s) of individual differences (i.e., between-subject variability) in fear conditioning has been relatively limited. Those studies that have investigated the neural basis of individual differences in fear conditionability have generally been plagued by small sample sizes, ranging from 5 to 27 participants [17–22]. Small sample sizes are problematic in studies of individual differences and the fMRI literature in particular has been criticized on this point [23,24]. Among the problems associated with small sample sizes are that lack of power may lead to erroneous conclusions about which brain regions are and are not associated with individual differences and that effects which *are* observed may capitalize on chance, which may lead to overestimations of effect size [23].

In the largest study yet published on the neural basis of individual differences in fear conditionability ($n = 27$), Petrovic and colleagues [21] sought to investigate neural mechanisms underlying affective evaluations of social stimuli. To this end, participants viewed pictures of 4 different faces over the course of an experiment. Two of the faces (CS+) were paired with mild electric shock (US) on 50% of trials; the other two faces (CS−) were never paired with shock. While they failed to observe an overall increase in SCR for the CS+ versus the CS−, Petrovic and colleagues [21] observed greater conditioning related increases in SCR from the second half of the experiment compared to the first half of the experiment that were positively correlated with BOLD activation in the bilateral amygdala, using a region of interest (ROI) approach focused on the amygdala and the fusiform gyrus, a region involved in face processing.

In the second-largest report on the neural basis of individual differences in fear conditionability published to-date, Schiller and Delgado [22] reanalyzed data from an earlier study [25]. In the original study, $n = 17$ participants viewed 2 faces, one of which (CS+) had been paired with a mild electric shock (US), and the other (CS−), which was never paired with shock. Using a whole-brain, between-subjects approach, Schiller and Delgado [22] found evidence of a positive correlation between CS+ SCR and activation in the striatum and the insula, suggesting that these brain regions, which have been implicated in the encoding of value signals, might underlie individual differences in fear conditionability.

The lack of congruence between results from these studies (e.g., lack of SCR-amygdala covariation in [22]) makes it difficult to draw firm conclusions about the neural correlates of inter-individual variation in fear conditionability. For example, it is unclear whether Schiller and Delgado [22] failed to observe a correlation between the amygdala and SCR because of a lack of power, and whether Petrovic and colleagues [21] might have observed correlations between SCR and BOLD activation in other brain regions (e.g., the insula, ventral striatum) had they not limited their analysis to the amygdala and the fusiform gyrus. Further, both studies used faces as the CS stimuli, which might vary in their perceived affective salience across individuals (e.g., [26]) and might therefore confound effects of social stimuli processing and fear conditioning. Further, conditioned faces might potentiate activity in stimulus-specific regions (e.g., the fusiform gyrus) that may or may not be otherwise implicated in inter-individual variation in fear learning.

Therefore, the goal of the present study was to further investigate the brain mechanism underlying inter-individual variation in fear conditionability. Current recommendations are that fMRI studies of individual differences employ a minimum sample size of $n = 40$, in order to achieve an acceptable trade-off between statistical power and data collection costs [24]. To this end, we used a sample of $n = 49$ healthy volunteers and simultaneous SCR recording and fMRI BOLD during Pavlovian fear conditioning, in which a neutral object (a street lamp) was paired with a mild electric shock (US) on some trials (CS+) and not others (CS−). To assess contingency awareness during fear learning, participants were also asked to rate US expectancy on each trial (prior to US onset). Previous work has implicated the amygdala, the insula and the ACC in fear learning [10], and the amygdala, insula, cerebellum, medial prefrontal cortex, precentral gyrus and the superior temporal gyrus in the expression of conditioned fear responding (i.e., SCR production [27]). Therefore, we hypothesized that individuals with greater fear conditionability (measured via SCR to the CS+ versus CS−) would show greater neural activation in these regions.

2. Materials and method

2.1. Participants

Fifty-one healthy, right-handed participants participated in the study. One participant was excluded from analyses because of a technical difficulty that compromised recording of the SCR data; another participant was excluded because he felt claustrophobic during the scan and was unable to continue. Therefore, 49 participants (28 female; M age = 25.3 years, range = 21–40 years, $SD = 4.8$; Caucasian = 23, Asian = 12, African American/Black = 3, Native American or Native Hawaiian = 3, more than one race = 8)