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# Fear and panic in humans with bilateral amygdala damage

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## Abstract

Decades of research have highlighted the amygdala's influential role in fear. Surprisingly, we found that inhalation of 35% $CO_2$ evoked not only fear, but also panic attacks, in three rare patients with bilateral amygdala damage. These results indicate that the amygdala is not required for fear and panic, and make an important distinction between fear triggered by external threats from the environment versus fear triggered internally by $CO_2$.

### Keywords

$CO_2$; interoception; emotion; feeling; lesion



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Conceived and planned experiments: JAW, MJW, JSF, RLF, DT, WHC, NSD
Provided financial support, equipment, and supplies: JAW, DT, RH, WHC
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Wrote and edited manuscript and figures: JAW, CB, MJW, JSF, RH, DT, RLF, WHC, NSD

A substantial body of evidence indicates the importance of the amygdala in fear [1,2]. In animals, amygdala-restricted manipulations interfere with the acquisition, expression, and recall of conditioned fear and other forms of fear and anxiety-related behaviors [1]. In humans, focal bilateral amygdala lesions are extraordinarily rare and such cases have been crucial for understanding the role of the human amygdala in fear. The most intensively studied case is patient SM, whose amygdala damage stems from Urbach-Wiethe disease (Supplementary Fig. 1). Previous studies have shown that SM does not condition to aversive stimuli [3], fails to recognize fearful faces [2], and demonstrates a marked absence of fear during exposure to a variety of fear-provoking stimuli including life-threatening traumatic events [4]. Patients with similar lesions have largely yielded similar results [5,6].

One stimulus not previously tested in humans with amygdala damage is $CO_2$. Inhaling $CO_2$ stimulates breathing and can provoke both air hunger and fear [7-9]. Furthermore, $CO_2$ can trigger panic attacks, especially in patients with panic disorder [9,10]. Recent work in mice found that the amygdala directly detects $CO_2$ and acidosis to produce fear behaviors [11]. Therefore, we hypothesized that bilateral amygdala lesions would reduce $CO_2$-evoked fear in humans.

In contrast to our prediction, patient SM reported fear in response to a 35% $CO_2$ inhalation challenge. To our knowledge, this was the first time SM experienced fear in any setting, laboratory or otherwise, since childhood [4]. Surprised by this result, we tested two additional patients (AM and BG), monozygotic twin sisters with focal bilateral amygdala lesions due to Urbach-Wiethe disease (Supplementary Fig. 1) [6]. Replicating the finding in SM, both AM and BG also reported experiencing fear during the $CO_2$ challenge.

Even more strikingly, $CO_2$ triggered a panic attack in all three amygdala-lesion patients. The patients panicked on the first $CO_2$ trial and also during subsequent challenges (Supplementary Table 1), indicating that the effect was reproducible and not simply the result of a novel experience. By contrast, only 3 of 12 panicked in the matched, neurologically-intact comparison group (Fig. 1a), a rate similar to that previously observed in adults without a personal or family history of panic disorder [10]. Self-reported levels of fear and panic in the amygdala-lesion patients were significantly higher than in non-panickers from the comparison group (Figs. 1b and 1c). In addition, the patients reported elevated levels of anxiety and found the $CO_2$ inhalation to be significantly more arousing and aversive than non-panickers (Supplementary Figs. 2 and 3). The patients denied experiencing any anger (with ratings of zero on all trials), suggesting that the emotional changes induced by $CO_2$ were largely confined to the fear domain. Moreover, during air trials, the patients reported absolutely no fear, panic, or anxiety, indicating that the induction of these emotions were specific to $CO_2$. The observation that $CO_2$ evoked multiple emotions in the fear domain suggests that the subjective experience could not be easily defined by a single emotional term such as fear, panic, or anxiety. Notably, the bilateral amygdala lesions did not interfere with the ability to express or experience any of these fear-related emotions.

Details of each patient's panic attack are described in the Supplementary Panic Descriptions. Several observations were consistent across patients. First, all patients found the feelings induced by the $CO_2$ to be novel and described the experience as "panic". Second, all patients

displayed similar behavioral responses to $CO_2$, including gasping for air, distressed facial expressions, and escape behavior (e.g., ripping off the inhalation mask).

To test whether the reports of fear and panic were accompanied by physiological changes, we also measured respiratory rate, heart rate, and skin conductance response (SCR). Compared to air trials, $CO_2$ increased physiological responses in both the lesion and comparison groups (Fig. 2). Notably, physiological responses in the amygdala-lesion patients were higher than the non-panickers, including a significantly greater rate of respiration (Fig. 2). In contrast, there were no significant differences between the amygdala-lesion patients and the comparison panickers. Together, these physiological measures paralleled the greater incidence of $CO_2$-evoked panic found in the amygdala-lesion patients.

Not all physiological responses were increased in the patients. In the comparison group, skin conductance and heart rate gradually rose prior to the inhalation, as participants observed the experimenters preparing to administer the inhalation challenge (Fig. 3). In the lesion patients, both of these anticipatory responses were deficient (Fig. 3), which stands in sharp contrast to their heightened responses following $CO_2$ inhalation. These results are consistent with the notion that the amygdala detects potential danger in the external environment and physiologically prepares the organism to confront the threat, a process closely linked to the generation of anticipatory anxiety [1,12].

Contrary to our hypothesis, and adding an important clarification to the widely held belief that the amygdala is essential for fear, these results indicate that the amygdala is not required for fear and panic evoked by $CO_2$ inhalation. Moreover, the higher rate of panic attacks in the amygdala-lesion patients suggests that an intact amygdala may normally inhibit panic. This apparent loss of inhibition might have occurred during development, as the amygdala damage is thought to have emerged during adolescence [4]. Another possibility is that the amygdala inhibits panic acutely. Such modulation is plausible given that the output from the central nucleus of the amygdala is GABAergic [13] and projects to a number of brainstem sites implicated in producing panic-like behavior [1,14].

The elevated incidence of panic attacks evoked by $CO_2$ in the lesion patients raises the possibility that loss of amygdala function might contribute to the development of panic disorder. Supporting this possibility, patients with panic disorder have been found to have localized atrophy of the amygdala [15], as well as amygdala hypoactivity [16,17]. Anecdotal accounts from a single patient suggest that spontaneous panic can occur despite amygdala damage [18]. However, the absence of prior spontaneous panic attacks in our lesion patients suggests that amygdala dysfunction alone is not sufficient to cause spontaneous panic attacks or panic disorder.

Finally, the patients reported being surprised by their reaction to $CO_2$, and found the induced feelings of fear and panic to be completely novel. This suggests that the high concentration of inhaled $CO_2$ activated a pathway that had remained mostly dormant up until the point of the experiment. These observations raise the question of what is different about $CO_2$ compared to the previous stimuli that failed to evoke fear or panic [4], as well as the stimuli in this study that failed to evoke anticipatory responses. One possibility is that all of these other

stimuli were exteroceptive in nature, mainly processed through visual and auditory pathways that project to the amygdala. In contrast, $CO_2$ acts internally at acid-activated chemoreceptors and causes an array of physiological changes [7,9,11]. Thus, $CO_2$ might engage interoceptive afferent sensory pathways that project to the brainstem, diencephalon, and insular cortex [19,20]. Additionally, many brain areas outside the amygdala possess $CO_2$ and pH-sensitive chemoreceptors including acid-sensing ion channels [7]. Thus, $CO_2$ may directly activate extra-amygdalar brain structures underlying fear and panic, which may help explain the apparent discrepancy between these findings and the previous work in mice [11]. In either case, the results described here indicate that in humans, the internal threat signaled by $CO_2$ is detected and interpreted as fear and panic despite the absence of an intact amygdala.

## Online Methods

### Subjects

We tested three female patients with bilateral amygdala damage due to Urbach-Wiethe disease (mean age = 39.33 years, s.d. = 4.04; mean years of education = 13.33, s.d. = 1.15) and 12 healthy, neurologically-intact females of comparable age (mean = 43.08, s.d. = 5.65) and education (mean = 14.33, s.d. = 1.87). All subjects were free of psychiatric diagnoses and medications, and reported no personal or family history of panic attacks. All subjects gave written informed consent, and all procedures were approved by the University of Iowa Institutional Review Board.

### Data Collection

Before the procedures, all subjects completed the Beck Anxiety Inventory as a measure of baseline anxiety, and both groups reported experiencing low levels of anxiety that were not significantly different (amygdala lesion mean raw score = 4, s.d. = 2; comparison group mean raw score = 3.4, s.d. = 3.8; $p = 0.365$). During each inhalation challenge, subjects were in a supine position while seated in a reclining chair. A plastic inhalation mask was comfortably placed over their nose and mouth and then strapped to the reclining chair to ensure that it would remain in place during the inhalation. Respiratory rate, heart rate, and skin conductance were recorded throughout each trial using a BIOPAC MP150 data acquisition system (BioPac Systems, Inc). Baseline recordings were taken during a two minute rest period before each inhalation and recordings continued for two minutes after each inhalation. The volume of each inhalation was recorded using an RSS 100 Research Pneumotach System (KORR Medical Technologies). Forced inspiratory vital capacity (FIVC) was calculated from height and weight as described previously [21]. During all challenges, subjects were required to inhale a minimum of 75% of their FIVC in order for the challenge to be considered valid. All subjects completed 4 single-breath FIVC challenges, two with compressed air and two with 35% $CO_2$ mixed with 21% oxygen (balanced with nitrogen). All bilateral amygdala lesion patients returned for a second visit to complete an additional set of challenges. The challenge order for each subject was air first followed by $CO_2$, and was repeated at least once. Subjects were blinded to trial order. Each trial was separated by an interval of at least 20 minutes.

At the end of each inhalation, subjects completed a number of different self-report questionnaires including: an inhalation symptom checklist containing all of the DSM-IV symptoms of a panic attack; four separate visual analog scales (VAS) asking them to rate their level of fear, panic, anxiety, and anger from 0 (not at all) to 100 (extremely); a bipolar valence scale asking them to rate the inhalation from 0 (extremely unpleasant) to 8 (extremely pleasant); an arousal scale asking them to rate the overall intensity of the inhalation from 0 (not at all) to 8 (extremely); and the state portion of the Spielberger State-Trait Anxiety Inventory. When completing the self-report questionnaires, subjects were instructed to rate how they felt during and immediately following the inhalation when symptoms were at their peak. The same measures were also completed before each inhalation (i.e., baseline) during which subjects were instructed to rate how they currently felt. After each trial, subjects were interviewed by a clinician or trained researcher and were asked to describe any symptoms they experienced before, during, and after the inhalation.

## Data Analysis

The threshold for a panic attack was based upon conservative criteria for differentiating panic attacks from the strong respiratory and physiological responses that many people have to $CO_2$ challenges [10]. This threshold required that the subject endorse at least four DSM-IV symptoms of panic, either express or enact a desire to escape or flee, and report at least a 25% increase in panic as measured by the panic VAS. Of note, VAS panic scores did not differ significantly between the first and second panic attacks described in Supplementary Table 1 (paired t-test, $p = 0.13$). Data from the comparison group was statistically compared to the amygdala-lesion group using two-tailed Mann-Whitney *U*-tests with Bonferroni-Holm correction for multiple comparisons (when appropriate) and a significance threshold of $p < 0.05$. The self-report ratings were converted to POMP scores (standardized units representing the "percent of maximum possible" for each scale, ranging from 0–100) [22], and the valence scale was reverse-scored. Several of the self-report measures were not collected in one of the non-panicking comparison participants. Evoked increases in heart rate were calculated by subtracting the baseline rate from the maximum rate during the minute following each inhalation. Baseline was calculated as the average heart rate during the 20 beats preceding the minute before inhalation, whereas maximum heart rate following inhalation was found by assessing each beat-to-beat interval averaged over three seconds. Evoked increases in respiratory rate were similarly calculated by subtracting the baseline rate from the maximum rate during the minute following inhalation. Baseline was calculated as the average respiratory rate during the two minutes prior to inhalation, whereas maximum respiratory rate was found by assessing each breath-to-breath interval during the minute following inhalation. Evoked skin conductance responses (SCR) were calculated by subtracting the average skin conductance level during the first second of inhalation from the peak skin conductance level during the minute following the start of inhalation. Differential increases in respiration, heart rate, and SCR were calculated in each subject by subtracting their maximum evoked response during the air trial from their maximum evoked response during the $CO_2$ trial.

Several factors affected the analysis of the physiological data in the lesion patients. We were unable to obtain skin conductance from anywhere on the palm of the hands or the fingers in

both SM and BG (likely due to epithelial pathology caused by Urbach-Wiethe disease), and thus, patient AM is the only lesion patient included in the SCR analysis and was compared to the comparison participants using a modified t-test [23]. Patient SM was excluded from the heart rate analysis since she was taking propranolol for treatment of hypertension. Additionally, the heart rate data for AM and BG during the first $CO_2$ inhalation could not be analyzed due to contamination by motion artifacts secondary to the patients' escape behavior, and thus, heart rate could only be analyzed during later trials.

Anticipatory physiological responses were also calculated. An anticipatory SCR was considered to be any upward deflection in skin conductance during the 10 seconds prior to inhalation. The magnitude of the response was calculated by subtracting the skin conductance level at the beginning of this deflection from the level at its peak during the 10 seconds prior to inhalation. Anticipatory heart rate was similarly calculated by subtracting the previously described baseline heart rate from the average heart rate calculated during each 3-second interval in the minute before inhalation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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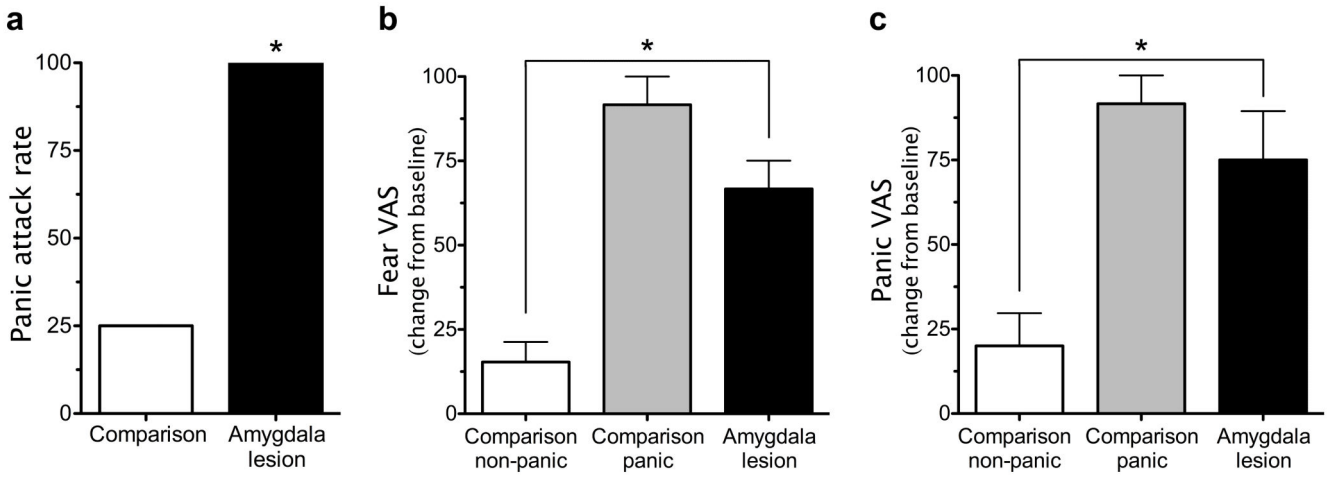


**Figure 1.**

Panic attack rate and self-reported levels of fear and panic during the first $CO_2$ inhalation. (**a**) Panic attack rate (%) in amygdala-lesion patients (n=3) versus the neurologically-intact comparison participants (n=12). All of the amygdala-lesion patients had a panic attack, whereas only 3 of the 12 comparison participants panicked (*p<0.05; Fisher's Exact Test). (**b**) Level of subjective fear and (**c**) level of subjective panic reported during $CO_2$ relative to baseline quantified with visual analog scales (VAS). Both the amygdala-lesion patients and the comparison participants who panicked reported significantly higher levels of fear and panic relative to the comparison participants who did not panic (*p<0.05; Mann-Whitney U-tests). There were no significant differences between the amygdala-lesion patients and the comparison panickers. Error bars represent the standard error of the mean.

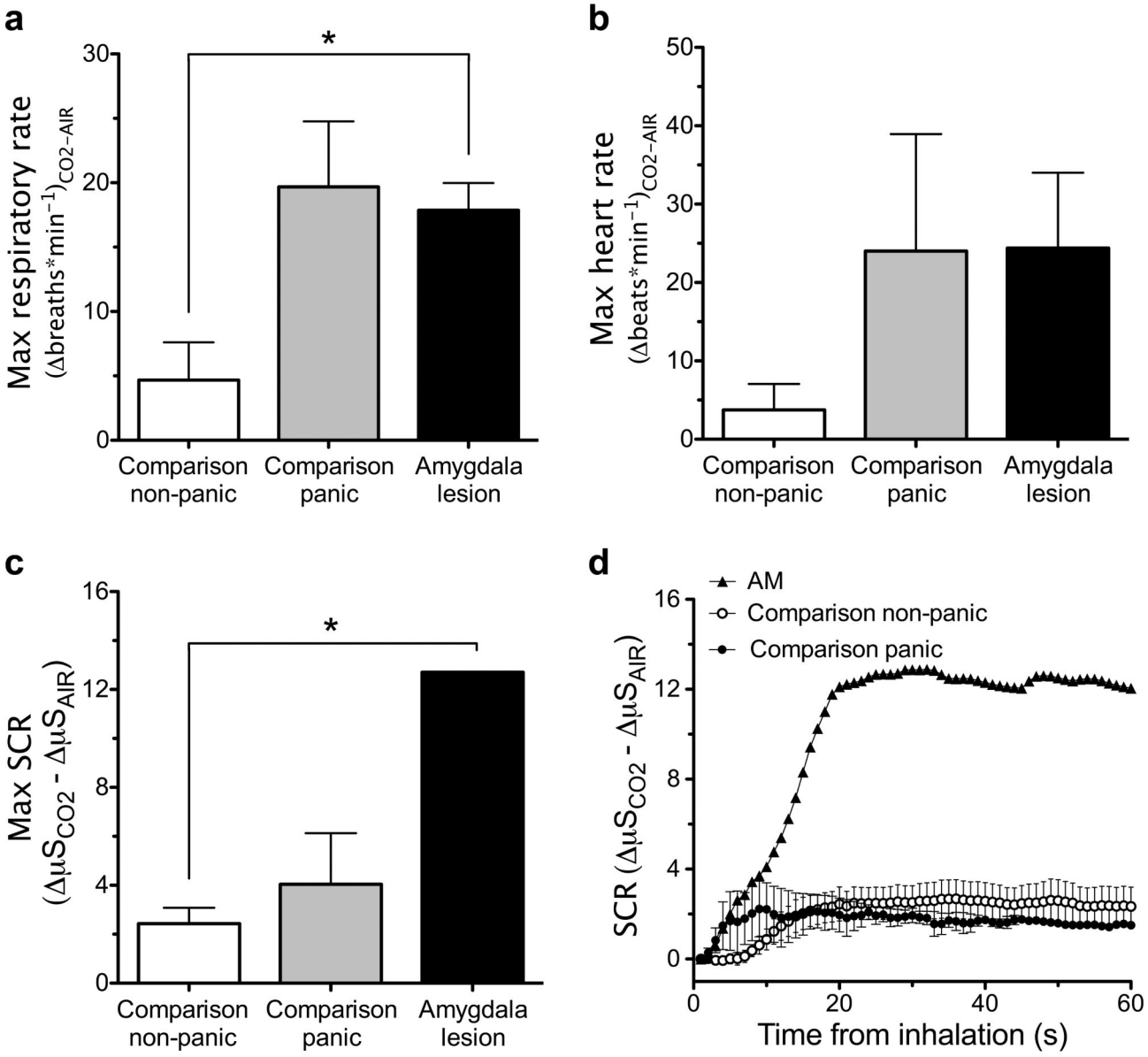


**Figure 2.**

$CO_2$–evoked physiological changes. (**a**) Change from baseline in maximum respiratory rate during the first $CO_2$ trial relative to the first air trial. Both the amygdala-lesion patients (n=3) and the comparison participants who panicked (n=3) demonstrated significantly higher increases in respiratory rate relative to the comparison participants who did not panic (n=9) (*p<0.05; Mann-Whitney U-tests). There was no significant difference between the amygdala-lesion patients and the comparison panickers. (**b**) Change from baseline in maximum heart rate during $CO_2$ relative to air trials. Both the amygdala-lesion patients (n=2) and the comparison participants who panicked (n=3) demonstrated higher increases in heart rate relative to the comparison participants who did not panic (n=9). (**c**) Change from baseline in maximum SCR during the first $CO_2$ trial relative to the first air trial. Patient AM

demonstrated a significantly higher maximum SCR than the comparison participants who did not panic (*p<0.001; modified t-test). (**d**) Change from baseline in SCR during the first $CO_2$ trial relative to the first air trial graphed during the first minute post-inhalation. Error bars represent the standard error of the mean.

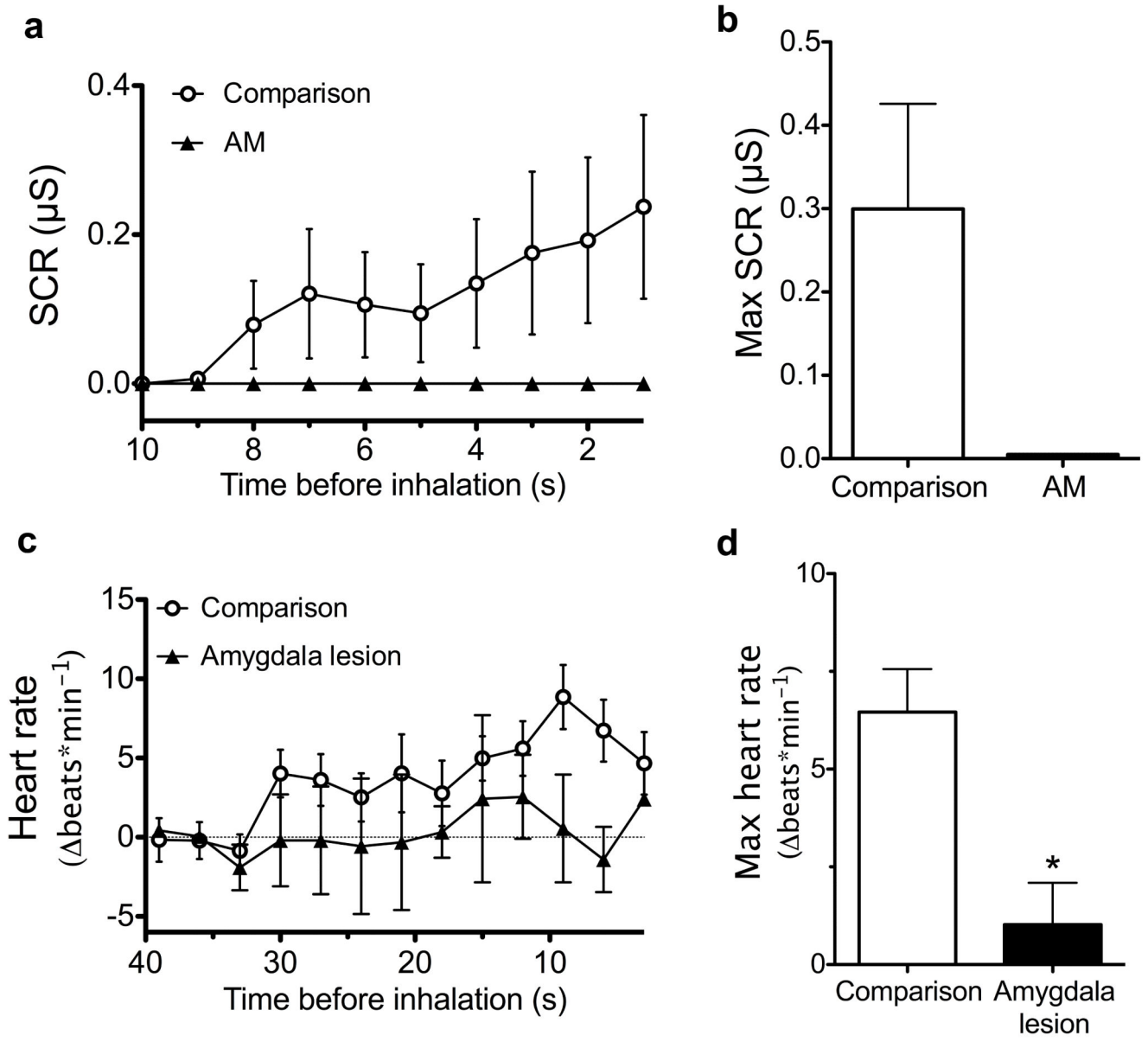


**Figure 3.**

Anticipatory physiological responses prior to inhalation. (**a**) SCR graphed during the 10 seconds prior to inhalation and (**b**) the maximum evoked-SCR during the same time period. Patient AM showed no anticipatory SCR response on any trials. (**c**) Change in heart rate relative to baseline during the 40 seconds prior to inhalation and (**d**) the maximum change in heart rate during the same time period. The amygdala-lesion patients (n=2) had a significantly lower anticipatory heart rate response relative to the comparison participants (n=12) (*$p<0.05$; Mann-Whitney U-test). Error bars represent the standard error of the mean.