Fear and panic in humans with bilateral amygdala damage

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Decades of research have highlighted the amygdala's influential role in fear. 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.

A substantial body of evidence has emphasized 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[2]. The most intensively studied case is patient SM, whose amygdala damage stems from Urbach-Wiethe disease (**Supplementary Fig. 1**). Previous studies have shown that patient 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 inhalation. 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]. Thus, we hypothesized that bilateral amygdala lesions would reduce CO_2-evoked fear in humans.

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

Notably, CO_2 triggered a panic attack in all three of the amygdala-lesion patients. The patients panicked on the first CO_2 trial and during a subsequent challenge (**Supplementary Table 1**), indicating that the effect was reproducible and not simply the result of a novel experience. In contrast, only 3 of the 12 matched, neurologically intact comparison participants panicked (**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 ($P < 0.05$) than in non-panickers from the comparison group (**Fig. 1b,c**). In addition, the patients reported elevated levels of anxiety and found the CO_2 inhalation to be substantially 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.
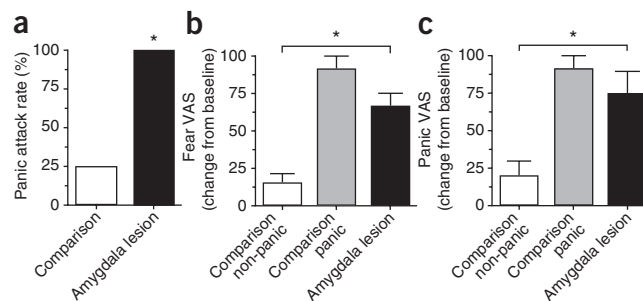

Figure 1 Panic attack rate and self-reported levels of fear and panic during the first CO_2 inhalation. (**a**) Panic attack rate (%) in amygdala-lesion patients ($n = 3$) versus neurologically intact comparison participants ($n = 12$). All of the amygdala-lesion patients had a panic attack, whereas only 3 of the 12 comparison participants panicked (*$P < 0.05$, Fisher's exact test). (**b,c**) Level of subjective fear (**b**) and level of subjective panic (**c**) 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 s.e.m.
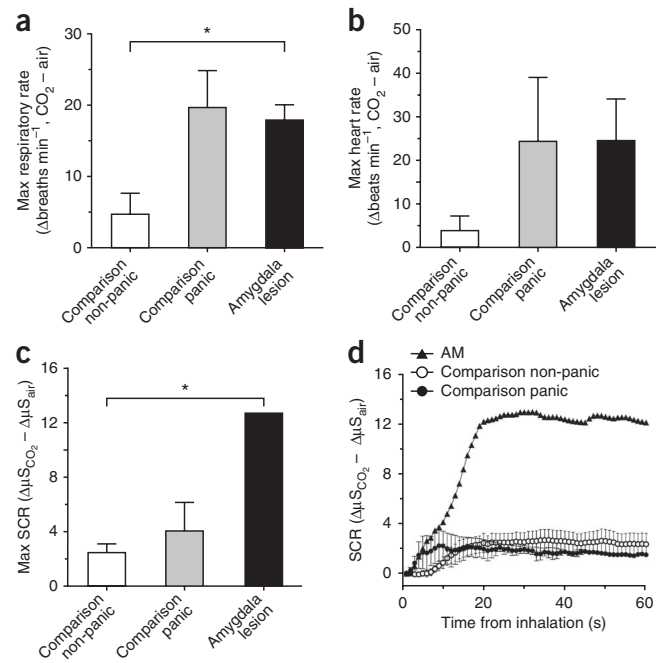
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Figure 2 CO_2-evoked physiological changes. (**a**) Change from baseline in maximum respiratory rate during the first CO_2 trial relative to the first air trial. Both the amygdala-lesion patients ($n = 3$) and the comparison participants who panicked ($n = 3$) 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 s.e.m.

We examined the details of each patient's panic attack (**Supplementary Panic Descriptions**). Several observations were consistent across patients. First, all of the patients found the feelings induced by the CO_2 to be novel and described the experience as "panic." Second, all of the patients displayed similar behavioral responses to CO_2, including gasping for air, distressed facial expressions and escape behavior (for example, 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 with 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 ($P < 0.05$; **Fig. 2**). In contrast, there were no significant differences ($P > 0.05$) 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, SCR and heart rate gradually rose before 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 with 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 that have been 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
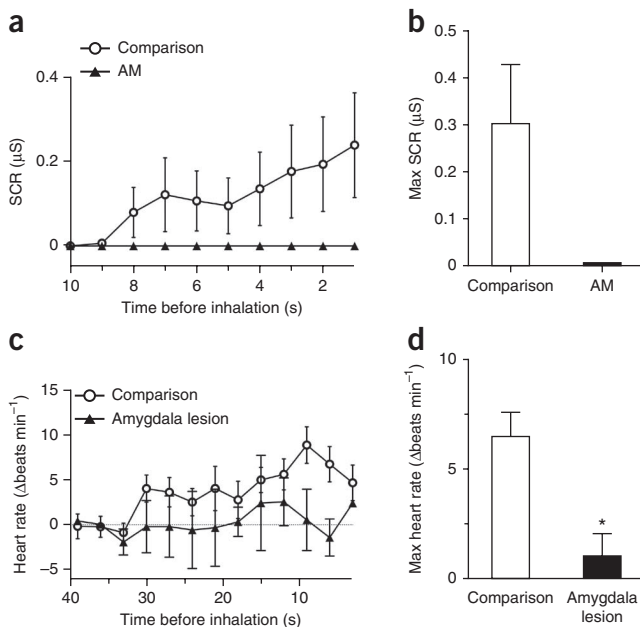

Figure 3 Anticipatory physiological responses before inhalation. (**a,b**) SCR graphed during the 10 s before inhalation (**a**) and the maximum evoked-SCR during the same time period (**b**). Patient AM showed no anticipatory SCR on any trials. (**c,d**) Change in heart rate relative to baseline during the 40 s before inhalation (**c**) and the maximum change in heart rate during the same time period (**d**). The amygdala-lesion patients ($n = 2$) had a significantly lower anticipatory heart rate response relative to comparison participants ($n = 12$) (*$P < 0.05$, Mann-Whitney U test). Error bars represent the s.e.m.

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 with 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]. In addition, 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 that underlie fear and panic, which may help to explain the apparent discrepancy between these findings and previous work in mice[11]. In either case, our results 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.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

AUTHOR CONTRIBUTIONS
J.A.W., M.J.W., J.S.F., R.L.F., D.T., W.H.C. and N.S.D. conceived and planned the experiments. J.A.W., D.T., R.H. and W.H.C. provided financial support, equipment and supplies. J.A.W., C.B., J.S.F., R.L.F., R.H. and N.S.D. recruited participants and performed the experiments. J.A.W., C.B., M.J.W., J.S.F., R.H., D.T., R.L.F., W.H.C. and N.S.D. wrote and edited the manuscript and figures.

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ONLINE METHODS

Subjects. We tested three female patients with bilateral amygdala damage resulting from 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). Baseline recordings were taken during a 2-min rest period before each inhalation and recordings continued for 2 min 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 for the challenge to be considered valid. All subjects completed four single-breath FIVC challenges, two with compressed air and two with 35% CO_2 mixed with 21% oxygen (balanced with nitrogen). All of the 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 min.

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 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 (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 on 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 with 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 3 s. 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 2 min before inhalation, whereas maximum respiratory rate was found by assessing each breath-to-breath interval during the minute following inhalation. Evoked SCR was 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 patients SM and BG (likely as a result of epithelial pathology caused by Urbach-Wiethe disease); thus, patient AM was 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 because she was taking propranolol for treatment of hypertension. In addition, the heart rate data for AM and BG during the first CO_2 inhalation could not be analyzed because of contamination by motion artifacts secondary to the patients' escape behavior; 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 s before 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 s before inhalation. Anticipatory heart rate was similarly calculated by subtracting the previously described baseline heart rate from the average heart rate calculated during each 3-s interval in the minute before inhalation.

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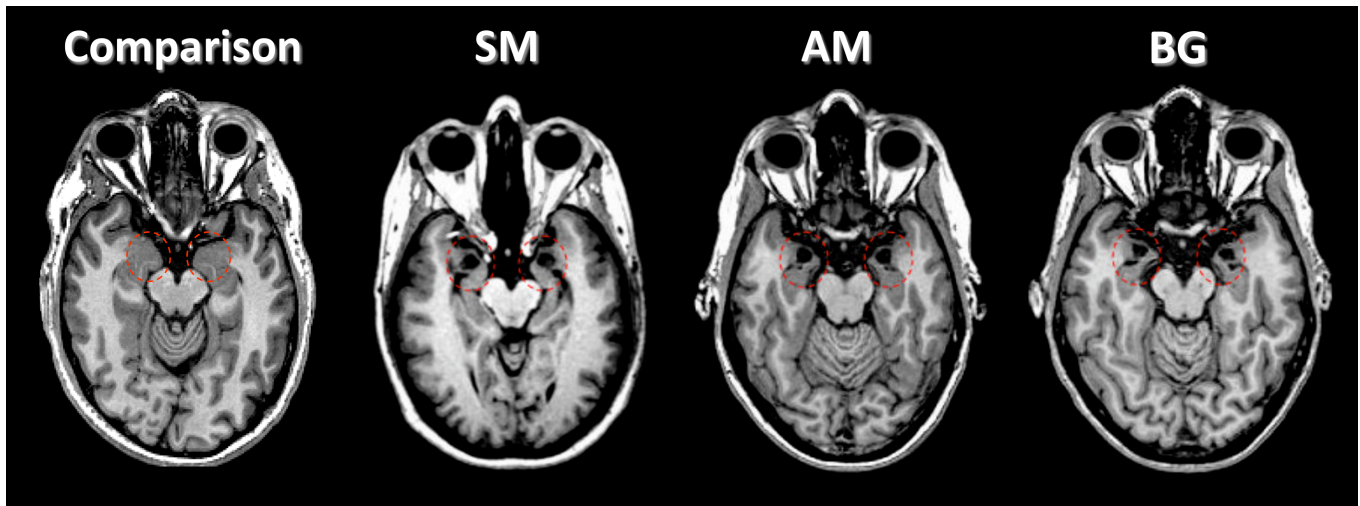# Fear and panic in humans with bilateral amygdala damage

Justin S. Feinstein*, Colin Buzza*, Rene Hurlemann*, Robin L. Follmer, Nader S. Dahdaleh,

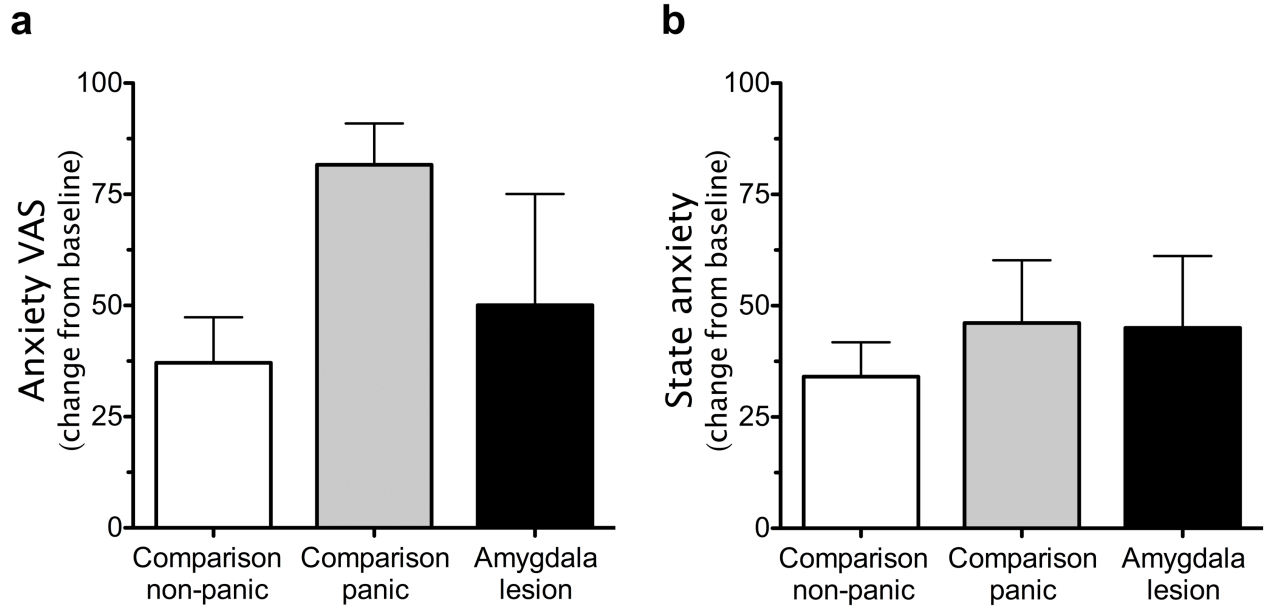William H. Coryell, Michael J. Welsh, Daniel Tranel, and John A. Wemmie

Supplementary Information

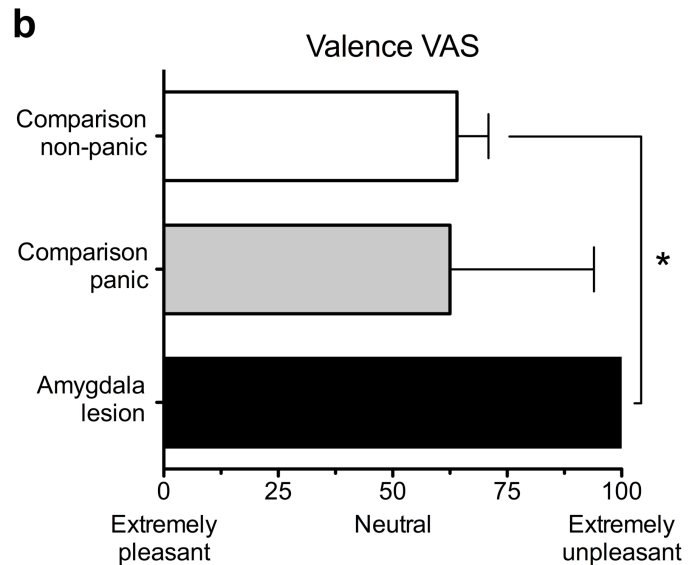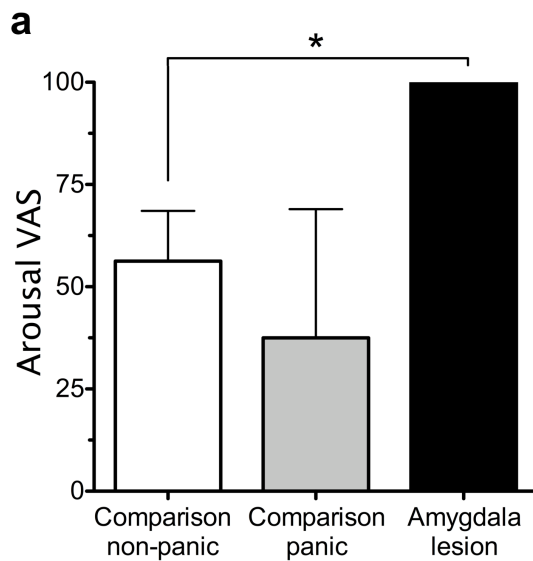*These authors contributed equally to this work

Supplementary Fig. 1. MRI scans acquired during the same time period as the CO_2 experiment revealed focal bilateral amygdala lesions in patients SM, AM, and BG (as highlighted by the red-dashed circles). For comparison, the amygdala of a healthy, neurologically-intact individual is also shown. Detailed neuroanatomical analyses of each patient's amygdala lesion have been previously published. Importantly, other key neural structures related to emotion remain intact, including the insular cortices, ventromedial prefrontal cortices, hypothalamus and brainstem (including the periaqueductal gray).

Supplementary Fig. 2. Change from baseline in self-reported anxiety during the first CO_2 inhalation as measured by (**a**) an anxiety visual analog scale (VAS), and (**b**) the Spielberger State Anxiety Inventory. Error bars represent the standard error of the mean.

Supplementary Fig. 3. Level of self-reported arousal and valence during the first CO_2 inhalation. (**a**) The amygdala-lesion patients rated the CO_2 inhalation as significantly more arousing than the comparison participants who did not panic (*$p<0.05$; Mann-Whitney U-test). (**b**) The amygdala-lesion patients rated the CO_2 inhalation as significantly more unpleasant than the comparison participants who did not panic (*$p<0.05$; Mann-Whitney U-test). Error bars represent the standard error of the mean.

Supplementary Table 1. DSM-IV panic symptoms endorsed by each patient during the panic attack evoked during the first CO_2 inhalation challenge (Panic #1), and during a subsequent CO_2 inhalation challenge (Panic #2).

	Panic #1	Panic #2
SM	-sensations of shortness of breath and smothering -palpitations -derealization (feelings of unreality) -fear of losing control	-sensations of shortness of breath and smothering -trembling and shaking -feeling unsteady -chills and hot flushes
AM	-sensations of shortness of breath and smothering -palpitations -trembling -feeling dizzy -fear of dying	-sensations of shortness of breath and smothering -palpitations -trembling -feeling dizzy -fear of going crazy
BG	-sensations of shortness of breath and smothering -feeling of choking -palpitations and accelerated heart -sweating -trembling -feeling dizzy and faint -derealization (feelings of unreality) -chills -fear of dying	-sensations of shortness of breath and smothering -feeling of choking -palpitations -trembling -feeling dizzy and faint -derealization (feelings of unreality) and depersonalization (being detached from oneself) -paresthesias (numbness or tingling sensations) -fear of dying

<center>**Supplementary Panic Descriptions**</center>

All patients were video recorded during the CO_2 inhalation. Below are detailed behavioral observations of each patient's first CO_2-induced panic attack, followed by excerpts taken from an interview conducted after the inhalation.

Patient SM

Immediately following the inhalation, SM began breathing at a rapid pace and gasping for air. Approximately 8 seconds following the inhalation, her right hand started waving frantically near the air mask. At 14 seconds post-inhalation, SM exclaimed, "Help me!" while her right hand gestured toward the mask. The experimenter immediately removed the mask from SM's face. As this was happening, her body became rigid, her toes curled, and her fingers on both hands were flexed toward the ceiling. As soon as the mask was removed, SM grabbed the experimenter's hand and in a relieved tone said, "Thank you." The skin on her face was flushed, her nostrils were flared, her eyes were opened wide, and her upper eyelids were raised. At 30 seconds post-inhalation, SM's breathing began to return to a normal rate, she let go of the experimenter's hand, and then said, "I'm alright."

SM: It felt like my throat was closing up... I couldn't breathe.

Clinician: What kind of emotions did that cause?

SM: Panic mostly, cause I didn't know what the hell was going on.

Clinician: This [feeling] was really bad?

SM: Yeah, this was the most, number one, worst.

Clinician: Were you surprised that you reacted the way you did?

SM: I was cause usually nothing happens to me.

Clinician: [During the inhalation] what were you worried about?

SM: Suffocating.

Patient AM

At the very beginning of the inhalation, AM's entire upper body (including both arms) slightly

jumped as if startled, her left hand clenched into a fist, and her breathing became pronounced.

Her facial expression formed into a grimace with eyebrows furrowed, eyelids tightly shut, mouth

stretched downward and horizontally, and neck muscles tightened. At 10 seconds post-

inhalation, AM attempted to escape from underneath the mask by contorting her head down and

to the left, while trying to grab the mask with her left hand. At 15 seconds post-inhalation, she

stopped trying to escape, but her eyes remained closed, and her left hand remained near the

mask. By 22 seconds post-inhalation, her body posture and facial expression became more

relaxed, as did her breathing.

Clinician: Can you verbally describe what that experience was like for you?

AM: Yes, fear. A strong fear of suffocation.

Clinician: Did you ever feel this before?

AM: No, never.

Clinician: Is this the strongest feeling of fear you have ever had?

AM: Yes, definitely.

Clinician: Did you have any thoughts that came to your mind during the peak of this

       experience?

AM: I was overwhelmed by the panic and fear of dying. There was nothing else.

Clinician: Did you actually have the thought that you might be dying.

AM: Yes.

<u>Patient BG</u>

During the inhalation, BG's eyelids closed and her eyebrows lowered and furrowed. At 8 seconds post-inhalation, she gasped for air, as her neck muscles clenched, and her facial expression became even more contorted with both eyes tightly shut and her mouth opened and stretched horizontally. Her hands briefly flailed upwards and then rested back down on top of her stomach. At 16 seconds post-inhalation, she ripped the mask off with both hands and started to take deep inhalations followed by quick exhalations as her fingertips gently touched her upper chest and her head slowly rocked back and forth on the headrest. At 36 seconds post-inhalation, BG moved her hands back down to her stomach and her breathing became less labored.

BG: When I breathed in, I didn't get any air. I thought that if it went on then it ends.

Clinician: Could you describe it in a bit more detail? What do you mean by it ends?

BG: Well, that if it went longer, then, I go away.

Clinician: Death?

BG: Yes.

Clinician: Have you ever had such a feeling in your life before?

BG: Totally new.

Clinician: What best describes what you experienced?

BG: Panic... the feeling of suffocation.