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Amygdala-driven apnea and the chemoreceptive origin of anxiety

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Abstract

Although the amygdala plays an important part in the pathogenesis of anxiety and generation of exteroceptive fear, recent discoveries have challenged the directionality of this brain-behavior relationship with respect to interoceptive fear. Here we highlight several paradoxical findings including: (1) amygdala lesion patients who experience excessive fear and panic following inhalation of carbon dioxide (CO_2), (2) clinically anxious patients who have significantly smaller (rather than larger) amygdalae and a pronounced hypersensitivity toward CO_2, and (3) epilepsy patients who exhibit apnea immediately following stimulation of their amygdala yet have no awareness that their breathing has stopped. The above findings elucidate an entirely novel role for the amygdala in the induction of apnea and inhibition of CO_2-induced fear. Such a role is plausible given the strong inhibitory connections linking the central nucleus of the amygdala with respiratory and chemoreceptive centers in the brainstem. Based on this anatomical arrangement, we propose a model of Apnea-induced Anxiety (AiA) which predicts that recurring episodes of apnea are being unconsciously elicited by amygdala activation, resulting in transient spikes in CO_2 that provoke fear and anxiety, and lead to characteristic patterns of escape and avoidance behavior in patients spanning the spectrum of anxiety. If this new conception of AiA proves to be true, and activation of the amygdala can repeatedly trigger states of apnea outside of one's awareness, then it remains possible that the chronicity of anxiety disorders is being interoceptively driven by a chemoreceptive system struggling to maintain homeostasis in the midst of these breathless states.

Keywords

respiration; brainstem; interoception; CO_2; fear; panic; suffocation alarm

Introduction

Anxiety disorders are the most common form of mental illness, affecting over a quarter of the population and representing the sixth leading cause of disability, worldwide (Bandelow & Michaelis, 2015; Baxter et al., 2014; Kessler et al., 2005). Age of onset is typically in adolescence and young adulthood, with symptoms often persisting throughout life without

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treatment, making anxiety one of the most chronic health conditions (Kessler et al., 2012). More than three-quarters of patients never receive treatment (Collins et al., 2004), and meta-analyses and large-scale clinical trials suggest that only about half of patients improve with existing treatments (Loernic et al., 2015; Springer, Levy, & Tolin, 2018; Warden et al., 2007).

Given the ubiquitous and debilitating nature of anxiety, and the insufficient treatment response to currently available therapies, it is imperative that we gain a better understanding of the pathophysiological mechanisms underpinning anxiety so that more targeted treatments can be developed (LeDoux & Pine, 2016). Yet, the etiology driving the chronic and unrelenting nature of anxiety continues to elude neuroscience, psychology, and psychiatry. This point was recently underscored in an article that interviewed a panel of the top researchers in the field and found very little consensus on the basic definition of what constitutes fear and anxiety, let alone the best way to probe its neural underpinnings (Mobbs et al., 2019). In order to avoid confusion, some neuroscientists have recommended that the terms *fear* and *anxiety* be used in an undifferentiated manner, and the focus should instead be on differentiating the specific parameters of the threat (Shackman & Fox, 2016), a recommendation which we intend to follow throughout this paper.

No threat is more proximal to survival than a threat from within the body. Yet, most neuroscience research investigating fear has focused almost exclusively on studying exteroceptive threats conveyed through canonical visual, auditory, olfactory, or somatosensory channels. In contrast, interoception is the process by which the nervous system senses, interprets, and integrates signals originating from within the body, especially the viscera, but very little is known about the neural basis of interoceptive fear (Berntson & Khalsa, 2021; Khalsa et al., 2018; Paulus, Feinstein, & Khalsa, 2019). This paper focuses on the chemoreceptive system, an often-neglected branch of interoceptive neurobiology that is foundational to our survival, and a potential source of the fear and anxiety that so often pervades the consciousness of clinically anxious patients.

Respiratory Chemoreception

Every moment of the day, breath by breath, the chemoreceptive system is regulating the pH of our blood and extracellular fluids within a tightly constrained range between 7.35–7.45 (Duffin, 2005; Shirakabe et al., 2012). Even small shifts in pH will rapidly trigger compensatory changes in respiration, as disruptions in acid-base homeostasis can quickly lead to organ failure and eventually death. Carbon dioxide (CO_2) is the primary driver of these respiratory changes. Increases in CO_2 reduce blood pH (via carbonic acid), triggering acidosis. CO_2 also provokes pronounced changes throughout the cardiovascular system including vasodilation and an increase in blood pressure and cerebral blood flow (Battisti-Charbonney, Fisher, & Duffin, 2011; Chang & Glover, 2009; Vickers et al., 2012). As aptly summarized by one of the original CO_2 physiologists, "*Carbon dioxide is the chief [para]hormone of the entire body; it is the only one that is produced by every tissue and that probably acts on every organ… carbon dioxide is, in fact, a more fundamental component of living matter than is oxygen*" (Henderson, 1940).

Respiration is regulated by the chemoreceptive system via feedback from peripheral and central chemoreceptors (Del Negro, Funk, & Feldman, 2018; Guyenet & Bayliss, 2015), in addition to acid-sensing ion channels found in neurons throughout the nervous system (Wemmie, Price, & Welsh, 2006). Peripheral chemoreceptors monitor the arterial blood for changes in the partial pressure of oxygen (PO_2), the partial pressure of carbon dioxide (PCO_2), and pH, and can be found in two primary locations: (1) the carotid body located near the bifurcation of the carotid arteries, and (2) the aortic bodies on the aortic arch. Signals from the peripheral chemoreceptors are directly transmitted to the nucleus tractus solitarii (NTS) in the brainstem, with signals from the carotid body conveyed via the glossopharyngeal nerve and signals from the aortic bodies conveyed via the vagus nerve. The carotid body is the primary peripheral chemoreceptor responsible for detecting states of hypoxemia (Iturriaga et al., 2021), with recent work also highlighting its role in both inflammation and metabolism (Conde, Sacramento, & Martin, 2020). Central chemoreceptors are largely located on the ventrolateral surface of the medulla, in regions such as the medullary raphe and the retrotrapezoid nucleus (Nattie & Li, 2012; Richerson, 2004). Since central chemoreceptors sense changes in PCO_2 and pH within the cerebrospinal fluid, the central nervous system is remarkably insensitive to detecting acute short-term changes in oxygen (Nattie & Li, 2012; but see Gestreau et al., 2010 for an example of how central chemoreceptors can respond to chronic hypoxia). In contrast, changes in CO_2 are readily detected by both central and peripheral chemoreceptors and rapidly alter respiration such that an increase in PCO_2 of 2–5 mmHg can increase ventilation more than twofold (Del Negro, Funk, & Feldman, 2018; Duffin, 2005; Rassovsky, Abrams, & Kushner, 2006). As PCO_2 rises and pH becomes more acidic, respiratory chemoreceptors will emit a cascade of "*suffocation alarms*" (Klein, 1993), a proverbial primal scream aimed at alerting the nervous system of impending demise. If corrective action is not immediately taken, unconsciousness can occur within as little as 30 to 40 seconds, and death within a matter of minutes (Sharp, Azar, & Lawson, 2006).

Fear and panic in patients with bilateral amygdala lesions

There is a large body of evidence in both humans and other animals showing that the amygdala plays a central role in the generation of fear and pathogenesis of anxiety (Davis, 1992; Etkin & Wager, 2007; Gorman et al., 2000; Kalin, Shelton, & Davidson, 2004; Oler et al., 2010; Shackman & Fox, 2016; Tovote, Fadok, & Lüthi, 2015). Much of this research utilized external threats, such as exposure to predators, in order to probe the behavioral manifestations of fear. For example, animals with amygdala lesions typically display reduced freezing and a striking lack of avoidance as exemplified by rats with amygdala lesions that readily approach cats (e.g., Blanchard & Blanchard, 1972), and monkeys with amygdala lesions that approach snakes (e.g., Meunier et al., 1999). Much less is known about the amygdala's "necessary" role in the conscious experience of fear (LeDoux & Pine, 2016). This is in large part because nonhuman animals with amygdala lesions are unable to verbally report on their internal subjective experience, and humans with amygdala lesions are extremely rare.

An exception is patient SM, a middle-aged woman with Urbach–Wiethe disease who is one of the best-characterized human cases with focal bilateral amygdala lesions. Over the

past three decades, there have been numerous attempts to probe SM's reaction to a host of different exteroceptive threats, in both the laboratory and the real-world (for a review of these publications, see Feinstein, Adolphs, & Tranel, 2016). Similar to amygdala-lesioned animals, SM exhibits a deficit in fear conditioning (Bechara et al., 1995), and an overall lack of fear and avoidance behavior to external threats including when exposed to snakes and tarantulas, horror films, haunted houses, and a range of traumatic life events (Feinstein et al., 2011). Beyond her inability to recognize and respond to dangerous situations, SM also reported that such situations failed to evoke feelings of fear. Her highly impoverished experience of fear dates back to adolescence, around the time when her amygdala lesions likely began to emerge. However, during early childhood, SM remembers several incidents that did evoke fear, and as a consequence, she maintains a basic conceptual understanding of what fear feels like (Feinstein et al., 2011).

After many unsuccessful attempts to scare SM using exteroceptive threats, we shifted course and decided to probe her reaction to interoceptive threat. In comparison to the wide range of paradigms probing exteroceptive fear, there are far fewer options for safely inducing interoceptive fear in humans. One method that has been well-studied entails the inhalation of an air mixture containing 35% CO_2 (Vickers et al., 2012), a quantity of CO_2 that is 875 times greater than the amount of CO_2 in the air we typically breathe (~.04%). Given such a high concentration, participants only take a single vital capacity inhalation, triggering a brief hypercapnic state that rapidly activates both central and peripheral chemoreceptors causing a marked increase in ventilation (Griez, van den Hout, & Verstappen, 1987; Rassovsky & Kushner, 2003; Vickers et al., 2012). The most commonly reported side effect of this chemoreceptive perturbation is a profound sense of 'air hunger' that is felt almost immediately after the inhalation and lasts for about a minute (Vickers et al., 2012). Since the gas mixture contains a normal amount of oxygen, O_2 levels within the body are unaffected, which means that the CO_2 manipulation triggers an illusion of air hunger. Despite its illusory nature, the feeling induced by 35% CO_2 is very potent and capable of inducing fear, anxiety, and even panic, in up to one-quarter of healthy individuals who undergo this challenge (Colasanti et al., 2012). In individuals with a history of panic disorder, the manipulation readily produces full-blown panic attacks that closely parallel those occurring in everyday life (Colasanti et al., 2012; Schruers, Van de Mortel, Overbeek, & Griez, 2004).

The amygdala has been shown to have the ability to directly detect changes in CO_2 and pH through acid-sensing ion channels, leading to CO_2-evoked fear behaviors (Ziemann et al., 2009). Moreover, several theories have highlighted a central role for the amygdala in the generation of panic attacks (Coplan & Lydiard, 1998; Gorman, Kent, Sullivan, & Coplan, 2000). Based on these theories and findings, we hypothesized that patient SM would experience abnormally low levels of CO_2-evoked fear and panic as a result of the damage incurred to her amygdala. To test this hypothesis, we arranged for SM to undergo a 35% CO_2 challenge, marking the first time we had ever directly exposed her to an interoceptive threat (Feinstein et al., 2013).

Immediately following the inhalation of 35% CO_2, SM began breathing at a rapid pace and gasping for air, exclaiming, "*I can't breathe*". She attempted to escape from the air mask (even though it was no longer delivering CO_2). During debriefing, she reported that

she felt an immense fear, labeling it as the "*worst*" fear she had ever felt in life. In one breath, our hypothesis was proven wrong, and we learned that the amygdala could not be the brain's quintessential and sole fear center. To test whether this result was reproducible, we collaborated with Dr. René Hurlemann, who had identified monozygotic twin sisters (AM and BG) who both had focal bilateral amygdala lesions due to the same genetic disorder as SM (Becker et al., 2012). Replicating SM's reaction, inhalation of 35% CO_2 triggered panic attacks in both twins characterized by an intense fear of suffocation, concomitant thoughts of death, heightened physiological arousal (including hyperventilation), and prominent signs of escape behavior (Feinstein et al., 2013). The amygdala-lesioned patients exhibited a significantly higher rate of CO_2-evoked fear and panic than a sample of demographically-matched healthy participants who did not panic when exposed to CO_2 (Figure 1). The procedure entailed single vital capacity inhalations of 35% CO_2 or compressed air, each administered twice in a blinded order. Subjective changes were assessed several minutes after each inhalation where participants reported how they felt during and immediately following the inhalation when symptoms were at their peak. Physiological changes were concurrently measured throughout each inhalation. The threshold for defining a panic attack used conservative criteria (Rassovsky & Kushner, 2003) that required a participant to endorse at least four DSM-IV symptoms of panic, exhibit signs of escape behavior, and report at least a 25% increase in self-reported panic.

The significantly higher level of panic experienced by the amygdala-lesioned patients raises the possibility that instead of inducing panic, the amygdala may be integrally involved in inhibiting panic, especially panic evoked by elevated levels of CO_2. Such an inhibitory role might also help explain how another patient with amygdala lesions spontaneously developed panic attacks in everyday life (Wiest, Lehner-Baumgartner, & Baumgartner, 2006). Likewise, amygdala-lesioned mice were recently found to exhibit an excessive amount of escape behavior (frenetically jumping off the walls and ceiling) in tandem with a lack of freezing behavior when placed in a chamber with 10% CO_2 (Taugher et al., 2020). Notably, this pattern of excessive escape behavior was eliminated by also lesioning the dorsal periaqueductal gray (PAG), suggesting that an intact amygdala normally inhibits CO_2-induced escape and promotes CO_2-induced freezing via its connections with the PAG (Kim et al., 2013). Interestingly, bilateral lesions to the bed nucleus of the stria terminalis (BNST) in mice also reduced freezing to 10% CO_2, as well as conditioned-place avoidance, however the BNST-lesioned mice did not show any sign of the excessive escape-like behavior that was seen in the amygdala-lesioned mice, suggesting that the amygdala may exert a preferential regulatory role over CO_2-induced escape (Taugher et al., 2014; Taugher et al., 2020).

In a follow-up study with the amygdala-lesioned twins (Khalsa et al., 2016), we examined their response to a different form of interoceptive threat entailing intravenous infusions of isoproterenol, a beta-adrenergic agonist akin to adrenaline. Shortly after receiving a 4 microgram bolus infusion of isoproterenol, both patients exhibited a large physiological response as evidenced by a rapid acceleration in their heart rate, on the order of 30 beats per minute faster than baseline. During this time period, both patients reported experiencing heightened levels of anxiety. One of the patients (BG) had a panic attack that was accompanied by intense feelings of breathlessness, a partial replication of what

was found during the CO_2 challenge. However, BG's level of self-reported panic was only about half the intensity of what she experienced during 35% CO_2, and neither patient reported having a fear of dying during isoproterenol, signifying that CO_2 was a more potent panicogen. One potential explanation for this difference in panic response could be due to the fact that isoproterenol bronchodilates the lungs (Tattersfield & McNicol, 1969) and thus would not be expected to elicit hypercapnia.

While definitive conclusions from the above lesion experiments with CO_2 and isoproterenol are limited by the small number of rare patients that were studied, the findings demonstrate that the amygdala is not always required for the conscious experience of fear, anxiety, and panic. Brain regions outside the amygdala may be the source of interoceptive fear and identifying their locus could provide key neural modulation targets for future anxiolytic treatments. These findings also stand in sharp contrast to prior research from our group demonstrating that these same lesion patients showed a marked absence of fear in response to threatening stimuli from the external environment (Becker et al., 2012; Feinstein et al., 2011; Feinstein et al., 2016; Scheele et al., 2012). Thus, there appears to be an important neural distinction between threats conveyed through exteroceptive sensory channels (e.g., visual and auditory pathways) versus threats conveyed through interoceptive sensory channels (e.g., chemoreceptive and cardiorespiratory pathways). Sensory and association cortices required for representing external stimuli are intact in the brain of SM and the other lesion patients, as are the brainstem and hypothalamic circuitry necessary for orchestrating the action program of a fear response. Their amygdala lesion in effect disconnects these two components, making it improbable, if not impossible, for external sensory representations of threat to trigger full-blown fear responses, leading to their deficits in the realm of exteroceptive fear. On the other hand, interoceptive threats are able to bypass the amygdala and directly stimulate the brainstem. Since the lesion patients have lost the amygdala's inhibitory control over brainstem circuitry, certain interoceptive threats (such as CO_2 and isoproterenol) can lead to a disinhibited fear response that likely engages an interoceptive pathway projecting from the brainstem to the diencephalon, insular cortices, anterior cingulate, and a network of other limbic and cortical structures, culminating in their conscious experience of fear, anxiety, and panic (Berntson & Khalsa, 2021; Davenport & Vovk, 2009). In summary, the amygdala may be critical for the generation of exteroceptive fear, but it does not appear to be necessary for the generation of interoceptive fear. Instead, the amygdala may play an important role in the inhibition of interoceptive fear, especially chemoreceptive fear evoked by elevations in CO_2.

Amygdala-driven apnea and the loss of awareness for elevations in CO_2

Recent findings from the field of neurosurgery (Dlouhy et al. 2015; Lacuey et al., 2017; Nobis et al. 2018; Rhone et al., 2020) have identified a remarkable brain-behavior relationship that has largely been overlooked for the better part of the past century; stimulation of the human amygdala inhibits breathing and triggers apnea, yet surprisingly, the patients had no awareness that their breathing had stopped, and did not report any fear or dyspnea as their CO_2 levels rose during the period of apnea. In other words, amygdala stimulation can quite literally 'take one's breath away' and they will not even know that it has happened. The neurosurgical studies defined an apnea as the involuntary cessation of

breathing following the onset of electrode stimulation where at least 2 breaths were missed with a drop in peak signal excursion ≥ 90% of baseline breathing (Lacuey et al., 2017) or at least 1 breath was missed with a flattened airflow trace (oral/nasal thermistor or nasal pressure transducer) and verified by the absence of chest wall movement as measured with plethysmography belts or video (Rhone et al., 2020). In this next section we review these findings in detail and discuss how they further highlight the strong inhibitory role of the amygdala with regard to both respiration and chemoreception.

The first study to clearly demonstrate amygdala-driven apnea was published in 2015 by Dlouhy and his colleagues at the University of Iowa (Dlouhy et al., 2015). They found that stimulation of electrodes in the amygdala would cause breathing to come to an immediate halt and often remain in a state of apnea until the stimulation was turned off (Figure 2). All three patients who were tested were awake and conscious throughout the stimulation, but were completely unaware that their breathing had stopped, and showed no signs of discomfort or distress. In one patient, the apnea lasted for 48 seconds, causing their oxygen saturation to drop from 97% to 87%. When this same patient was asked to voluntarily hold their breath for the same amount of time, but without the amygdala stimulation, they had great difficulty doing so and reported experiencing severe dyspnea during the breathhold, suggesting that the amygdala stimulation was somehow inhibiting their normal response to elevations in CO_2.

This finding of amygdala-driven apnea has now been replicated by two other neurosurgical departments (Lacuey et al., 2017; Nobis et al. 2018), and in all cases the patients were completely unaware that their breathing had stopped. In one case the apnea lasted for 56 seconds and caused the patient's end-tidal CO_2 to increase by 10 mmHG (Lacuey et al., 2017). Most recently, these results were replicated in patients with pediatric epilepsy (Rhone et al., 2020), which found that all patients "*were completely unaware that they had stopped breathing and did not report any shortness of breath, air hunger, desire to breathe, or display any visible signs of respiratory distress during or after the periods of stimulation-induced apnea*" (Rhone et al., 2020, p. 3). The researchers stimulated a number of different electrodes, both within and outside of the amygdala, and found a remarkable degree of specificity such that apnea only occurred when the amygdala was stimulated. Using machine learning with a multiclass support vector, the researchers identified a specific site in the basomedial amygdala that consistently induced apnea. Notably, the basomedial amygdala has been shown to mediate the top-down control of fear and freezing via projections from the ventromedial prefrontal cortex (Adhikari et al., 2015). In the study by Nobis et al. (2018), they found that apnea was most reliably induced when the most medial electrodes were stimulated, corresponding to activation of the central nucleus of the amygdala. Prior research stimulating the central nucleus of the amygdala in rabbits (Applegate et al., 1983) and cats (Harper et al., 1984) found that brief pulses of stimulation (< 1 second in duration) often led to transient increases in respiration, whereas the human neurosurgical studies all delivered trains of electrical stimulation over a prolonged period (between 5 to 60 seconds). This suggests that the amygdala has the potential to both excite and inhibit respiration, depending on the duration of stimulation.

While most neurosurgical studies have found that apnea was only elicited following amygdala stimulation, there have been sporadic reports of apnea following stimulation to other regions in the medial temporal lobe (Lacuey et al., 2019) and adjacent limbic structures (Kaada & Jasper, 1952). A retrospective analysis of epilepsy patients who had seizures while being monitored with intracranial electrodes found a high incidence of ictal central apnea as the seizure spread into the amygdala (Nobis et al., 2019). These findings have important implications for understanding the etiology of sudden unexpected death in epilepsy (SUDEP), the most common cause of death in patients with refractory epilepsy (Buchanan, 2019; Massey, Sowers, Dlouhy, & Richerson, 2014). In line with this notion, a mouse model of SUDEP found that electrolytic lesions to the amygdala significantly reduced the incidence of seizure-induced respiratory arrest (Marincovich, Bravo, Dlouhy, & Richerson, 2019), adding further evidence that amygdala-driven seizures are inducing apnea and playing a causal role in the sudden death of patients with epilepsy, often times without their awareness.

It is quite remarkable that we are only learning about this strong relationship between the amygdala and apnea in recent years, as researchers have been stimulating the amygdala for many decades. However, a close inspection of the literature reveals several documented instances of amygdala-driven apnea. The first report by W.G. Spencer in 1894 found that respiration in non-human animals "*can be slowed and arrested by excitation of a certain spot… to the outer side of the olfactory tract just in front of the junction of the tract with the uncinate. And this arrest can be constantly obtained and the experiment repeated again and again under certain conditions*" (Spencer, 1894, p.629). In 1899, Hughlings Jackson commented on this prescient observation, "*I presume that the arrest is by great cortical inhibition of the respiratory medulla… watching patients in slight paroxysms of epilepsy with regard to degrees of asphyxia… there is sometimes turning blue, as the friends may say. Here comes, I submit, the importance of that part of Mr. W.G. Spencer's research which I have quoted; his is very near to the uncinate gyrus. So that if an epileptic discharge does begin in some part of that gyrus it may spread to and may soon reach the arrest centre*" (Jackson, 1899). The first report of intracranial stimulation in humans causing apnea came in 1952, where mechanical stimulation "*in and about the anterior portion of the hippocampal gyrus resulted in complete respiratory arrest… in one instance for as long as 56 seconds*" (Kaada & Jasper, 1952). There was also another case where respiratory arrest for as long as 40 seconds could be reliably evoked following stimulation "*near the center of the left amygdala*" (Nelson & Ray, 1968). In rats, the intensity of hypercapnic response to CO_2 was inversely correlated with *c-fos* expression in the medial amygdala consistent with the amygdala having an inhibitory influence on chemoreception (Tenorio-Lopes et al., 2017). In anesthetized squirrel monkeys, stimulation of the amygdala caused prolonged apneas, leading to significant increases in PCO_2 and decreases in pH (Reis & McHugh, 1968). Remarkably, the respiratory inhibition "*persisted long enough to cause myocardial hypoxia and even death from lethal arrythmias*", yet signs of the monkey struggling were notably absent. Similar changes in PCO_2 and pH were reproduced via occlusion of the trachea, however without concurrent stimulation of the amygdala, the tracheal occlusion elicited a strong increase in respiratory effort and behavioral signs of struggle in the monkey. Reis &

McHugh (1968) concluded that the amygdala stimulation had selectively blocked respiratory and behavioral chemoreceptor responses.

Amygdala projections to the brainstem are inhibitory

The amygdala is one of the most highly connected structures in the brain (Pessoa, 2008). It is comprised of 13 different subnuclei, each with their own unique pattern of connectivity (Freese & Amaral, 2009). Neuroanatomical connections linking the amygdala with the brainstem are inhibitory in nature and prominently feature brainstem nuclei involved in both respiration and chemoreception. Much of our understanding of amygdala neuroanatomy comes from studies conducted in non-human animals such as rats and monkeys (Freese & Amaral, 2009). Since there are differences between species in the physiological properties of amygdala neurons (Dumont et al., 2002), it will be important to conduct more anatomical studies in human brains (including postmortem approaches) to verify the connectivity patterns (Mori et al., 2017).

The central nucleus provides the amygdala's primary output to the brainstem and is quite distinct from other amygdala nuclei due to its 'striatal-like' medium spiny neurons that form a continuum with the bed nucleus of the stria terminalis (BNST) in what has come to be known as the *extended amygdala* (Davis, Walker, Miles, & Grillon, 2010; Shackman & Fox, 2016). Notably, the central nucleus and BNST share many connections to brainstem nuclei and also appear to share an overlapping timing of impulses to these nuclei (Nagy & Paré, 2008). It is important to recognize that the cells in the central nucleus of the amygdala are primarily GABAergic inhibitory neurons (Babaey, Chatain, & Krueger-Berg, 2018; Ciocchi et al., 2010). These GABAergic neurons are innervated by GABAergic interneurons from the adjacent intercalated cell islands, as well as GABAergic projections from the insula (Cassell, Freedman, & Shi, 1999; Sun, Yi, & Cassell, 1994), and this dense GABAergic circuitry appears to underlie the anxiolytic effect of benzodiazepines (Griessner et al., 2018; Paulus et al., 2005).

As a consequence of this arrangement, the projections from the central nucleus of the amygdala to the brainstem are also GABAergic, and thus, inhibitory in nature (Jongen-Rêlo & Amaral, 1998; Liu et al., 2021). The most prominent projections are to brainstem nuclei critically involved in regulating autonomic functioning (Price & Amaral, 1981). These include direct projections to nuclei that regulate the rhythm of respiration including the parabrachial nucleus and preBötzinger complex, as well as projections to a site in the midline of the medulla that has been shown to elicit apnea (Dutschmann & Dick, 2012; Jia, Zhang, & Wan, 2005; Verner, Pilowsky, & Goodchild, 2008; Yang et al., 2020). The central nucleus also innervates nuclei that mediate sympathetic arousal, including asphyxia-induced and CO_2-induced arousal; these include projections to adrenergic and noradrenergic neurons in the rostral ventrolateral medulla, locus coeruleus, and the dorsal motor nucleus of the vagus (Cassel & Gray, 1989; Guyenet & Abbott, 2013; Liu et al., 2021; Wallace, Magnuson, & Gray, 1992). The central nucleus has additional projections to the dorsal periaqueductal gray (PAG), dorsal raphe, as well as the lateral and dorsomedial hypothalamus, regions which are integrally involved in orchestrating the full repertoire of defensive behaviors that characterize states of fear, anxiety, and panic including freezing, avoidance, and escape (Del-

Ben & Graeff, 2009; Keifer et al., 2015; Spiacci, Coimbra, & Zangrossi, 2012; Schimitel et al., 2012; Weera et al., 2021; Weissbourd et al., 2014). In terms of chemoreception, the central nucleus has projections to both the retrotrapezoid nucleus (Rosin, Chang, & Guyenet, 2006) and the medullary raphe (Mason, 2001; Richerson, 2004), the primary sites of the brain's central chemoreceptors (Nattie & Li, 2012). It also projects to the NTS (Saha, Batten, & Henderson, 2000), a region which is the primary recipient of signals from peripheral chemoreceptors (Zoccal et al., 2014) and vagal sensory afferents from the lungs (Chang et al., 2015). This unique pattern of connectivity combined with strong GABAergic projections make the central nucleus of the amygdala ideally situated to: (1) inhibit respiration, (2) inhibit chemoreceptive awareness for elevations in CO_2, and (3) inhibit the associated fear and arousal spurred by CO_2-induced suffocation alarms.

Apnea-induced Anxiety

In the current section we discuss how amygdala activity fits within a model of Apnea-induced Anxiety (AiA). The AiA model predicts that similar to the neurosurgical stimulation studies, states of apnea are being unconsciously triggered by amygdala activation, resulting in transient spikes in CO_2 that can provoke anxiety and lead to avoidance behavior. We hypothesize that varying degrees of AiA is happening on a recurring basis in day-to-day life in all individuals who have a functioning amygdala capable of inhibiting downstream structures within the brainstem. The basis of the model is that once amygdala activation surpasses a certain threshold, breathing will be inhibited and a transient episode of apnea will be triggered. One prediction stemming from this model is that individuals who have a hyperactive amygdala (Swartz, Knodt, Radtke & Hariri, 2015), especially patients with clinical anxiety (Bruehl, Delsignore, Komossa, & Weidt, 2014; Etkin & Wager, 2007; Hayes, Hayes, & Mikedis, 2012; Ipser, Singh, & Stein, 2013), will be most at risk of having recurrent episodes of amygdala-driven apnea. Like the neurosurgical stimulation studies, the model predicts that most individuals will be entirely unaware of the fact that their breathing has temporarily stopped. Their first sign of disturbance would only become apparent after amygdala activation had subsided and its inhibition over the brainstem was lifted, at which point they would resume breathing but would suddenly feel anxious due to the unforeseen build-up of CO_2 generated during the episode of apnea. From this perspective, the well-documented hypersensitivity that anxious patients have in response to CO_2 may not entirely be due to suffocation false alarms, as originally theorized (Klein, 1993), but rather real alarms firing to transient spikes in CO_2 caused by recurring episodes of amygdala-driven apnea (Figure 3).

The amygdala's ability to elicit apnea could be an evolutionarily determined manifestation of the broader freezing response that the amygdala is well-known to coordinate (Janak & Tye, 2015). For instance, when central amygdala circuits receive signals of imminent threat, respiration might be reflexively paused to help the prey avoid being detected by the predator. Given the amygdala's strong inhibitory input over key respiratory and chemoreceptive nuclei, this arrest of respiration can be rapidly enacted and sustained, even as CO_2 levels escalate. The amygdala-lesioned patients may have lost this ability, as their lesion has effectively severed the amygdala's inhibitory connections to the brainstem. As a consequence, they experience a disinhibited state of fear to elevations in CO_2 characterized

by excessive escape behavior and hyperventilation. When queried afterwards, the lesion patients all reported that the feelings induced by CO_2 could be best described as a profound fear of suffocation (Feinstein et al., 2013).

These observations support aspects of Donald Klein's suffocation false alarm theory of spontaneous panic, which hypothesizes that "*a physiologic misinterpretation by a suffocation monitor misfires an evolved suffocation alarm system. This produces sudden respiratory distress followed swiftly by a brief hyperventilation, panic, and the urge to flee. Carbon dioxide hypersensitivity is seen as due to the deranged suffocation alarm monitor*" (Klein, 1993, p. 306). The data from the lesion patients as well as the intracranial stimulation studies all point to the amygdala as being integrally involved in monitoring and regulating suffocation alarms emerging from chemoreceptive centers in the brainstem. However, the proposed physiologic misinterpretation that leads to "false" suffocation alarms may not be a misfire after all, but rather, an entirely appropriate response to an actual alarm. In other words, the amygdala could be triggering episodes of apnea outside of one's awareness, and the subsequent build-up of CO_2 would activate chemoreceptors and trigger the suffocation alarm system. This reinterpretation of Klein's theory suggests that CO_2 hypersensitivity may actually be a byproduct of real suffocation alarms being repeatedly incited by episodes of amygdala-driven apnea.

CO_2 hypersensitivity across the spectrum of anxiety

According to the AiA model, CO_2 hypersensitivity likely develops over time as a consequence of recurring episodes of amygdala-driven apnea leading to hypercapnia. Due to the amygdala's inhibition over the chemoreceptive system during the actual episode of apnea, hypercapnic states would seem to suddenly emerge out of the blue, after amygdala activation has subsided and its inhibition over the brainstem has lifted. This in turn triggers a much larger suffocation alarm than if the chemoreceptors' warnings had been heeded during the initial moments of apnea. Over time, these unforeseen homeostatic disruptions to the acid-base balance may cause the chemoreceptive system to respond disproportionately to small increases in CO_2, such that even short periods of apnea can induce feelings of anxiety and suffocation fear in anxious individuals (such as during a voluntary breath hold: Asmundson & Stein, 1994; Lapidus et al., 2020). Moreover, since a key component of anxiety is apprehensive worry about uncertain events in the future, the repeated occurrence of unexpected hypercapnic states would undoubtedly heighten one's level of apprehension, leading to more anxiety and greater levels of hypersensitivity toward CO_2.

CO_2 hypersensitivity is most commonly tested by having patients inhale an air mixture containing elevated levels of CO_2. This simple procedure will often trigger anxiety across the spectrum including in patients with panic disorder (Colasanti et al., 2012; Rassovsky & Kushner, 2003), posttraumatic stress disorder (Kellner et al., 2018; Muhtz et al., 2011; Telch et al., 2012), and social anxiety disorder (Blechert et al., 2010; Caldirola et al., 1997; Gorman et al., 1990). Importantly, in the studies above, the demographically-matched healthy participants experienced significantly less anxiety than the patients when exposed to the same exact dose of CO_2, confirming that the anxious patients' CO_2-response was indeed hypersensitive. In addition, patients will often report that the feelings induced by CO_2 are

remarkably similar to the anxiety and panic that they experience in everyday life (Rapee et al., 1992; Schruers et al., 2004). This same observation was actually highlighted in one of the first studies to ever expose anxious patients to CO_2 (Cohen & White, 1951), with the patients reporting that the feeling induced by CO_2 was "*identical*" to the surges in anxiety that they felt in everyday life.

The fact that CO_2 induces anxiety across the spectrum of anxiety disorders is sometimes overshadowed by early research efforts that aimed to use CO_2-reactivity as a specific marker for panic disorder. In these early studies, the primary outcome was usually focused on whether or not the manipulation provoked a panic attack, often times using high doses of 35% CO_2 (Colasanti et al., 2012; Perna et al., 1995; Rassovsky & Kushner, 2003; Verburg et al., 1998). This panicogenic focus may have caused the field to overlook CO_2's ability to induce less intense forms of acute anxiety. Indeed, one study found that the clearest way to discriminate panic disordered patients from healthy controls during a 35% CO_2 challenge was using an anxiety scale rather than the number or intensity of induced symptoms of panic (Battaglia & Perna, 1995); a modest 20-point change in ratings of subjective anxiety on a 100-point visual analogue scale proved to be the ideal threshold for differentiating the two groups.

CO_2 is not just a panicogen, but it is also anxiogenic, especially at lower doses. Studies that have utilized lower doses of CO_2 (ranging from 5.5% to 20%) have all found that CO_2 induces heightened levels of anxiety in anxious patients and little to no anxiety in healthy participants (Blechert et al., 2010; Rapee et al., 1992; Seddon et al., 2011). These studies lend support to a continuum model of CO_2 sensitivity. On one end of the continuum are healthy individuals who report minimal anxiety in response to CO_2, especially healthy participants with no family history of panic disorder (Colasanti et al., 2012). In the middle of the continuum are patients with generalized anxiety disorder and social phobia, who typically report mild-to-moderate levels of anxiety when exposed to CO_2 (Blechert et al., 2010; Rapee et al., 1992; Seddon et al., 2011). At the extreme end of the continuum are patients with panic disorder and agoraphobia who will often report the highest levels of anxiety to CO_2 (Blechert et al., 2010; Colasanti et al., 2012; Rapee et al., 1992; Rassovsky & Kushner, 2003). Regardless of diagnosis, we postulate that individuals who have a hypersensitivity to CO_2 will attempt to minimize chemoreceptive disturbances by deploying a range of strategies to prevent hypercapnia. These compensatory strategies (described in the subsequent sections) may help abate hypercapnia in the short-term, but over time will lead to maladaptive outcomes that may contribute to the chronicity of anxiety disorders.

CO_2-induced avoidance behavior

Heightened experiences of fear and anxiety and the pervasive avoidance of stimuli capable of inducing such experiences are perhaps the two most common themes that unite all anxiety disorders. As the previous section described, CO_2 inhalation elicits a heightened experience of fear and anxiety across the spectrum of anxiety disorders. As it turns out, CO_2 is also a potent stimulus for eliciting avoidance behavior. The innate avoidance triggered by CO_2 appears to be evolutionarily hardwired into the nervous system and conserved across species. Drosophila fruit flies have specialized olfactory sensory neurons that are able to

detect minute changes in the outside levels of CO_2 in their local environment, and rapidly trigger a change in flight pattern in order to avoid that area of air space (Suh et al., 2004; Suh et al., 2007). Similar patterns of innate avoidance to environments containing high levels of CO_2 can be found in species ranging from *C. elegans* (Bretscher et al., 2011) to rats (Améndola & Weary, 2020; Kirkden et al., 2008). In humans, although speculative, the AiA model highlights the possibility that certain patterns of avoidance behavior are actually a byproduct of the specific situations and circumstances that activate one's amygdala and trigger episodes of apnea and spikes in CO_2. And similar to the fruit fly, heightened levels of CO_2 may motivate the anxious patient to escape from their surrounding environment. For example, in the case of social phobia, the AiA model would predict that social contexts would most readily stimulate states of amygdala-driven apnea, and the subsequent increases in CO_2 would provoke socially anxious patients to escape from these environments and avoid them in the future. This largely unconscious process of attributing internal suffocation alarms to external environmental cues is really a form of fear generalization that could lead to avoidance of a multitude of different stimuli and contexts (McMurray et al., 2020), culminating in the widespread pattern of avoidance characteristic of agoraphobia.

Hyperventilation to minimize AiA

Individuals struggling to adapt to the repeated and unforeseen buildups of CO_2 stemming from AiA may compensate by simply lowering their baseline level of PCO_2 so that future spikes are less likely to elicit a full-blown suffocation alarm. Consistent with this prediction, it has long been known that anxious patients have a tendency toward hyperventilation at rest (Kaplan, 1997; Saltzman, Heyman, & Sieker, 1963), and patients with panic disorder (Meuret & Ritz, 2010), as well as other types of anxiety disorders (Henje Blom et al., 2014; Van den Hout et al., 1992), have been found to have low resting end-tidal CO_2. This has led to much discussion and debate as to whether hyperventilation is a cause or consequence of panic (Klein, 1993; Ley, 1985; Meuret & Ritz, 2010). According to the AiA model, hyperventilation would be a consequence of recurring episodes of amygdala-driven apnea and a form of chemoreceptive avoidance aimed at reducing the occurrence of chemoreceptors firing following an episode of apnea. Unfortunately, this compensatory strategy is maladaptive and may actually lead to more episodes of apnea, and even greater levels of anxiety and panic. For example, patients with low resting end-tidal CO_2 have an even greater panic response to elevations in CO_2 than patients with normal levels of CO_2 (Papp et al., 1997) and hyperventilation often leads to more apneas rather than less (Meah & Gardner, 1994). Hyperventilation can also acutely induce symptoms of panic, including heart palpitations, shortness of breath, dizziness, trembling, tingling or numbness in the extremities, and depersonalization/derealization (Meuret & Ritz, 2010). And prolonged hyperventilation can lead to an enduring state of hypocapnia and a host of health issues (Meuret, Kroll, & Ritz, 2017), including exacerbation of anxiety (Brashear, 1983). In addition, low baseline levels of CO_2 across the spectrum of anxiety disorders is a predictor of poor treatment response to psychotherapy (Davies & Craske, 2014; Tolin et al., 2017), highlighting the need for a more targeted treatment approach. Remarkably, when such an approach was undertaken by combining capnometry-assisted biofeedback with hypoventilation breathing training, not only were panic disordered patients able to normalize

their levels of end-tidal CO_2, but by doing so they were able to significantly reduce their symptoms of panic disorder (Meuret, Wilhelm, Ritz, & Roth, 2008).

Amygdala volumetric reductions in anxious psychopathology

A cursory review of the literature examining amygdala volumes in clinically anxious patients shows that the notion of a larger amygdala being associated with greater levels of fear and anxiety is not just overly simplistic, but in many cases opposite to reality. This was most evident in panic disorder, where four studies showed that panic patients have significantly smaller amygdala volumes than demographically-matched healthy individuals (Asami et al., 2018; Hayano et al., 2009; Massana et al., 2003; Yoon et al, 2016). Smaller amygdala volumes were also found in a group of participants with spider phobia (Fisler et al., 2013). The findings were mixed with regard to generalized anxiety disorder and social anxiety disorder, with some studies showing significant decreases in amygdala volume (Irle et al., 2010; Milham et al., 2005) and others showing significant increases or no significant differences (De Bellis et al., 2000; Machado-de-Sousa et al., 2014; Suor et al., 2020). In general, most of these studies were underpowered, with average sample sizes ranging between 20 to 30 participants per group. A meta-analysis of studies in patients with major depression (which is often comorbid with anxiety), found significantly reduced amygdala volumes in depressed patients who were unmedicated (Hamilton et al., 2008). More recently, an analysis of nearly 1000 individuals with and without alcohol use disorder (which is also highly comorbid with anxiety), found that alcohol-dependent males had significantly smaller amygdala volumes, especially in the basolateral nucleus (Grace et al., 2021). There is also a high comorbidity between asthma and panic disorder (Meuret & Ritz, 2010; Meuret, Kroll, & Ritz, 2017), and it was recently found that asthmatics with smaller amygdala volumes tended to catastrophize more about future asthma attacks and reported less ability to control their asthma (Ritz et al., 2019). Smaller amygdala volumes were also found in autistic children, but only in those who had clinically significant anxiety (Herrington et al., 2017). Finally, with regard to trauma exposure, there is further evidence of decreased amygdala volume, both in children exposed to trauma (Hanson & Nacewicz, 2021; Nogovitsyn et al., 2020; Weissman et al., 2020), as well as in adults with posttraumatic stress disorder (Morey et al., 2012; O'Doherty et al., 2015). Thus, across the spectrum of anxiety disorders, as well as in other disorders that are often comorbid with anxiety, a relatively consistent pattern of reduced amygdala volume has been found. The etiology, cellular mechanism, and developmental trajectory underlying these volumetric reductions remains to be determined. It will also be important for future studies to examine the volume of specific amygdala subnuclei, especially the central nucleus given its direct projections to the brainstem. Based on the AiA model and the data from the amygdala-lesioned patients, it seems plausible that a smaller amygdala volume would confer less downstream inhibition over brainstem chemoreceptive centers, making it harder to inhibit suffocation alarms. Viewed in this light, the smaller amygdala volumes found in clinically anxious patients may be a neural marker for CO_2 hypersensitivity.

Evidence of apnea in real-world anxiogenic contexts

The AiA model predicts that chronically anxious individuals will experience frequent episodes of apnea induced centrally via the amygdala, especially when exposed to anxiogenic contexts. Of note, this centrally-induced form of apnea during waking states is quite different than the apnea that occurs during sleep, which is most commonly caused by an obstruction of the airways and also appears to be associated with anxiety (Garbarino et al., 2020). While evidence for amygdala hyperactivity has been found across the spectrum of anxiety disorders (Bruehl et al., 2014; Etkin & Wager, 2007; Hayes, Hayes, & Mikedis, 2012; Ipser, Singh, & Stein, 2013), very little research has examined whether recurring episodes of apnea are also evident in anxious populations. There are, however, some notable exceptions. An ambulatory monitoring study assessing individuals with flying phobia while onboard an actual airplane found evidence of increased pauses in breathing, sometimes lasting up to 20 seconds (Wilhelm & Roth, 1998). A sleep study conducted in a group of patients with panic disorder found an increased rate of "*microapneas*" entailing brief 5–10 second pauses in breathing (Stein et al., 1995). Another study in patients with panic disorder found evidence of frequent "*breathing pauses*" lasting anywhere between 20–60 seconds (Bystritsky et al., 2000). Notably, the pauses were longest in those patients who experienced panic attacks during a subsequent CO_2 challenge. These data add to other research showing marked breathing irregularities in panic disorder (Papp et al., 1997), including hyperventilation (Meuret & Ritz, 2010) and frequent sighs (Abelson et al., 2001), which might be part of a compensatory response to help clear the build-up of CO_2 following an episode of apnea. Another ambulatory monitoring study was able to capture a series of panic attacks in a group of patients with panic disorder (Meuret et al., 2011). Shortly before the onset of the panic attack, they found significant decreases in tidal volume followed by abrupt increases in PCO_2. In contrast, the panic attack itself was characterized by heart rate and tidal volume increases and a corresponding reduction in PCO_2. Although the occurrence of apnea was not specifically analyzed, it remains possible that the noted drop in tidal volume and increase in PCO_2 that preceded a panic attack was actually triggered by episodes of apnea.

There have also been real-world studies using ambulatory monitoring in healthy individuals that found a significant increase in patterns of "*sustained inhibitory breathing*" while participants were in anxiogenic settings such as at work or during social gatherings as compared to when they were alone (Anderson et al., 1992). Interestingly, these patterns of inhibitory breathing were also associated with higher blood pressure (Anderson et al., 1993), which is in line with other studies that have found frequent episodes of apnea of 10–20 seconds in duration in individuals with hypertension (Anderson et al., 2008; Novak et al., 1994; Wu et al., 2016), suggesting that even short periods of apnea are sufficient to elicit hypercapnia-induced increases in blood pressure. There have also been anecdotal reports of apnea arising while reading emails or engaging in social media, with one empirical study finding evidence that individuals "*held their breath*" at the onset of receiving a text message (Lin & Peper, 2009). Taken together, these initial findings suggest that apneas can spontaneously occur in everyday life, especially in anxiogenic contexts. And although it was

not explicitly explored in these prior studies, it remains possible that most individuals were entirely unaware of the fact that their breathing had stopped.

It is important to emphasize that the proposed model of AiA is still speculative and there are many unknowns that need to be tested. While the above studies provide initial evidence that episodes of apnea can occur in everyday life, they also highlight the importance of utilizing ambulatory monitoring to assess respiration in real-world anxiogenic contexts where AiA is most likely to occur. Future studies will need to conduct more granular analyses on the respiratory data to discern the presence, frequency, and duration of the apnea episodes. In addition, the above studies all lacked a clear definition of apnea making it difficult to determine whether a true episode of apnea was actually induced. In the sleep apnea literature, apnea is defined as a period of breathing cessation that is ≥ 10 seconds based on a drop in the peak signal excursion by ≥ 90% of pre-event baseline (Berry et al., 2012), and a similar definition could potentially be applied to future ambulatory monitoring studies. Finally, experience sampling will need to be collected in conjunction with ambulatory monitoring in order to ascertain whether the episodes of apnea are temporally-linked to fluctuations in state anxiety as the AiA model predicts.

Treatment implications of AiA

In the event that AiA is a real phenomenon being surreptitiously driven by amygdala hyperactivity, then new interventions could be readily developed to interrupt or prevent the apnea before it cascades into CO_2-induced anxiety. Wireless wearable sensors could be used to identify apneas, relaying respiratory-associated signals to monitoring algorithms that can quickly alert the patient whenever an episode of apnea or hypercapnia is detected. For example, a wireless and portable pulse oximeter could send real-time feedback using vibrations or sounds anytime levels of O_2 saturation drop, alerting the patient to resume breathing. Likewise, a portable capnometry system could detect sudden spikes in end-tidal CO_2 and alert the patient to exhale before anxiety escalates or to breathe slower if abnormally low levels of CO_2 were detected (Meuret & Ritz, 2021). Devices that incorporate accelerometry or respiratory inductive plethysmography into the fabric of one's shirt may be able to rapidly detect an apnea at its onset. One noteworthy observation from the recent neurosurgical stimulation studies found that patients could stop amygdala-driven apnea simply by purposefully breathing through their mouth (Nobis et al., 2018), suggesting that there are regulatory circuits that can override the amygdala's inhibition over nasal breathing. Tapping into these alternate respiratory circuits could potentially help overcome AiA, but real-time feedback will be imperative since most people will be unaware that their breathing has stopped.

Conclusion

The physiological processes driving the chronic and unrelenting nature of anxiety remain elusive. Here we outlined the parameters of Apnea-induced Anxiety (AiA), a neurobiological model that attempts to provide a plausible explanation for the chronicity of anxiety disorders. The model is predicated on the newly discovered ability of the amygdala to induce apnea and inhibit suffocation fear. This dual brain-behavior relationship is not

well-known in the fields of psychiatry and psychology, but it can be formally tested in future studies in both humans and non-human animals, and it may have substantial implications with regard to both the etiology and treatment of anxiety.

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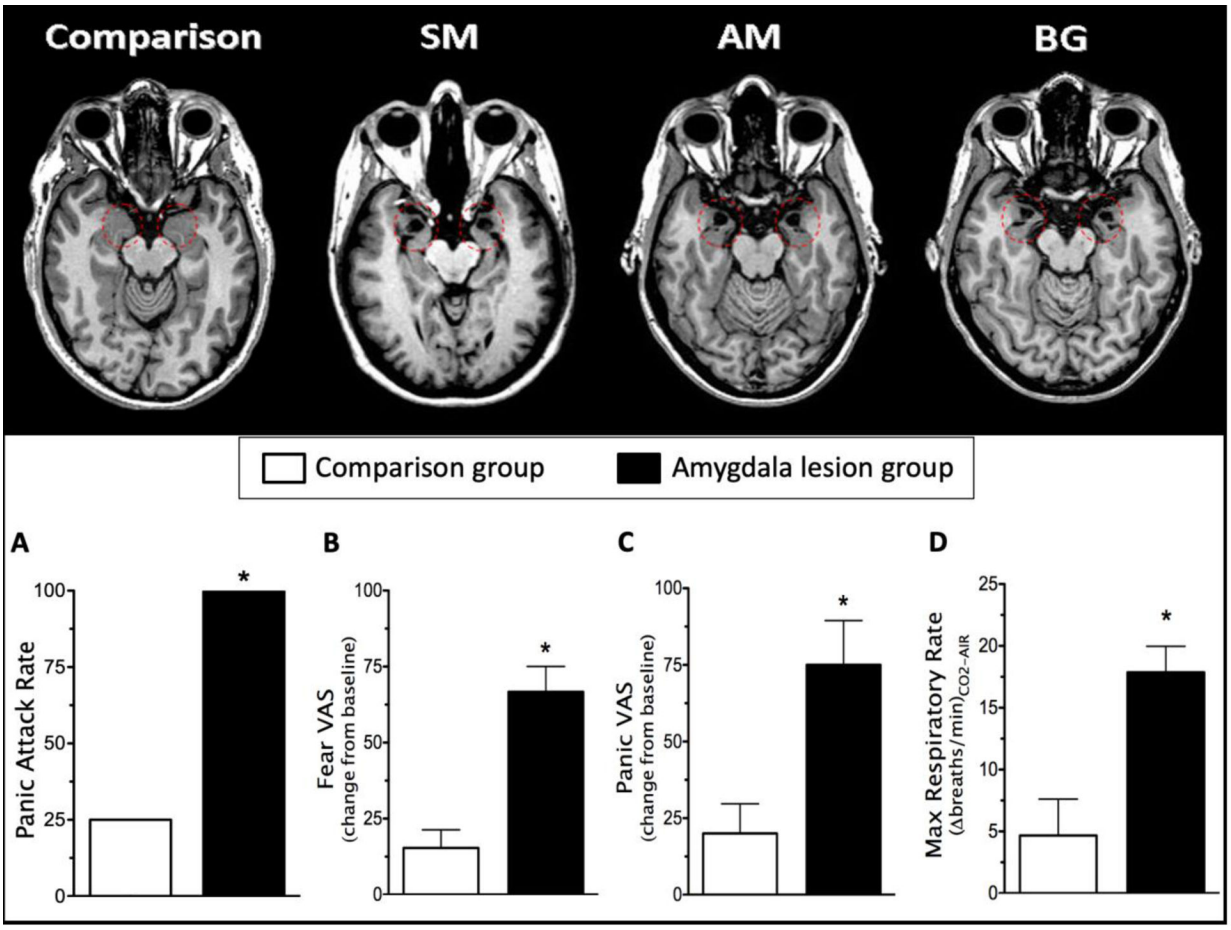

Figure 1. Heightened fear and panic to 35% CO_2 in three rare lesion patients with focal bilateral amygdala damage

(Feinstein et al., 2013). The amygdala is highlighted by red-dashed circles on the MRI scans in the top panel. A single vital capacity inhalation of 35% CO_2 triggered a panic attack in all of the patients with amygdala damage (A), as well as significantly higher levels of self-reported fear (B) and panic (C), and a significantly higher rate of respiration (D). *p < .05; error bars represent the standard error of the mean. VAS, visual analogue scale.

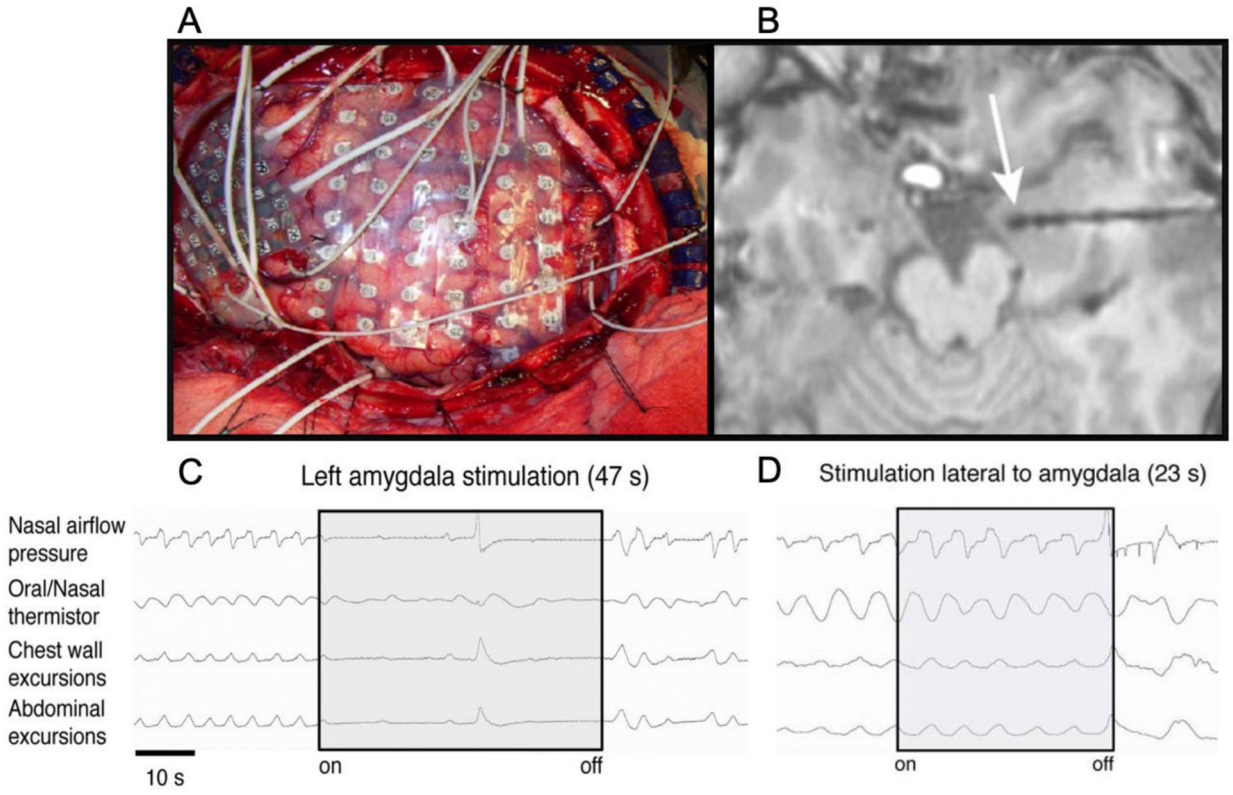

Figure 2. Intracranial stimulation of the human amygdala induces apnea

(images from Dlouhy et al., 2015). (A) For many years, neurosurgeons have applied large arrays of electrodes inside the brain of epilepsy patients to identify the source of their seizures prior to resecting the epileptogenic tissue. These intracranial electrodes were mainly used for passively recording neuronal activity. More recently, neurosurgeons have started using the electrodes to stimulate the underlying tissue by applying extended trains of electrical pulses at 50 Hz while simultaneously recording changes in respiration. (B) Depth electrodes stimulated in the vicinity of the amygdala (white arrow) reliably trigger apnea (C), whereas stimulation of electrodes outside of the amygdala does not disrupt respiration (D).

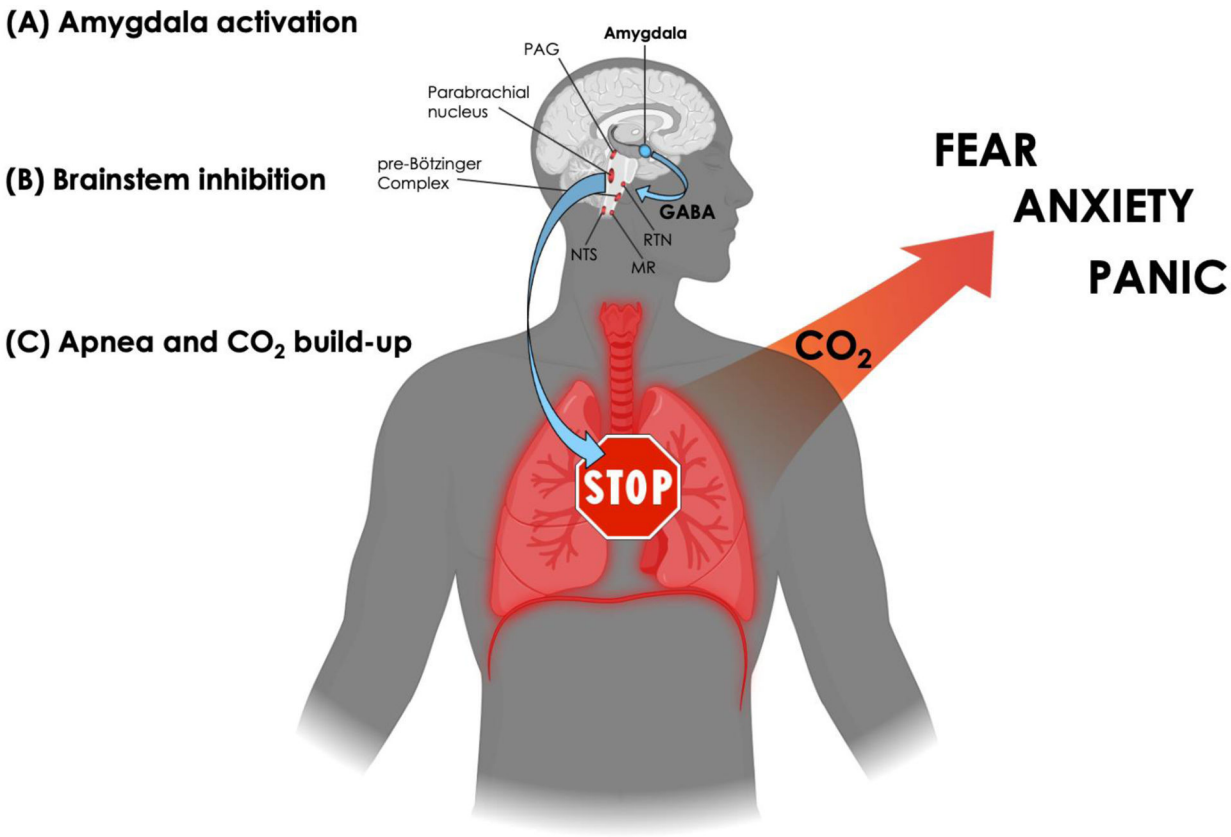

Figure 3. A model of Apnea-induced Anxiety

(A) Amygdala activation. The model applies to situations in which amygdala activation surpasses the necessary threshold to elicit apnea. Since a myriad of emotionally laden stimuli can activate the amygdala (Costafreda et al., 2008), the model allows for the possibility that any individual, healthy or anxious, could find themselves in a situation that triggers an episode of apnea.

(B) Brainstem inhibition. The central nucleus of the amygdala will flood downstream targets in the brainstem with GABA, leading to inhibition over respiratory-related nuclei that regulate the rate of breathing (including the periaqueductal gray (PAG) in the midbrain, the parabrachial nucleus in the pons, and the pre-Bötzinger complex in the medulla) as well as inhibition over chemoreceptive-related nuclei that sense changes in CO_2 (both centrally in the retrotrapezoid nucleus (RTN) and medullary raphe (MR), and peripherally in the nucleus tractus solitarii (NTS) via projections from the carotid and aortic bodies).

(C) Apnea and CO_2 build-up. As inhibition over brainstem respiratory centers accumulates, breathing eventually stops, leading to a transient state of apnea and rising levels of CO_2. However, due to amygdalar inhibition over chemoreceptive centers in the brainstem, the individual remains unaware of the CO_2 build-up and unaware that their breathing has stopped. Once amygdala activation subsides, and inhibition over the brainstem is lifted, chemoreceptive awareness and respiratory drive returns. The unforeseen build-up of CO_2 generated during the episode of apnea rapidly activates suffocation alarms, triggering

a state of anxiety characterized by varying degrees of fear and panic, hyperventilation, and avoidance/escape behavior. (Created with BioRender.com)