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Review

Lifelong opioidergic vulnerability through early life separation: A recent extension of the false suffocation alarm theory of panic disorder

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ABSTRACT

The present paper is the edited version of our presentations at the "First World Symposium On Translational Models Of Panic Disorder", in Vitoria, E.S., Brazil, on November 16–18, 2012. We also review relevant work that appeared after the conference.

Suffocation-False Alarm Theory (Klein, 1993) postulates the existence of an evolved physiologic suffocation alarm system that monitors information about potential suffocation. Panic attacks maladaptively occur when the alarm is erroneously triggered. The expanded Suffocation-False Alarm Theory (Preter and Klein, 2008) hypothesizes that endogenous opioidergic dysregulation may underlie the respiratory pathophysiology and suffocation sensitivity in panic disorder. Opioidergic dysregulation increases sensitivity to CO_2, separation distress and panic attacks. That sudden loss, bereavement and childhood separation anxiety are also antecedents of "spontaneous" panic requires an integrative explanation. Our work unveiling the lifelong endogenous opioid system impairing effects of childhood parental loss (CPL) and parental separation in non-ill, normal adults opens a new experimental, investigatory area.

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We briefly reference previous material on Klein's suffocation false alarm theory (SFA) of panic disorder (Klein, 1993) and its amplification in 2008 (Preter and Klein, 2008). We then discuss a recent finding showing a fundamental difference in opioidergic reactivity to a naloxone challenge in psychiatrically and medically healthy adults, based on the presence or absence of childhood separation/parental loss.

In 1993, Klein published the original SFA theory of panic disorder (Klein, 1993), attempting to integrate the multiplicity of apparently unrelated clinical and laboratory observations. We posited "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. If other indicators of potential suffocation provoke panic, this theoretical extension is supported." In the original paper, we tested "the theory by examining Ondine's curse as the physiologic and pharmacologic converse of panic disorder, splitting panic in terms of symptomatology and challenge studies, reevaluating the role of hyperventilation, and reinterpreting the contagiousness of sighing and yawning, as well as mass hysteria" (Klein, 1993). Original SFA focused on relating the observed lactate and carbon dioxide hypersensitivity in panic disorder to a putative dysfunction in a hypothesized suffocation alarm. At the time, the underlying pathophysiology that might connect the apparent disparate "phenomena of panic during relaxation

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and sleep, late luteal phase dysphoric disorder, pregnancy, childbirth, pulmonary disease, separation anxiety, and treatment", was unknown.

Over the intervening decades, much data evolved linking Separation Anxiety, Panic, and respiratory dysfunction. This suggested a potential missing link:

> "Klein and Fink (1962) posited a developmental pathophysiological link between [clinical levels of] separation anxiety and PD and subsequent agoraphobia, since 50% of hospitalized agoraphobics reported severe early separation anxiety that often prevented school attendance. Further, panic, in this group, was frequently precipitated by bereavement, or separation [...]" (Preter and Klein, 2008). This was also noted by others, e.g., Faravelli and Pallanti (1989), Kaunonen et al. (2000), Milrod et al. (2004).

We noted that "[p]atients highly comorbid for multiple anxiety disorders are particularly likely to recall childhood SAD (Lipsitz et al., 1994)", and that "[c]laims that separation anxiety equivalently antecedes other anxious states (van der Molen et al., 1989) may be due to diagnostically ambiguous limited symptom attacks and the unreliability of the questionnaire method". We concluded that "in the only controlled, long-term, direct, blind, clinical interview follow-up of separation-anxious, school-phobic children, the only significant finding was an increased PD rate" (Preter and Klein, 2008).

Adding further support, Battaglia et al. (1995) showed that "[s]eparation anxiety correlates with increased familial loading and early onset of PD." More recently (2012), as part of their series of brilliant twin studies, Robertson-Nay et al. demonstrated that, "[childhood] separation anxiety disorder and adult onset panic attacks share a common genetic diathesis".

1. Panic and comorbid conditions

There has been a regained awareness of the relevance of panic states to other clinical contexts, as Freud suggested in his pioneering statement (Freud, 1895).

In the US, nearly half of panic patients are initially seen in the medical emergency room of a hospital. They may undergo extensive diagnostic medical procedures, such as MRI scans of the brain for headaches, or coronary angiograms for chest pain. Cardiovascular symptoms, particularly pseudo-anginal chest pain resembling a heart attack are the most common symptoms in these PD patients' experience. Accordingly, 25% or more of outpatients seen by a cardiologist have a current diagnosis of PD (Ballenger, 1998). Since primary complaints are of distress, rather than anxiety, they have been termed "non-fearful" panics. This seemingly oxymoronic term nevertheless indicates that fearfulness is not essential to panic disorder (Beitman et al., 1990).

Migraine and other chronic headaches are highly comorbid with panic disorder (Breslau et al., 2001; Hamelsky and Lipton, 2006). Having PD increases the risk of migraine four-fold, and vice versa. This bidirectionality suggests that the migraine-panic association is unlikely to be merely coincidental and that shared environmental and familial factors are involved (Breslau et al., 2001). In a longitudinal study, separation and parental loss early in life increased the risk of both headaches and psychiatric morbidity, mainly anxiety and depression, in adulthood (Fearon and Hotopf, 2001).

Panic disorder is also comorbid with other somatic pain syndromes (Johnson et al., 2006). In a cross-sectional survey of 1219 female veterans studying the prevalence and frequency of mastalgia, women reporting frequent mastalgia were much more likely to have comorbid panic disorder (OR 7.1), but also post-traumatic stress disorder, mood disorders, and other somatic pain syndromes, such as fibromyalgia, chronic pelvic pain or irritable bowel syndrome.

Although panic attacks as they occur in panic disorder often prominently feature air hunger, other panic subtypes have prominent vestibular symptoms and unspecific dizziness/lightheadedness. True vertigo was historically recognized as a common presentation of panic disorder (Benedikt, 1870; Frommberger et al., 1994). The current rigid distinction between psychiatry and neurology (Staab, 2006) interferes with proper assessment (Preter and Bursztajn, 2009).

In Mandarin Chinese, *tou yun* refers to the disabling sensation of a constant state of movement of oneself or one's surroundings. This dizziness (note that *tou yun* also describes vertigo), is probably the most common expression of panic disorder in Chinese patients (Park and Hinton, 2002), so by sheer numbers, this may well be the most prevalent panic subtype worldwide.

Taken together, the various comorbidities of panic disorder and untreated sequelae massively impact people's quality of life (Sareen et al., 2006).

One prominent characteristic of the panic attack and subthreshold panic-related anxiety is respiratory dysregulation and chaotic breathing. This can be experimentally reproduced in adult panic sufferers, but also in children with separation anxiety disorder (Pine et al., 2000, 2005; Preter and Klein, 2008).

Air hunger and chronic sighing outside of the acute attack are hallmarks of panic that rarely occurs under acute, external-threat initiated fear (Klein, 1993; Preter and Klein, 1998). Increasing hypercapnia is a more salient indicator of potential suffocation than hypoxia, but hypoxia also serves this alarm function. "Beck et al. (1999, 2000) showed that panic patients respond with increased panic symptoms not only to CO_2 inhalation, but also to normocapnic hypoxia, as predicted by SFA" (Preter and Klein, 2008). Unsurprisingly, numerous studies found that panic disorder and lung disease commonly occur together (Goodwin and Eaton, 2003; Goodwin et al., 2004; Katon et al., 2004; Nascimento et al., 2002; Klein, 2001; Roy-Byrne et al., 2006; Valença et al., 2006; Wingate and Hansen-Flaschen, 1997; Yellowlees and Kalucy, 1990; Yellowlees et al., 1988). More specifically, we wrote, "early lung disease, including asthma and COPD may predispose to PD (Craske et al., 2001; Goodwin and Eaton, 2003; Hasler et al., 2005; Karajgi et al., 1990; Perna et al., 1997; Verburg et al., 1995), or present solely with panic symptoms (Edlund et al., 1991; Sietsema et al., 1987). Asthma and PD are both characterized by acute episodes, salient respiratory symptoms and anxiety with avoidance of situations related to acute attacks (Klein, 1993; Yellowlees and Kalucy, 1990). There is a significantly higher (6.5–24%) prevalence of PD in asthmatics (Goodwin et al., 2005; Shavitt et al., 1992; Yellowlees et al., 1988) than the 1–3% reported in the general population (Kessler et al., 2006; Weissman, 1988). Perna et al. (1997) found a significantly higher prevalence of PD, sporadic panic attacks, and social phobia in asthmatics than the general population. In 90% of asthmatics with PD, asthma appeared first. Panic symptomatology during the asthmatic attack predicted longer hospitalizations in asthmatic patients (Baron et al., 1986; Brooks et al., 1989; Jurenec, 1988)" (Preter and Klein, 2008).

The recent amplification of SFA centers on the observation that separation anxiety and suffocation sensitivity are both under endogenous opioidergic control. We amplified the SFA theory by suggesting that PD may be due to an episodic functional endogenous opioid deficit (Preter and Klein, 1998). The following is a necessarily brief explanation.

The endogenous opioid system was discovered in the early 1970s. Electrical stimulation the periaqueductal gray (Mayer et al., 1971) produced analgesia that was reversed by naloxone, suggesting an endogenous opioid system. Opioid molecules are among the oldest evolved signaling substances, functioning in many

physiological processes e.g., pain perception, respiration (Stefano et al., 1996). Dyspnea is modulated by central and peripheral opioid levels in both rodents and humans (Santiago and Edelman, 1985).

In mice, exposure to intermittent, severe hypoxia prolonged survival during subsequent lethal suffocation (Mayfield and D'Alecy, 1992). This effect was blocked by naloxone, implying that endogenous opioids increase adaptability to hypoxic environments. Opioid receptors, including 'non-conventional' ones, can be found throughout the respiratory tract. Nebulized morphine is an outstanding treatment for chronic dyspnea (Baydur, 2004; Bruera et al., 2005; Zebraski et al., 2000; Mahler, 2011).

In our 2008 paper, we summarized data from developmental psychobiology and neuroanatomy that point to a possible link between separation and the endogenous opioid system, as follows:

> "Following birth, mammalian infants cannot survive independently. Survival requires reliable distress signaling mechanisms to elicit parental care and retrieval. Distress vocalizations (DVs) are a primitive form of audio-vocal communication (Panksepp, 1998). A common neuroanatomy subserving DVs may be shared by all mammals, although substantial functional variations depend on the ontogenetic niche. The latter (West and King, 1987) signifies the ecological and social legacies ("the inherited environment") in which a given set of genes develops. For instance, isolated altricial (developmentally immature) infants do not emit DVs compared to other species, since it is not likely they will stray from the nest (Panksepp et al., 1992)."

Immature human infants practically never get lost for their first six months. Despite frequent maternal absence, separation anxiety in humans develops only after their motor system matures. Young rats are not specifically attached to their mother, i.e. any mother will do as heater or feeder. Only once mobile do they socially bond, but their responses do not compare with the vigor seen in other species. Rats also differ from other species, including primates, dogs and chicks in their greater DV suppression by benzodiazepines (Kalin et al., 1987; Panksepp et al., 1992; Scott, 1974). Since benzodiazepines differentially alleviate anticipatory anxiety, social isolation in young rodents, as compared to many other mammals, may activate anxiety mechanisms other than separation distress. Thus, Panksepp emphasizes that when using cross-species analogies, it is important to keep in mind that the type and degree of social separation distress depends on ecological and developmental parameters (Panksepp et al., 1992).

The developmental phase of separation anxiety serves as a biologic leash for the increasingly mobile, but helpless infant who continually checks for the mother's presence, becomes acutely distressed on discovering her absence, and immediately attempts to elicit retrieval by crying. In humans, separation anxiety usually wanes around age four when the now verbally skilled child can successfully elicit care even from non-relatives.

Using electrical brain stimulation (ESB), DVs have been elicited in many species from homologous areas, including the midbrain, dorsomedial thalamus, ventral septum, preoptic area, and the bed nucleus striae terminalis (BNST). In some higher species, one can obtain separation calls by stimulating the central amygdala and dorsomedial hypothalamus. All these sites have high opioid receptor densities and figure heavily in sexual and maternal behaviors (Panksepp, 1998). Cortically, electrical stimulation of the rostral cingulate gyrus in monkeys consistently elicits distress calls (Jurgens and Ploog, 1970; Ploog, 1981). The cingulate cortex, found exclusively in mammals, is particularly well developed in humans and contains high densities of opioid receptors (Wise and Herkenham, 1982).

Naloxone-blockable opioid agonists reduce isolation-induced distress vocalizations (DVs) across mammalian species (Hofer and Shair, 1978; Kalin et al., 1988; Kehoe and Blass, 1986; Panksepp et al., 1978). In beagles, imipramine, the classic anti-panic agent, and morphine were the only psychotropic drug that yielded specific DV reduction at nonsedating doses (Scott, 1974; Panksepp et al., 1978).

Naloxone given to guinea pigs and young chicks (Panksepp et al., 1978) increased baseline vocalizations (by 600%), but only when the animals were in a group, since isolates already emitted maximum DVs.

Kalin et al. (1988) studied opioid modulation of separation distress in primates, showing morphine (0.1 mg/kg) significantly decreased separation distress vocalizations without changes in autonomic and hormonal activation. Naloxone (0.1 mg/kg) blocked this effect. Sympathetic blockade using the $\alpha(2)$ agonist, clonidine, and the β adrenergic antagonist, propranolol, had no specific effect on separation-induced "coos" in infant rhesus monkeys (Kalin and Shelton, 1988)" (Preter and Klein, 2008).

2. Testing the panic-suffocation-false alarm-endogenous opioid connection

"Panic Disorder is unique among psychiatric disorders in that its salient component, the panic attack, can be reliably incited in laboratory settings by specific chemical challenges as well as having challenges specifically blocked by anti-panic agents, e.g. imipramine. We can experimentally turn panic on and off, producing trenchant causally related data rather than inferences from naturalistic data" (Preter and Klein, 2008). Specifically, sodium lactate infusions and CO_2 inhalation regularly produce panic attacks in patients with panic disorder (Liebowitz et al., 1984b; Gorman et al., 1984; Papp et al., 1993). However, while normal controls or patients with other anxiety disorders rarely show such reactivity (i.e., progress to a full-blown panic attack) (Klein, 1993), higher concentrations of inhaled CO_2 are highly aversive and can produce respiratory panic symptomatology in a dose-dependent fashion (Griez et al., 2007; Esquivel et al., 2010; Leibold et al., 2013).

Both spontaneous and lactate induced panic attacks in panic patients produce air hunger and marked, objective increases in tidal volume (Vt) (Goetz et al., 1993; Martinez et al., 1996). Since sodium lactate infusion causes a metabolic alkalosis, a compensatory decrease in ventilation would be expected. This would homeostatically buffer blood pH, by increasing CO_2 retention. However, the converse actually occurs indicating a specific lactate stimulating effect on respiration.

The usual response of healthy control subjects to a sodium lactate infusion is a minor, but definite increase in Vt (Liebowitz and others, 1984b). The lesser tidal volume response in lactate challenged normal subjects may be due to buffering by their intact endogenous opioid system.

An open pilot study showed that naloxone infusion (ranging from an initial 0.5 mg/kg to a maximum of 2 mg/kg) followed by lactate (N + L), caused significant tidal volume increments similar to those observed during clinical and lactate induced panic attacks in 8 of 12 normal subjects, supporting the hypothesis that opioidergic deficiency might be necessary for lactate to produce a marked increase in tidal volume in normal subjects (Sinha et al., 2007).

Based on these initial findings, and cognizant that previous experiments using smaller doses of both intravenous and oral opioid blocking agents had shown little results (Liebowitz et al., 1984a; Esquivel et al., 2009) we decided to conduct a controlled, randomized experimental study to investigate whether high-dose naloxone, an intravenous opioid receptor antagonist, could change the regularly resistant normal controls to become more sensitive to intravenous lactate as a respiratory stimulus to tidal volume increment. Study design and statistical analysis are detailed elsewhere (Preter et al., 2011), but in addition to the usual standard

recruitment procedure for healthy research subjects, "eligible volunteers were further interviewed about potentially significant individual and family antecedents and comorbidities of panic, such as near-suffocation, pulmonary disease, and migraine headache. Recent and childhood loss and separation events (parental divorce or death, childhood abuse) were specifically reviewed" (Preter et al., 2011).

Results showed that "normal subjects, usually relatively insensitive to the tidal volume effects of lactate infusion, [. . .] given opioid antagonist pretreatment, developed tidal volume and respiratory rate increments resembling those occurring in both spontaneous clinical panic attacks and in panic patients who panic during lactate infusions (Gorman et al., 1984; Papp et al., 1993). The hypothesis that a functioning endogenous opioid system buffers normal subjects from the behavioral and physiological effects of lactate is consonant with these results. [. . .]"

The most interesting aspect of this study is that "for the first time the prolonged physiological effects of actual separations and losses during childhood, i.e. parental death, parental separation or divorce, on the endogenous opioid system of healthy adults have been objectively, experimentally shown. Presence or absence of childhood parental loss (CPL) antecedents determined the response to the naloxone-lactate probe" (Preter et al., 2011).

A history of CPL decreased the naloxone + lactate effect implying that there was an antecedent decrement in opioidergic activity, so that the naloxone had nothing to block. We however note these normal subjects had been carefully screened for lack of psychiatric or medical disorder. It was the subjects that had not suffered such separation events that showed the expectable naloxone blockade and tidal volume increment.

"The import of these findings is that analyses attempting to relate CPL to other baseline variables may well fail since CPL impact may be specific to challenges to the endogenous opioid system" (Preter et al., 2011). Also it implies that separation-induced, baseline opioidergic deficiency, while it may not be sufficient to induce overt disease, confers lifetime vulnerability even in healthy adults. Whether it is longitudinally, or cross-sectionally relevant to somatic pain syndromes such as migraine, and to opiate abuse ought to be determined.

Again, we "emphasize that these CPL effects were apparent in a 'normal' sample. In a society where divorce rates approach 50%, the results raise the question whether current psychiatric classification and diagnostic scales are sensitive enough to detect the effects of CPL. This applies as well to developing societies like China, where the massive migration of mostly young individuals from the countryside to urban areas has left approximately 30 million small children behind (Liu et al., 2009).

CPL is a risk factor for adult anxious and depressive psychopathology (Kendler et al., 1992; Bandelow et al., 2002). However, its detrimental long-term effect is not limited to psychiatric illness (Shonkoff et al., 2009). Using criteria similar to ours, the Adverse Childhood Experiences (ACE) Study, a CDC supported prospective cohort study of 16,908 adults found a significant relationship between CPL and premature death in adulthood (Brown et al., 2009). Retrospective (e.g., Juang et al., 2004; Kopec and Sayre, 2005) and prospective longitudinal data (Fearon and Hotopf, 2001; Harter et al., 2003; Katerndahl, 2008; Jones et al., 2009), link family disruption, physical abuse, separation and maternal loss in early life to chronic physical pain in adulthood. Whether the NL vs. SL probe has a differential effect on pain perception and physiological pain measures, and whether CPL status modifies this interaction should be explored. Unfortunately, our exploratory pain measure was limited to a single item, and in retrospect, was clearly inadequate.

CPL as related to childhood separation anxiety, adult panic disorder (PD) and suffocation hypersensitivity was studied by Battaglia et al. (2009). In a large sample of twins from Norway, CPL accounted in no small part for "the covariation between separation anxiety in childhood, hypersensitivity to CO_2 (as indexed by the anxiety response to a 35% CO_2/65% O_2 mixture), and PD in adulthood". Note that in Battaglia's study, CPL increased reactivity to the 35% CO_2 probe" (Preter et al., 2011) [. . .]

> "Testing the specificity of the naloxone-lactate model of clinical panic requires double-blind investigation whether specific anti-panic drugs, but not panic irrelevant drugs, block this effect." If found, this has practical and heuristic implications.

First, there is currently no specific, screening method for testing putative anti-panic drugs except by the experimental treatment of panic disorder patients. The naloxone + lactate effect in normal humans may afford such a screening method, and may be extended to preclinical studies. Second, these data offer heuristic support for the theory that an opioidergic dysfunction is the pathophysiological mechanism underlying panic disorder. If so, the appropriateness of opioidergic therapeutic agents comes into question. The use of morphine or other simple agonists would probably be rejected for fear of inducing addiction, although the evidence for addiction during indicated medical treatment is slim. However, recent work with opioidergic mixed agonist-antagonists (Gerra et al., 2006; Wallen et al., 2006), e.g. buprenorphine, may be relevant. The concern about addiction would be mitigated by the fact that higher doses become receptor blockers rather than agonists. Positive results would foster investigations into basic molecular mechanisms. For instance, we note that the dose of naloxone used in our study (2 mg/kg) substantially exceeds that needed for μ opioid receptor (MOR) blockade (Sluka et al., 1999), suggesting a role for the δ opioid receptor (DOR). This could spark interest in the development of specific DOR agonists suitable for human use. Currently, such agents have not been developed, although agents suitable for animal use are available" (Preter et al., 2011).

Since the publication of our paper, exciting new work in panic disorder has emerged, notably from Brazil. Appropriately, the "First World Symposium On Translational Models Of Panic Disorder", was held in Vitoria, E.S., in November of 2012. Moreira et al. (2013) present a thoughtful review of the use of rodents in panic disorder research. Graeff (2012), studying an animal model of panic disorder found that the inhibitory action of serotonin is connected with activation of endogenous opioids in the periaqueductal gray (PAG). Schenberg and colleagues (Schimitel et al., 2012) suggest "[the PAG] harbors an anoxia-sensitive suffocation alarm system". Activation precipitates panic attacks and potentiates the subject's responses to hypercapnia. Notably, the resemblance of these effects to panic disorder was supported by their pharmacological parallel to panic disorder treatment. This model was also previously supported by demonstrating a lack of stress hormone release during DPAG stimulation thus paralleling panic disorder (Schenberg et al., 2008). The utility of opioidergic mixed agonist-antagonists in animal models of panic disorder and in treatment refractory patients would seem promising.

The lack of hypothalamic pituitary adrenal (HPA) activation during the panic attack, as it occurs in panic disorder, is a striking peculiarity since it contradicts the belief that the panic is an expression of a hypersensitive fear mechanism that would stimulate the HPA anti-stress response, supposedly reactive to all dangers. This is usually understood as dependent on hyper-responsiveness of the amygdala. For instance, both Stein (2008), and Gorman et al. (2000) neglect or dismiss the incongruity of the lack of HPA response, claiming a supposed amygdala-based hypersensitive fear system as central to panic.

Further damage to the amygdalocentric fear system theory is provided by Feinstein et al. (2013) who studied three patients with

amygdala damage produced by Urbach–Wiethe syndrome. It is worth extensive citation:

> "A substantial body of evidence has emphasized the importance of the amygdala in fear [...]. In animals, amygdala-restricted manipulations interfere with the acquisition, expression and recall of conditioned fear and other forms of fear and anxiety-related behaviors. 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 [...] Previous studies have shown that patient SM does not condition to aversive stimuli [...], fails to recognize fearful faces [...] and demonstrates a marked absence of fear during exposure to a variety of fear-provoking stimuli, including life-threatening traumatic events [...]. Patients with similar lesions have largely yielded similar results [...].

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 [...] Furthermore, CO_2 can trigger panic attacks, especially in patients with panic disorder [...]. Recent work in mice found that the amygdala directly detects CO_2 and acidosis to produce fear behaviors [...]. 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 [...]. 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 [...] As with patient SM, both patients also reported experiencing fear during the CO_2 challenge" (Feinstein et al., 2013).

These startling observations affirm that the reaction to carbon dioxide must be due to an alternative alarm system, such as has been proposed for possible suffocation. We have suggested that under conditions of threatened asphyxia the activation of the HPA system would produce a counterproductive hyperoxidative state and is therefore inactivated. This is in keeping with the observation that the tachycardia during panic is produced by vagal withdrawal rather than a counterproductive sympathetic oxidative surge (Preter and Klein, 2008).

In conclusion, we objectively, experimentally showed a physiological link between endogenous opioid system deficiency and panic-like suffocation sensitivity in healthy adults. This is consonant with the expanded Suffocation-False Alarm Theory of panic suggesting an episodic functional endogenous opioid deficit (Preter and Klein, 1998). The specificity of the naloxone + lactate model of clinical panic should be tested using specific anti-panic components, possibly including opioidergic mixed agonist-antagonists such as buprenorphine. If specific, the naloxone + lactate effect in normal humans affords a screening method for testing putative anti-panic drugs which is currently not available. This could obviate the experimental treatment of panic disorder patients in drug development.

Our data also show for the first time that actual separations and losses during childhood, such parental death, parental separation or divorce (CPL), effect lifelong alterations in the physiological reactivity of the endogenous opioid system of healthy adults.

This result encourages epigenetic inquiry into the effects of CPL on endogenous opioid systems, and their role in resilience under extreme stress. In addition, a redefinition of what constitutes a (truly) healthy control in clinical research protocols may be called for.

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