Threat from the inside:

Characterization of defensive responses to interoceptive threats

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Breathing

Kuush Puhhrrrr…

Kuush Puhhrrrr…

Kuush Puhhrrrr…

Kuush Puhhrrrr…

Kuush Puhhrrrr…

- Darth Vader

Star Wars: Episode VI - Return of the Jedi

Contents

Abstract

The processing of signals from within the body is crucial for maintaining the bodily homeostasis, i.e., to ensure adequate body regulation and survival. Previous research has recognized the dysfunctional perception of these interoceptive signals as an important hallmark of anxiety and health problems, when even slight and harmless body sensations are interpreted as threat and, thus, elicit excessive defensive response mobilization. Even though the scientific interest in processing interoceptive threats has strongly increased recently, the defensive dynamics to these sensations have rarely been studied. Therefore, the present thesis targeted to study the behavioral and psychophysiological dynamics of defensive mobilization to interoceptive threats, as well as the moderating effect of dispositional factors and biobehavioral markers.

The first study compared defensive responses to an approaching external, predator-like threat relative to an approaching internal respiratory threat in dependence on the threat proximity and the opportunity to avoid the threat on subjective, autonomic, respiratory, behavioral and brain-circuit levels of expression. Moreover, the second study analyzed defensive response mobilization during repetitive avoidance of culminating dyspnea for a detailed analysis of initiating and maintaining active avoidance behavior. Extending these findings, the third study investigated the role of maximal voluntary breath-holding time as a possible predictor of excessive defensive threat mobilization to an approaching interoceptive threat, depending on whether it is possible to avoid such threat or not. Finally, in the fourth study predictors of active defensive behavior (i.e., escape/active avoidance) during culminating dyspnea, evoked by increasing inspiratory resistive loads, were examined.

The first Study revealed common patterns of defensive response mobilization to approaching external and internal threats, irrespective of a given opportunity of avoidance, and a threat-specific respiratory mobilization when the respiratory was inevitable. The data from the second study demonstrated that the initiation of first avoidance behavior from culminating

dyspnea is accompanied by indications of response preparation and physiological arousal. Those indications diminished with repetitive avoidance, suggesting a developing habituational avoidance behavior. Moreover, the third study demonstrated that excessive defensive response mobilization to an approaching inevitable respiratory threat was predicted by shorter maximal voluntary breath-holding time, but not when the threat was avoidable. Finally, the fourth study revealed that higher anxiety sensitivity and shorter breath-holding time were associated with active avoidance behavior during culminating dyspnea.

Taken together, the present data suggest that defensive mobilization for exteroceptive and interceptive threats are comparable, as well as varying as a function of threat proximity and the behavioral repertoire at hand. Moreover, the proneness to fear body sensations and reduced distress tolerance during breath-holding are associated with elevated anxious response to the sensation of dyspnea. Therefore, these dispositional and biobehavioral factors might facilitate the switch from culminating body sensations into defensive action. This, if performed in a habitual way, might increase the risk for the emergence of psychopathology, as persistent avoidance behavior might be developed.

Zusammenfassung

Körpersignale sind elementar für die Aufrechterhaltung der Homöostase, um eine angemessene Regulation der Körperfunktionen zu ermöglichen und dadurch das Überleben des Individuums sicherzustellen. Die bisherige Forschung hat die dysfunktionale Wahrnehmung dieser interozeptiven Signale als wichtigen Bestandteil vieler Angst- und Gesundheitsprobleme identifiziert, da selbst leichte und harmlose Körperempfindungen eine übermäßig starke Mobilisierung von Abwehrreaktionen hervorrufen können. Obwohl das wissenschaftliche Interesse im Bereich Interozeption in den letzten Jahren stark gewachsen ist, wurde die Dynamik von Abwehrreaktionen als Reaktion auf Körpersignale bisher selten untersucht. Daher hatte die vorliegende Arbeit zum Ziel, die verhaltensbezogene und psychophysiologische Dynamik der defensiven Mobilisierung auf bedrohliche interozeptive Signale sowie den moderierenden Effekt von Dispositionsfaktoren und biologisch determinierten Verhaltensmarkern zu untersuchen.

In der ersten Studie wurden die Dynamik defensiver Mobilisierung auf eine näherkommende externe Bedrohung mit einer sich annähernden interozeptiven respiratorischen Bedrohung, in Abhängigkeit von der Bedrohungsnähe und der Möglichkeit zur Vermeidung, bezüglich subjektiver, autonomer und respiratorische Reaktionen sowie Gehirnreaktionen und defensiver Reflexe verglichen.

In der zweiten Studie wurde die Mobilisierung defensiver Reaktionen während der wiederholten Vermeidung von kulminierender Atemnot analysiert, um eine detaillierte Analyse der Initiierung und Aufrechterhaltung von aktiven Vermeidungsverhalten zu erhalten.

Die dritte Studie unterweiterte die diese Befunde, indem die Rolle der maximalen freiwilligen Luftanhaltezeit als möglicher Prädiktor für eine übermäßig starke Mobilisierung defensiver Reaktionen bei der Konfrontation mit einer näherkommenden respiratorischen Bedrohung, in Abhängigkeit der Möglichkeit zur Vermeidung, untersucht wurde.

In der vierten Studie wurden die Prädiktoren für aktives Abwehrverhalten (d.h., Flucht oder aktive Vermeidung bei Konfrontation) während ansteigender Atemnot, induziert durch in der Intensität ansteigende inspiratorische Atemwiderstände gefolgt von einer kurzen Blockade der Einatmung, untersucht.

Die erste Studie zeigte, dass das defensive Aktivierungsmuster bei der Mobilisierung defensiver Reaktionen auf eine sich annähernde externe Bedrohung annähernd vergleichbar ist wie bei einer interozeptiven respiratorischen Bedrohung, unabhängig von der Möglichkeit zur Vermeidung. Zusätzlich wurde eine bedrohungsspezifische Mobilisierung des respiratorischen Systems bei der Konfrontation mit der unvermeidbaren interozeptiven Bedrohung beobachtet.

Die Daten der zweiten Studie demonstrierten, dass die Initiierung von erstmaligen Vermeidungsverhalten als Reaktion auf ansteigende Atemnot begleitet wird von physiologischen Erregungen als Indikatoren für eine Reaktionsvorbereitung. Diese verschwanden zunehmend mit wiederholter Vermeidung, was auf die Entwicklung von gewohnheitsmäßiger Vermeidung hindeutet.

Darüber hinaus wurde in der dritten Studie gezeigt, dass eine übermäßig starke Mobilisierung von Abwehrreaktionen auf eine sich annähernde unvermeidbare respiratorische Bedrohung durch eine reduzierte maximale freiwillige Luftanhaltezeit vorhergesagt wird, jedoch nicht, wenn die Möglichkeit zur Vermeidung vorhanden war.

Die vierte Studie demonstrierte, dass eine höhere Angstempfindlichkeit und eine kürzere freiwillige maximale Luftanhaltezeit mit aktivem Vermeidungsverhalten während ansteigender Atemnot assoziiert sind.

Zusammenfassend zeigen die vorliegenden Daten, dass die defensive Mobilisierung für eine exterozeptive Bedrohung vergleichbar ist wie für eine interozeptive Bedrohung und sich in Abhängigkeit der Bedrohungsnähe und dem verfügbarem Abwehrrepertoire ändert. Darüber hinaus ist die Neigung, Erregungsgefühle zu befürchten und eine verminderte Belastungs-toleranz während freiwilligem Luftanhaltens mit einer erhöhten Angst- und Furchtreaktion auf

Atemnotsymptome verbunden. Daher könnten diese dispositionellen und biologischen Verhaltensmarker bei der Konfrontation mit ansteigender Atemnot aktives Vermeidungsverhalten begünstigen und, wenn sie gewohnheitsmäßig ausgeführt werden, kann sich persistentes Vermeidungsverhalten entwickeln, welches das Risiko für die Entstehung einer ernsthaften psychischen Erkrankung erhöht.

1 Introduction

Fear and anxiety are closely related and they are adaptive responses to a threat to ensure our everyday survival (Barlow, 2002). More detailed, the term 'fear' describes an emotional response to a real or perceived threat, which is associated with "*surges of autonomic arousal necessary for fight of flight, thoughts of immediate danger, and escape behavior*" (American Psychiatric Association, 2013). Moreover, fear increases in intensity with increasing proximity of a threat and decreases when the threat has vanished. In contrast, 'anxiety' is defined as an emotional response to an anticipated or future threat, often accompanied with "*muscle tension and vigilance in preparation for future danger and cautious or avoidance behaviors*" (American Psychiatric Association, 2013). Thus, anticipation of and confrontation with feared stimuli or situations elicit defensive responses, which are mediated by defensive brain circuits (Barlow, 2002; Fanselow, 1991; Lang, Bradley, & Cuthbert, 1997).

While the origin of most threats are external (e.g., predator, wild animal, gun, heights), threats might also arise from inside our body (e.g., suffocation), as various studies showed that healthy individuals react with elevated fear and anxiety to body symptoms (Benke, Hamm, & Pané-Farré, 2017; Eifert, Zvolensky, Sorrell, Hopko, & Lejuez, 1999; Eke & McNally, 1996; Kroeze et al., 2005; McNally & Eke, 1996; Norton, Pidlubny, & Norton, 1999; Rassovsky, Kushner, Schwarze, & Wangensteen, 2000; Shipherd, Beck, & Ohtake, 2001; Zvolensky & Eifert, 2001). Moreover, it has been discussed that stronger defensive mobilization to body sensations might facilitate the emergence of an anxiety-related disorder or mental comorbidities in individuals with respiratory diseases (Vogele & von Leupoldt, 2008; von Leupoldt & Kenn, 2013), as defensive mobilization increases the proneness for safety seeking behavior and thereby might establishing persistent avoidance behavior (Leyro, Zvolensky, & Bernstein, 2010; Salkovskis, 1991).

According to the present diagnostic system DSM-5 (American Psychiatric Association, 2013), excessive and persistent fear and anxiety, as well as related behavioral disturbances are

core features of all anxiety disorders (e.g., in social phobia, panic disorder, or specific phobia). Thus, patients with anxiety disorders are characterized by excessive defensive mobilization towards the feared threat, along with increased safety seeking behavior, which can, unfortunately, result into high individual suffering as well as high socio-economic costs due to increased health care utilization or absences from work (Barlow, 2002).

Etiological models of anxiety disorders propose that defensive survival circuits in the brain might be dysregulated or hypersensitive, thus eliciting excessive and dysfunctional defensive mobilization even in response to safe stimuli (Bouton, Mineka, & Barlow, 2001; Lang, Davis, & Öhman, 2000; Lang, McTeague, & Bradley, 2016). In fact, patients with anxiety disorders often react with an exaggerated defensive response to low threat-levels or threats at great distance (Hamm, Richter, & Pané-Farré, 2014; Perusini & Fanselow, 2015), possibly contributing to dysfunctional and persistent avoidance behavior (Hamm et al., 2016).

Therefore, it is assumed that persons with pathological anxiety and fear of body sensations, as observed in patients with panic disorder (PD), are reacting to actually innocuous body sensations (e.g., palpitations, pounding heart or accelerated heart rate) or early indicators of an anticipated critical somatic state (e.g., dyspnea signaling suffocation) with a strong or even excessive activation of the defensive system (Bouton et al., 2001; Hamm et al., 2014; Hamm et al., 2016; Meuret et al., 2011).

The present thesis targets to reveal new insights about the dynamics of defensive mobilization to interoceptive threats. Moreover, this work aimed to examine personality and biobehavioral factors that might contribute to excessive defensive activation, thus increasing the risk for the emergence of anxiety-related disorders. In the first part of this work, I will give an overview of the current knowledge about defensive mobilization and their possible role in the etiology of pathological fear and anxiety. Afterwards, I will present experimental studies of this thesis and discuss them in light of the current literature, as well as their application to the *Threat Imminence Model* of panic disorder.

2 Defensive mobilization

2.1 Threat imminence

Animal studies revealed that defensive behavior varies as a function of threat proximity, whereby the predator's imminence is determined by physical, temporal, and probabilistic closeness (R. J. Blanchard & Blanchard, 1989b; Fanselow, 1994, 2018; Fanselow & Lester, 1988; Perusini & Fanselow, 2015). Based on these findings, models like the *Threat Imminence Model* (Fanselow, 1994) distinguish three sequential stages of defensive behavior, dependent on the perceived threat distance (see table 1):

Table 1: The three different stages of the Threat Imminence Model (adapted from Fanselow (2018)).

Predator imminence continuum in the rat			
Stage	Pre-encounter	Post-encounter	Circa-strike
Location	Home/nest	Foraging ground	Prey and predator in contact
Examples of defensive behavior primarily based on rodents	Stretched approach, nocturnal feeding	Freezing, Thigmotaxis	Protean escape attempts from predator, vocalization, biting, thrashing
Emotional experience	Anxiety	Fear	Panic

Pre-encounter. If an animal enters an environment in which it has previously encountered a predator without having detected it yet, the prey typically shows preemptive behavior with antipredator defensive strategies, like generalized hypervigilance, withdrawal, and passive avoidance (R. J. Blanchard & Blanchard, 1989a; Fanselow, Lester, & Helmstetter, 1988). As the anticipated predator is at furthest distance, the mode of pre-encounter defense is more permissive of flexibility to allow to, or more precisely, to be able to go into a potential dangerous situation (Mobbs, Hagan, Dalgleish, Silston, & Prévost, 2015) by reducing the probability of encounter (Fanselow, 2018).

Post-encounter. When the prey-animal encounters a predator, attention is immediately shifted towards the threat (attentive immobility) and motoric movement stops simultaneously in order to evade detection. The engaged motor freezing is typically associated with bradycardia, while defensive reflexes are potentiated and arousal increases with increasing threat proximity (Campbell, Wood, & McBride, 1997; Fanselow, 1994; Marks, 1987; Timberlake, 1993). At this stage, the prey-animal will try to prevent an attack by displaying

active avoidance (Mowrer, 1940), or, as the predator approaches, preparing for defensive fight or flight (R. J. Blanchard, Flannelly, & Blanchard, 1986; Cannon, 1915; Fanselow, 1994; Marks, 1987).

Circa-strike. When it comes to contact with a predator, defensive fight or flight reactions are engaged, depending on the opportunity of escape routes and the species-specific defensive strategy (Marks, 1987). Under attack, prey-animals are typically displaying protean escape behavior, as in rodents for example vocalization, biting or thrashing (Perusini & Fanselow, 2015), or they are showing an extreme fear reaction – tonic immobility or faint – in which they are 'paralyzed with fear' when an escape is not possible (Marks, 1987; Volchan et al., 2017). Thus, the animal gets unresponsive to intense or even painful stimulation (e.g., when the predator bites), and some species are rolling themselves in a tight motionless ball (e.g., armadillo *Tolypeutes conurus* or pangolin *Manus tricuspis*). In doing so, they are trying to increase their possibility to escape and survive, as most predators are triggered by prey-movements and refuse to eat dead meat (e.g., hawks) (Marks, 1987).

2.2 Defense Cascade Model

Lang et al. (1997) proposed the D*efense Cascade Model*, in which they transferred the theoretical assumptions of the *Threat Imminence Model* from animals to humans, based on findings about physiological reactions during picture viewing. Their theoretical deductions are presented and discussed in the following.

Pre-encounter defense – generalized hypervigilance. At early stages of defense, when the threat is not encountered and the emotional intensity is low, the sympathetic and parasympathetic systems are co-activated and perceptual processing is facilitated, indicated by orienting reactions (heart rate deceleration, moderate electrodermal increases, and inhibition of the defensive startle reflex).

In line with the theoretical assumptions of Lang et al. (1997), the pre-encounter stage can be conceptualized as anxiety, as individuals are at a sustained state of apprehension about a

potential future threat, resulting into worry, (muscle) tension, feeling of insecurity and threat-nonspecific hyper-vigilance, as well as hesitating or avoidance behavior (American Psychiatric Association, 2013; Barlow, 2000; Davis, Walker, Miles, & Grillon, 2010; Perusini & Fanselow, 2015; Rachman, 2004). In contrast to the proposed model from Lang et al. (1997), individuals who experience anxiety are already showing a non-specific potentiation of the startle reflex in a context where they are told that an aversive electric shock might be delivered (Grillon, Baas, Lissek, Smith, & Milstein, 2004; Schmitz & Grillon, 2012). This indicates a greater activation of the defensive system in an unpredictable/uncertain situation in comparison to a neutral/safe situation. Moreover, this effect is pronounced and more generalized in individuals with an anxiety disorder than in healthy controls (Grillon, 2002). For example, Vietnam veterans with posttraumatic stress disorder (PTSD), in contrast to healthy control individuals, reacted with a potentiated startle reflex in experimental periods, when they were not at risk of receiving an electric shock. This baseline-effect was only observed after the patients with PTSD had associated the initially innocuous context of the experimental setting as threatening in a second experimental session (Grillon, Morgan, Davis, & Southwick, 1998). Similar findings were reported when individuals with high spider fear were told that pictures of spiders might be presented during an experiment (Michalowski et al., 2009; Michalowski, Pané-Farré, Löw, & Hamm, 2015). The resulting generalized hypervigilance even to safety cues is discussed to be a key symptom of anxiety disorders (Davis & Whalen, 2001; Weymar, Keil, & Hamm, 2014), which might have its origin in an increased afferent sensory gaining during pre-encounter defense (Bublatzky & Schupp, 2012; Cornwell, Garrido, Overstreet, Pine, & Grillon, 2017; Weymar et al., 2014; Weymar, Bradley, Hamm, & Lang, 2013).

Post-encounter defense – defensive freezing. When the threat is encountered and 'approaches', or the emotional intensity increases, the defensive system gets more activated and the sympathetic system dominates. Thereby, the electrodermal activity and the startle response increase with increasing threat proximity and/or emotional intensity. Additionally, to prepare

for fight or flight, the heart rate switches from an initial deceleration (orienting and freezing) to acceleration in order to be able to compensate for the higher metabolic rate during defensive action.

In accordance, as soon as a real or perceived threat is detected, fear along with a fear response is elicited (Davis et al., 2010; Perusini & Fanselow, 2015; Schmitz & Grillon, 2012). Thereby, humans are often experiencing the feeling of fear and are mostly able to report the specific fear trigger (e.g., spider) (American Psychiatric Association, 2013). The response pattern is typically characterized by selective attention towards the threat, accompanied by motoric freezing and a heart rate deceleration ('fear bradycardia', Campbell et al., 1997), a surge of autonomic arousal (necessary preparation for fight or flight behavior), thoughts of immediate danger (realistic up to unrealistic catastrophizing concerns), and escape behavior (American Psychiatric Association, 2013).

Importantly, the characteristics of defensive mobilization during fear depend on the proximity of the threat. For example, participants who are anticipating an electric shock are showing an increasing potentiation of the startle reflex with increasing proximity to the delivery of the aversive stimuli (Grillon, Ameli, Merikangas, Woods, & Davis, 1993). New insights about the dynamics of defensive mobilization were revealed by Löw, Weymar, and Hamm (2015). They developed an instructed fear paradigm in which they used symbols increasing in size to create an impression of approach. The symbols signaled whether the participants were safe or whether they could get an electric shock at the end of the symbol-looming. Moreover, a colored frame displayed if the threat-delivery could be avoided or not. When participants were confronted with an approaching inevitable threat, motoric and attentive freezing was observed, as indicated by fear bradycardia, an increase in skin conductance and a potentiated startle reflex. Remarkably and in contrast to these results, when participants had the opportunity to avoid an 'attack', the pattern of defensive response mobilization substantially changed to response preparation, along with an attentional shift. Most importantly, and irrespective of an avoidance

opportunity, both defensive response mobilizations were more pronounced with increasing proximity of threat.

Circa-strike defense – fight/flight or fright. When the threat is most imminent (perceived or spatial proximity), or at a certain threshold of emotional intensity, fight-or-flight behavior is engaged, depending on the available behavioral options (Marks, 1987).

Indeed, most humans are reporting feelings of panic and an immediate urge to escape at this stage of defensive responding (American Psychiatric Association, 2013). If escape is possible, the patterns of defensive mobilization change dramatically in comparison to an inevitable threat, as autonomic arousal sharply increases, along with a strong heart rate acceleration. Moreover, defensive reflexes are strongly inhibited and attention is shifted towards fight or flight by blocking action-irrelevant stimuli (Löw et al., 2015; Löw, Lang, Smith, & Bradley, 2008; Wendt, Löw, Weymar, Lotze, & Hamm, 2017) in order to facilitate successful escape or, at least, increasing the probability to do so. These results are in line with findings from animal research (e.g., see Fanselow, 1994) and therefore indicating a global mechanism.

In contrast, when escape is not an option, as the life-threatening danger is inescapable (e.g., during a traumatic event, like a physical or sexual assault), defensive strategy switches to tonic immobility (TI; also described as fright or immobility under attack) to reduce the risk of harmful injuries and a continuing attack in order to increase the probability to survive (Schauer & Elbert, 2010; Volchan et al., 2011; 2017). This defensive strategy is characterized by profound motor inhibition and relative unresponsiveness to external stimuli, which is mostly experienced by patients with PTSD during the initial traumatic event. Those individuals reported that they had the urge to move while they find themselves 'locked-in' as they were involuntarily immobilized by their defensive system (see Volchan et al., 2011).

2.3 Defensive brain network

The processing of threat-related stimuli and thus, the orchestration of defensive responses along the continuum of threat proximity and the behavioral options at hand to ensure survival, is mediated by defensive brain circuitry (Johnson, Federici, & Shekhar, 2014; LeDoux, 2012;

Maren, 2007). These circuits have been extensively studied in animals and humans (for overviews see for example Fanselow, 1994; Perusini and Fanselow, 2015; LeDoux, 2012; LeDoux and Pine, 2016). Especially the amygdala, the anterior cingulate cortex (ACC), the anterior insula, the ventromedial prefrontal cortex (vmPFC), and the periaqueductal gray (PAG) have been identified as important anatomical structures in mediating anxiety and fear responses (Bandler & Shipley, 1994; Benarroch, 2012; Fullana et al., 2015; Sehlmeyer et al., 2009).

In general, when a threat is distant, neural activity is increased in the vmPFC and the lateral amygdala (LA), mediating avoidance behavior (Mobbs et al., 2007; 2009; for an overview see Maren, 2007 and figure 1). In the case that the threat approaches, a shift in neural activity from forebrain to midbrain has been observed, whereas cerebral blood flow increased especially in the central amygdala (CeA) and the PAG (for an overview see Maren, 2007). Previous findings suggest that this shift might be mediated in the amygdala, and be controlled by the prefrontal cortex (Martinez et al., 2013; Moscarello & LeDoux, 2013). Moreover, this results in a dynamic recruitment of brain areas along the threat imminence continuum, as explained in the following:

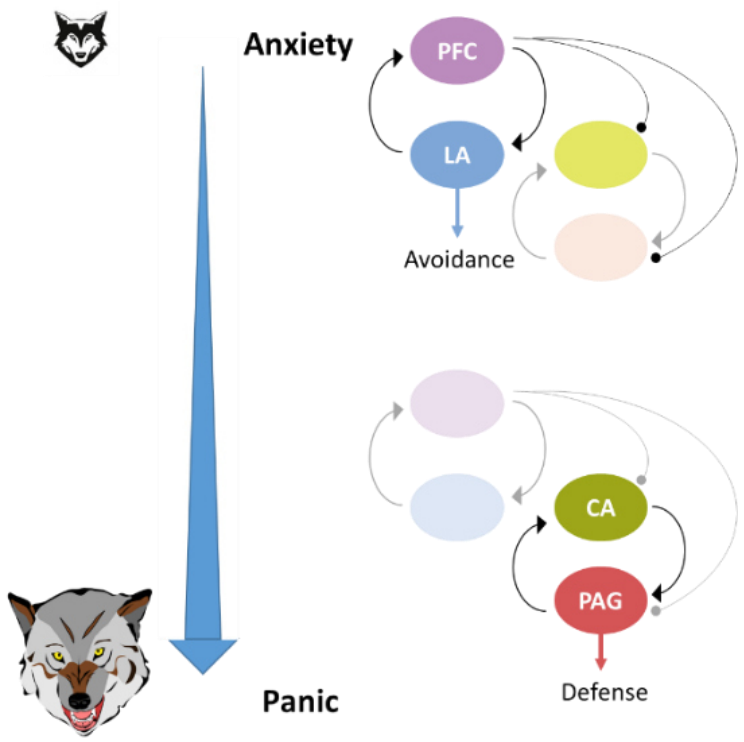

Figure 1. The shift in human brain activity from forebrain to midbrain with increasing threat proximity (adapted from Maren, 2007).

Pre-encounter. As previously described, general hypervigilance and precaution behavior are elicited during pre-encounter defense. At this early defensive stage, neural activity has been found to be increased in the primary sensory areas and the bed nucleus of the stria terminalis (BNST) to facilitate the processing of external stimuli (see Cornwell et al., 2017; Rosen and Schulkin, 1998). Thus, individuals are capable of faster threat detection as well as faster initiation of avoidance or escape behavior. As this process is activated by threat stimuli, contexts, or situations (uncertain or unsafe), the rate of false alarm reactions is increased according to the motto: 'better safe than sorry'. Moreover, initiated escape or passive avoidance at this stage are mediated by projections from the LA via the basal amygdala (BA) to the nucleus accumbens in the ventral striatum (see also figure 2; Amorapanth, LeDoux, and Nader, 2000; Ramirez, Moscarello, LeDoux, and Sears, 2015).

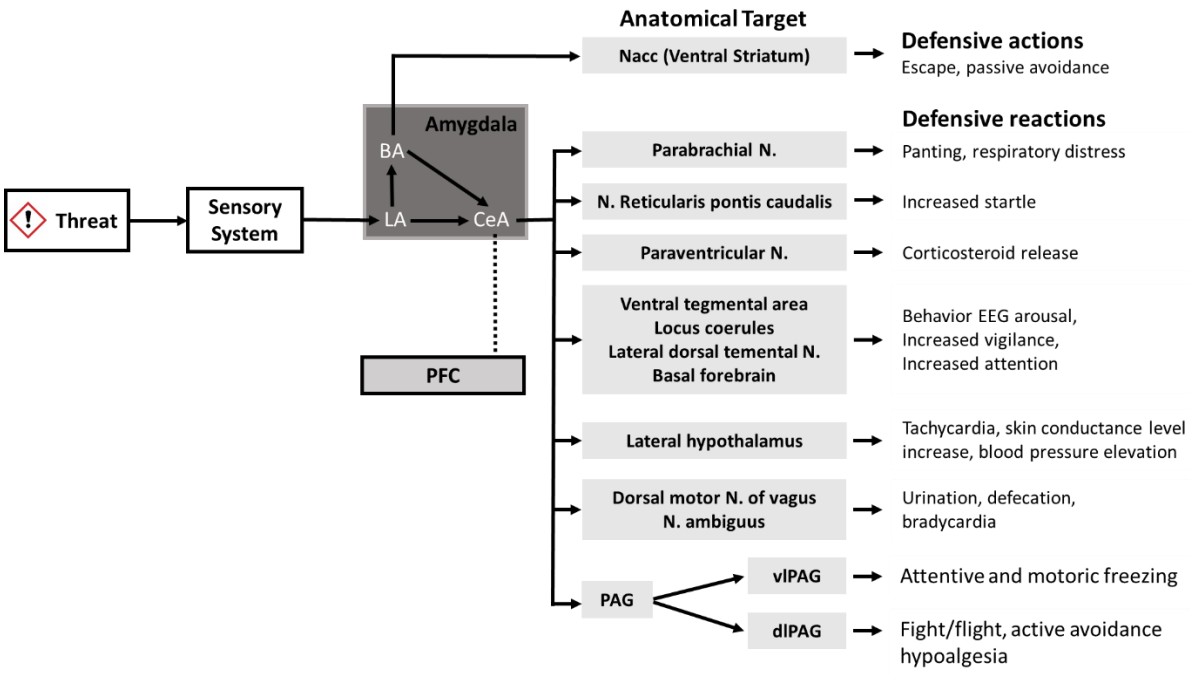

Figure 2. Pathways underlying defensive reactions and defensive actions (adapted from LeDoux and Pine, 2016; Davis and Whalen, 2001; and Fanselow, 1991). Abbreviations: LA, lateral amygdala; CeA, central amygdala; BA, basal amygdala; NAcc, nucleus accumbens, PFC, prefrontal cortex; PAG, periaqueductal gray; vl, ventrolateral; dl, dorsolateral.

Post-Encounter. The neural circuits mediating post-encounter and circa-strike defense have been extensively studied (for an overview see LeDoux, 2000). Using Pavlovian fear conditioning, animal research revealed that threat-cues are capable of activating the LA, and

that activation is directly or indirectly (via the BA) conveyed to the CeA, which controls the expression of defensive responses (behavior, autonomic, endocrine and somatic reflexes) (LeDoux, 2000). In order to do so, the CeA is targeting anatomical structures in the brainstem and the hypothalamus to effectively respond to danger, depending on the threat proximity and the behavioral repertoire at hand.

Especially the PAG has been identified as an important anatomical structure in controlling defensive behavior during post-encounter and circa-strike defense (for a meta-analysis and review see Linnman, Moulton, Barmettler, Becerra, and Borsook, 2012). The ventrolateral part of the PAG (vlPAG) is activated by the CeA during post-encounter defense, interrupting ongoing behavior (motoric freezing), promoting attentive freezing, as well as potentiating defensive reflexes like the startle reflex (Gross & Canteras, 2012; Hamm, 2015; Tovote, Fadok, & Luthi, 2015), and decelerating the heart rate (fear-bradycardia; Bandler, Keay, Floyd, and Price, 2000).

Circa-strike. If the threat is most imminent, defensive response will change from defensive freezing to action (e.g., fight, flight, active avoidance), mediated by a switch from the vlPAG to the dorsal part of the PAG (dlPAG; de Oca, DeCola, Maren, and Fanselow, 1998; Fanselow and Poulos, 2005). This circa-strike defense mobilization is accompanied by a general discharge of the sympathetic nervous system (Cannon, 1932).

2.4 Interoception – the possible threat from inside

Previous research has mainly focused on defensive mobilization to external threats. However, as the scientific interest on signals from inside the body increased recently (Khalsa et al., 2017; Khalsa & Lapidus, 2016), the knowledge about interoceptive threats expands.

In general, interoception refers to the perception of the physiological condition of the body and is vital for maintaining the bodily homeostasis (Craig, 2002; Khalsa et al., 2017). Bodily disturbances, such as dyspnea (air hunger, breathlessness) can elicit adaptive behavior to regain homeostatic balance in order to ensure survival (Craig, 2002, 2009; Strigo & Craig, 2016) as

well as evoking defensive response mobilization (Alius, Pané-Farré, von Leupoldt, & Hamm, 2013; Benke, Alius, Hamm, & Pané-Farré, 2018; Pané-Farré et al., 2015; Richter et al., 2012). The dysfunction of interoception has been recognized by previous research as a central component of different mental health conditions, including anxiety disorders (Khalsa et al., 2017). Thus, besides the important life-saving and maintaining function of interoception, excessive fear and anxiety in response to recurrent or chronic experiences of interoceptive signals (e.g., dyspnea), along with related dysfunctional behavioral changes, can cause great individual suffering as well as high socio-economic costs. This is the case as in mental disorders (e.g., PD), or in various somatic diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD); Barlow, 2002; Dalal, Shah, Lunacsek, and Hanania, 2011; Lehrer, Feldman, Giardino, Song, and Schmaling, 2002; Wittchen and Jacobi, 2005).

Moreover, already small and harmless interoceptive signals are capable of eliciting strong defensive behavior in order to prevent potentially life-threatening risks (e.g., suffocation, critical somatic state; Acheson, Forsyth, and Mosley, 2012; Bouton et al., 2001; Cort, Griez, Buchler, and Schruers, 2012; Pappens, Vandenbossche, Van den Bergh, and Van Diest, 2015). Especially, elevated defensive mobilization to the perception of interoceptive threats has been considered as an important etiological factor for PD (Briggs, Stretch, & Brandon, 1993; Klein, 1993; Preter & Klein, 2008; Vickers & McNally, 2005), and for somatic symptom disorders (Olatunji et al., 2014; Thomson & Page, 2007), as well as for mental co-morbidities in individuals suffering from different somatic diseases (Elsenbruch et al., 2010; Fond et al., 2014; Vogele & von Leupoldt, 2008; von Leupoldt, Chan, Esser, & Davenport, 2013; von Leupoldt & Kenn, 2013; Zaman et al., 2016). The extend of the defensive response is determined by the individual believes about the consequences and the fear of the body sensation (Alius et al., 2013; Pané-Farré et al., 2015; Smits, Tart, Rosenfield, & Zvolensky, 2011), and they also mediate the impact on the perception of sensations and behavior (e.g., physical activity, avoidance; Smits et al., 2011).

2.5 Neurobiological dynamics of interoception

Previous research has tried to shed light on the defensive network which is involved in the detection and orchestration of defensive mobilization to interoceptive signals that might indicate danger to the body's integrity (Craig, 2002, 2009; Schenberg et al., 2014; Schimitel et al., 2012; Strigo & Craig, 2016).

In case of dyspnea, where the threat is arising in the respiratory system, the defensive network seems to be linked to a much wider network of respiration. Following the analysis from Evans (2010) and his proposed cortico-limbic model for respiratory sensorimotor integration, there are two distinguishable sub-networks. The first network is for volitional control of breathing and is mediated within motor cortical, supplement-motor areal, cerebellar, and subcortical regions. The second network has been extensively discussed to be crucial for processing dyspnea (Hayen, Herigstad, & Pattinson, 2013), and, moreover, for processing of emotions in general (Holzschneider & Mulert, 2011; Paulus, 2008; Sehlmeyer et al., 2009). This second network is mediated by a cortico-limbic network, consisting of the anterior insula, ACC, PAG, and the amygdala.

Interestingly, the neurobiological dynamics of defensive mobilization to an interoceptive threat that is approaching or culminating might be comparable with those to an exteroceptive threat (von Leupoldt et al., 2009). In fact, discrete projections from the vmPFC to different columns in the PAG have been found to mediate defensive responses (e.g., freezing or fight/flight) to both exteroceptive and interoceptive threats (for reviews see Bandler et al., 2000 and Faull, Subramanian, Ezra, and Pattinson, 2019).

Moreover, as the anticipation or the perception of dyspnea can evoke anxiety and/or fear, the insula, the ACC, and the amygdala are discussed for the processing of these arousing and motivational relevant emotions (Adolphs et al., 2005; Phillips, Drevets, Rauch, & Lane, 2003; Takahashi et al., 2008; Vogt, 2005). Therefore, the anterior insula seems to play a central role in the integration and representation of interoceptive signals (e.g., dyspnea), as well as for the

regulation of the internal state (Cameron, 2009; Craig, 2002; Davenport & Vovk, 2009; Oppenheimer & Cechetto, 2016; Saper, 2002). Interestingly, this region has been found to be hyperactive in patients with anxiety (e.g., PD) or mood disorders (e.g., depression), possibly indicating increased interoceptive awareness due to altered interoceptive states (Craig, 2002; Craig, 2009; Paulus & Stein, 2010). Additionally, the anterior insula has found to be stronger activated in healthy individuals with high anxiety during the anticipation of a respiratory challenge that evoke unpleasant and potentially threatening body symptoms (Holtz, Pané-Farré, Wendt, Lotze, & Hamm, 2012). Moreover, the right mid-insula was found to be associated with sympathetic arousal, heart rate increase, and cardiorespiratory sensation (Hassanpour et al., 2018). Furthermore, new insights about the neurobiological dynamics during culminating and escalating dyspnea were presented in a talk by Krause (2017; unpublished data). He and his colleagues adapted and transferred the experimental design from Benke et al. (2017) into the MRI-environment. They recruited women with low or high suffocation fear (tendency to fear suffocation-associated stimuli; Radomsky, Rachman, Thordarson, McIsaac, and Teachman, 2001) and asked them to participate in a respiratory challenge of increasing inspiratory resistance (individually adjusted) and a subsequent short forced breath-holding task. During the respiratory challenge, Krause (2017; unpublished data) found dynamic changes in the areas of the proposed networks from Evans (2010), including the ACC, the anterior insula, the PAG, the amygdala, and, additionally the vmPFC. Moreover, they observed a shift from forebrain to midbrain with culminating dyspnea, along with respiratory adjustment and increased reported fear. In contrast to the low suffocation fear group, persons with high suffocation fear terminated trials prematurely, reported significantly higher fear, and reacted with elevated skin conductance during the forced breath-holding. Moreover, they showed a stronger forebrain-to-midbrain shift, along with increased activation of the right anterior insula. In contrast, the group of low suffocation fear showed successively increasing activation in the vmPFC and the ACC. These findings suggest that higher suffocation fear is associated with elevated activation of the

defensive brain circuits to respiratory threats, which might facilitate avoidance behavior. However, the concrete neurobiological and physiological defensive mechanisms, especially of avoidance behavior, in response to a culminating respiratory threat, remain to be elucidated.

3 Experimental studies of defensive responses to interoceptive signals

3.1 Comparable defensive response mobilization to external and internal threats

As previously described, anxiety and fear in the face of an external threat (e.g., predator or criminal) are organized along a dimension as they change from one to another, depending on the perceived threat imminence and the available behavioral repertoire at hand. Additionally, and importantly, survival-relevant threats can also arise from inside the body. For example, suffocation-like experiences of dyspnea (e.g., evoked by inhalation of CO_2, increased respiratory loading or blocked inspiration) are eliciting defensive mobilization across species (Alius, Pané-Farré, Löw, & Hamm, 2015; Berquin, Bodineau, Gros, & Larnicol, 2000; Blechert, Wilhelm, Meuret, Wilhelm, & Roth, 2010; Leibold et al., 2013; Schimitel et al., 2012; Teppema et al., 1997; von Leupoldt et al., 2009; Winter, Ahlbrand, Naik, & Sah, 2017). Moreover, even early indicators of respiratory distress are capable of evoking comparable adaptive defensive responses, as observed for exteroceptive threats (Fullana et al., 2015; Milad & Quirk, 2012).

Recently, Krause et al. (2017) demonstrated that the patterns of dynamic defensive mobilization to an approaching interoceptive and exteroceptive threat are comparable. They adapted the instructed fear paradigm from Löw et al. (2015) and included an additional interoceptive threat as a third condition – a forced breath holding that evoke dyspnea by culminating CO_2. Thus, three different symbols indicated whether an external threat (electric shock – highly annoying, but not painful), an interoceptive threat (forced breath holding – individually adjusted to 40 % of individual maximal voluntary breath holding time after expiration, minimum 15 s), or a safe condition. Moreover, each trial consisted of a cascade of five looming stages (duration per stage 2000 ms), whereas each stage started with the presentation of a colored frame (blue or yellow; 500 ms). While the frame remained on the screen, a white symbol (e.g., circle, star, or triangle) appeared in the center of the frame (1500 ms). With each stage, the symbol increased in size in order to create an impression of approach

towards the participant. Importantly, the color of the frame indicated whether the participants had the opportunity to avoid the threat delivery by a fast button-press after the most proximal threat-cue or not. After the last stage, the frame disappeared and thereby signaled the participant that they had to press the button in the active/avoidable conditions. Thus, irrespective of the condition, the symbol remained alone on the screen for 1000 ms (response window in the active/avoidable conditions). Afterwards, the threats in the inevitable conditions were delivered in 50 percent of the trials (electric shock after 500 ms of the response window (symbol only); forced breath holding was manually started by the experimenter at the end of the first expiration after the response window). In contrast, a computer algorithm dynamically adjusted the time window for successful avoidance behavior in the avoidable conditions to also targeting a delivery rate of 50 percent for each threat. Overall, fifty-three healthy students participated the study and the final sample consisted of 48 participants.

In line with previous findings (Löw et al., 2015), they observed an increasing potentiation of blink magnitudes with increasing proximity of the inevitable exteroceptive threat, as well as a strong bradycardia and an increase in skin conductance level. Moreover, the N100 amplitude, as evoked by the startle probe, increased while the inevitable external threat approached, indicating higher general alertness. The same dynamic pattern of post-encounter freezing was observed for an approaching inevitable interoceptive threat. In contrast, when participants could avoid the interoceptive or the exteroceptive threat by a fast button-press, blink magnitudes, and probe-evoked P3 amplitudes were substantially suppressed with greater proximity of the response generation, while heart rate strongly accelerated. This suggests a mechanism to facilitate the action by focusing attention towards the fight or flight response and blocking action-irrelevant stimuli, supported by an increased sympathetic activation. Interestingly, defensive responses to external and interoceptive threats only differed on the level of respiration, as minute ventilation only strongly increased during the anticipation of an inevitable interoceptive threat and decreased when active avoidance was possible. At the same time,

minute ventilation was not modulated by an inevitable or avoidable external threat. This possibly has an important implication for the understanding of the etiology of anxiety disorders, especially the PD, and for understanding mental comorbidities in individuals with respiratory diseases (e.g., COPD, Asthma), as already a distant threat, i.e., the cue, which does not evoke respiratory discomfort, might trigger a false suffocation alarm (Klein, 1993; Preter & Klein, 2008, 2014).

Taken together, this study revealed mostly comparable dynamics of defensive response mobilization to interoceptive and exteroceptive threats during post-encounter freezing and circa-strike action. However, these results did not answer the questions if and how defensive response mobilization is modulated by repeated avoidance performance.

3.2 The change of defensive responses during repeated avoidance behavior

The evolutionary function of avoidance and escape behavior is to ensure survival (Marks, 1987), as it allows an individual to adapt to changing environmental conditions as well as to protect itself from a life-threatening situation (Cain & LeDoux, 2008; Hamm & Weike, 2005). However, a wide spectrum of mental disorders, especially anxiety disorders, are characterized by excessive avoidance or safety behavior in order to prevent a confrontation with or termination of exposure to a perceived threat (American Psychiatric Association, 2013; Craske et al., 2009; Krypotos, Effting, Kindt, & Beckers, 2015). Unfortunately, these maladaptive behaviors (e.g., taking medication, avoiding crowded places or arousing activities) are persistent as they are consistently elicited by threat-related cues (e.g., phobic objects or body sensations). Moreover, they are inflexible when they are performed through the expected negative outcomes while the environmental conditions may have changed (Dickinson, 1985; LeDoux, Moscarello, Sears, & Campese, 2016). A key component in the maintenance of anxiety disorders is that patients with persistent avoidance behavior prevent themselves from disconfirming their central concerns about the consequences of a specific situation. Thus, as a result of avoidance behavior, the extinction of previously learned association between a threat-

signaling cue and an associated threat might be prevented (Barlow, 2002; Craske et al., 2008; Helbig-Lang & Petermann, 2010; Mineka & Zinbarg, 2006).

In order to prevent the development of an anxiety disorder, it is crucial to understand the mechanism of emerging avoidance behavior. Data from animals and humans suggest that fear might initiate instrumental avoidance behavior and get less important for its maintenance (Campese et al., 2016; LeDoux & Pine, 2016; Solomon, Kamin, & Wynne, 1953; Vervliet & Indekeu, 2015). Interestingly, there is evidence that reactive fear responses (i.e., freezing) are mediated by the amygdala, whereas the prefrontal cortex (i.e., infralimbic prefrontal cortex) coordinates instrumental defensive action by inhibiting the amygdala (Martinez et al., 2013; Moscarello & LeDoux, 2013). Thus, it is possible that avoidance behavior can become amygdala-independent when it is performed repeatedly, and thus, lose its adaptive function (Campese et al., 2016; LeDoux et al., 2016).

New insights about the dynamics of spontaneous avoidance learning have been revealed by Benke, Krause, Hamm, and Pané-Farré (2018), using a respiratory challenge with successively increasing dyspnea. First, inspiratory resistive loads (IRLs) were presented to the participants and they had to rate the intensity and unpleasantness of each IRL. After an IRL was rated as maximally tolerable, three IRLs were selected (previously rated as producing slight [1st IRL], moderate [2nd IRL] and maximally tolerable [3rd IRL] unpleasantness). These three IRLs were presented each for 60 s in an ascending order, immediately followed by a breathing occlusion (15 s) as the ultimate respiratory threat and a recovery phase (30 s). This sequence was repeated eight times and the participants had the opportunity to press a button to terminate each trial prematurely. Overall, 69 healthy individuals participated in the experiment, whereas 24 participants terminated the exposure more than once. While most participants initially terminated during the ultimate respiratory threat, they successively terminated earlier in order to avoid being exposed to the breathing occlusion.

The first termination was preceded by a strong surge in autonomic arousal and reported anxiety, as well as by a strong inhibition of the startle reflex and the probe evoked P3-component right before the avoidance action. This indicates preparation for the defensive action. In contrast, autonomic arousal alleviated with repetitive termination and thus, no physiological indication of the response generation for performing the avoidance behavior could be observed anymore. In comparison, no indication of any defensive response preparation, nor any changes in physiological response patterns were observed for the matched controls (matched for age, sex, and level of suffocation fear, who never terminated any trial) at all, only an increase in anxiety levels with repeated exposure. The pattern of active response preparation prior to the first termination are in line with data from Krause et al. (2017) and Löw et al. (2015). Interestingly, the same pattern has been observed in patients with PD when they escaped entrapment during a standardized behavioral avoidance test, as well as right before a panic attack (Hamm et al., 2016; Richter et al., 2012).

With each repetition, participants terminated the exposure at lower threat levels to avoid the ultimate respiratory threat, accompanied by alleviation of the defensive response pattern. These results are in line with previous research (Krypotos, Effting, Arnaudova, Kindt, & Beckers, 2014; Solomon et al., 1953; Solomon & Wynne, 1954), as, for example, a decrease in autonomic arousal was observed during avoidance learning (Boeke, Moscarello, LeDoux, Phelps, & Hartley, 2017; Delgado, Jou, LeDoux, & Phelps, 2009; Lovibond, Saunders, Weidemann, & Mitchell, 2018; Vervliet & Indekeu, 2015). Thus, in this study slight dyspnea might have become an indicator for the upcoming ultimate respiratory threat and therefore avoidance behavior was successively initiated at lower intensity levels (Lovibond, 2006; Pappens, Smets, Vansteenwegen, Van den Bergh, & Van Diest, 2012). Unfortunately, when slight interoceptive sensations are resulting in avoidance behavior in order to prevent an anticipated threat, individuals are unable to re-evaluate the learned dysfunctional association to disconfirm their central concerns (Craske, Hermans, & Vansteenwegen, 2006; Craske, Treanor,

Conway, Zbozinek, & Vervliet, 2014; Vervliet, Craske, & Hermans, 2013). Thus, this maladaptive behavior can get manifested. However, the question arise which factors contribute to the occurrence of individually performed avoidance behavior.

3.3 Prediction of excessive defensive response mobilization and avoidance behavior to internal threats

As previously demonstrated, internal and external threats are eliciting mostly comparable adaptive defensive responses (Krause et al., 2017) to ensure survival (Marks, 1987; Strigo & Craig, 2016). However, the adaptive response may become dysregulated as threat associated cues, which are at great distance (e.g., spider) or are at low symptom level (e.g., slight body symptom) might be perceived as a threat and thus lead to strong or even excessive defensive mobilization. For example, persons who suffer from anxiety disorders or cardiopulmonary diseases are prone to react with excessive anxiety and defensive arousal to even benign respiratory signals (American Psychiatric Association, 2013; Hamm et al., 2014; Parshall et al., 2012). Individuals with anxious apprehension about body symptoms and strong fear reactions typically show “preventive” avoidance behavior, as they evade situations or contexts which are associated with these symptoms (e.g., drinking caffeine or physical activities), as well as slight interoceptive signals (e.g., mild dyspnea), that might indicate a potential culmination of feared symptoms into a critical somatic state (Barlow, 2002; Craske & Barlow, 1988; Craske, Rapee, & Barlow, 1988; Hamm et al., 2014). In the case of a confrontation with the feared symptoms, individuals react with strong defensive mobilization, facilitating flight or avoidance behavior (Barlow, 2002; Richter et al., 2012). Excessive avoidance behavior to respiratory signals as a result of excessive defensive mobilization might be an important etiological factor for PD, and more generally for mental comorbidities in individuals with respiratory diseases (Bouton et al., 2001; Hamm et al., 2016; Klein, 1993; Vogele & von Leupoldt, 2008; von Leupoldt & Kenn, 2013).

In order to find predictors for these maladaptive defensive mobilization, the maximal voluntary breath-holding time (mvBHT) has been discussed as a biobehavioral marker (Asmundson and Stein, 1994; Eke and McNally, 1996; McNally and Eke, 1996). During breath-holding, endogenous CO_2 accumulates, thus evokes unpleasant respiratory symptoms. Therefore, the duration of mvBHT is discussed to reflect the (in-)tolerance of the increasing levels of CO_2 and the accumulating sensation of dyspnea (Zvolensky & Eifert, 2001). According to Klein's false suffocation alarm theory (Klein, 1993), shorter mvBHT might indicate higher CO_2 sensitivity of a suffocation alarm monitor system. Thus, defensive responses (e.g., panic or hyperventilation) are prompted at smaller changes in CO_2-levels to prevent potential suffocation. Indeed, healthy persons were found to display longer mvBHT than patients with PD (Asmundson & Stein, 1994; Zandbergen, Strahm, Pols, & Griez, 1992), and it has been demonstrated that persons with PD more frequently reported a panic attack after a breath-holding challenge as patients with other anxiety disorders (Nardi et al., 2003). Moreover, higher frequency of PAs in patients with PD during a respiratory challenge is associated with shorter mvBHT (Masdrakis, Markianos, Vaidakis, Papakostas, & Oulis, 2009).

In line with this, Krause, Benke, Hamm, and Pané-Farré (Under review) demonstrated that mvBHT is predicting defensive response mobilization during increasing proximity of an anticipated interoceptive threat by examining healthy individuals with short and long mvBHT, using the experimental design from Krause et al. (2017). Replicating previous findings (Krause et al., 2017), Krause et al. (Under review) demonstrated that startle response magnitudes potentiated with increasing proximity of the inevitable exteroceptive threat, indicating freezing, and that they were strongly inhibited right before the action to avoid threat delivery, indicating preparation for escape. Moreover, this defensive reflex mobilization was comparable for both mvBHT groups, regardless of the behavioral repertoire at hand. Also, when participants had the opportunity to avoid the approaching interoceptive threat, Krause et al. (Under review) could again observe an inhibition of startle magnitudes right before action, independent of mvBHT.

On the other hand, when the participants were confronted with an approaching inevitable respiratory threat, defensive response mobilization was only elicited in individuals with short mvBHT, but not for those with long mvBHT. This indicates a stronger defensive activation with shorter mvBHT and, therefore, a potentially more (hyper-)sensitive suffocation alarm monitor (Klein, 1993; Preter & Klein, 2008).

Moreover, the trait-like psychological variable anxiety sensitivity (AS) has been identified as a trait-like psychological variable that modulates defensive mobilization to interoceptive sensations (Benke, Blumenthal, Modess, Hamm, & Pané-Farré, 2015; Eifert et al., 1999; Eke & McNally, 1996; McNally & Eke, 1996; Melzig, Holtz, Michalowski, & Hamm, 2011; Shipherd et al., 2001; Zvolensky & Eifert, 2001). By definition, AS describes the tendency to fear anxiety-related sensations based on believes about potential harmful consequence of these sensations (McNally, 2002). It has been demonstrated that AS is related to increasing defensive mobilization to different interoceptive threats, as well as that elevated AS is a risk factor for panic attacks and the onset of PD (for an overview see McNally, 2002).

Interestingly, an interaction of the psychological variable AS and the biobehavioral marker mvBHT has been demonstrated by Benke, Krause, Hamm, and Pané-Farré (2019) for healthy individuals, who were confronted with a respiratory challenge with culminating dyspnea (see chapter 3.2 for experimental details). In the beginning of the experiment, the individual mvBHT after expiration was determined and IRLs, producing slight, strong and maximally tolerable dyspnea, were individually selected. During repetitive confrontation with increasing intensity of dyspnea (evoked by three IRLs, presented in ascending order, immediately followed by a short post-expiratory breath-holding task), participants had the opportunity to terminate each repetition of the respiratory challenge with a button-press. The analysis of the spontaneously occurring avoidance behavior to prevent a further culmination of the provoked symptoms revealed that high AS and shorter mvBHT were associated with premature termination of the respiratory challenge, while suffocation fear and trait anxiety were not related. Especially the

interaction of AS and mvBHT predicted the avoidance behavior, as participants with shorter mvBHT were more likely to avoid the symptom provocation when they also reported high AS as those who reported low AS.

Taking together, the results from Krause et al. (Under review) and Benke et al. (2019) demonstrated that mvBHT is associated with defensive response mobilization during the anticipation of an approaching inevitable respiratory threat, while the interaction of mvBHT with the psychological factor AS predicts avoidance behavior during the confrontation with culminating dyspnea in healthy individuals. Thus, already healthy individuals with high AS and shorter mvBHT seem to be more sensitive or even hypersensitive to anticipated or actual sensations of dyspnea and, therefore, react with elevated or even excessive defensive mobilization. This is in accordance with Klein's false suffocation alarm theory (Klein, 1993), as defensive responses (i.e., defensive mobilization and fight/flight responses) are facilitated in individuals with a hypersensitive suffocation alarm monitor to prevent a potential life-threatening suffocation.

Avoidance behavior is primarily motivationally driven by the anticipation of the expected outcome or the potential worst case (Reiss, 1991), which is in this context death by suffocation. Additionally, excessive defensive mobilization is accompanied by an increased tendency for safety seeking behavior (Leyro et al., 2010; Salkovskis, 1991), which could facilitate the development of behavioral disturbances (i.e., avoidance and safety seeking behavior) and, thereby, may initiated a spiral of decline (Hayen et al., 2013; Reiss, 1991; Simon et al., 2006). Through this, the possible resulting vicious circle of mutual increasing hypervigilance, facilitated defensive response mobilization and more frequent avoidance behavior (Leyro et al., 2010; Salkovskis, 1991) may contribute to the emergence and maintenance of a serious anxiety or somatic symptom related disorder.

4 Application to the Threat Imminence Model of panic disorder

According to the DSM-5 (American Psychiatric Association, 2013), the panic disorder is characterized by "*recurrent, unexpected panic attacks*" – a brief period of intense fear or discomfort, which reaches a peak in a few minutes, accompanied by at least four out of 13 symptoms (e.g., heart palpitations; sensations of shortness of breath; sweating; feeling dizzy, unsteady, lightheaded, or faint). Moreover, anxious apprehension about the consequences of these panic attacks or about a recurrent attack, or the emergence of maladaptive behavior must follow after a panic attack for at least one month.

The theoretical framework of the *Threat Imminence Model* from Fanselow (1994; see also Lang et al., 1997; Blanchard, 1997) has been translated to a trans-diagnostic model for conceptualizing PD and agoraphobia (Hamm et al., 2014; Hamm et al., 2016), which will be presented in the following:

A panic attack can get associated with a previously innocuous mild interoceptive stimulus (Schimitel et al., 2012) and, thus, this conditioned cue is now also able to elicit anxious apprehension (conditioned response). When a conditioned context is detected (e.g., alone in a crowded place), pre-encounter defense is engaged along with hypervigilance. As soon as a mild body symptom is encountered (e.g., slight dyspnea) – conceptualized as a distant threat – post-encounter defense elicits freezing and selective attention towards the body symptom. If the intensity of the interoceptive symptom increase, i.e., proximity of the threat increases, post-encounter defense can switch to circa-strike responses and, thus, elicit active defensive behavior and/or a panic attack as a circa-strike defense.

Of course, individuals are trying to stop the escalation of this cascade by developing and displaying persistent avoidance behavior, like avoiding the conditioned context or escaping the situation as soon as a mild body sensation is detected, or by using safety signals/behavior (e.g., medication). Unfortunately, avoidance and safety seeking behavior are the key components in the maintenance of anxiety orders, as the conditioned cue – the mild interoceptive signal –

cannot be extinctioned (Barlow, 2002; Craske et al., 2008; Helbig-Lang & Petermann, 2010; Mineka & Zinbarg, 2006).

Thus, the results of Krause et al. (2017) are in line with the theoretical assumption of freezing and selective attention during post-encounter defense of a respiratory threat, as well as with the attentional and sympathetic switch to overt action during avoidance/escape. Furthermore, the study from Benke, Krause et al. (2018) revealed that initial avoidance behavior is elicited by fear and gets more fear-independent with repeated avoidance, and, therefore, might facilitates the development of dysfunctional safety behavior. Additionally, the trans-diagnostic model was further specified by Krause et al. (Under review) and Benke et al. (2019), who revealed that lower mvBHT predicts elevated defensive mobilization during the anticipation of a respiratory threat, whereas higher AS and lower mvBHT predict avoidance behavior during exposure to dyspnea. Thus, individuals with these psychological and biobehavioral traits/factors might be at higher risk to develop a PD or another anxiety or somatic symptom related disorder.

5 Summary and future directions

The present thesis extents the current knowledge about defensive mobilization to interoceptive signals as well as about dispositional factors and etiological mechanism that may contribute to the emergence of pathological anxiety. The data from Krause et al. (2017) demonstrated that the dynamic organization of a defensive mobilization to an approaching exteroceptive threat is comparable to an approaching interoceptive threat. Additionally, the study from Benke, Krause et al. (2018) indicates that the first avoidance of a culminating respiratory threat is initiated by a physiological fear response, whereas repetitive avoidance behavior seemed to become more intended to avoid the worst threat in advance. Furthermore, the study from Krause et al. (Under review) revealed that increased defensive mobilization to an anticipated respiratory threat is associated by reduced mvBHT, while actual avoidance behavior during the confrontation with culminating dyspnea is predicted by the interplay of reduced mvBHT and elevated AS. Taken together, the studies provided new insights about the dynamics of defensive mobilization to body sensations and about possible risk factors that might contribute to the etiology of pathological anxiety. While providing fundamental support for the trans-diagnostic translation of the *Threat Imminence Model* to PD, several new questions arise. For example, further research should address to which degree excessive defensive threat mobilization during anticipation and culmination of body symptoms is associated with the risk to actually develop an anxiety disorder. Thus, the results have to be replicated within a high-risk (e.g., persons with a panic attack without meeting the criteria for PD) and a clinical population. Furthermore, future research should study the specificity of the observed effects by including different intero- and exteroceptive threats. Moreover, future studies ought to extend the findings by investigating the neurobiological defensive dynamics during culminating dyspnea in healthy individuals with low and high SF, as well as in patients with PD and dyspnea-experts (e.g., divers). Thereby, the neurobiological mechanisms underlying initial avoidance behavior should be targeted, as they might contribute to the developing of persistent avoidance behavior.

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Appendix A: Publications

Overview of publications discussed in this thesis

Publication 1

Krause, E., Benke, C., Koenig, J., Thayer, J. F., Hamm, A. O., & Pané-Farré, C. A. (2017). Dynamics of Defensive Response Mobilization to Approaching External Versus Interoceptive Threat. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.* Advance online publication. https://doi.org/10.1016/j.bpsc.2017.12.002

Publication 2

Benke, C., **Krause, E.**, Hamm, A. O., & Pané-Farré, C. A. (2018). Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat. International journal of psychophysiology: official journal of the International Organization of Psychophysiology, 131, 44–56. https://doi.org/10.1016/j.ijpsycho.2017.09.013

Publication 3

Krause, E., Benke, C., Hamm, A.O., Pané-Farré C.A. (Under review). Hold your breath: voluntary breath-holding time predicts defensive activation to approaching internal threat.

Publication 4

Benke, C., **Krause, E.**, Hamm, A. O., & Pané-Farré, C. A. (2019). Predictors of behavioral avoidance during respiratory symptom provocation. *Behaviour Research and Therapy*, *112*, 63–67. https://doi.org/10.1016/j.brat.2018.11.012

Publication 1

Dynamics of Defensive Response Mobilization to Approaching External Versus Interoceptive Threat

Elischa Krause, Christoph Benke, Julian Koenig, Julian F. Thayer, Alfons O. Hamm & Christiane A. Pané-Farré

Biological Psychiatry – Cognitive Neuroscience and Neuroimaging

Published in 2017

Author contributions:

CPF, AOH, CB and EK designed the experiment. EK and CB supervised the data acquisition. EK analyzed the data and provided the first draft of the manuscript. All authors contributed to the interpretation of the data and wrote the manuscript.

Archival Report

Biological Psychiatry: CNNI

Dynamics of Defensive Response Mobilization to Approaching External Versus Interoceptive Threat

Elischa Krause, Christoph Benke, Julian Koenig, Julian F. Thayer, Alfons O. Hamm, and Christiane A. Pané-Farré

ABSTRACT

BACKGROUND: Excessive fear and anxiety are core features of anxiety disorders. Defensive response mobilization varies dynamically with threat proximity.

METHODS: We analyzed defensive responses in 48 healthy students to an approaching external, predator-like threat (an electric shock resembling a predator attack) versus an approaching threat from inside the body (feeling of dyspnea as evoked by forced breath-holding). Threats either were inevitable or could be avoided by button press.

RESULTS: Autonomic changes (heart rate, skin conductance), defensive reflex priming (startle eyeblink response), respiratory responses, and event-related potentials were assessed. Regardless of its source, when an approaching threat was inevitable, a defensive pattern emerged characterized by an increase in skin conductance, a potentiation of the startle reflex, and bradycardia. Minute ventilation increased only with approaching dyspnea. In preparation for active avoidance of either threat, startle magnitudes were inhibited and probe-elicited P3 wave amplitudes were reduced. Moreover, generation of avoidant action resulted in heart rate acceleration.

CONCLUSIONS: This study demonstrates common and specific defensive activation patterns for approaching external and respiratory threats. The specific modulation in respiration in response to an inevitable respiratory threat may have important implications for our understanding of the etiology of anxiety disorders, especially panic disorder.

Keywords: Avoidance, Breath-holding, Fear, Startle response, Threat imminence, Threat proximity

https://doi.org/10.1016/j.bpsc.2017.12.002

According to DSM-5 (1), excessive fear and anxiety and related behavioral disturbances are core features shared by all anxiety disorders. The term "fear" is used to describe a feeling state associated with detection of a threatening object. Fear increases in intensity with increasing proximity of the threat and decreases when the threat stimulus is removed. The term "anxiety" refers to an emotional state elicited in a context in which potential threats might occur without knowing when this will be. While these two feeling states often guide patients' symptom reports and thus categorizations of anxiety disorders, animal data suggest that fear and anxiety are organized along a dimension changing from one to another (2,3) depending on the perceived proximity or imminence of the threat and thus the probability of actual strike and the available response repertoire at hand.

When an organism enters an environment where a predator has previously been encountered but has not yet been detected, rodents show typical patterns of generalized hypervigilance, an inhibition of appetitive behaviors, and passive avoidance (4,5). As soon as the predator is detected, attention is focused on the threat and—to evade detection—motor freezing, typically associated with bradycardia (6), and potentiation of defensive reflexes, is initiated. If possible, animals will display active avoidance behavior to prevent an attack (7) or, with increasing proximity, prepare for defensive fight or flight (3,8–10). In contrast, if escape routes are blocked, the prey will show tonic immobility or faint once it is attacked (11). It has been demonstrated that different neural circuitries organize these different defensive behaviors (12). Recent studies have demonstrated that the described defensive patterns are highly preserved in humans (13–18). Moreover, if a threat can be actively avoided, preparation for action is accompanied by an increase in sympathetic arousal and binds attentional resources, thus limiting the processing of other, irrelevant contextual stimuli (13,19,20).

Across species, it is known that survival-relevant threats may arise not only from external sources (e.g., a predator attack) but also from inside the body. Suffocation-like experiences of dyspnea as a result of inhalation of carbon dioxide (CO_2)-enriched air or increased respiratory loading have been demonstrated to be powerful elicitors of defensive action across species (21–28). The human brain entails numerous neuronal networks that ensure detection of subtle interoceptive signals that indicate danger for the body's integrity (21,29–31). It has been demonstrated that via associative learning processes, early indicators of respiratory threat may

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elicit adaptive defensive responses as observed for external threats (22,32–38). Moreover, they entail specific components, such as the initiation of hyperventilation to counteract possible suffocation (39). Perception of feared mild respiratory symptoms evoked by various respiratory provocation procedures reliably evokes general defensive response mobilization, i.e., sympathetic arousal and potentiation of the startle reflex (33,34,40–42), as well as an increase in respiratory rate, which has been discussed as compensatory adjustment (32,36,42–45).

Excessive defensive mobilization to interoceptive threats is considered to be an important etiological factor not only for panic disorder (37,39,46–48) but also for somatic symptom disorders (49,50) and mental comorbidities in individuals with respiratory (51–53) or gastrointestinal (54–56) diseases. Hyperventilation-related symptoms are frequently found in spontaneous panic attacks (46) for which interoceptive threats are assumed to be primary elicitors (37), whereas such symptoms are not as frequently reported in specific phobia where the threat is clearly external (57). Recently, defensive mobilization and its dysregulation in pathological anxiety, especially panic disorder, was theoretically conceptualized, suggesting that different symptom patterns can be related to the dynamics of defensive mobilization evoked by approaching threat (11,16,58–62).

The present study advances this line of reasoning by investigating this dynamic organization of defensive mobilization to an internal, respiratory threat that is progressively approaching. We used forced breath-holding to establish a respiratory threat—the feeling of dyspnea that emerges when breathing is terminated. Geometric symbols of increasing size indicated the increasing proximity of the threat. We also assessed defensive response mobilization to an approaching external threat, i.e., an electric shock resembling a predator attack, to investigate the general and the specific aspects of defensive mobilization to both threats. In addition, we explored defensive response activations if individuals had the opportunity to actively avoid the encounter with the threat.

Based on previous findings (13,34,63), we expected a clear potentiation of startle reflex—an index of the activation of the central nucleus of the amygdala (64) that would linearly increase with approaching external threat as well as respiratory threat. Moreover, we expected activation of the autonomic nervous system during mobilization of defensive behavior, which should also not differ between threat modality. More specifically, we expected an increase in skin conductance level (SCL) in combination with heart rate (HR) deceleration as an index of attentive freezing with approaching respiratory and external threat.

When individuals were given the opportunity to actively avoid breath-holding by a timely button press, we expected—as observed earlier for active avoidance of an electric shock (13) or entrapment (59)—an inhibition of the startle response, a relative acceleration of HR, an increase in SCL, and a decrease in the P3 component of the event-related brain potential evoked by the startle-eliciting stimulus. Again, we did not expect any differences for the different threat modalities. In contrast, defense-specific adjustments in the respiratory system were expected only for the respiratory threat. Based on observations from symptom provocation studies using inspiratory loading (43), we expected adjustments of respiratory rate or volumes specifically in the inevitable respiratory threat condition, i.e., an increase just preceding breath-holding. Moreover, as respiration is associated with body movement, we expected a suppression of respiration during motor freezing (65) when expecting an immediate inevitable threat as well as during attentive immobility preceding the avoidance button press (66).

METHODS AND MATERIALS

Participants

Participants were recruited from a subject pool of more than 400 students at the University of Greifswald, Germany. In a telephone screening, participants were excluded (27 of 104 contacted participants) if they reported any mental health problems (e.g., any treatment related to psychological or emotional problems or alcohol abuse) or physical conditions (including cardiovascular, respiratory, or neurological diseases; severe hearing impairment; and pregnancy). All participants provided written informed consent to the research protocol approved by the ethics committee of the German Psychological Society. Students received either course credit or payment (25€) for study participation.

Fifty-three Caucasian students participated in the laboratory assessment. Five participants were excluded from the data analyses owing to premature termination of the procedure (n = 3), not adhering to instructions (n = 1), or technical problems (n = 1). The final sample consisted of 48 students (24 women; mean age 23.6 years [SD 4 years]; range, 18–34 years).

Materials, Tasks, and Procedure

We used an instructed fear paradigm, in which each 10-second trial consisted of a cascade of five looming stages. Each stage started with the presentation of a colored frame (500 ms) that remained on screen while a symbol (e.g., circle, star, or triangle) appeared in the center of the frame (1500 ms) (Figure 1). With each stage, the symbol successively increased in size creating an impression that it was approaching the participant. All three symbols had identical luminance and covered an identical area of the screen for the corresponding stages. The symbols served as threat and safety cues, signaling whether the cascade would potentially end with an aversive electric shock, a breath-holding task, or no aversive stimulation (safe condition). The color of the frame (yellow or blue; combinations of symbols and frames balanced out across participants) indicated whether the threat could be avoided by pressing a button (active/avoidable condition) or whether the threats were inevitable (passive/inevitable condition). In the active/avoidable condition, participants were instructed to press a button as quickly as possible after offset of the colored frame. During the response window (1000 ms), the last symbol remained on-screen. The electric shock was delivered 500 ms after symbol offset, and breath-holding was manually set at end of expiration of the first breathing cycle. The time window for successful active avoidance of threat delivery was initially set to 240 ms and—depending on the performance of the participant—dynamically adjusted per

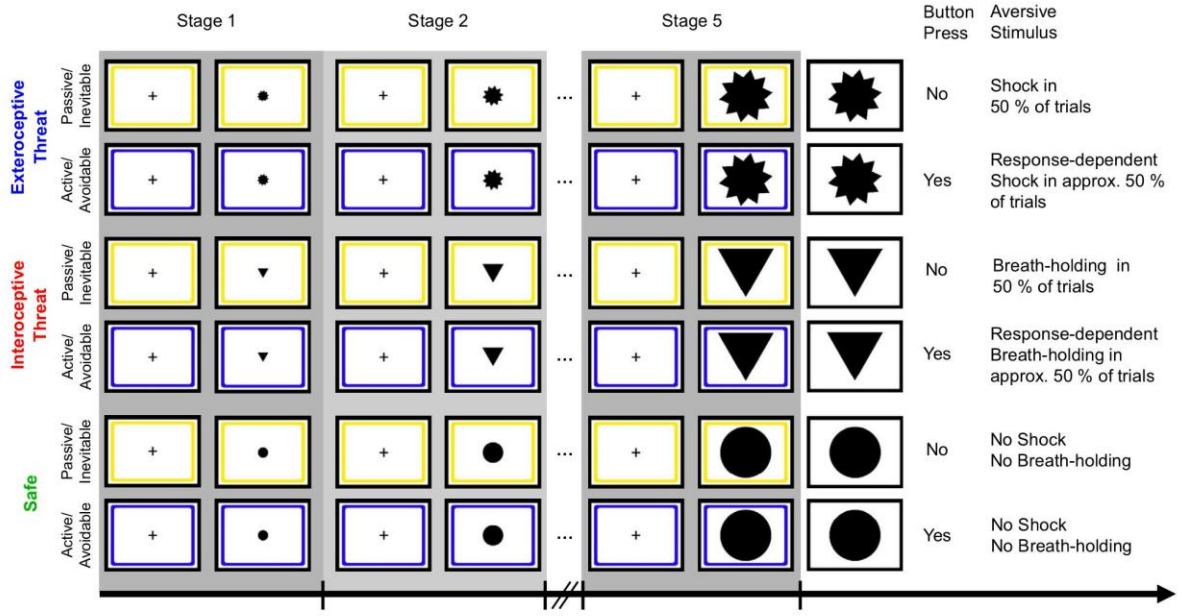

Figure 1. Experimental design. In each of five looming stages, a colored frame was displayed (500 ms), and then a symbol (e.g., circle, star, or triangle) appeared in the center of the frame (1500 ms). With each stage, the symbol successively increased in size, creating an impression of approach. The symbols served as threat and safety cues, signaling whether the cascade would potentially end with an aversive electric shock, a forced breath-holding task, or no aversive stimulation (safe). The color of the frame indicated whether the threat could be avoided by a fast button press (active/avoidable condition) or not (passive/inevitable condition). approx., approximately.

threat condition to reach a target delivery rate of 50% of trials for shocks and breath-holds. Threat delivery also occurred in 50% of threat trials in the passive/inevitable conditions. If avoidance was successful, participants received visual feedback 500 ms after the offset of the symbol. In the active safe condition, the button press had no consequences, but participants were instructed to respond as fast as possible because reaction times would be assessed. Twenty trials for each of the six resulting experimental conditions (inevitable vs. avoidable shock; inevitable vs. avoidable breath-holding; passive vs. active safe) were presented in two pseudo-randomized orders with a variable intertrial interval of 5 to 7 seconds between each looming/threat exposure sequence. To ensure adequate respiratory recovery, each breath-hold was followed by a 30-second recovery phase. See the Supplement for further details on stimulus materials, tasks, and procedure.

Data Acquisition and Response Definition

See the Supplement for data acquisition and response definition.

Data Analyses

All physiological data were analyzed using analyses of variance with repeated measures of time (28 half-second bins for HR and electrodermal activity, seven 2-second bins for all respiration parameters, and 5 data points for the startle reflex and the probe event-related potentials [ERPs]), threat condition (safe vs. breath-holding vs. shock), and defensive behavior (active/avoidance vs. passive/inevitable exposure). To ensure that performance of the breath-holding task and the delivery of the shock had no impact on the physiological data, we split the recorded trials into trials with and without delivery of the threat. Only the latter trials were analyzed. Whenever significant interactions with threat condition and/or defensive behavior were detected, effects were followed up targeting our main research questions. Responses to the inevitable external versus respiratory threats were characterized by calculating a threat minus safe difference to compare the two threat conditions. We characterized the effect of active avoidance by contrasting the avoidable minus inevitable threat conditions. Significant results were followed up by trend and preplanned contrast analyses. Statistical tests used a significance level of $p < .05$. Whenever necessary, Greenhouse-Geisser corrections of *df* were applied. Effect sizes are reported as η_p^2.

RESULTS

Autonomic arousal, HR, respiration, startle reflex magnitudes, and ERP amplitudes changed dynamically for the different threat conditions and the behavioral repertoire at hand (Table 1).

Defensive Response Mobilization in Response to Approaching Inevitable Shocks and Breath-Holding

Autonomic Arousal. SCL significantly increased with approaching inevitable threat (Figures 2A and 3A, Table 2)

Table 1. Statistical Significance for Relevant Main Effects and Interactions

Parameter	*F* Test	*F (df)*	*p*	η_p^2
Skin Conductance Level	Threat × behavior × time	7.24 (54,2538)	< .001	.13
Heart Rate	Threat × behavior × time	8.52 (54,2538)	< .001	.15
Minute Ventilation	Threat × behavior × time	4.72 (12,564)	.001	.09
Tidal Volume	Threat × behavior × time	5.81 (12,564)	< .001	.11
Respiratory Rate	Threat × behavior × time	1.77 (12,564)	.14	.04
	Threat × time	3.86 (12,564)	.01	.08
	Behavior	9.51 (1,47)	.003	.17
$P_{ET}CO_2$	Threat × behavior × time	0.66 (12,564)	.79	.01
	Threat × time	4.44 (12,564)	.001	.09
	Behavior × time	3.85 (6,282)	.024	.08
Blink Magnitudes	Threat × behavior × time	5.00 (8,280)	< .001	.13
Startle/ERP N1	Threat × behavior × time	0.87 (8,280)	.542	.02
	Threat	14.51 (2,70)	< .001	.29
	Time	29.49 (4,140)	< .001	.46
Startle/ERP P3	Threat × behavior × time	1.21 (8,280)	.29	.03
	Behavior × time	2.71 (4,140)	.045	.07
	Threat	4.76 (2,70)	.012	.12

ERP, event-related potential; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide.

(linear trend: $p < .001$), with an additional increase when a threat was immediately expected to occur (linear trend: $p < .001$). This increase in SCL was larger for approaching shock than for breath-holding. After an initial HR acceleration (Figures 2C and 3C) (linear trend: $p < .001$) that was greater for approaching breath-holding than for approaching shock, there was a strong HR deceleration immediately before the inevitable threat ($F_{1,47} = 133.73$ [*F* test: time], $p < .001$, $\eta_p^2 = .74$). The magnitude of this HR deceleration was comparable for shock and breath-holding (mean $[SD]_{breath\text{-}holding} = -6.37$ [5.11] vs. mean $[SD]_{shock} = -6.19$ [3.71]; $F < 1$).

Changes in Respiration. With approaching inevitable threat, minute ventilation (Figures 2D and 3D) gradually increased for breath-holding (linear trend: $p < .001$) but not for shock. This increase in minute ventilation was driven by an increase in tidal volume (Supplemental Figures S3A and S4A) (linear trend: $p < .005$) and accompanied by a successive reduction of expired CO_2 (Supplemental Figures S3C and S4C) (linear trend: $p < .001$). Minute ventilation decreased when the threats were expected to immediately occur (linear trend: $p < .001$). This effect was driven by a decrease in respiratory rate for breath-holding (Supplemental Figures S3B and S4B) (linear trend: $p < .001$) and a decrease in tidal volume for shock (linear trend: $p = .013$) but not for breath-holding (linear trend: not significant) and accompanied by an overall CO_2 recovery (linear trend: $p < .001$).

Defensive Reflex Mobilization. As expected, the approach of any inevitable threat resulted in a continuously increasing startle potentiation (Figures 2B and 3B) (linear trend: $p < .001$). Startle potentiation emerged earlier and grew more accentuated for the external threat than for the approaching breath-holding.

Modulatory Effects of Active Avoidance

Autonomic Arousal. SCL was relatively reduced (Figure 4A, Table 3) when an avoidable shock approached compared with when it was inevitable (linear trend: $p < .001$). No such effect was observed for breath-holding. During the time window of possible threat delivery (as expected for a button press performed too slowly), SCL was unaffected for shock (linear trend: not significant) but increased for breath-holding (linear trend: $p = .005$). HR decelerated immediately before the required action in all active conditions ($F_{2,94} = 21.84$ [*F* test: time], $p < .001$, $\eta_p^2 = .32$, linear trend: $p < .001$; $F_{4,188} = 1.34$ [*F* test: threat × time], $p = .266$, $\eta_p^2 = .03$). With action performance, HR increased in both avoidable threat conditions relative to the corresponding time window of inevitable threat (linear trend: $p < .001$) (Figure 4C).

Respiratory Mobilization. Preparation for action resulted in a general decrease in minute ventilation for all threat/non-threat conditions ($F_{4,188} = 25.76$ [*F* test: time], $p < .001$, $\eta_p^2 = .35$, linear trend: $p < .001$) that was primarily driven by a decrease of tidal volume (Supplemental Figure S3A) ($F_{4,188} = 17.57$ [*F* test: behavior × time], $p < .001$, $\eta_p^2 = .27$) and accompanied by a decrease in expired CO_2 (Supplemental Figure S3C) ($F_{4,188} = 4.03$ [*F* test: behavior × time], $p = .034$, $\eta_p^2 = .08$). Thus, a net suppression of minute ventilation emerged when preparing for an avoidable threat compared with an inevitable threat (Figure 4D) (linear trend: $p < .001$). This effect was stronger for the breath-holding than for the shock condition.

Defensive Reflex Mobilization. When participants were given the opportunity to actively avoid delivery of the threats, startle responses grew increasingly suppressed with increasing proximity of the required response generation (Figure 4B) (linear trend: $p < .001$). This evolving suppression

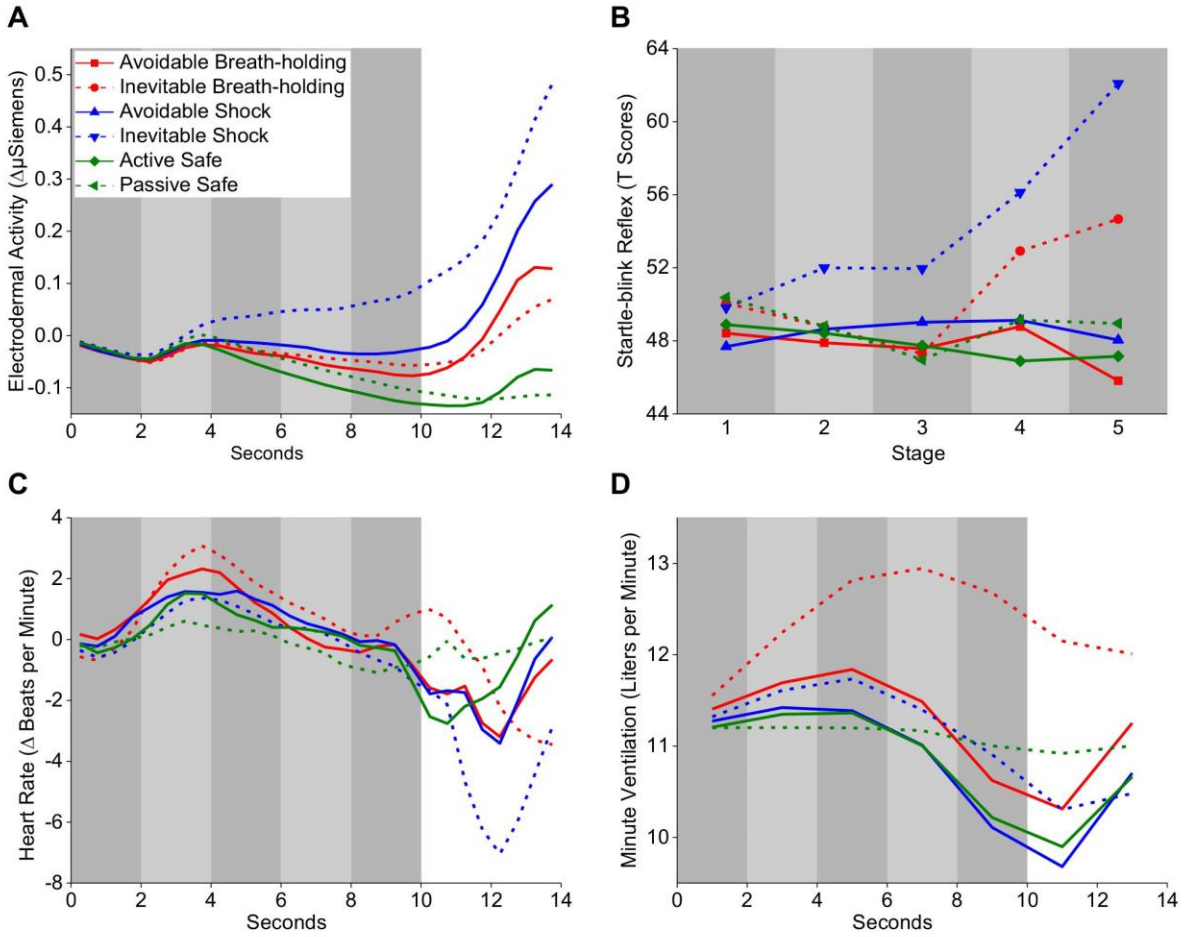

Figure 2. Defensive mobilization as a function of threat imminence, type of threat, and behavioral response options at hand. External threat (blue) vs. respiratory threat (red) or safety (green) is illustrated in dotted lines if inevitable (passive/inevitable condition) or solid lines if a button press was required (active/avoidable condition). Results are shown across the five looming stages and the subsequent period of the possible shock delivery or breath-holding separately for **(A)** electrodermal activity, **(B)** startle eyeblink response, **(C)** heart rate, and **(D)** minute ventilation. Panels **(A)** and **(C)** depict changes relative to baseline.

(stage 3 vs. stage 5) was similar in magnitude for both threat conditions. The overall suppression of startle response magnitudes was more accentuated for shock than for breath-holding.

Brain Responses

Figure 5A shows the grand average of the ERP to the acoustic startle probes across the five looming stages. The N1 component significantly increased with increasing imminence for any approaching stimulus (Figure 5B and D, Table 1) (linear trend: $p < .001$), suggesting that general alertness to external stimuli increased with increasing proximity of threat. Indication of threat versus safety generally elevated N1 amplitudes (Table 4). The availability of avoidance generally reduced N1 amplitudes. In contrast, P3 amplitudes (Figure 5C and E, Tables 1 and 4) were suppressed at early stages, when the threats were inevitable in contrast to safe. In accordance with startle findings, P3 amplitudes were suppressed with greater proximity of the response generation.

DISCUSSION

The present study demonstrates that defensive behavior changes dynamically with increasing proximity of approaching threat. These dynamic changes in defensive mobilization do not occur only during approaching external threat, i.e., a mild electric shock, replicating previous findings (13), but also occur if the threat originates from inside the body, in this case, feelings of dyspnea evoked by forced breath-holding. Extending previous research, it was demonstrated that defensive response mobilization during approach of external and respiratory threat shares common patterns. In addition, we also observed defensive response mobilization that was specific for approaching respiratory threat. Also, replicating

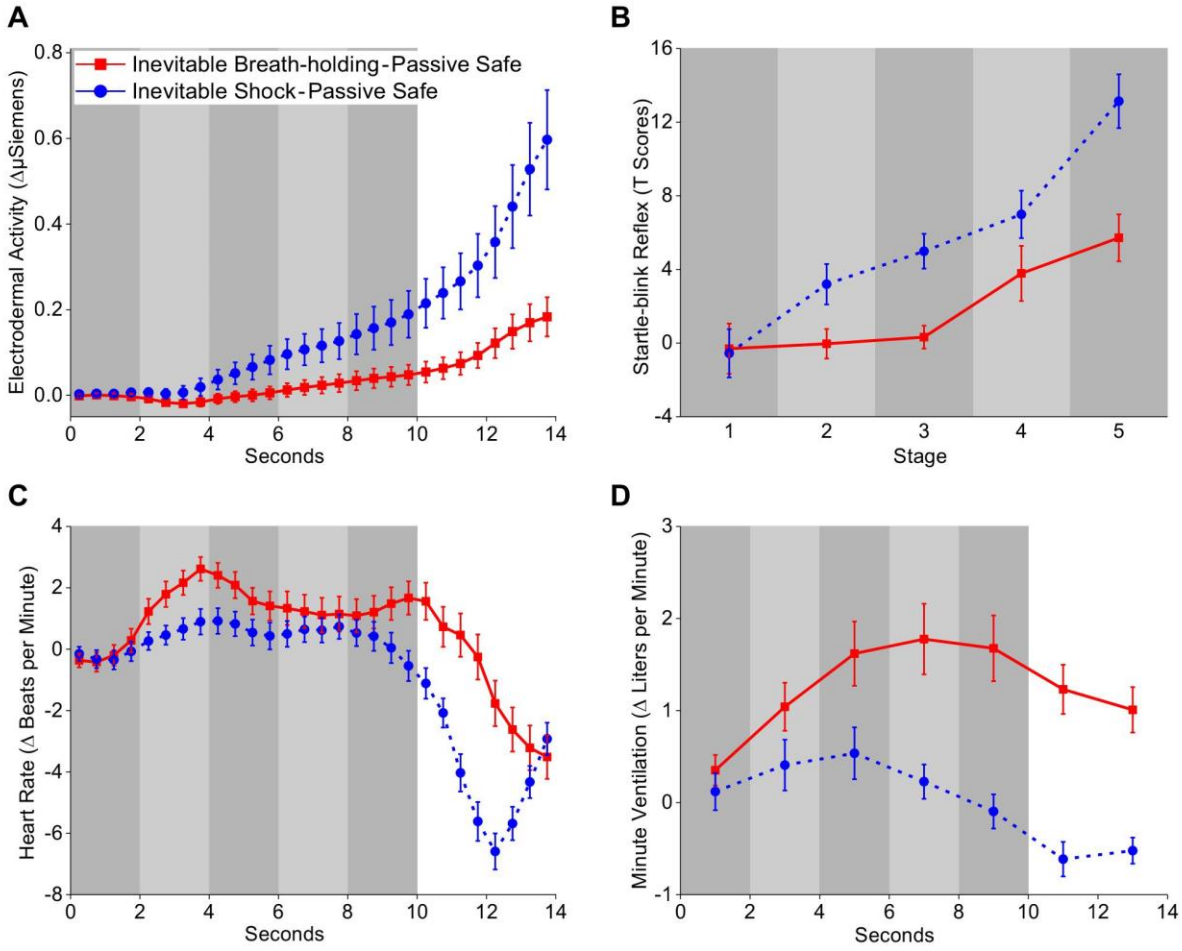

Figure 3. Mean difference in response magnitude between inevitable threat and passive safe conditions (blue line for external threat minus safe, red line for respiratory threat minus safe). Results are shown across the five looming stages and the subsequent period of the possible shock delivery or breath-holding separately for **(A)** electrodermal activity, **(B)** startle eyeblink response, **(C)** heart rate, and **(D)** minute ventilation. Panels **(A)** and **(C)** depict changes relative to baseline.

previous findings, defensive response mobilization was modulated depending on the behavioral options at hand.

Defensive Mobilization to Inevitable Threat

In line with previous research (67), we observed a potentiation of startle responses when these were elicited during cues signaling the occurrence of an electric shock. This startle potentiation increased linearly with increasing temporal proximity of the inevitable threat, replicating previous findings (13,17). There is ample evidence from animal research that the cue-specific potentiation of this protective reflex is mediated by the central nucleus of the amygdala (68,69). The same linear increase in startle potentiation—albeit with a slight delay—was observed if visual cues predicted the temporal proximity of dyspnea, a typical threat emerging from inside the body. This temporal delay might be explained by the extension of the threat delivery window for breath-holding because the occlusions were set at the end of expiration. These data suggest that fear-potentiated startle is highly sensitive to the temporal dynamics of the approaching threat (15). In addition, the facilitation of the protective reflex was independent of whether the threat came from outside or inside the body, suggesting that freezing, as indicated by startle potentiation, can be observed not only during predatory defense but also when there is threat signaling potential suffocation. The HR data were in line with this interpretation.

Replicating previous findings, HR decreased just before the delivery of shock (13,17,19). The same decrease in HR was also observed immediately before the occlusion. This interpretation is in line with experimental animal data as well as theoretical models of neural pathways responsible for regulating defensive mobilization (62,70–73). Again, this pattern of defensive response mobilization was independent

Table 2. Effects of Inevitable Threats: Statistical Significance for Relevant Main Effects and Interactions

Parameter	Effect	Time Window[a]	*F* Test	*F (df)*	*p*	η_p^2
Skin Conductance Level	Complete trial	1–28	Threat × time	11.47 (27,1269)	.001	.2
			Threat	8.37 (1,47)	.006	.15
	Threat looming	1–20	Threat × time	5.26 (19,893)	.021	.1
			Time	14.54 (19,893)	< .001	.24
	Immediate threat	21–28	Threat × time	19.25 (7,329)	< .001	.29
			Time	34.94 (7,329)	< .001	.43
			Threat	10.70 (1,47)	.002	.19
Heart Rate	Complete trial	1–28	Threat × time	13.37 (27,1269)	< .001	.22
	Initial acceleration	1–8	Threat × time	7.57 (7,329)	.001	.14
			Time	21.05 (7,329)	< .001	.31
			Threat	4.64 (1,47)	.036	.09
	Immediate threat	21 vs. min[b]	Threat × time	0.07 (1,47)	.788	< .01
			Time	133.73 (1,47)	< .001	.74
		min[c]	Threat	0.22 (1,47)	.638	.01
Minute Ventilation	Complete trial	1–7	Threat × time	8.24 (6,282)	< .001	.15
	Threat looming	1–5	Threat × time	9.32 (4,188)	< .001	.17
			Threat	14.92 (1,47)	< .001	.24
	Threat looming for shock	1–5	Time	12.05 (4,188)	< .001	.2
	Threat looming for breath-holding	1–5	Time	2.41 (4,188)	.098	.05
	Immediate threat	5–7	Threat × time	1.8 (2,94)	.0176	.04
			Threat	32.43 (1,47)	< .001	.41
			Time	11.43 (2,94)	< .001	.2
Tidal Volume	Complete trial	1–7	Threat × time	16.44 (6,282)	< .001	.26
	Threat looming	1–5	Threat × time	10.77 (4,188)	< .001	.19
	Threat looming for shock	1–5	Time	3.12 (4,188)	.062	.06
	Threat looming for breath-holding	1–5	Time	8.18 (4,188)	.001	.15
	Immediate threat	5–7	Threat × time	12.2 (2,94)	< .001	.21
	Immediate threat for shock	5–7	Time	6.54 (2,94)	.005	.12
	Immediate threat for breath-holding	5–7	Time	3.71 (2,94)	.047	.07
Respiratory Rate	Complete trial	1–7	Threat × time	16.44 (6,282)	< .001	.26
	Immediate threat	5–7	Threat × time	6.99 (2,94)	.005	.13
	Immediate threat for shock	5–7	Time	13.52 (2,94)	< .001	.22
	Immediate threat for breath-holding	5–7	Time	0.18 (2,94)	.772	< .01
$P_{ET}CO_2$	Complete trial	1–7	Threat × time	1.59 (6,282)	.197	.03
			Time	8.11 (6,282)	< .001	.15
	Threat looming	1–5	Threat × time	2.92 (4,188)	.057	.06
			Time	10.75 (4,188)	< .001	.19
	Threat looming for shock	1–5	Time	4.56 (4,188)	.008	.09
	Threat looming for breath-holding	1–5	Time	11.43 (6,282)	< .001	.2
	Recovery	5–7	Threat × time	1.57 (2,94)	.218	.03
			Time	13.19 (2,94)	< .001	.22
Blink Magnitudes	Complete trial	1–5	Threat × time	4.69 (4,140)	.006	.12
			Time	17.02 (4,140)	< .001	.33
			Threat	22.50 (1,35)	< .001	.39

min, minimum; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide.

[a]Time in half-seconds (skin conductance level, heart rate), in 2-second bins (minute ventilation, tidal volume, respiratory rate, $P_{ET}CO_2$), or in stages (blink magnitudes).

[b]The minimum was detected in the time window from half-second 22 to 28.

[c]The magnitude of heart rate deceleration was calculated by detecting the minimum in the time window from half-second 22 to 28 and subtracting it from half-second 21.

of the source of threat. Along with the startle potentiation and bradycardia, we observed an increase in autonomic arousal as indexed by a linear increase in SCL, again supporting previous findings (13,17). This increase in sympathetic arousal was also found during the approaching breath-holding task, suggesting that this part of defensive

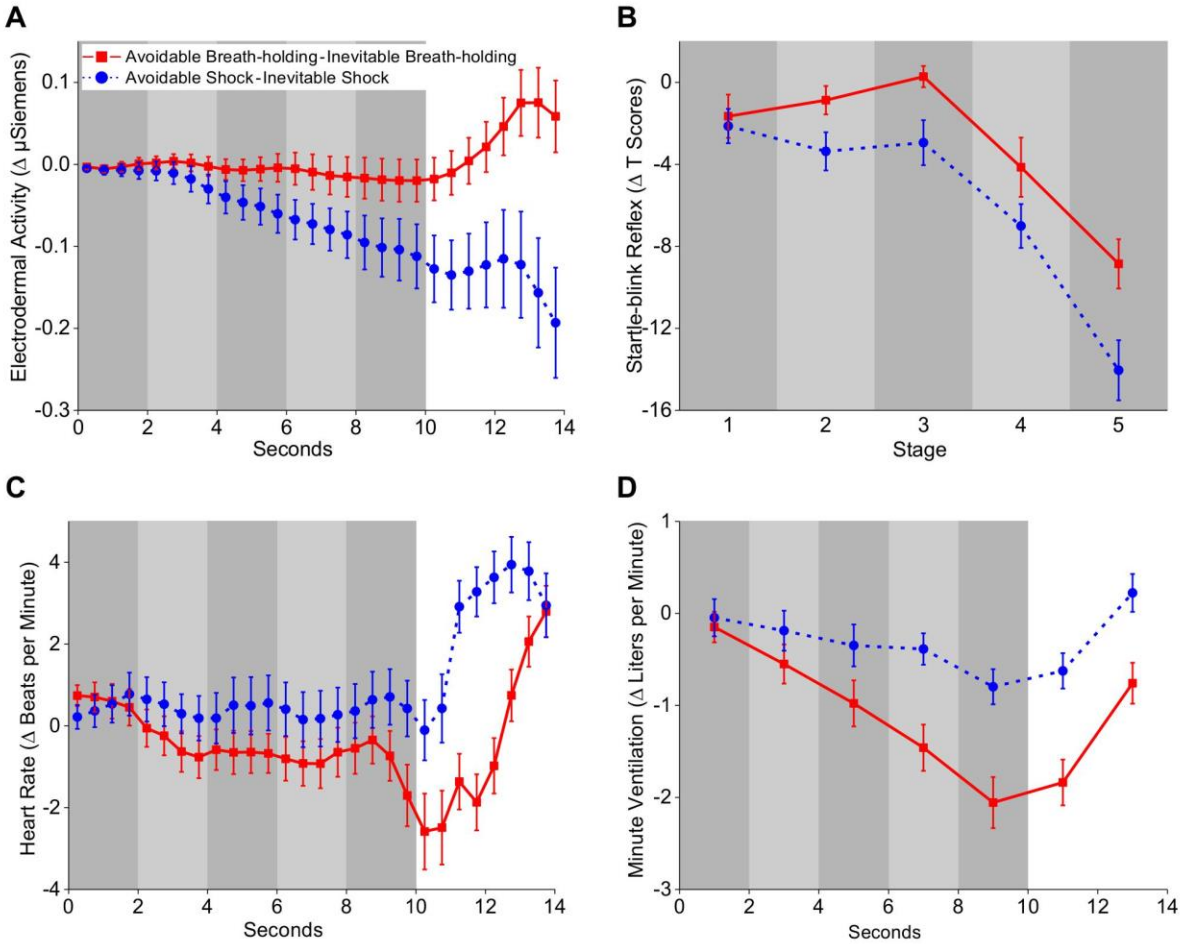

Figure 4. Mean difference in response magnitude between avoidable and inevitable threat conditions (blue line for external threat, red line for respiratory threat). Results are shown across the five looming stages and the subsequent period of the possible shock delivery or breath-holding separately for **(A)** electrodermal activity, **(B)** startle eyeblink response, **(C)** heart rate, and **(D)** minute ventilation. Panels **(A)** and **(C)** depict changes relative to baseline.

response mobilization is also independent of the source of threat.

The described pattern of defensive response mobilization to inevitable threat, that is, bradycardia in combination with an increase in SCL and startle potentiation, has been termed a freezing response in the literature (5,9,10,74). Freezing is a defensive behavior highly preserved across species that was described for rodents, birds, larger mammals, and humans and has functionally been linked to evasion of detection. As a characteristic observable component, the freezing reaction is dominated by a motor inhibition. We did not assess gross motor movement in the present study; however, we observed a depression of respiratory movement when a threat was immediately expected to occur. Such reduction of respiratory movement has previously been interpreted as an indicator of motor inhibition (65) and thus further supplements our observation of a freezing response in the present experimental setting.

Over and above a comparable general pattern of defensive activation, we expected a specific defensive response pattern to approaching dyspnea in the respiratory system, possibly emerging from a defensive control system responsible for protecting the organism from suffocation threat. We observed a progressive increase in minute ventilation, primarily driven by an increase in tidal volume, accompanied by a reduction of expired CO_2. This respiratory pattern may be interpreted as a read-out of an evolving suffocation alarm, which has been described as a lifesaving reaction to suffocation threat (39). Interestingly, it has been argued that a false suffocation alarm is triggered in patients with panic disorder (39). From the perspective of threat proximity models, these alarms may be conceived as essentially functional defensive mobilization patterns that are evoked at low levels of threat proximity (thus turning dysfunctional). According to the suffocation alarm theory, the alarm is triggered by a network that integrates various physiological data for which the neuronal basis has

Table 3. Effects of Active Avoidance: Statistical Significance for Relevant Main Effects and Interactions

Parameter	Effect	Time Window[a]	*F* Test	*F (df)*	*p*	η_p^2
Skin Conductance Level	Complete trial	1–28	Threat × time	9.84 (27,1269)	< .001	.17
	Threat looming	1–20	Threat × time	3.44 (19,893)	.05	.07
	Threat looming for shock	1–20	Time	8.59 (19,893)	.002	.15
	Threat looming for breath-holding	1–20	Time	0.42 (19,893)	.613	.01
	Immediate threat	21–28	Threat × time	11.1 (7,329)	< .001	.19
	Immediate threat for shock	21–28	Time	1.66 (7,329)	.203	.03
	Immediate threat for breath-holding	21–28	Time	7.85 (7,329)	.002	.14
Heart Rate	Complete trial	1–28	Threat × time	7.34 (27,1269)	< .001	.14
	Response preparation	19–21	Threat × time	6.67 (2,94)	< .001	.08
			Time	7.66 (2,94)	.005	.14
	Response preparation for shock	19–21	Time	3.57 (2,94)	.054	.07
	Response preparation for breath-holding	19–21	Time	8.36 (2,94)	.003	.15
	Response generation	21–28	Threat × time	11.75 (7,329)	< .001	.2
			Time	21.23 (7,329)	< .001	.31
	Response generation for shock	21–28	Time	16.02 (7,329)	< .001	.25
	Response generation for breath-holding	21–28	Time	19.87 (7,329)	< .001	.3
Minute Ventilation	Complete trial	1–7	Threat × time	4.34 (6,282)	.013	.08
	Threat looming	1–5	Threat × time	5.4 (4,188)	.005	.1
			Time	18.83 (4,188)	< .001	.29
			Threat	9.85 (1,47)	.003	.17
	Threat looming for shock	1–5	Time	3.6 (4,188)	.025	.07
	Threat looming for breath-holding	1–5	Time	20.69 (4,188)	< .001	.31
Tidal Volume	Complete trial	1–7	Threat × time	19.74 (4,188)	< .001	.30
			Time	9.7 (6,282)	< .001	.17
	Threat looming	1–5	Threat × time	3.64 (4,188)	.027	.07
			Time	13.35 (4,188)	< .001	.22
	Threat looming for shock	1–5	Time	2.06 (4,188)	.14	.04
	Threat looming for breath-holding	1–5	Time	18.3 (4,188)	< .001	.28
Blink Magnitudes	Complete trial	1–5	Threat × time	1.23 (4,140)	.303	.03
			Time	32.3 (4,140)	< .001	.48
			Threat	17.55 (1,35)	< .001	.33
	Response generation	3 vs. 5	Threat × time	0.8 (1,35)	.376	.02

[a]Time in half-seconds (skin conductance level, heart rate), in 2-second bins (minute ventilation, tidal volume), or in stages (blink magnitudes).

been well described (21,29). This hardwired survival system can also be activated by environmental or context information (48,75), such as cues indicating the proximity of a suffocation threat. In the present experiment, geometric symbols were used that relayed, by increasing size, information regarding proximity of a breath-holding task. The observed defensive respiratory pattern supports the hypothesis that such a breath-holding task is a good model for a suffocation threat. Based on observations from interoceptive cue and context conditioning studies (32,38), it is conceivable that a variety of external or interoceptive cues (and generalization cues) (76,77) or contexts may convey this information [see (58) for a theoretical model] and thus trigger successively evolving defensive mobilization in preparation for encounter with the respiratory threat.

The respiratory system is only one of many sources within the body where interoceptive threat may occur. Thus, it needs to be determined whether respiratory mobilization turns out to be a specific component of defensive mobilization to respiratory threat or whether this finding also generalizes to other interoceptive threats. In accordance with the suffocation alarm idea, it is conceivable that respiratory mobilization may be a specific preparatory strategy to oppose the effects of threat of suffocation by decreasing blood carbonation and increasing blood oxygenation before the suffocation threat is imminent. However, other specific response patterns may be detected for threats from the cardiovascular system. In line with this idea, compensatory cardiovascular adjustments that occur in anticipation of cardiovascular events have been described (78). Moreover, further research is needed to identify specific response components to external, predator-like threats. For instance, a decrease of blood flow to the periphery (as observed in its extreme in a vasovagal syncope in individuals with blood phobia) or an increase in local muscle tone (79,80) may be conceivable responses to prepare for shock delivery.

Active Avoidance

The pattern of defensive response mobilization changed substantially when there was a possibility to actively avoid

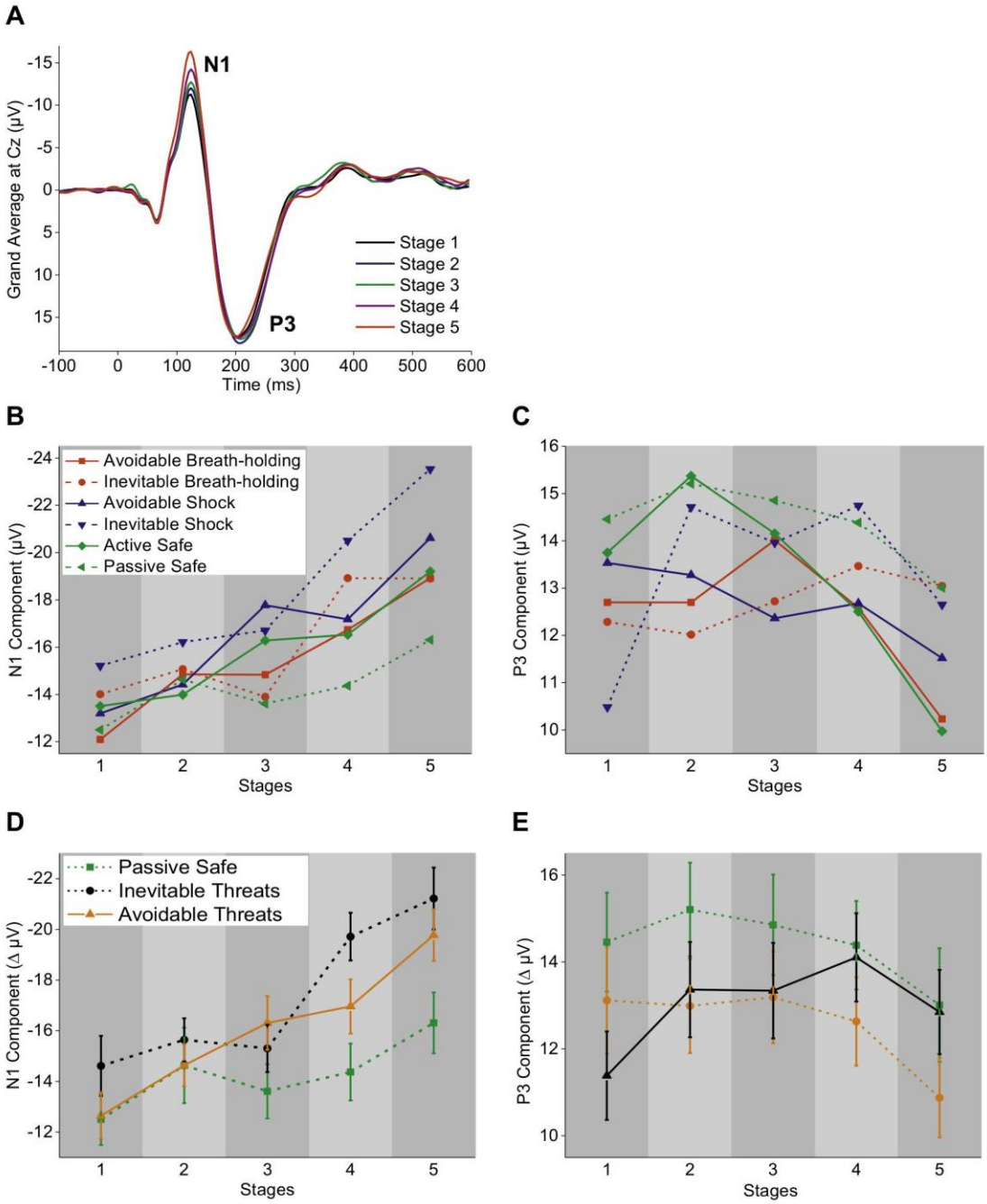

Figure 5. Event-related potentials evoked by the startle probes. The waveforms **(A)** depict the mean brain potentials evoked by startle probes at each of the five stages. Grand averaged event-related potentials for each of the five looming stages. Defensive mobilization as a function of threat imminence, type of threat, and behavioral response options at hand are shown separately for the probe-evoked N1 component **(B)** and the probe-evoked P3 component **(C)**. External threat (blue) vs. respiratory threat (red) or safety (green) is illustrated in dotted lines if inevitable (passive/inevitable condition) or solid lines if a button press was required (active/avoidable condition). Results are shown across the five looming stages and the subsequent period of the possible shock delivery or breath-holding. Mean amplitudes of the probe-evoked N1 component **(D)** and the P3 component **(E)** are shown as a function of looming stage and whether or not threats could be avoided (active/avoidable threats [averaged across avoidable shock and avoidable breath-holding], orange line) or not (passive/inevitable threats [averaged across inevitable shock and inevitable breath-holding], black line).

Table 4. Effects of Inevitable Threats and Active Avoidance on Electroencephalogram Components: Statistical Significance for Relevant Main Effects and Interactions

Parameter	Effect	Time Window[a]	*F* Test	*F (df)*	*p*	η_p^2
Startle/ERP N1	Complete trial	1–5	Threat × time	2.50 (8,280)	.012	.07
	Inevitable[b] threats vs. passive safe	1–5	Threat × time	2.87 (4,140)	.025	.08
			Time	11.62 (4,140)	< .001	.25
			Threat	39.01 (1,35)	< .001	.53
	Inevitable[b] vs. avoidable[c] threats	1–5	Behavior × time	2.14 (4,140)	.079	.06
			Time	27.31 (4,140)	< .001	.04
			Behavior	8.66 (1,35)	.006	.20
Startle/ERP P3	Complete trial	1–5	Threat × time	1.17 (8,280)	.33	.03
			Time	2.54 (4,140)	.04	.07
			Threat	8.31 (2,70)	.001	.19
	Inevitable[b] threats vs. passive safe	1–5	Threat × time	1.30 (4,140)	.271	.04
			Time	1.51 (4,140)	.204	.04
			Threat	9.49 (1,35)	.004	.21
		1–3	Threat	13.07 (1,35)	.001	.27
	Inevitable[b] vs. avoidable[c] threats	1–5	Behavior × time	2.54 (4,140)	.043	.07

ERP, event-related potential.
[a]Time in stages.
[b]Inevitable corresponds to the calculated mean of inevitable respiratory and external threats.
[c]Avoidable corresponds to the calculated mean of avoidable respiratory and external threats.

the threat. HR accelerated in the time window where avoidant action was performed. These data support findings from animal experiments. Moreover, there was a reversal of fear-potentiated startle. Blink magnitudes were inhibited when individuals could actively avoid the aversive stimulus regardless of whether this was an external or internal aversive event, replicating and extending previous findings (13). This pattern of the fear-modulated startle is remarkably consistent with findings from animal experiments relating the switch from startle potentiation to startle inhibition to different patterns of behaviors in rodents (freezing vs. escape) that are modulated by the periaqueductal gray (81–83). Recent data from Wendt *et al.* (17) show that there is a switch from forebrain to midbrain activation when threat is becoming more proximal and that activation of the periaqueductal gray is specifically pronounced during active avoidance. Interestingly, the same switch from startle potentiation to inhibition is observed in patients with panic disorder just before escape from entrapment or during panic attacks (59).

In line with startle response magnitude data, we observed a reduction of the P3 component of the ERPs to the startle-eliciting probe stimuli. A comparable reduction of probe P3 amplitudes is observed when individuals view emotional cues (84) or have to breathe through an aversive respiratory load (22,85), thus suggesting that attentional resources are allocated to these respective foreground stimuli and, as a consequence, reduce the elaborated processing of the secondary acoustic probe stimuli. The reduction of the P3 component was specific for the active avoidance condition, which suggests that irrelevant stimuli are blocked to promote effective action. Again, this effect might explain why attention channels to irrelevant stimuli (e.g., voice of the therapist) are blocked during an acute panic attack.

Limitations

As participants were provided with a button to terminate the occlusions of the inspiratory port if they could not hold their breath any longer, the breath-holding condition may have been perceived as more controllable or not entirely inevitable. Although the fear ratings indicate that both threat conditions provoke comparable fear, physiological responses might have been influenced by this difference in controllability.

Conclusions

The present study demonstrated that defensive response mobilization changes dynamically with the proximity of approaching threat. Some patterns of defensive response mobilization are comparable for respiratory versus external threat, whereas defensive mobilization in the respiratory system is specific for suffocation threat. Moreover, defensive response mobilization is modulated depending on the behavioral repertoire at hand. Our findings are consistent with animal and human experiments, relating different patterns of defensive behaviors to different neural network activation (16,61,81–83,86). This neuroscience-based approach to describing different patterns of defensive behaviors might be used for a transdiagnostic description of anxiety disorders based on the proximity of threat. Understanding the mechanisms of how these dynamic changes in defensive responding are modulated by interoceptive threats might help in gaining a better understanding of the mechanisms of panic disorder and anxiety disorders in general. The present study was performed in a nonclinical sample. Further research is warranted in exploring defensive mobilization in clinical populations. These studies will allow a description of specificity of response patterns, their magnitude, and timing. Exploring the perspective of response dynamics to threat represents a clearly mechanistic approach to the study of psychopathology. It may prove

helpful in assessment, early risk identification, design of individualized treatments, or treatment monitoring. Such tests are lacking in current clinical practice.

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Dynamics of Defensive Response Mobilization to Approaching External vs. Interoceptive Threat

Supplementary Information

SUPPLEMENTARY METHODS

Materials, tasks, and procedure

External threat (shock). The electric shock (a 1 ms pulse of electrotactile stimulation) was generated by a commercial stimulator (S48K; Grass Instruments, West Warwick, RI) and transmitted via a constant current unit (CCU1, Grass Instruments) to a bipolar electrode attached to the participant's left forearm. The intensity of the stimulation was individually adjusted using a standard procedure (1–8) to a level that was described as "highly annoying but not painful". In the present sample the average shock intensity was set to 8.67 mA (*SD* = .99).

Interoceptive threat (Forced breath-holding[1]). Participants were breathing through a tightly fitting soft silicone face mask (7400 series; Hans Rudolph, Inc., Kansas City, MO) connected to a rigid tube with sensors for measuring respiration parameters. A flow sensor was mounted to the common port of the two-way y-shaped non-rebreathing valve (no. 2630; Hans Rudolph, Inc.). The expiratory port of the y-valve was always left open. The inspiratory port was connected to a plastic tube (length = 2.75 m; diameter = 35 mm) which led to the common port of a Five-Way Gatlin-Shape™ valve (no. 2440; Hans Rudolph, Inc.), located in the adjacent experimenter room, which was controlled by an Inflatable-Balloon-Type™ controller (no. 2430; Hans Rudolph, Inc.). Breath-holding tasks were set manually at the end of expiration by simultaneously shutting all four valve ports via VPM software (9). The breath-holding time to be used for the breath-holding tasks was individually determined based on two

1. For ethical reasons, the participants had the opportunity to press a button to immediately terminate breath-holding at any time during the experiment.

criteria. First, individual maximal breath-holding time was assessed in four separate trials prior to the start of the experiment during which participants were instructed to hold their breath as long as possible after expiration (see supplemental results, below). Based on previous fear conditioning studies using breath-holding as an unconditioned stimulus (10–13) breath-holding time was then set to 40% of this individually determined maximal post-expiratory breath-holding time. In case 40% of the maximal breath-holding time was shorter than 15 seconds, breath-holding time was set to 15 seconds during the experiment. Based on these two criteria average breath-holding time during the experiment was ($M[SD]_{Breath\text{-}holding}$ = 17.14[5.55]). It needs to be noted that the present setup (occluding a balloon at the end of a long tube) theoretically allowed minimal consumption of the dead-space oxygen at the cost of strongly increased inspiratory workload.

Startle probes. A 50 ms burst of white noise (95dB, rise/fall time < 1ms) was delivered via headphones and served as a startle eliciting stimulus throughout the experiment. Per 10 s looming/threat exposure sequence one startle probe was presented, either at stage 1, 2, 3, 4, or 5 (900 - 1200 ms after onset of the corresponding symbol). Overall, four startle probes were delivered per stage and per condition. In addition, 36 startle probes were presented during ITIs (2000 - 2200 ms after ITI onset).

Procedure. All participants were seated in a reclining chair in a dimly lit, sound-attenuated room. The sensors were attached, the face mask tightly and comfortably fitted, and signal quality checked. Then, the shock intensity and breath-holding duration were individually determined as described above. Participants were instructed and each type of looming sequence presented and explained once. Then, each type of looming sequence was presented again and the experimenter verified that the participants correctly understood the meaning of symbols and colors. If participants had no further questions, the headphones were comfortably fitted. Before the experimental procedure started, eight startle probes were delivered with a mean ITI of 9.1 s (5.8-14 s range) to reach a stable baseline level of startle response magnitudes. Then, the experimental assessment started as explained above.

Data acquisition and response definition

Skin conductance level (SCL). Electrodermal activity was recorded using two Ag/AgCl electrodes (8 mm diameter; Marquette Hellige) filled with a sodium chloride electrolyte medium. Sensors were placed 15 mm apart on the hypothenar eminence of the participant's palmar surface of the left hand. A constant voltage of 0.5 V was applied across sensors by a Coulbourn S71-22 skin-conductance coupler. The signal was digitized with a sampling rate of 10 Hz. Digital values were converted to µS and change scores were computed in half-second bins by subtracting the mean 1 s SCL baseline prior to the start of the looming sequence.

Heart rate. An electrocardiogram (ECG) was recorded with two electrolyte (Hellige electrode cream) filled Ag/AgCl standard electrodes (8 mm diameter; Marquette Hellige) placed in an Einthoven-II setup. The ECG signal was band-pass filtered (1-13 Hz) and amplified using a Coulborn S75-01 amplifier (Coulborn Instruments, Whitehall, PA). Digital sampling rate was set to 100 Hz. Using ANSLAB (Autonomic Nervous System Laboratory, University of Basel, Switzerland) version 2.4 the ECG signal was visually inspected for artifacts and corrected whenever misplaced R-wave triggers had occurred. Then HR and inter-beat-intervals (IBI) were derived from the ECG signal. In a next step, change scores for HR were computed in half-second bins as a deviation from a 1 s baseline preceding each looming trial and then averaged for each condition.

Breathing parameters. Respiratory flow**,** mouth pressure (P_I) and fractional CO_2 (FCO_2) were continuously measured using a ZAN 600 pneumotachograph (nSpire Health, Inc., Oberthulba, Germany). Three 5-m long plastic tubes reached from three ports of the flow sensor to the recording unit of the pneumotachograph that also performed the gas analyses. In addition, two respiration belts (Respiband Plus, distributed by Cardinal Health, Germany) connected to an inductance plethysmography system (Respitrace Q.D.C., SensorMedics, distributed by NewMedics GmbH, Öhringen, Germany) were placed over the thorax and the abdomen to visualize in- and expiration in real-time to be able to manually set the respiratory occlusion at the end of expiration. First, the fractional CO_2 was converted to partial pressure

CO_2 (pCO_2) and together with the mouth pressure, visually inspected and corrected for artifacts (e.g., coughing). Breath-holding intervals were manually set missing and thus did not enter the analyses. Then, end-tidal pCO_2 and the maximal mouth pressure during inspiration were automatically detected and if necessary, manually corrected, using BrainVision Analyzer 2.0 software. Afterwards, respiration rate, tidal volume, and minute ventilation rate were calculated using ANSLAB 2.4. All parameters were exported in weighted 2 s means.

Startle reflex. The acoustic startle probe, a 95 dB(A) burst of white noise generated by a Coulbourn S81-02 noise generator (Coulbourn Instruments, Whitehall, PA) was presented binaurally over AKG K-66 headphones for 50 ms. The eye-blink component of the startle response was measured by recording an electromyogram over the left orbicularis oculi muscle with two electrolyte-filled (Hellige electrode cream) Ag/AgCI miniature surface electrodes (Sensormedics, Yorba Linda, CA). The signal was amplified using a Coulborn V75-01 amplifier, high pass (30 Hz) and low-pass filtered (400 Hz) and digitally sampled at 1000 Hz using a 12-bit A/D converter. Sampling started 100 ms before the onset of the acoustic startle stimulus and lasted until 400 ms after probe onset. The raw EMG signal was filtered off-line with a 60 Hz high-pass filter, rectified, and integrated with a time constant of 10 ms. Responses were visually inspected and scored using a computer program (14) that identified latency of blink onset (in milliseconds) and peak amplitude (in microvolts). Trials in which blinks started 20–100 ms after stimulus onset and reached their peak amplitude within 150 ms were scored as valid startle responses. If no blinks were detected the magnitudes were scored as zero. Trials with excessive baseline activity or movement artifacts were rejected and treated as missing values (0.77%). To ensure that each participant contributed equally to the groups mean all raw magnitudes were transformed to T-scores (M=50, SD=10) as recommended by the guidelines for human startle eye-blink studies (15).

Event-related potentials. The electroencephalogram was recorded using Ag/AgCI electrodes (8 mm diameter; Marquette Hellige) filled with EC2 Genuine Grass Electrode Cream (West Warwick, RI) and placed at Cz, Fz and Pz according to the international 10-20-system. All channels were referenced to Pz and re-referenced offline to a linked ear lobe reference (two

linked Ag/AgCl ear-clip electrodes; Klaus Schuler GmbH, Germany). An electrooculogram (EOG) was registered with two electrolyte-filled (Hellige electrode cream) Ag/AgCl electrodes (8 mm diameter; Marquette Hellige), placed above and on the right side of the right eye with Pz as reference. The impedance of the electrodes was kept below 20 kΩ. Signals were amplified using a 12-channel isolated Bioelectric AC/DC Amplifier System (San Diego Instruments, San Diego, CA) with a time constant of 1 s and a low-pass filter of 35 Hz. The signals were sampled at a rate of 250 Hz. BrainVision Analyzer 2.0 software (Brain Products GmbH, Gilching, Germany) was used for analyzing EEG data. First, the signals were filtered offline with a 50 Hz notch filter and a 0.1–35 Hz band-pass filter. Afterwards, the signal was corrected for vertical and horizontal eye movements using the Gratton-Coles algorithm (16). Then, stimulus-synchronized epochs starting 100 ms before the onset of the acoustic startle probe stimulus until 600 ms after the probe stimulus onset were extracted. For artifact removal, data were visually inspected and epochs with movement artifacts or technical failures were excluded. For statistical analyses, the N1 component of the ERP was determined with an automatic peak detection (time window 80 to 150 ms). The P3 component of the ERP was calculated as the mean activity in the time window from 180 to 280 ms.

Reaction time. Reaction time was assessed using a 4-button response pad (Electrical Geodesics, Inc, Eugene, OR) controlled by Presentation software (Version 17.2 Build 08.11.14; Neurobehavioral Systems Inc., Berkeley, CA).

Fear ratings. Fear ratings were presented on the screen at the beginning of the experiment and every 30 trials. Participants had to rate their fear for both threat conditions (shock, breath-holding) as well as the safe condition on a scale from 1 (no fear) to 6 (maximum fear).

Data analyses

All statistical analyses reported in this supplement were performed using repeated measures analyses of variance (ANOVAs). To analyze effects of the repeated breath-holding trials that preceded the experiment and aimed at determining the individual maximal breath-

holding duration, a repeated-measures factor *trials* (1 through 4) was used. To compare reaction times across the three active/avoidable conditions that required a button press, a repeated measures factor *condition* (avoidable breath-holding vs. avoidable shock vs. active safe) was applied. The change of fear ratings across the experiment was tested with repeated-measures factors *time* (1 through 5) and *condition* (safe vs. breath-holding vs. shock).

SUPPLEMENTARY RESULTS

Determination of maximal breath-holding time prior to the experiment

Post-expiratory breath-holding time increased over the four trials (see **Figure S1**; $F(3,129)_{time} = 45.48$, $p < .001$, $\eta_p^2 = .51$, linear trend: $p < .001$). The range of maximal breath-holding time varied between 9 and 102 seconds.

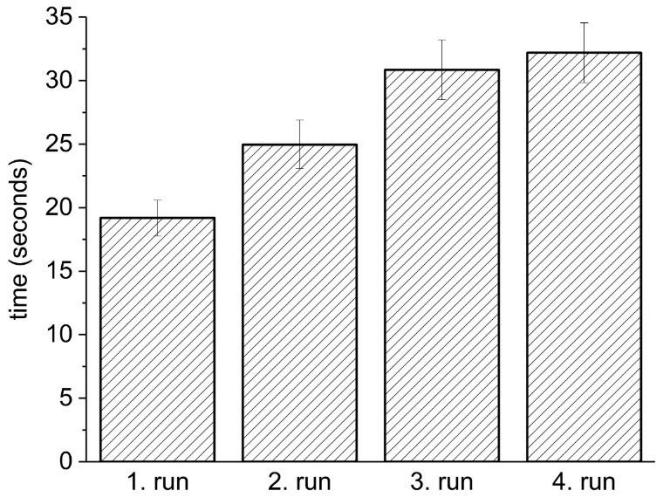

Figure S1. Post-expiratory breath-holding time (means and standard errors) for the four determination trials preceding the experiment.

Manipulation check

The reaction times (in ms) for the button presses in response to the visual go-signal, the offset of the colored frame, were significantly shorter in both threat conditions ($M[SD]_{Breath-holding} = 284.45[48.78]$; $M[SD]_{Shock} = 279.4[45.4]$) than in the safe condition ($M[SD]_{Safe} = 310.06[55.25]$), $F(2, 94)_{threat} = 9.37$, $p < .001$, $\eta_p^2 = .17$, $F(1, 47)_{shock\_vs\_safe} = 15.31$, $p < .001$, $\eta_p^2 = .25$, $F(1, 47)_{Breath-holding\_vs\_safe} = 9.53$, $p = .003$, $\eta_p^2 = .17$, indicating greater motivational significance of the threat conditions for the participants. Reaction times did not differ between shock and breath-holding, $F < 1$.

Fear ratings

Subjective fear was rated higher for the breath-holding than for the shock and lowest for the safe condition ($F(2,47)_{threat} = 66.88$, $p < .001$, $\eta_p^2 = .59$; $F(1,47)_{shock\_vs\_breath\text{-}holding} = 6.23$, $p = .016$, $\eta_p^2 = .12$, $F(1,47)_{shock\_vs\_safe} = 79.64$, $p < .001$, $\eta_p^2 = .63$; $F(1,47)_{breath\text{-}holding\_vs\_safe} = 144.26$, $p < .001$, $\eta_p^2 = .75$; see **Figure S2**). Fear ratings decreased during the experiment for the breath-holding condition only ($F(4,47)_{time} = 10.53$, $p < .001$, $\eta_p^2 = .18$), but not for the shock ($F < 1$) or the safe condition ($F(4,188)_{time} = 1.12$, $p = .33$, $\eta_p^2 = .02$; $F(8,376)_{threat*time} = 8.54$, $p < .001$, $\eta_p^2 = .15$). Differences between both threat conditions were only present before the start of the experiment and disappeared with repeated presentations of the threats ($F(1,47)_{threat} = 2.29$, $p = .14$, $\eta_p^2 = .05$).

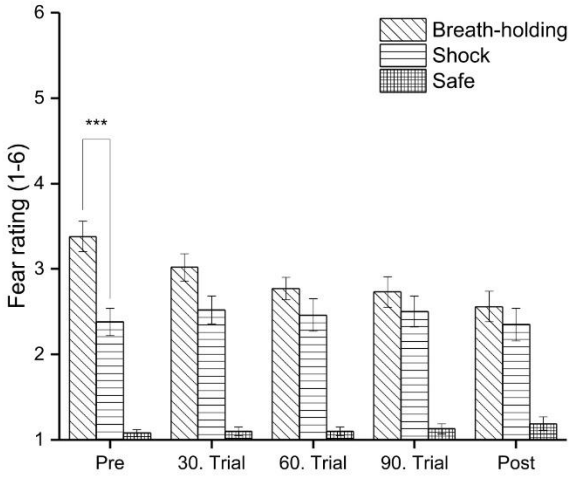

Figure S2. Fear ratings (means and standard errors) for the safe and both threat conditions reported on a scale from 1 (no fear) to 6 (maximum fear). *** indicates $p \leq .001$

Breathing parameters

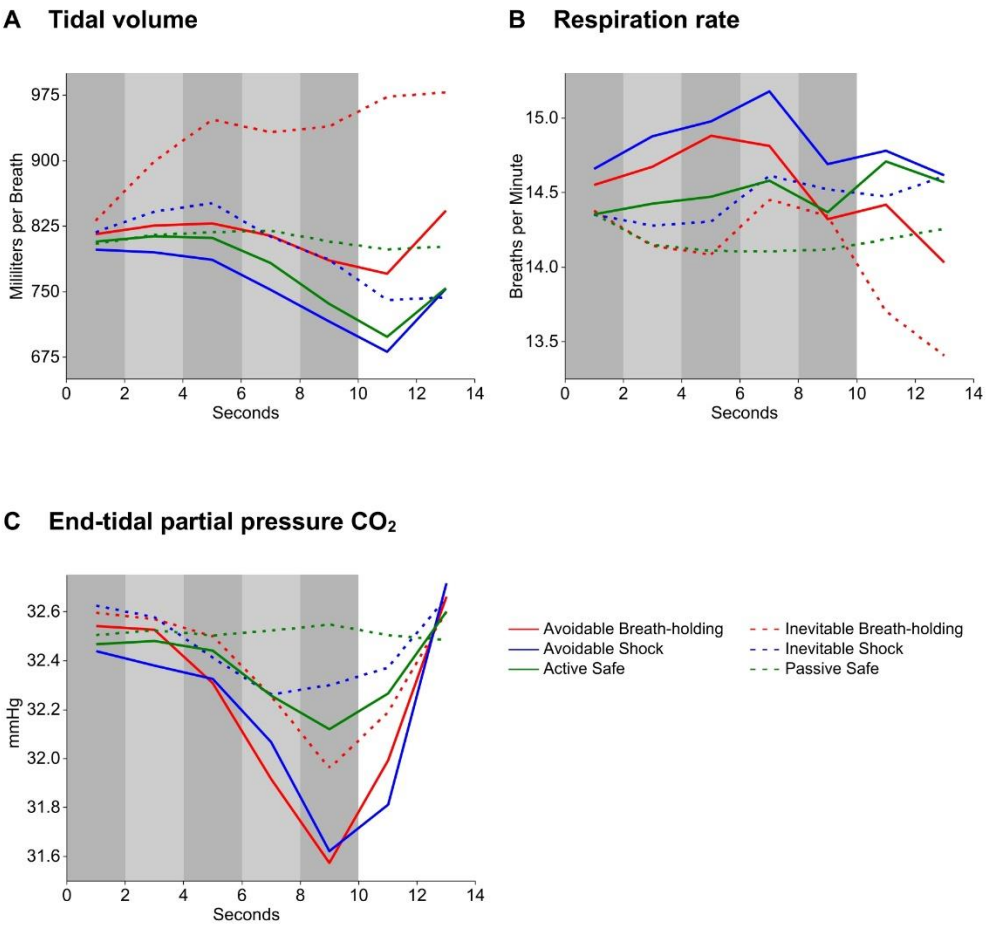

Figure S3. Defensive mobilization as a function of threat imminence, type of threat, and behavioral response options at hand. External threat (blue) vs. interoceptive threat (red) or safety (green) are illustrated in dotted lines if inevitable ("passive/inevitable condition") or solid lines if a button press was required ("active/avoidable condition"). Results are shown across the five looming stages and the subsequent period of the possible shock or breath-holding delivery, separately for (A) Tidal volume, (B) Respiration rate, (C) End-tidal partial pressure CO_2.

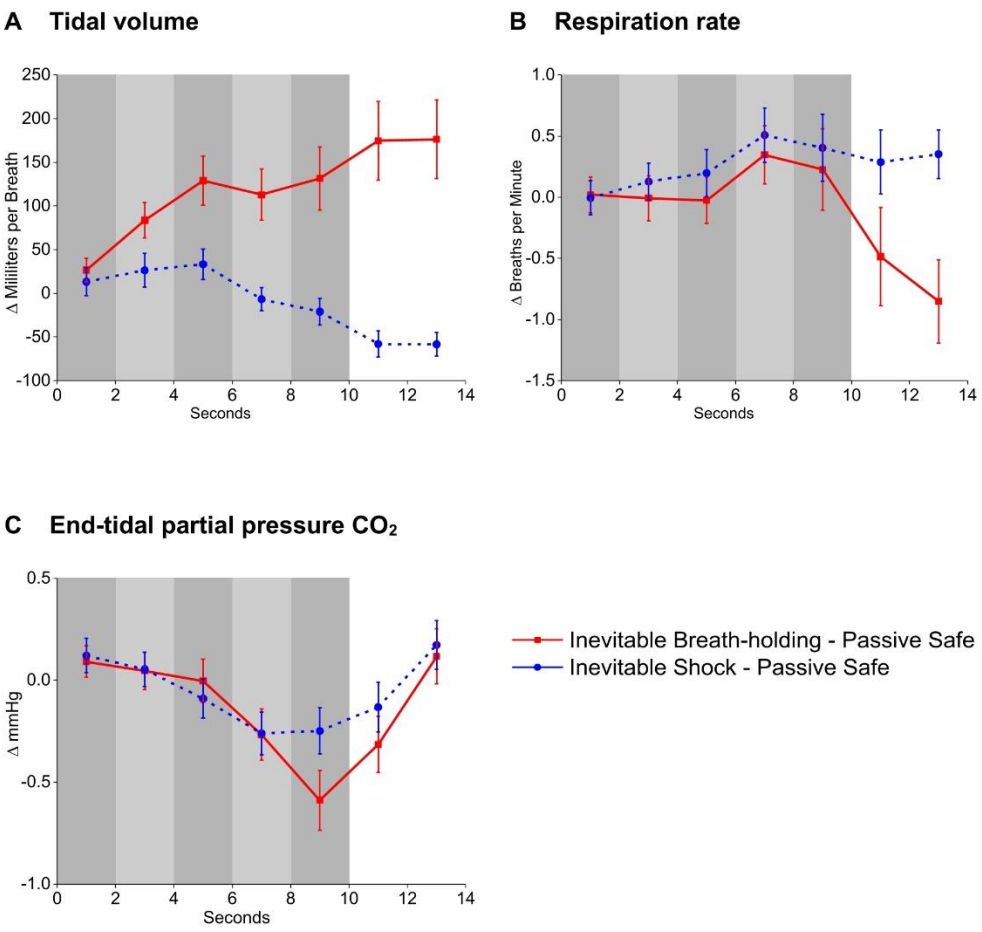

Figure S4. Mean difference in response magnitude between inevitable threat and passive safe conditions (blue line for external threat minus safe, red line for respiratory threat minus safe). Results are shown across the five looming stages and the subsequent period of the possible shock delivery or breath-holding, separately for (A) Tidal volume, (B) Respiration rate, (C) End-tidal partial pressure CO_2.

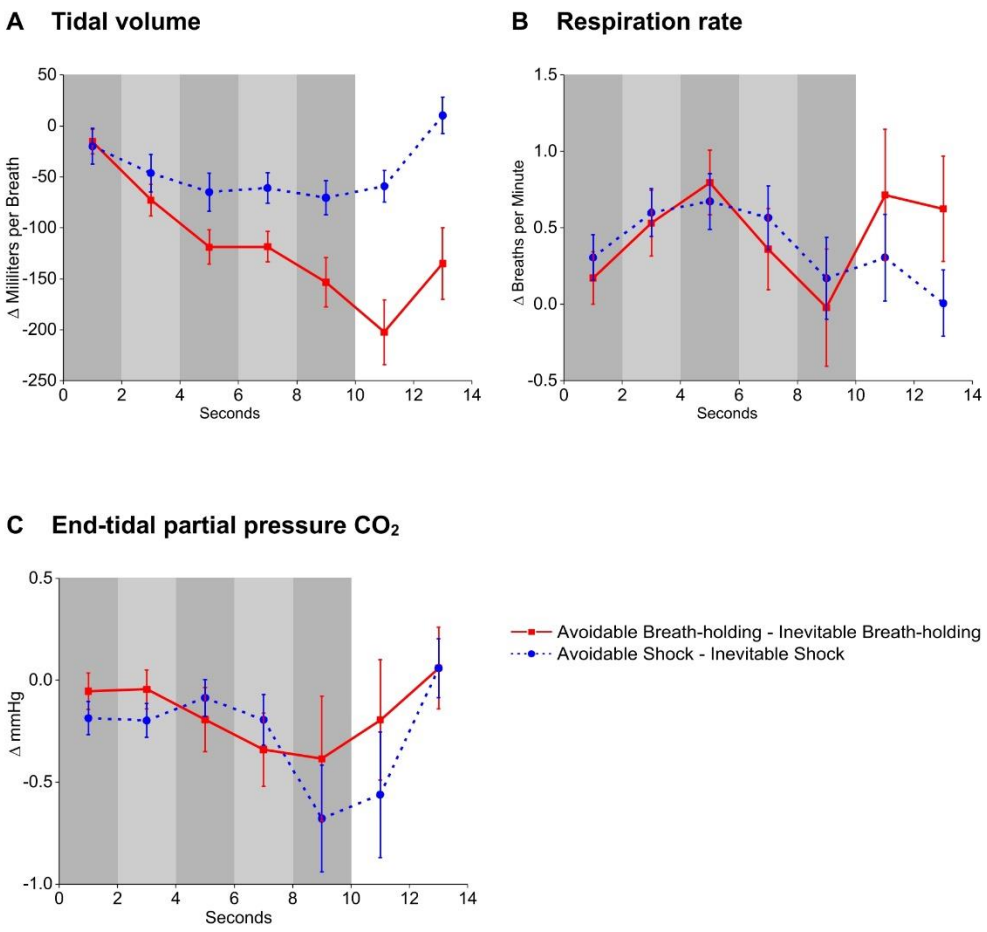

Figure S5. Mean difference in response magnitude between avoidable and inevitable threat conditions (blue line for external threat, red line for respiratory threat). Results are shown across the five looming stages and the subsequent period of the possible shock delivery or breath-holding, separately for (A) Tidal volume, (B) Respiration rate, (C) End-tidal partial pressure CO_2.

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Publication 2

Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat

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CB, CFP and AOH designed the experiment. CB and EK supervised the data acquisition. CB analyzed the data with help from EK and CB provided the first draft of the manuscript. All authors contributed to the interpretation of the data and wrote the manuscript.

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Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat

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ABSTRACT

Resistant avoidance behaviors play a crucial role in the maintenance of anxiety disorders and are therefore central targets of therapeutic interventions. In the present study, the development of avoidance behavior was investigated in 24 healthy participants who repeatedly prematurely terminated the exposure to increasing interoceptive threat, i.e., the feeling of dyspnea induced by increasing inspiratory resistive loads that were followed by the ultimate threat, a short breathing occlusion. Physiological responses and subjective anxiety preceding terminations were compared to matched intervals of a matched control group (N = 24) who completed the exposure. Initially, participants terminated during the ultimate threat, i.e., during occlusion. This first termination was preceded by a strong surge in autonomic arousal and reported anxiety. Startle reflex and the P3 component of event-related brain potentials to startle probes were strongly inhibited, indicating preparation for defensive action. With repetitive terminations, individuals successively terminated earlier, avoiding exposure to the occlusion. This avoidant behavior was accompanied by alleviated autonomic arousal as compared to the first termination. In addition, no indication of physiological response preparation was found implying that the avoidance behavior was performed in a rather habitual way. Matched controls did not show any indication of a defensive response surge in the matched intervals. In matched controls, no changes in physiological response patterns were detected while anxiety levels increased with repetitions. The present results shed new light on our understanding of the motivational basis of avoidance behavior and may help to refine etiological models, behavioral analysis and therapeutic strategies in treating anxiety disorders.

1. Introduction

The avoidance of a threat (e.g., pain, suffocation) is an adaptive instrumental defense behavior to protect the individual from life-threatening consequences, thus ensuring the adaptation to changing environmental conditions (Skinner, 1953; Hamm and Weike, 2005; Cain and LeDoux, 2008). However, if avoidance behaviors become too dominant they may impair psychosocial functioning and quality of life (Barlow, 2002; American Psychiatric Association, 2013). In fact, maladaptive changes in behavior that prevent exposure to or terminate confrontation with a perceived threat are one of the core features of a wide spectrum of mental disorders (Craske et al., 2009; American Psychiatric Association, 2013; Krypotos et al., 2015). These maladaptive behaviors (e.g., avoiding eye contact or taking medication) are typically persistent and inflexible in nature, automatically elicited by threat-related cues (e.g., body sensations or phobic objects), and thus performed in a habit-like manner (Dickinson, 1985; Gillan et al., 2016c; LeDoux et al., 2016). Most importantly, avoidance behavior is often not adaptive and consistently performed even though expected negative outcomes and environmental conditions may have changed (Dickinson, 1985; LeDoux et al., 2016). Of clinical importance is that in patients with anxiety disorders persistent avoidance prevents the disconfirmation of central concerns about the consequences (e.g., the mental representation of the unconditioned stimulus) of a specific situation. As such, avoidance plays a key role in preventing extinction of a learned association and maintaining anxiety and irrational fears (Barlow, 2002; Mineka and Zinbarg, 2006; Craske et al., 2008; Helbig-Lang and Petermann, 2010).

In modern exposure-based therapies, the prevention of safety-seeking behaviors including avoidance and escape is a key prerequisite to facilitate extinction (Barlow et al., 2004; Craske et al., 2014; Pittig et al., 2016). Persistent avoidance, therefore, interferes with extinction learning - one central mechanism of exposure based therapies (Powers et al., 2004; Craske et al., 2008; Lovibond et al., 2009; Helbig-Lang and Petermann, 2010). Possibly, resistant avoidance behavior accounts for the relatively high rates of dropouts or refusals, nonresponders and

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relapses in exposure-based therapies (Craske et al., 2006; Gloster et al., 2013; Fernandez et al., 2015). As such, it becomes clear that a comprehensive analysis of human avoidance behavior and its underlying mechanisms and motivational basis is of high relevance and could help to enhance the effectiveness of exposure therapy.

Early animal data, as well as recent findings from humans, suggest that avoidance behaviors can persist following fear extinction (Solomon et al., 1953; Vervliet and Indekeu, 2015) suggesting that fear might initiate instrumental avoidance behavior but might be less important for its maintenance (see LeDoux et al., 2016 for a review). It has been demonstrated that as rodents start to exert behavioral control over a threat (e.g., show instrumental avoidance responses) defensive fear responses (e.g., freezing) elicited by the threat-predicting cues will diminish (see Campese et al., 2016 for a review). Moreover, there is increasing evidence that different neural networks are involved in regulating freezing and defensive action (Amorapanth et al., 2000; Choi et al., 2010; Ramirez et al., 2015). The switch from reactive responses to instrumental defensive action is assumed to be coordinated by the prefrontal cortex (infralimbic prefrontal cortex) that actively inhibits central amygdala mediated expression of conditioned freezing and thus facilitates defensive action (Martinez et al., 2013; Moscarello and LeDoux, 2013). Finally, when avoidance behavior is performed repeatedly, defensive actions may become inflexible, stimulus-triggered and automatic, i.e., become amygdala-independent defensive habits (Campese et al., 2016; LeDoux et al., 2016).

The findings in animals are consistent with recent human brain imaging data suggesting that the amygdala, prefrontal cortex, and striatum are involved in avoidance learning (Schlund et al., 2010; Schlund and Cataldo, 2010; Schlund et al., 2011; Levita et al., 2012; Schlund et al., 2013; Collins et al., 2014; Boeke et al., 2017). Indeed, in addition there is evidence from human research demonstrating that autonomic arousal decreases during avoidance learning (Lovibond et al., 2008; Delgado et al., 2009; Vervliet and Indekeu, 2015; Boeke et al., 2017). While these data are promising, in most studies individuals are instructed or trained specifically to exhibit avoidance behavior. In contrast, although highly clinically relevant, there are almost no data on spontaneously occurring avoidance behavior and its maintenance in humans. The present study therefore aimed at characterizing defensive behaviors, physiological arousal, and reported anxiety associated with spontaneously occurring repeated termination of exposure to a threat.

In the present study, we used an interoceptive threat increasing in intensity because such threat bears high relevance for a variety of anxiety and health problems. For example, bodily symptoms may spiral into panic and may elicit defensive action in persons with panic disorder (Goodwin et al., 2005; Kessler et al., 2006; Pané-Farré et al., 2013; Pané-Farré et al., 2014). In our study, the increasing interoceptive threat was established by evoking increasing feelings of dyspnea using increasing respiratory loads to impede inspiration and a complete breathing occlusion, a model for a suffocation experience that has been shown to be a potent unconditioned internal threat (Nardi et al., 2006; Pappens et al., 2012; Pappens et al., 2014). Participants were provided with a response button that they could press (during the presentation of increasing loads and the occlusion) to terminate the trial. In the present analysis we explored (1) at which threat intensity (increasing loads vs. occlusion) participants terminated the exposure, (2) how the behavioral pattern, (3) reports of anxiety, (4) physiological responses and brain stem reflex measures as well as (5) startle probe evoked brain potentials as an index of selective attention changed with repetitions of premature terminations of the exposure sequences. To control for the possibility that changing response patterns during repeated terminations could be the result of the mere repetitions of exposure to increasing interoceptive threat, defensive responses prior to terminations were compared to responses during matched control intervals of individuals who completed all exposure sequences.

Based on previous findings and clinical observations, we assumed that after the initial defensive action at the ultimate threat level (e.g., during occlusion) successive defensive actions would be initiated increasingly earlier at lower threat levels. We also predicted that repetitive defensive actions would be accompanied by different autonomic response patterns. We expected that the first termination would be motivated by a strong fear response elicited at the highest threat level, characterized by a surge in sympathetic arousal (increased heart rate and skin conductance level) (Richter et al., 2012; Hamm et al., 2016), as would be predicted by Mowrer's two-factor model (Mowrer, 1939). In contrast, no such strong autonomic responses were expected during later premature terminations supporting animal data and initial evidence in humans, that the maintenance of avoidance is not motivated by fear and therefore not accompanied by strong autonomic indices of fear (Lovibond et al., 2008; Delgado et al., 2009; Campese et al., 2016). In matched control persons, we predicted that there would be no increase in autonomic arousal during the first and subsequent matched control intervals. Besides autonomic measures, we also assessed the modulation of the startle response – an additional rather low-level brain stem measure of fear (see Hamm, 2015 for a review) prior to exposure terminations.

There is evidence showing that if individuals have the option to actively avoid exposure to a threat by performing a motor task (button press), startle response magnitudes are inhibited during the acute preparation for action (Löw et al., 2008; Richter et al., 2012; Löw et al., 2015; Wendt et al., 2017). This inhibition of the startle blink magnitudes was associated with a sharp drop of the probe-elicited P3 component of the evoked brain potentials, suggesting that attentional resources are allocated to the visual cue that signals the critical time window for the initiation of the avoidance response, thus reducing the selective attention to the irrelevant secondary acoustic startle probe (see Löw et al., 2015). Based on these results, we expected an inhibition of the startle eyeblink response and a reduction of the P3 component of the ERP to the acoustic probe stimuli prior to initial defensive action as a result of binding of attentional resources in the context of response preparation. In contrast, we expected that repetitive avoidance would be performed rather automatically or in a habit-like manner, thus not requiring allocation of attentional resources to facilitate the preparation and initiation of the behavioral response (Solomon et al., 1953; Lovibond, 2006; Ilango et al., 2014; Krypotos et al., 2015; Gillan et al., 2016c; LeDoux et al., 2016). As such, we assumed that the startle eyeblink responses would no longer be inhibited and the probe-evoked P3-component would no longer be reduced.

2. Methods and materials

2.1. Participants

Participants were recruited from a pool of 400 university students. Exclusion criteria were cardiovascular, respiratory (e.g., asthma, COPD), or neurological (e.g., epileptic or apoplectic seizures, multiple sclerosis) diseases, current or past psychotherapeutic treatment for anxiety problems, hearing impairment, or pregnancy. Overall, 69 participants took part in the laboratory assessment. Twenty-eight participants prematurely terminated the exposure to the restricted breathing at least once as described in the procedures section. The sample included in this analysis consisted of those 24 individuals who *repeatedly* (more than once) terminated the exposure. Verbal reports of anxiety and physiological responses of repeated terminations were compared with matched exposure sequences from 24 control individuals matched for age, sex, and level of suffocation fear who completed all experimental procedures. A description of the group characteristics is presented in Table 1, indicating that the groups did not differ by age, sex, body weight, height, body mass index, trait anxiety, anxiety sensitivity, suffocation fear, agoraphobic cognitions, fear of bodily sensations or the vigilance to body sensations. All participants provided written informed consent prior to the study and either received course credit or

Table 1
Means and standard deviations of demographic characteristics and questionnaires for persons who prematurely terminated exposure and matched controls.

	Premature terminations	Exposure completed	*p*-Value
CLQ – SF [0–46]	10.4 (7.7)	10.8 (8.6)	$p = 0.874$
ASI – 3 [0–72]	24.0 (11.0)	20.5 (12.2)	$p = 0.296$
BSQ [1–5]	2.4 (0.6)	2.2 (0.7)	$p = 0.481$
ACQ [1–5]	1.6 (0.4)	1.6 (0.4)	$p = 0.658$
BVS [0–40]	15.8 (5.5)	15.9 (6.7)	$p = 0.965$
STAI - trait [20–80]	38.3 (7.8)	42.8 (11.4)	$p = 0.121$
Age	22.8 (3.8)	23.2 (3.4)	$p = 0.691$
Sex (female/male)	20/4	20/4	$p = 1.000$
Weight (kg)	68.5 (12.6)	67.6 (12.7)	$p = 0.803$
Height (cm)	173.5 (6.9)	172.3 (8.6)	$p = 0.570$
Body mass index	22.8 (4.2)	22.7 (3.3)	$p = 0.937$

Note: CLQ: Claustrophobia Questionnaire; ASI: Anxiety Sensitivity Index; BVS: Body Vigilance Scale; STAI: State-Trait Anxiety Inventory; BSQ: Body Sensations Questionnaire; ACQ: Agoraphobic Cognition Questionnaire; possible questionnaire score ranges are listed in parentheses.

financial compensation (20 €) for their participation. The study protocol was approved by the ethics committee of the German Psychological Society.

2.2. Materials and measurements

2.2.1. Breathing circuit

Participants breathed through a tightly fitting face mask (7400 series; Hans Rudolph, Inc., Kansas City, MO) connected to a rigid tube with sensors for measuring respiration. A flow sensor was mounted to the mouth port of the two-way y-shaped non-rebreathing valve (no. 2630; Hans Rudolph, Inc.) which enabled unrestricted expiration. A plastic tube (length: 2.75 m; diameter: 35 mm) connected the inspiratory port of the y-valve to the common port of a Five-Way Gatlin-Shape™ Inflatable-Balloon-Type™ valve (2440 series, Hans Rudolph, Inc.), placed in the adjacent control room. Closing and opening of the 4 ports of this valve was controlled via VPM software triggering a pneumatic controller (2430 series, Hans Rudolph, Inc.). This system allowed a prompt and easy switching between three different inspiratory resistive loads, unrestricted breathing, and total occlusion (all ports closed).

2.2.2. Inspiratory resistive loads (IRL)

For the induction of dyspnea, nylon flow resistors of linear type (7100 series, Hans Rudolph, Inc., range: 0.5–236.5 $cmH_2O/l/s$) were attached to three ports of the valve.

2.2.3. Breathing occlusion

Breathing occlusions of 15 s duration were manually triggered at the end of expiration as indicated by visual display of the respiration curve generated by thoracic and abdominal respiration belts connected to an inductive plethysmography system (Respitrace, Q.D.C., SensorMedics, NewMedics GmbH, Öhringen, Germany).

2.2.4. Startle stimulus

The startle probes, 50 ms bursts of broadband white noise (rise/fall time $<$ 1 ms), were presented binaurally with an intensity of 95 dB(A) through AKG K-66 headphones.

2.2.5. Subjective reports

Using a computer keyboard, participants rated the experienced intensity and unpleasantness of dyspnea as well as the anxiety and severity of panic symptoms as listed in the DSM-5 during loaded breathing and occlusion on the following scale: 1 (not at all), 2 (slight), 3 (moderate), 4 (strong), 5 (very strong), and 6 (maximally tolerable). Moreover, using a touchpad (Intuos PEN & Touch S, Wacom Europe GmbH, Krefeld, Germany) participants were asked to draw a line indicating the course of their subjective anxiety during exposure to restricted breathing in a coordinate system which was labeled “time” on the x-axis and “anxiety intensity” on the y-axis (0 − 10). Rating options were projected onto a 1.50 × 1.30 m screen in front of the participants.

2.2.6. Physiological recordings

To measure the eyeblink component of the startle response, electromyographic (EMG) activity was recorded with two electrolyte-filled (Marquette Hellige, Freiburg, Germany) Ag/AgCl miniature surface electrodes (Sensormedic, Yorba Linda, CA) attached over the orbicularis oculi muscle beneath the lower left eyelid. The amplification of the raw EMG signal was realized using a Coulbourn S75-01 amplifier. The signal was filtered using a 30 Hz high-pass and a Kemo KEM-VBF8-03400 Hz low-pass filter. Digital sampling at a rate of 1000 Hz was carried out via a 12-bit A/D converter starting 100 ms before the onset of the startle stimulus and lasting 400 ms following the startle probe.

An electroencephalogram (EEG) was recorded with Ag/AgCl electrodes (8 mm diameter; Marquette Hellige) filled with EC2 Genuine Grass Electrode Cream (West Warwick, RI) and placed at Pz, Cz, and Fz according to the international 10–20 system. All channels were referenced to Pz and re-referenced offline to a linked ear lobe reference (two linked Ag/AgCl ear-clip electrodes). Vertical and horizontal eye movements (electrooculogram, EOG) were registered with two electrolyte-filled (Hellige electrode cream) Ag/AgCl electrodes (8 mm diameter; Marquette Hellige) placed above and on the right side of the right eye. Electrode impedance was kept below 20 kΩ. Both the EOG and the EEG were amplified (20,000-fold for EEG and 2000 for EOG, resp.) using a 12-channel Isolated Bioelectric AC/DC Amplifier System (San Diego Instruments, San Diego, CA) with a time constant of 1 s and a low-pass filter of 35 Hz. The signals were digitally sampled at 250 Hz.

Skin conductance was recorded from the hypothenar eminence on the palm of the participants' non-dominant hand using two Ag/AgCl standard electrodes (8 mm diameter, Marquette Hellige) filled with a 0.05 M sodium chloride electrolyte medium. A constant DC voltage of 0.5 V was applied across electrodes (attached 15 mm apart) by a Coulbourn S71–22 skin conductance coupler that processed the signal with a resolution of 0.01 μS. The DC voltage amplified signal was continuously sampled at 10 Hz by a 12-bit A/D-converter.

Electrocardiogram (ECG) was measured with electrolyte filled Ag/AgCl standard electrodes (Marquette Hellige) placed in an Einthoven-II-setup. The raw ECG signal was amplified and filtered through a 0.1–13 Hz band-pass filter using a Coulbourn S75-01 bioamplifier. The digital sampling rate was set to 100 Hz.

2.3. Procedure

Following the attachment of the breathing mask and all sensors, the experiment proceeded as follows.

(1) *Determination of breath-holding time*. The maximal post-expiratory breath-holding time (breath-holding at functional residual capacity as suggested by Asmundson and Stein, 1994) was determined using a standardized procedure. At the end of an expiration, the examiner signaled via a computer screen to hold the breath as long as possible, while the breathing circuit was occluded. Hence, during this period no breathing was possible until the participants terminated the breathing occlusion by button press which automatically initiated opening of the inspiratory port.
(2) *Determination of load detection threshold*. Next, for the determination of the individual's detection threshold of loaded breathing, IRLs were separately presented for 20 s, each followed by a 20 s recovery phase and stepwise increased until participants noticed any change in respiration (for a detailed description see Alius et al., 2013).
(3) *Presentation and selection of increasing IRLs*. Subsequently, to get acquainted with the range of possible loads, participants were asked

to rate the intensity and unpleasantness of dyspnea elicited by presentation of a mild (5 cmH2O/l/s above threshold) and a more severe load (50 cmH2O/l/s above threshold). In the next step, inspiratory resistive loads were gradually increased following an exponential curve. Loads were presented 30 s and each followed by a recovery phase lasting 30 s. After each load presentation participants rated the intensity and unpleasantness of experienced dyspnea. After an IRL was rated with an unpleasantness of 6 (= maximally tolerable) loads were not further increased. Finally, participants were exposed to one post-expiratory breathing occlusion lasting for 15 s, and, again, ratings of intensity and unpleasantness of dyspnea were obtained.

(4) *Repeated presentation of increasing IRLs followed by occlusion.* The assessment phase started with a one-time-only startle habituation phase (110 s) during which 8 startle probes were presented to reach a stable baseline for startle response magnitudes. Then, three loads of increasing intensity (previously rated as producing slight [load1], strong [load2] and maximally tolerable [load3] unpleasant feelings of dyspnea) were consecutively presented for 60 s each. During each load, three startle probes were presented with a randomized inter-stimulus-interval varying between 10 s and 30 s. Presentation of the third load was immediately followed by a post-expiratory breathing occlusion for 15 s and a 30s recovery phase. Two startle probes were presented during occlusion and recovery, respectively, with an inter-probe-interval of 5–20 s. Then, participants were asked to draw the course of anxiety they experienced during the exposure trial. The described load-occlusion-recovery sequence (trial) was repeated eight times.

Participants were informed that during the sequences of increasing loads and the occlusion they could press a termination button if, at any point in time, they were unable to tolerate the exposure any longer. However, it was stressed to the participants that it is crucial for the experiment to complete the sequences. A button press immediately terminated the presentation of loads or an occlusion and initiated a forward skip to the next recovery and anxiety-rating phase. From there, the experimental procedure (next sequence) was resumed normally. Thus, as eight load-occlusion sequences were presented, participants were able to terminate up to eight times at maximum. Note: Participants also had the option to terminate the entire experiment by calling the experimenter via intercom at any time.

(5) *Individual presentations and ratings of IRLs and occlusion*. During a final rating phase, the three previously selected loads and the breathing occlusion were presented separately for 30 s each, followed by a 30 s recovery phase and per-load/occlusion ratings of panic and respiratory symptoms were obtained.

At the end of the laboratory session, participants completed the Anxiety Sensitivity Index – 3 (ASI-3, Taylor et al., 2007), the Claustrophobia Questionnaire (CLQ, Radomsky et al., 2001), Body Sensations Questionnaire (BSQ, Chambless et al., 1984), the Agoraphobic Cognition Questionnaire (ACQ, Chambless et al., 1984), the State-Trait Anxiety Inventory (STAI, Spielberger et al., 1983) and the Body Vigilance Scale (BVS, Schmidt et al., 1997), and were fully debriefed by the experimenter.

2.4. Data reduction and analysis

The raw EMG signal was filtered off-line with a 60 Hz high-pass filter, rectified and smoothed using a 1st-order low-pass filter with a time constant of 10 ms. Then, the startle eyeblinks were scored using a computer program (Globisch et al., 1993) that identified blink onset and peak amplitude. Only trials in which blinks started during 20–100 ms after delivery of the startle probe and reached their peak amplitude within 150 ms were scored as valid startle responses. If no blink was detected in the defined time window the trials were scored as zero responses. Trials were rejected and treated as missing values if there was excessive baseline activity or movement artifacts. Digital values were converted to μV and then exported. To remove inter-individual variability not related to the experimental manipulation, for further analyses all values were transformed to T-scores ($M = 50$, $SD = 10$) as recommended by the guidelines for human startle eyeblink studies (Blumenthal et al., 2005).

EEG and EOG signals were filtered offline using a 0.1–35 Hz bandpass filter and a 50 Hz notch filter. The EEG signal was then corrected for vertical and horizontal eye movements using the Gratton-Coles algorithm (Gratton et al., 1983). Epochs of 700 ms (including a 100 ms pre-stimulus baseline) were extracted relative to startle probe onset, baseline corrected, and excluded from further analysis whenever the maximum-minimum difference of the EEG activity was larger than 100 μV. Additionally, all data were visually inspected and epochs with movement artifacts or technical failures were excluded. EEG analysis was processed with Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany). The P3 component of the ERP was determined as the mean activity between 170 and 310 ms.

Digital values of skin conductance level (SCL) were converted to μS and exported in half-second means.

The ECG signal was visually inspected, movement artifacts set to missing, and misplaced R-wave triggers were corrected using ANSLAB version 2.4 (Autonomic Nervous System Laboratory, University of Basel, Switzerland). Inter-beat-intervals were calculated, converted to heart rate (HR in bpm), and exported in half-second bins.

Data from persons who prematurely terminated exposures were analyzed time-locked to the button press. Reported anxiety, as well as physiological data, were analyzed for 90 s preceding the button press averaged in blocks of ten seconds, thus providing 10 data points prior to the premature termination of the trial. Blink magnitudes were averaged into blocks across three acoustic probes. Proximal response magnitudes were calculated as the mean of responses to three probes immediately prior to premature termination and distal response magnitudes were averaged over the preceding three probes presented during the load. Evoked brain potentials to the acoustic probes were analyzed using the same logic. Physiological and verbal report data were only analyzed for trials from which data were available for at least 90 s (at least 6 probe stimuli) prior to premature termination. Due to technical problems, analyses of startle responses and ERPs were based on data from 21 participants per group. The physiological and subjective data from matched control persons were analyzed applying the same trial and timing information used for analyses of premature termination trials.

Linear mixed models were chosen for the statistical analyses as this approach corresponds to the special structure of the data (trials nested in participants and missing data points) and allows a flexible and powerful analysis of the repeated-measures data with missing data points (Blackwell et al., 2006; Tabachnick and Fidell, 2007; West, 2009). In persons who prematurely terminated exposure and matched control persons, changes in reported anxiety and physiological responses prior to premature terminations or during matched control intervals were analyzed with linear mixed models including the repeated measures factors *proximity* (ten 10s–blocks [from -90s to 0 s], resp., two blocks [distal vs. proximal] for startle responses and ERP analyses), *trial* (first to eighth termination, resp., first to eighth matched interval) and the between-subject factor *group* (persons who terminated exposure vs. matched completer) as well as their interactions. For the analyses of the P3 component of the probe-evoked potentials electrode *location* (Pz vs. Cz vs. Fz) was entered as an additional repeated measures factor. The random part of the models included a person-specific intercept and repeated-measures effects for proximity and number of terminations (and location for ERP data) with a first-order autoregressive covariance structure (homogeneous variances and correlations that decrease with time). To check whether the experimental manipulation was successful in the present study, the change in

physical intensity of IRLs as well as in anxiety and panic symptom intensity during increasing loads and the occlusion was analyzed using a mixed-model ANOVA with the repeated-measures factor *load* (first vs. second vs. third load, resp., first vs. second vs. third load vs. occlusion for anxiety and symptom ratings) and the between-subject factor *group*. To evaluate whether with increasing number of terminations the behavioral pattern changed, i.e., whether the frequency of terminations decreased during occlusion and increased during loaded breathing, an ANOVA was run with the repeated-measures factor *number of terminations* (first to eighth termination). Whenever physiological and verbal report data significantly changed prior to terminations or during loads as indicated by a significant main effect of proximity or load, linear and quadratic trends were analyzed to test for significant increases in physiological or verbal report data. All statistical tests used a significance level of $p < 0.05$. Whenever necessary, a Greenhouse-Geisser correction was applied. All data were processed using SPSS 22.0 (SPSS for Windows, IBM).

3. Results

3.1. Manipulation check

In persons who prematurely terminated exposure and matched controls, the physical intensity of inspiratory resistive loads increased while the reported unpleasantness of dyspnea of the selected loads increased from slight to strong to maximally tolerable, $F(2, 92) = 72.00$, $p < 0.001$, Group × load $F(2, 92) = 2.71$, $p = 0.106$, group $F(2, 92) < 1$, $p = 0.495$, linear and quadratic trend $p < 0.001$. In both groups anxiety and symptom intensity continuously increased from load1 to occlusion, load $F(3, 138) = 39.81, p < 0.001$, Group x Load $F(3, 138) = 1.02$, $p = 0.372$, linear trend: $p < 0.001$, quadratic trend: $p = 0.076$ and load $F(3, 138) = 50.96$, $p < 0.001$, Group × load $F(3, 138) = 1.13$, $p = 0.324$, linear trend: $p < 0.001$, quadratic trend: $p = 0.286$ for anxiety and symptom ratings, respectively. However, persons who prematurely terminated exposures reported overall higher anxiety and symptom intensity as compared to matched controls, group $F(1, 46) = 5.88$, $p = 0.019$ and group $F(1, 46) = 3.87$, $p = 0.055$ for anxiety and symptom ratings, respectively.

3.2. Behavioral data

As depicted in Fig. 1, the frequency of terminations during the occlusion decreased with repeated trials, $F(7, 98) = 5.14$, $p < 0.001$, $\eta_p^2 = 0.27$, $\chi^2(7) = 28.20$, $p < 0.001$, linear trend: $p < 0.001$, quadratic trend: $p = 0.617$. Instead, participants more frequently terminated the trials already during the loaded breathing period.

3.3. Anxiety ratings

As depicted in Fig. 2,[1] both groups reported a continuous increase in the intensity of anxiety during the analyzed 90 s interval of termination or matched control trials, $F(9, 327.71) = 18.99$, $p < 0.001$, Group x Proximity $F(9, 327.71) = 1.09$, $p = 0.373$, linear trend: $ps < 0.001$ and quadratic trend: $ps > 0.262$ for both groups. Moreover, in both groups, the reported intensity of anxiety increased with the number of termination and matched control trials, respectively, $F(7, 927.64) = 6.82, p < 0.001$, Group x Trial $F(7, 927.64) < 1, p = 0.521$, linear and quadratic trends for both groups: $ps < 0.004$. Persons who prematurely terminated exposure reported a higher anxiety intensity immediately prior to the first and second termination as compared to during matched points in time of the matched control persons, e.g., at 0 s: group $Fs > 6.84$, $ps < 0.011$. Interestingly, autonomic indices of fear did not correspond with the verbal report data and showed a different pattern.

3.4. Autonomic arousal

As depicted in the upper left panel of Fig. 3, the pattern of SCL differed between persons who prematurely terminated exposure and matched controls, Group x Trial $F(7, 263.90) = 2.65$, $p = 0.012$. In persons who terminated exposure, the increase in SCL prior to premature terminations significantly changed with increasing number of terminations, $F(63, 712.12) = 4.83$, $p < 0.001$. There was a strong increase in SCL across the 90s prior to the first termination of exposure, $F(9, 603.07) = 4.19$, $p < 0.001$, linear trend: $p < 0.001$, quadratic trend: $p = 0.005$, while the second, $F < 1, p = 0.950$, and subsequent terminations were not preceded by significant changes in skin conductance level, $Fs < 1$, $ps > 0.870$. In contrast, there was no significant change in skin conductance during the first matched trial, $F < 1$, $p = 0.995$, nor did SCL change during subsequent matched control intervals (see right upper panel of Fig. 3), $Fs < 1, ps > 0.722$.

Supporting electrodermal data, persons who prematurely terminated exposure and matched control persons showed a different pattern of changes in heart rate, Group x Proximity x Trial $F(63, 1425.25) = 1.32$, $p = 0.052$. In persons who prematurely terminated exposure, heart rate increased significantly prior to the first termination (see lower left panel of Fig. 3), $F(9, 940.48) = 3.44$, $p < 0.001$, linear trend: $p < 0.001$, quadratic trend: $p = 0.023$. However, this increase in heart rate diminished with increasing number of terminations, $F(63, 985.46) = 1.33$, $p = 0.049$. Supporting the skin conductance data heart rate did not change significantly prior to the second, $F(9, 958.04) = 1.61$, $p = 0.107$, and subsequent terminations, $Fs < 1.50$, $ps > 0.144$. In contrast, in matched completers, heart rate did not change during the first matched control intervals, $F < 1, p = 0.555$, or during subsequent trials, $Fs < 1.88$, $ps > 0.070$.

3.5. Probe-evoked potential[2]

As depicted in Fig. 4, the pattern of the probe-evoked P3 amplitudes differed between persons who terminated exposure and matched controls, Group x Proximity x Trial $F(7, 709.89) = 4.62$, $p < 0.001$. The probe-evoked P3 amplitudes decreased significantly immediately prior to the first premature termination (see left panel of Fig. 4), $F(1, 224.92) = 25.88$, $p < 0.001$. However, this pattern changed with repeated terminations, Proximity x Trial $F(7, 474.17) = 11.90$, $p < 0.001$. There was no significant reduction of probe-evoked P3 amplitudes prior to the second, $F(1, 224.92) = 1.02$, $p = 0.314$, or subsequent terminations, $Fs < 2.53$, $ps > .112$. In contrast to the pattern found in persons who terminated exposure, in matched controls the P3 amplitudes did not decrease during the first matched non-termination trial, $F(1, 305.55) < 1$, $p = 0.366$, nor did P3 amplitudes change during subsequent trials, $Fs < 2.60$, $ps > 0.107$.

3.6. Startle response magnitudes

In line with the probe-evoked P3 data, startle response magnitudes decreased just before the first premature termination of exposure (see left panel of Fig. 5), $F(1, 244.89) = 7.42$, $p = 0.007$. Interestingly, increased inhibition of the startle response (proximal minus distal to the button press) was significantly correlated with reported anxiety just prior to the first termination, $r = -0.687$, $p = 0.001$. Again, startle response magnitudes did not change prior to the second, $F(1,$

[1] As reported for the subjective and physiological data, the response pattern did not change between the second and eighth termination. For a clear and consistent presentation of the data and effects found in the present study, only data from the first, second and eighth termination were depicted in Fig. 2 and all following figures. Data from all terminations are depicted in Fig. S1 to S4 (see online Supporting information).

[2] No significant interactions were found involving the factor location, all $Fs < 1.03$ and $ps > 0.421$.

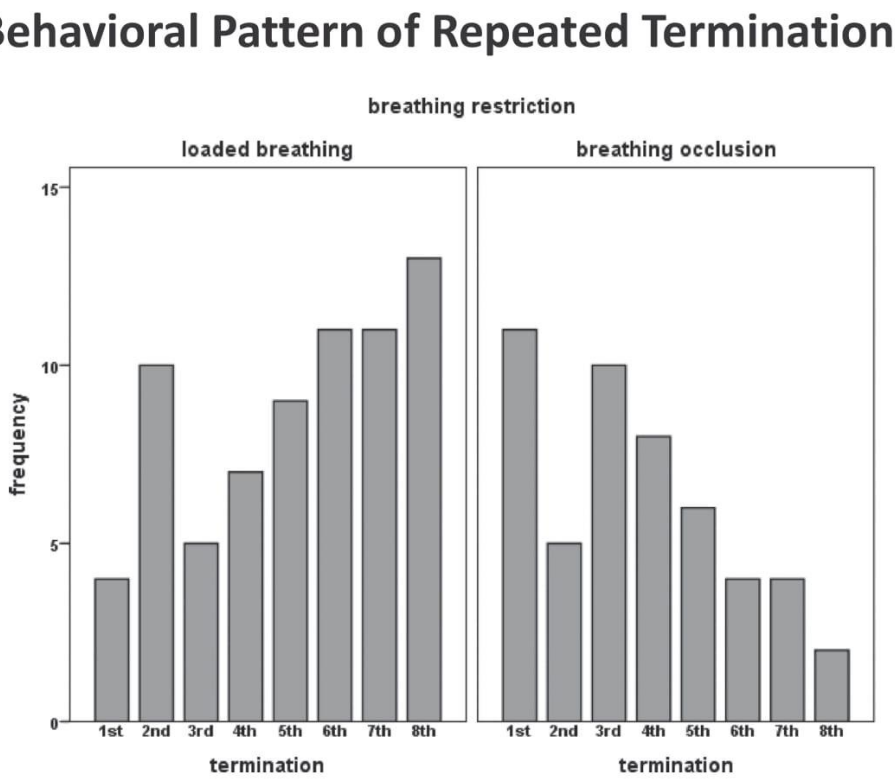

Fig. 1. The frequency of terminations either during loaded breathing or during a total breathing occlusion in the course of repeated terminations.

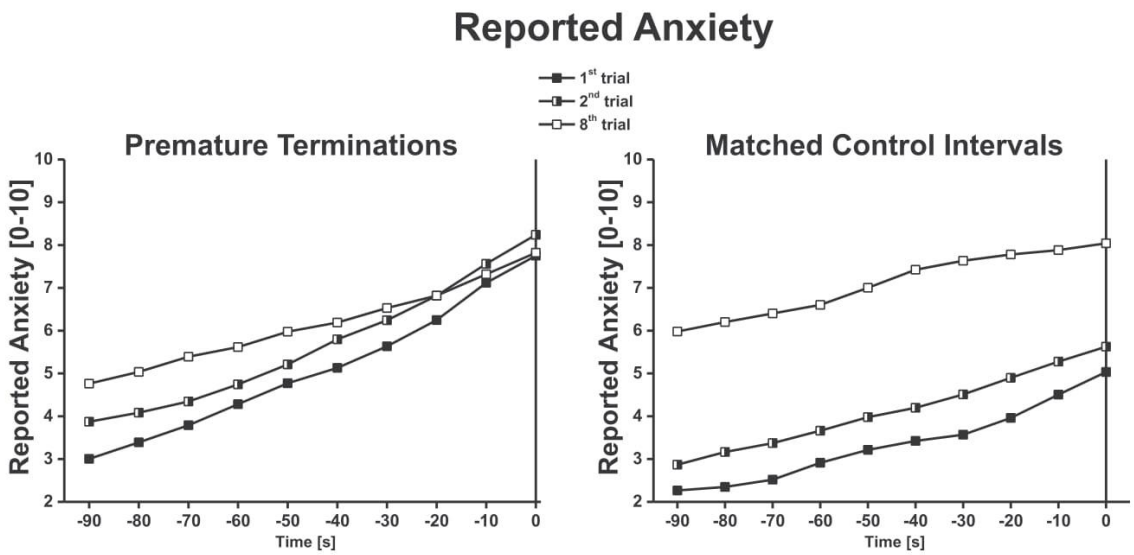

Fig. 2. Means of the reported anxiety during the 90s prior to the 1st, 2nd and 8th termination of increasing interoceptive threat (left panel) and during matched control intervals in matched controls (right panel).

244.89) < 1, $p = 0.567$, or subsequent terminations, $Fs < 1.04$, $ps > 0.309$. In accordance with the probe-evoked P3 amplitudes, in matched control subjects, no changes were observed in startle response magnitudes during matched time intervals (see right panel of Fig. 5), $Fs < 2.58$, $ps > 0.109$.

4. Discussion

The present study examined changes in defensive behavior during repeated premature terminations of exposure to an increasing interoceptive threat. In accordance with early animal data, we observed that with repeated terminations participants ceased the exposure to increasing interoceptive threat at increasingly lower threat levels.

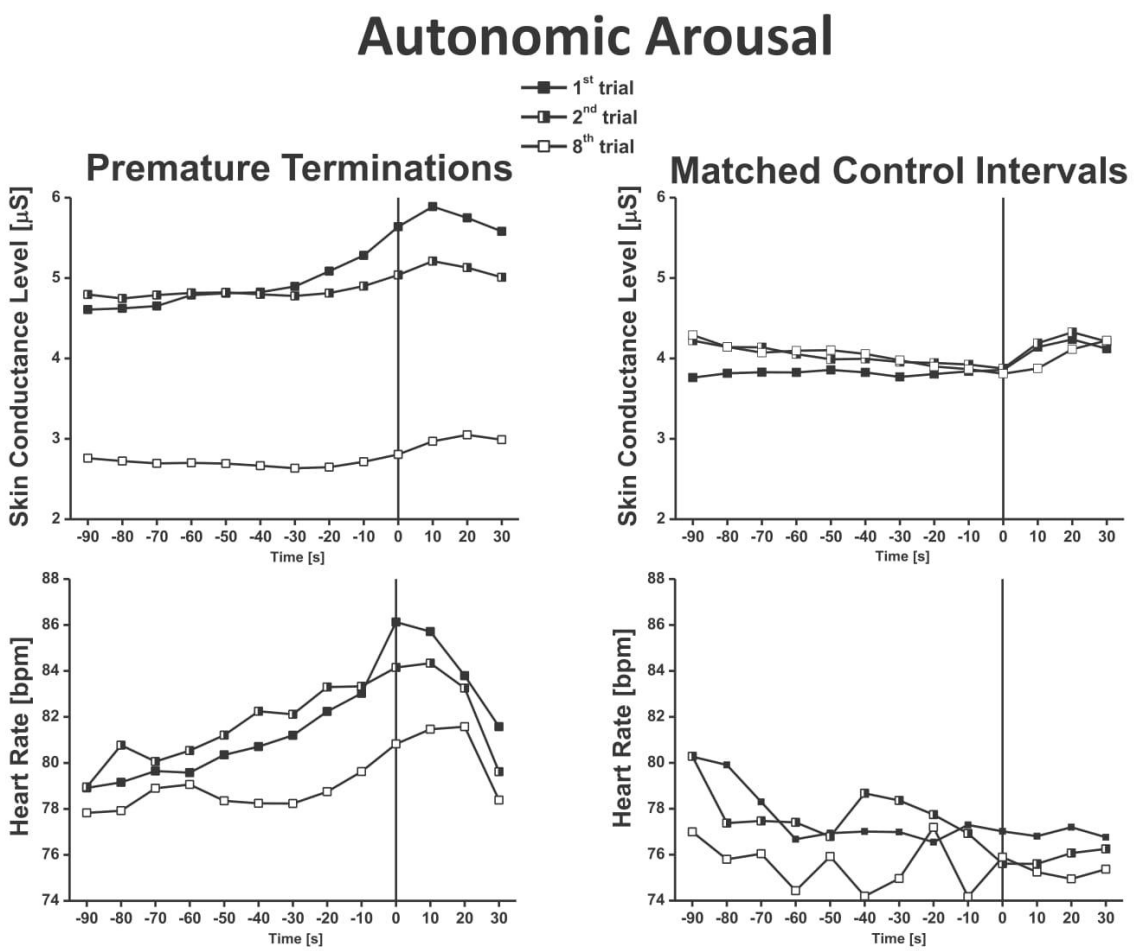

Fig. 3. Changes in autonomic arousal during the 1st, 2nd and 8th termination (left panel) or matched control trial (right panel). Mean skin conductance level (upper panel) and heart rate (lower panel) 90s before, during, and 30s after the button press.

Associated with these behavioral changes, autonomic and reflex measures of defensive behaviors changed from preparation for defensive action to habitual behavior. These changes in defensive patterns went along with corresponding changes in selective attention as indexed by evoked brain potentials. The first termination typically occurred at the highest level of threat (i.e., during occlusion) and was preceded by a surge of sympathetic arousal and an increase in reported anxiety. In addition, we observed a strong inhibition of the startle response magnitudes just prior to the premature termination supporting previous data from Löw et al. (2015). Moreover, attention to irrelevant and interfering cues in the threat environment was blocked as indicated by a reduced P3-component of the evoked potentials to the probe stimuli. A fundamentally different pattern of defensive reactivity emerged with repetition of premature terminations. The behavioral pattern changed in that participants terminated the exposure earlier in the sequences of increasing interoceptive threat, i.e., at lower levels of threat intensity, preventing the occurrence of the full occlusion. With increasing number of repetitions of premature terminations, we did not observe any increases in autonomic arousal or changes in blink magnitudes. Moreover, selective attention as indexed by the probe-P3 amplitudes was no longer modulated proximal to the button press. Importantly, this response pattern emerged exclusively in persons who prematurely terminated exposure but not in matched control persons, suggesting that the observed effects were not due to either the physiological state at the specific time of termination (i.e., during occlusion in the first termination) or the repeated confrontation with increasing interoceptive threat.

4.1. Defensive response patterns during the first termination of interoceptive threat

On a behavioral level, individuals terminated the first exposure of increasing threat at the highest threat level, i.e., the total breathing occlusion. This initial termination was preceded by strong increases in skin conductance level and heart rate. In contrast, this increase was not observed in matched control persons. These results are in line with observations in a subgroup of patients with panic disorder who escaped from a situation of entrapment during a standardized behavioral avoidance test (Richter et al., 2012; Hamm et al., 2016). These patients also showed a strong increase in heart rate and skin conductance level steadily increasing one minute prior to escape.

Startle magnitudes were inhibited prior to the first termination but not during the matched control interval, i.e., not just because of the present occlusion at this point of time. A similar relative inhibition of the startle reflex was also observed in panic disorder patients just prior to escape from entrapment (Richter et al., 2012). This decrease was even stronger for patients who escaped from the dark, narrow chamber during a self-reported panic attack (see Hamm et al., 2016). This

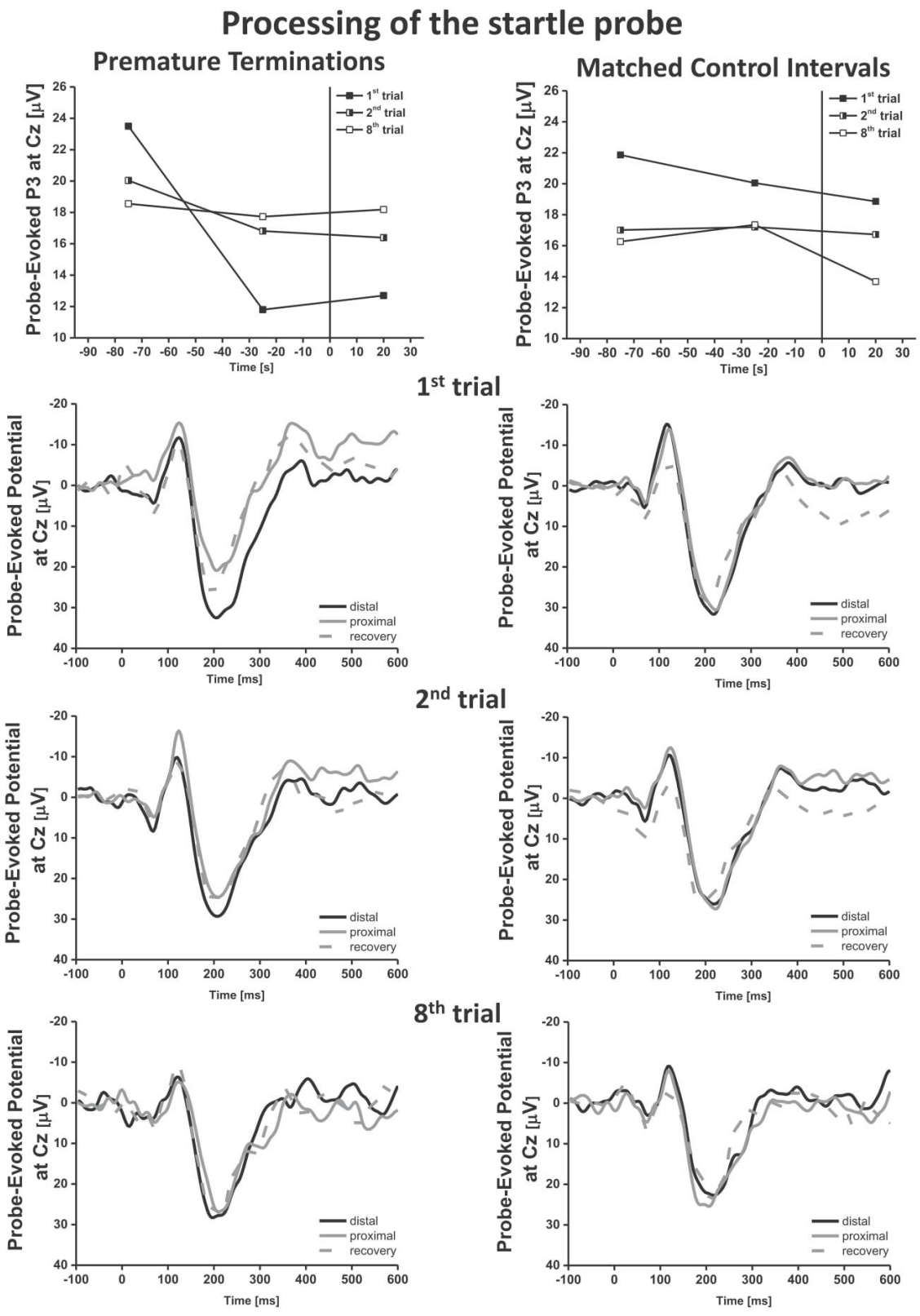

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Fig. 4. Event-related potentials evoked by startle probes distal and proximal to the button press of the 1st, 2nd, and 8th termination of exposure or matched control interval. Grand average waveforms (lower panels) and mean amplitude of the probe-evoked P3 component (upper panel) for Cz in persons who prematurely terminated exposure (left panel) and in matched control persons (right panel).

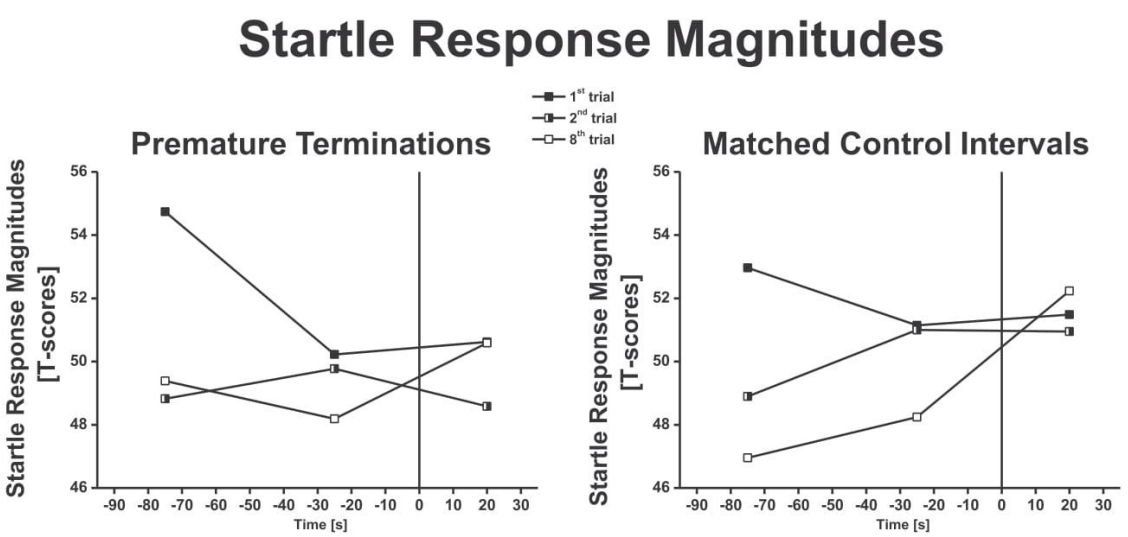

Fig. 5. Startles response magnitudes distal (responses to three startle probes) and proximal (responses to three startle probes) to the 1st, 2nd, and 8th premature termination of exposure by button press (left panel). Startle response magnitudes during matched control trials in matched controls (right panel).

corroborates animal data demonstrating that startle responses were relatively inhibited during cues predicting very intense foot shocks as compared to cues associated with mild shocks (Walker et al., 1997; Walker and Davis, 1997). In line with this evidence, we observed a stronger inhibition of the startle response when participants reported higher anxiety immediately prior to the first termination of exposure. Alternatively, this pattern of startle inhibition can be interpreted as an indicator of active response preparation that requires allocation of attentional resources to interoceptive threat cues and thus decreases available resources for processing of the auditory startle probe. This assumption goes in line with cross-modality experiments which demonstrated that startle response magnitudes were decreased when attention was allocated to stimuli that diverged from the sensory modality of the startle-eliciting probe (Anthony and Graham, 1985; Filion et al., 1998; Alius et al., 2014; Benke et al., 2015). Interestingly, the inhibition of blink magnitudes was associated with a linear increase in heart rate, replicating previous research (Löw et al., 2008; Löw et al., 2015). According to the cardiac-somatic coupling hypothesis (Obrist, 1981), we interpret the strong increase in autonomic arousal as a preparation for an effective motor response during defensive action.

In contrast to the matched control interval, the P3 component to probes presented prior to the first premature termination was significantly reduced. A similar attenuation of probe-evoked P3 amplitudes has been observed in picture viewing paradigms where affective foreground stimuli capture attentional resources thus limiting resources available for processing of the startle probe (Schupp et al., 1997; Cuthbert et al., 1998). Moreover, this pattern has also been described during exposure to interoceptive threat (Alius et al., 2014), unpredictable as well as predictable threat (Nelson et al., 2015) or while individuals were preparing for a motor response to actively avoid presentation of a threat (Löw et al., 2015). Thus, during the preparation of active avoidance attentional resources to the irrelevant acoustic stimuli are blocked and may be allocated to the interoceptive threat stimuli (including dyspnea and autonomic symptoms) to promote initiation of effective avoidance.

4.2. Defensive behavior during repeated terminations of interoceptive threat

With increasing repetitions of terminations, participants terminated the exposure sequences at successively lower threat levels (i.e., already during lower intensities of inspiratory resistive loads), avoiding the occurrence of the ultimate threat (i.e., the complete breathing occlusion). This change in defensive behavior is similarly observed in animal as well as in human avoidance learning experiments (Solomon and Wynne, 1953, 1954; Krypotos et al., 2014). From a learning perspective, one could argue that increasing dyspnea possibly became an indicator of the occurrence of the complete breathing occlusion and thus defensive action was initiated already at lower intensities of dyspnea to prevent the further increases in dyspnea (Lovibond, 2006; Pappens et al., 2012).

According to the two-factor theory postulated by Mowrer (1939), terminations of stimuli predicting imminent danger are negatively reinforced by the reduction of the conditioned fear response, which in turn would lead to the maintenance of the avoidance behavior (Mowrer and Lamoreaux, 1946; Mowrer, 1951). Based on this theory, several animal and human studies have investigated whether avoidance behavior is motivated by fear. In a line of influential studies, dogs learned to avoid shocks, however, no signs of fear (e.g., defecation, pupillary dilatation, suppression of operant appetitive behavior) were observed while avoidance behavior was maintained (Solomon et al., 1953; Solomon and Wynne, 1954; Kamin et al., 1963; Starr and Mineka, 1977; Mineka and Gino, 1980). Similarly, signs of fear were absent in humans who learned to effectively avoid a shock (Lovibond et al., 2008; Delgado et al., 2009; Lovibond et al., 2009; Vervliet and Indekeu, 2015). The present study extended these findings for spontaneously occurring avoidance behavior that was initiated by strong indices of fear but was maintained in the absence of any indices for physiological arousal.

The current data support previous data suggesting that fear responses might be an important motivator for the initiation of avoidance while alternative processes might be involved in the maintenance of avoidance behavior (for review see Krypotos et al., 2015). For example, cognitive (expectancy) accounts of avoidance learning stressed that

propositional knowledge is acquired about the presentation or omission of an aversive stimulus if no action is emitted or an avoidance response is performed (Seligman and Johnston, 1973; Lovibond, 2006). The present results are in line with these accounts predicting a reduction in fear once the expectancy of experiencing a breathing occlusion decreases after successful initiation of avoidance behavior (Lovibond et al., 2008). Following this perspective, persistent avoidance behavior is maintained – without any signs of fear - as individuals do not experience a disconfirmation of their expectancies regarding the presentation of the threat if no avoidance response is performed (Lovibond, 2006).

More importantly, Solomon et al. (1953) reported that the avoidance behavior of dogs was not only persistent but also became stereotyped, i.e., the behavior was performed in a habitual way. Interestingly, the chronic and repetitive avoidance behavior in patients with anxiety disorders, which is commonly performed in an inflexible and automatic rather than in a goal-directed way often resembles such stereotypical behaviors. Thus, avoidance behavior might be rather conceptualized as a (stimulus-driven) habit (Gillan et al., 2016c) than as a fear motivated behavior. This might explain why avoidance behavior persists while the reinforcing qualities of the response outcome (e.g., fear reduction) diminish. Most importantly, it has been suggested that the transition from defensive action to defensive habits is characterized by a shift in activated underlying neural circuits (LeDoux et al., 2016). This view is supported by experimental studies in humans showing that active avoidance is mediated by similar neural circuits involved in habit formation (e.g., the dorsal striatum) (Delgado et al., 2009; Schlund et al., 2013; Collins et al., 2014; Ilango et al., 2014).

It has been suggested that habit-like performances do not require planning or organization, thus demanding low processing capacity in contrast to goal-directed behavior (Evans and Stanovich, 2013; Wood and Runger, 2016). In contrast to the first termination, we did not find any reductions in the probe-evoked P3 amplitudes during the repeated terminations. This may indicate that later terminations did not require any reallocation of attentional resources. Instead, the motor avoidance responses might have been evoked rather automatically by the dyspnea signaling the upcoming occlusion not affecting attention to the acoustic probe stimuli. It is to note that formation of habit-like avoidance behavior not only evolve from extended training or repetitions of responses but might also result from dysfunctional goal-directed control over actions (Gillan et al., 2014; Gillan et al., 2015). In fact, this failure in goal-directed control may show early during avoidance learning as observed in the present study (Gillan et al., 2015).

The present data are also in line with cognitive accounts of avoidance learning supporting the view that less cortical processing resources are captured by avoidance performances once propositional knowledge about the relationship between the avoidance performance and the omission of an expected breathing occlusion is acquired (Lovibond, 2006). However, the rapid shift in attentional and startle response pattern might be mediated by decision-making processes. The decision to terminate exposure might initially depend on the appraisal of the increasing interoceptive threat which requires more cortical capacity for processing of the interoceptive threat cues. Once the decision was made to terminate subsequent exposures, the occurrence of the ultimate threat, i.e., a possible suffocation, would be definitively prevented. Thus, the appraisal and processing of interoceptive cues was no longer necessary. Moreover, as startle inhibition in rodents was only evident during cues associated with highly intense shocks (Walker et al., 1997; Walker and Davis, 1997) the observed startle inhibition might have disappeared once participants terminated the exposure sequence at lower threat intensities during repeated defensive actions.

4.3. Avoidance and self-reported anxiety

Although participants exhibited alleviated physiological arousal the retrospectively reported anxiety increased prior to repeated terminations and the overall anxiety level even increased upon subsequent terminations. An increase in the reported intensity of anxiety was also observed within and across matched control intervals of matched control persons. Thus, in both groups reported anxiety seemed to be associated with the expectations and therefore more related to the central concerns about what could ultimately happen than to the physiological arousal symptoms. This would explain why verbal reports and physiological or behavioral indices of fear are often discordant (Rachman and Hodgson, 1974; see Cook et al., 1988). From the viewpoint of a two-system framework of fear, it has been proposed that defensive responding and subjective feelings of fear and anxiety in the presence of threat were mediated by two different neural circuits (LeDoux and Pine, 2016). Thus, it becomes clear that defensive responding and reported feelings of fear diverge in the face of threat (LeDoux and Pine, 2016). Interestingly, the maximal reported anxiety was higher during initial termination trials compared to during control intervals in matched control persons.

4.4. Implications for exposure-based therapy

Exposure-based therapies aim at disconfirming patients' central concerns about the expected threat and establishing a new inhibitory learning association (e.g., dyspnea does not necessarily predict imminent suffocation) (Craske et al., 2006; Vervliet et al., 2013; Craske et al., 2014). This inhibitory learning process might be impaired by habit-like avoidance behaviors (Craske et al., 2008; Lovibond et al., 2009; Vervliet and Indekeu, 2015). However, it has been reported that the elimination of avoidance behavior is challenging in exposure therapy (Helbig-Lang and Petermann, 2010; Vervliet and Indekeu, 2015). Response prevention is typically recommended as an effective technique to mitigate avoidance behavior. However, avoidance behavior and threat beliefs often return after response prevention in the context of fear extinction training (Lange, 2016; Rodriguez-Romaguera et al., 2016; Lovibond et al., 2009; Bravo-Rivera et al., 2015; Vervliet and Indekeu, 2015).

For optimizing exposure the expectancy model of avoidance suggests to alleviate anxiety and avoidance by reducing the subjectively perceived costs of harmful outcomes (reinforcer devaluation) (Lovibond, 2006). However, since avoidance behaviors can be resistant to extinction, insensitive to reinforcer devaluation, inflexible and performed automatically (Gillan et al., 2016b; Gillan et al., 2016c; Wood and Runger, 2016), it might be helpful to initiate a shift from habit-like avoidance performances to goal-directed control (Quinn et al., 2010; Wood and Runger, 2016). As a first step, it could be useful to identify idiosyncratic habitual avoidance behaviors via behavioral experiments. To change habits, it has been demonstrated that the inhibition or control of habit responses might be facilitated by vigilant monitoring of responses (Quinn et al., 2010), forming implementation intentions (if-then plans) (Gollwitzer, 1999; Karsdorp et al., 2016), contexts change (Thrailkill and Bouton, 2015) or enacting actions oppositional to patients' fear action tendencies (Wolitzky and Telch, 2009). Implementing these techniques in exposure-based therapy might alleviate habit-based avoidance behaviors which in turn may facilitate inhibitory learning and prevent relapses. Of course, the effectiveness of the use of these interventions in exposures-based therapy warrants experimental proof.

4.5. Limitations

The current study aimed at examining dynamical changes of defensive response mobilization during repeated defensive action. Importantly, participants were not instructed to terminate exposures of increasing interoceptive threat but spontaneously expressed this response pattern. As a consequence, the presented analyses are based on a self-selected population, i.e., avoidance behavior was not experimentally varied and randomized within and across participants. This limits the interpretation of the data and thus the generalization of the results

in understanding the processes involved in avoidance learning. In future research, an experimentally-controlled design would help to resolve these limitations. Although defensive response mobilization changed even after a very few terminations, future research should consider to include more exposure trials to specifically investigate the formation of avoidance behavior. In contrast to previous studies investigating avoidance learning with exteroceptive stimuli (e.g., pictures, shocks), aversive interoceptive stimuli, i.e. different intensities of dyspnea, were used in the current experiment. Thus, the observed effects in the present study might be specific for avoidance learning by interoceptive threat and may not be generalized to avoidance behavior in the context of an exteroceptive threat. Future research should include both interoceptive and exteroceptive threats to reveal possible differences in defensive response mobilization during avoidance learning. In the current study, participants were matched for trait anxiety and thus did not differ in measured anxiety-related questionnaire data. However, it has been shown that individual differences including compulsive behavior and intrusive thoughts, neuroticism or distress tolerance affect avoidance learning or habit formation which might be responsible for avoidance behavior or the different response profiles in avoiders and matched controls in the present study (Lommen et al., 2010; Krypotos et al., 2015; Gillan et al., 2016a; Vervliet et al., 2017). Thus, future studies ought to include these specific factors to reveal possible individual differences.

5. Conclusion

In the present study, we observed naturally occurring repetitive terminations of exposure to increasing interoceptive threat in humans. The study design proved useful to assess changes in defensive response patterns preceding repeated terminations of threat. In contrast to commonly used paradigms investigating avoidance, the present results did not originate from a classical avoidance conditioning task with consecutive instructed avoidance but rather resulted from naturally occurring terminations in an ecologically valid and translational paradigm. In contrast to the initial defensive action which might be conceptualized as an escape response, subsequent defensive actions were performed at lower threat levels to prevent the occurrence of the ultimate threat. Persistent defensive actions were characterized by the absence of physiological arousal, elevated anxious apprehension and in comparison to the initial defensive action an increased availability of cortical processing capacity. The data support the view that fear might not be a primary motivator of avoidance behavior. In contrast, the present results support the view that avoidance behavior might be better conceived as a habit like behavior that, however, prevents violation of contingency expectancies that is important for extinction learning to occur. Further research should focus on the underlying mechanisms and the factors that possibly set the stage for developing habitual avoidance behavior. To foster our understanding of these processes and mechanisms the results need to be replicated in a larger sample as well as in patients with mental disorders (e.g., anxiety or pain disorder). We proposed techniques that might facilitate extinction of habitual avoidance, thus augmenting the effects of exposure-based therapy. However, the impact of these techniques in exposure therapy warrants experimental proof.

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The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2017.09.013.

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Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat

Supplemental materials

Supplemental results

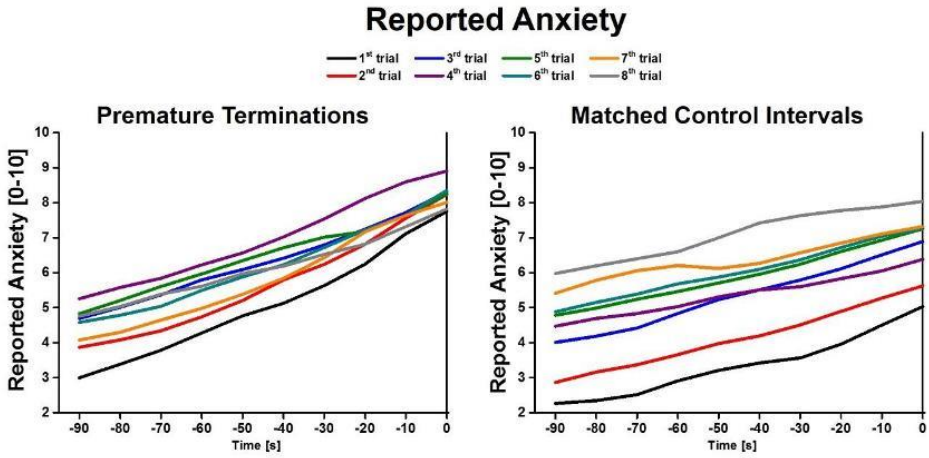

Fig. S1. Means of the reported anxiety during the 90s prior to terminations of increasing interoceptive threat (left panel) and during matched control intervals in matched controls (right panel).

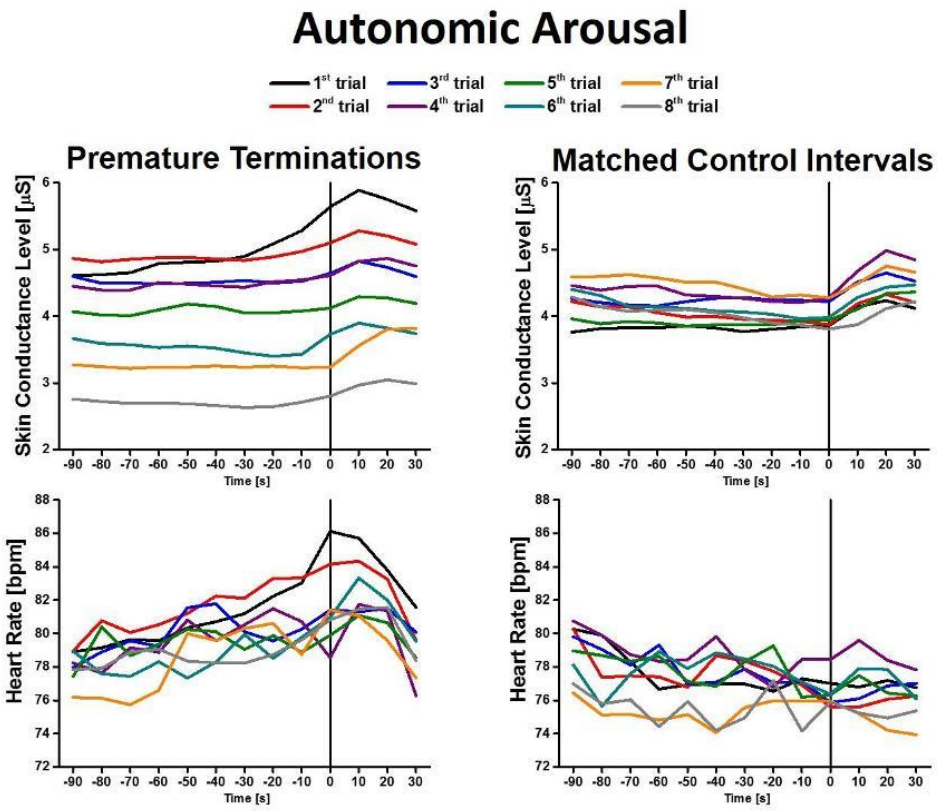

Fig. S2. Changes in autonomic arousal during terminations (left panel) or matched control trials (right panel). Mean skin conductance level (upper panel) and heart rate (lower panel) 90s before, during, and 30s after the button press.

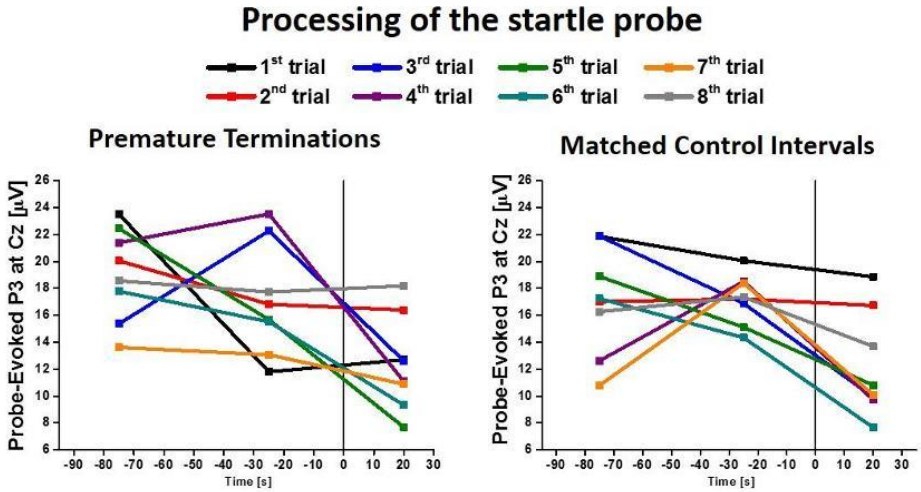

Fig. S3. Event-related potentials evoked by startle probes distal and proximal to the button press during terminations of exposure (left panel) or matched control intervals (right panel).

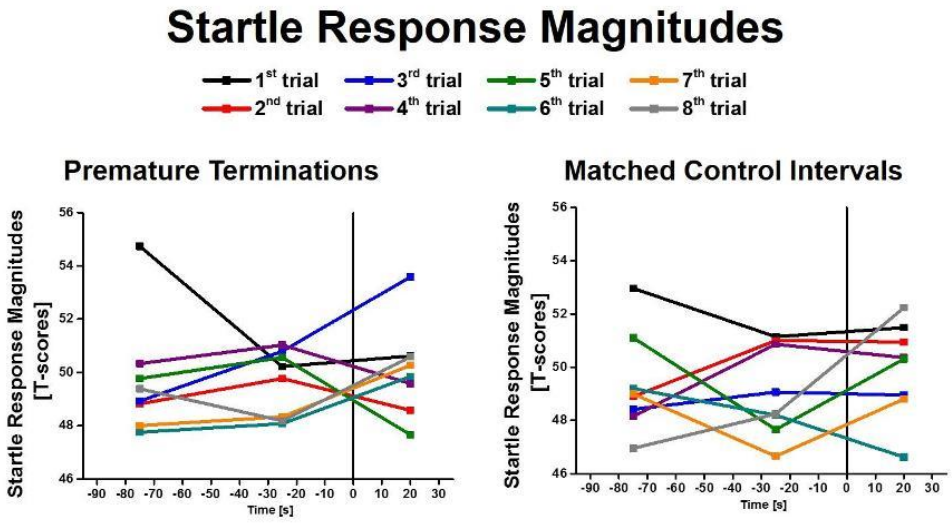

Fig. S4. Startles response magnitudes distal (responses to three startle probes) and proximal (responses to three startle probes) to premature terminations of exposure by button press (left panel). Startle response magnitudes during matched control trials in matched controls (right panel)

Publication 3

Hold your breath: voluntary breath-holding time predicts defensive activation to approaching internal threat.

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Under review

Author contributions:

CPF, AOH, CB and EK designed the experiment. EK supervised the data acquisition. EK analyzed the data with help from CB and EK provided the first draft of the manuscript. All authors contributed to the interpretation of the data and wrote the manuscript.

Title

Hold your breath: voluntary breath-holding time predicts defensive activation to approaching internal threat

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Keywords: defense cascade, fear, panic disorder, startle, breath-holding

Abstract

Bodily disturbances, like dyspnea, elicit adaptive responses to regain homeostasis and ensure survival. However, this life-saving function can become dysregulated when it is initiated at low intensity or large distance of respiratory threats, which may lead to the emergence of psychopathology. This study investigated whether voluntary maximal breath-holding time, a biobehavioral marker that characterizes sensitivity to respiratory stimulation, predicts defensive mobilization to an approaching mild electric shock vs. an approaching respiratory threat (induction of a feeling of shortness of breath by forced breath-holding) in 60 healthy participants. While the startle reflex, a brainstem measure of defensive mobilization, generally increased with the proximity of threat, shorter breath-holding time was specifically associated with greater startle potentiation when anticipating an approaching respiratory threat but not an electric shock. This study suggests that breath-holding time is a specific predictor for a hypersensitive responding to an approaching respiratory threat.

1. Introduction

Respiratory sensations of severe dyspnea (breathlessness, air hunger) elicit adaptive defensive behaviors to ensure survival (Strigo & Craig, 2016). However, these adaptive responses to dyspnea may become dysregulated, with even benign respiratory signals being perceived as a potential threat and thus leading to defensive mobilization that exceed situational demands (Hamm, Richter, & Pané-Farré, 2014), i.e., excessive fear, anxiety, and avoidance (Barlow, 2002; Craske & Barlow, 1988; Craske, Rapee, & Barlow, 1988; Hamm et al., 2014) or even panic and hyperventilation (Klein, 1993; Preter & Klein, 2008). Defensive mobilization may occur with direct perception of air hunger, i.e., with imminent threat, but also during anticipation of possible confrontation with the feared body sensations (Benke, Alius, Hamm, & Pané-Farré, 2018; Krause et al., 2017), i.e., when the threat is still distant.

Defensive responses for external threats are well described, as they dynamically cascade with increasing proximity of the threat (Fanselow, 1994; Lang, Bradley, & Cuthbert, 1997). Thus, when a threat is expected, but has not been detected yet, preemptive behavior along with threat-nonspecific vigilance is engaged. As soon as a threat is encountered, selective attention is allocated to the potential threat and the organism freezes. When the threat is most imminent or about to strike, defensive responses abruptly switch to overt fight-or-flight behavior. Typically, the perceived threat proximity depends upon the temporal or spatial distance of the threat, or the probability of its strike. Furthermore, for interoceptive threats, it has been proposed that the intensity of internal symptoms may be the indicator for the proximity of the threat (Hamm et al., 2014). Additionally, there is first indication (Alius, Pané-Farré, Löw, & Hamm, 2015; Benke, Hamm, & Pané-Farré, 2017; Krause et al., 2017) that the cascade of defensive mobilization is expressed similarly as for external threats.

Dysfunctional defensive mobilization is characterized by a mismatch of threat proximity and the initiated defensive response, i.e., intense defensive mobilization or imminent threat programs are initiated already at low intensity and greater distance of threat, along with dysregulated activation of brain's survival circuits (Lang, McTeague, & Bradley, 2014; Young & Craske, 2018). Moreover, excessive defensive mobilization to dyspneic sensations or

associated cues and contexts has frequently been described for persons suffering from cardiopulmonary diseases (e.g., asthma, COPD) or anxiety disorders (e.g., panic disorder (PD); American Psychiatric Association, 2013), and is known to cause great individual suffering and high socio-economic costs (Barlow, 2002; Carr, 1999; Dalal, Shah, Lunacsek, & Hanania, 2011).

Recent experimental studies in rodents and humans have helped to shed light on the brain circuits being implicated in defensive response mobilization to such respiratory threat or interoceptive signals and contextual cues that signal the possible occurrence of respiratory threat (Faull, Jenkinson, Ezra, & Pattinson, 2016; Faull, Subramanian, Ezra, & Pattinson, 2019; Holtz, Pané-Farré, Wendt, Lotze, & Hamm, 2012; Schimitel et al., 2012; Schimitel, Müller, Tufik, & Schenberg, 2014; Stoeckel et al., 2015). These studies highlight the pivotal role of the periaqueductal gray (PAG) in integrating physiological (e.g., CO_2 levels) and cortical input for orchestrating adaptive breathing mobilization (e.g., an increase in minute ventilation) and a variety of defensive behaviors in response to respiratory threats (Faull et al., 2016; Faull et al., 2019; Faull & Pattinson, 2017; Schimitel et al., 2012). Importantly, the PAG has been suggested to involve a suffocation alarm system that continuously monitors CO_2 levels (Schimitel et al., 2012). Klein (1993) proposed that a misfiring of this suffocation alarm system results in excessive defensive mobilization, i.e., hyperventilation (respiratory mobilization, indexed by increased minute ventilation that exceed respiratory demands) and panic, in case of circa-strike defense (Hamm et al., 2014; Richter et al., 2012). According to Klein's false suffocation alarm theory (Klein, 1993; Preter & Klein, 2008), individuals with pathological panic might have an increased CO_2 sensitivity that triggers a suffocation alarm and thus elicits defensive mobilization at lower intensity or greater distance of respiratory threat, which is in line with the assumption of dysfunctional defensive mobilization outlined above.

To assess CO_2 sensitivity in humans, in previous studies, a breath-holding test was used in which participants are asked to hold their breath as long as possible (Asmundson & Stein, 1994; McNally & Eke, 1996). As breath-holing leads to the accumulation of endogenous CO_2, voluntary breath-holding time (BHT) was introduced as a biological marker for the (in)tolerance

toward increasing levels of endogenous CO_2 (Asmundson & Stein, 1994; Masdrakis, Markianos, Vaidakis, Papakostas, & Oulis, 2009; McNally & Eke, 1996). In line with the false suffocation alarm theory (Klein, 1993), it has been demonstrated that persons with PD have lower BHT than healthy controls (Asmundson & Stein, 1994; Zandbergen, Strahm, Pols, & Griez, 1992), and reported more frequent panic attacks after breath-holding than patients with other anxiety disorders (Nardi et al., 2003). Moreover, lower BHT in PD is associated with a higher frequency of panic attacks during related respiratory challenges (Masdrakis et al., 2009). Most importantly, it was repeatedly demonstrated that lower BHT is a strong predictor of self-reported anxiety and avoidance behavior during respiratory challenges in healthy individuals (Benke, Krause, Hamm, & Pané-Farré, 2019; Eke & McNally, 1996; McNally & Eke, 1996; Rassovsky, Kushner, Schwarze, & Wangensteen, 2000). In view of this evidence, BHT might be a potential biological marker of dysfunctions in the suffocation alarm monitor that may manifest in defensive response mobilization to respiratory threat, thereby increasing the risk to develop panic and anxiety pathologies. Thus, BHT might be an important marker to identify individuals at risk to show increased defensive mobilization, i.e., anxiety or avoidance, during situations that signal the upcoming occurrence of respiratory sensations. These persons could be targeted in early intervention studies to prevent emergence of clinically relevant fear and anxiety. Therefore, the present study is aimed at examining the role of voluntary BHT, as a potential marker of dysfunctions in the suffocation alarm monitor, in defensive response mobilization to early indicators of upcoming respiratory threat.

In order to elucidate the role of maximal voluntary BHT capacity for defensive mobilization as an index for a (hyper-)sensitive suffocation alarm monitor, we used in the present study an instructed fear paradigm (Krause et al., 2017) that allowed to investigate defensive mobilization dependent on the proximity (distant to imminent) of respiratory threat and the behavioral repertoire at hand, i.e., whether threat could be avoided by a fast button press (active condition) or not (passive condition). Different geometric symbols were used which successively increased in size, thus indicating the proximity of the respiratory threat. In the present study, we used a forced breath-holding task as a respiratory threat – forcing the participant to hold

their breath by occluding the inspiratory port of an attached face mask, leading to the accumulation of endogenous CO_2 along with unpleasant respiratory symptoms. It has been demonstrated that forced breath-holding reliably induces respiratory symptoms and leads to a strong defensive mobilization (Benke et al., 2017; Krause et al., 2017; Pappens et al., 2014; Pappens, Smets, Vansteenwegen, Van den Bergh, & Van Diest, 2012). Based upon Klein's suffocation alarm theory (Klein, 1993; Preter & Klein, 2008), we hypothesized that an oversensitive suffocation alarm monitor as indicated by a greater CO_2 sensitivity will specifically manifest in defensive mobilization to cues signaling an approaching respiratory threat, i.e., a suffocation episode. To examine the specificity of this effect, we compared the defensive mobilization to a respiratory challenge (i.e., respiratory occlusion resulting in air hunger) with the dynamics of defensive mobilization to an approaching external threat (a mild pain stimulus to the forearm, i.e., an electric shock). Defensive response mobilization was indexed by the potentiation of the startle eyeblink reflex – a cross-species readout of activity of the defensive brain network centered on the amygdala (Davis, 2006; Hamm, 2015; Kuhn et al., 2020). Using this and related designs, previous studies demonstrated an increasing potentiation of startle reflex with increasing proximity of an inevitable respiratory threat as well as for approaching threat of shock (Krause et al., 2017; Löw, Weymar, & Hamm, 2015; Wendt, Löw, Weymar, Lotze, & Hamm, 2017).

Based on previous findings (Krause et al., 2017; Löw et al., 2015; Melzig, Michalowski, Holtz, & Hamm, 2008; Wendt et al., 2017), we expected an increasing defensive mobilization to an approaching inevitable threat of shock for all participants, indicated by a potentiation of startle reflex with increasing threat proximity. In line with Klein's false suffocation alarm theory and previous evidence that demonstrated that shorter BHT is related to anxious responding to respiratory symptom provocations (e.g. Benke et al., 2019; Eke and McNally, 1996; McNally and Eke, 1996; Rassovsky et al., 2000; Masdrakis et al., 2009; Asmundson and Stein, 1994), we expected that shorter maximal voluntary breath-holding time (mvBHT) would be associated with stronger startle reflex potentiation for an approaching inevitable respiratory threat, i.e., participants with longer maximal voluntary breath-holding time would show less defensive

response activation in this context. Moreover, in accordance with our previous findings (Krause et al., 2017), we expected that minute ventilation (an index of respiratory mobilization) will initially show a greater increase for an inevitable respiratory threat than for an inevitable shock or passive safe. Following the rational stated above, we expect this effect to be more accentuated in persons with shorter mvBHT.

In contrast, when participants are given the opportunity to actively avoid any threat delivery, defensive reflexes should be comparably inhibited across threats - a pattern repeatedly observed when individuals are required to generate active responses to avoid threat delivery (Benke, Krause, Hamm, & Pané-Farré, 2018; Krause et al., 2017; Löw et al., 2015; Löw, Lang, Smith, & Bradley, 2008; Wendt et al., 2017). As this inhibition is supposed to be driven by a switch from forebrain to midbrain activation (Wendt et al., 2017), where the dorsolateral PAG is mediating active responses (such as fight/flight) for internal and external threats (Benarroch, 2012; Fanselow, 1991, 1994; Faull et al., 2019; Faull & Pattinson, 2017; Walker, Cassella, Lee, Lima, & Davis, 1997), we would expect that mvBHT will not affect this attention-driven inhibition of the startle response. Moreover, in accordance with Krause et al. (2017), we expected a stronger reduction in minute ventilation for the respiratory threat, while respiratory dynamics for shock and safe are assumed to be comparable. Additionally, in line with Klein's suffocation alarm system (Klein, 1993; Preter & Klein, 2008) we would expect that minute ventilation will not be affected by mvBHT as the suffocation alarm monitor only triggers an alarm to an inevitable respiratory threat to initiate escape.

Based on our previous study (Krause et al., 2017), we expected higher subjective fear ratings for the breath-holding than for the shock condition at the beginning of the experiment, while these differences between threats are expected to diminish with repeated confrontations with threats. Given that, in previous studies, individuals at-risk for PD and patients with PD did not show higher panic or fear ratings during anticipation of threat as compared to non-fearful healthy controls (Grillon et al., 2008; Melzig et al., 2008), it was predicted that fear ratings will not be modulated by mvBHT.

2. Methods

2.1. Participants

Participants were recruited from a subject pool of over 500 students at the University of Greifswald, Germany. Exclusion criteria were cardiovascular, neurological (e.g., epileptic or apoplectic seizures, multiple sclerosis), or respiratory diseases (e.g., asthma, COPD), mental health problems (e.g., any treatment related to psychological problems), hearing impairment, or pregnancy as reported during a telephone screening. All participants provided written informed consent to the study and received either payment (25 €) or course credit for study participation. Overall, 65 Caucasian participants took part in the laboratory assessment. Five participants were excluded from analyses due to premature termination of the experiment (n = 3), noncompliance with the experimental procedure (n = 1) or due to extreme upward outlier status in determined voluntary breath-holding time (n = 1). The final sample consisted of 60 students (30 women; age M[SD] = 22.9[3.6] years) and was characterized by typical scores for students in the State-Trait Anxiety Inventory (STAI; $M[SD]_{trait\text{-}anxiety}$ = 40.08[7.89]), the Claustrophobia Questionnaire (CLQ; $M[SD]_{total}$ = 22.12[11.97]; $M[SD]_{Restriction}$ = 12.98[8.04]; $M[SD]_{Suffocation\ Fear}$ = 9.13[6.28]), and the Anxiety Sensitivity Index (ASI–3; M[SD] = 20.33[11.12]). The research protocol was approved by the ethics committee of the German Psychological Society.

2.2. Materials, Tasks, and Procedure

Forced breath-holding. Participants were breathing through a tightly fitting soft silicone face mask (7400 series; Hans Rudolph, Inc., Kansas City, MO) that was connected via a short plastic tube (length = 25.4 cm; diameter = 35 mm) to a respiratory flow sensor. The sensor was mounted to the mouth port of a two-way y-shaped non-rebreathing valve (no. 2630; Hans Rudolph, Inc.). The expiratory port of the y-valve was left open to enable unrestricted expiration. The inspiratory port was connected via a plastic tube (length = 2.75 m, diameter = 35 mm) to the common port of a Five-Way Gatlin-Shape™ valve (no. 2440; Hans Rudolph, Inc.), placed in the adjacent control room. The four valve ports could be simultaneously closed with an Inflatable-Balloon-Type™ controller (no. 2430; Hans Rudolph, Inc.) via VPM software

(Cook, 1987) to fully block inspiration and force the participant to hold their breath (for previous applications of this breath-holding procedure see Benke et al. (2017) and Krause et al. (2017)).

To individually determine maximal voluntary post-expiratory breath-holding time (mvBHT in seconds) participants were asked to hold their breath as long as possible in four consecutive trials separated by recovery periods. Each breath-holding trial was manually started by the experimenter at the end of an expiration and signaled by a visual cue. To assure adherence to the breath-holding procedure the inspiratory port of the breathing valve was closed during breath-holding and immediately reopened when the participant pressed a computer keyboard button to signal the end of breath-holding capacity. In compliance with standard procedure (Krause et al., 2017; Pappens et al., 2012) the BHT used during the latter forced breath-holding task was set to 40% of the individually determined mvBHT (M[SD] for mvBHT in the present sample = 33.71[14.6]) with a minimum criterion of 15 seconds. In result, the mean forced BHT applied in the present study was 16.93 [SD = 5.00] seconds. Furthermore, the individually determined mvBHT was later used as a continuous predictor for defensive mobilization in the statistical analyses.

Electric shock. The electric shock (a 1 ms pulse of electrotactile stimulation), generated by a commercial stimulator (S48K; Grass Instruments, West Warwick, RI), was transmitted via a constant current unit (CCU1, Grass Instruments) to a bipolar electrode attached to the participant's left inner forearm. Using a standard procedure (Hamm & Vaitl, 1996; Krause et al., 2017), the intensity of the stimulation was individually adjusted to be "highly annoying but not painful". The average shock intensity in the present sample was 8.95 mA (SD = 6.34).

Experimental procedure. We used an instructed fear paradigm (Krause et al., 2017; Löw et al., 2015), where each trial (10s) consisted of a cascade of five looming stages (see **Figure 1**). During each of the five looming stages, a colored frame was presented (500 ms) and followed by a symbol (e.g., circle, star, or triangle) presented in the center of the frame (1500 ms). The symbols successively increased in size with each stage to create an impression of approach. The symbols signaled, whether the cascade would potentially end with a forced breath-holding task, an aversive electric shock, or no aversive stimulation (safe). The color of

the frame (blue or yellow; combinations of symbols and frames balanced out across participants) indicated, if a threat could be avoided by a fast button press (active/avoidable condition) or not (passive/inevitable condition). The initial time window for successful active avoidance of threat delivery was set to 240 ms and dynamically adjusted during the experiment to reach a target threat delivery rate of 50 % of trials for breath-holds and shocks, separately. In the passive/inevitable conditions, threats were delivered in 50 % of the trials. Successful avoidance was signaled by visual feedback 500 ms after the offset of the symbol, otherwise, the breath-holding was manually set at the end of the first expiration and the electric shock was delivered 500 ms after the offset of the corresponding symbol. The button press in the active safe condition had no consequences, but participants were instructed to respond as fast as possible. The six resulting experimental conditions (inevitable vs. avoidable shock; inevitable vs. avoidable forced breath-holding; passive vs. active safe) were presented twenty times each in two pseudorandomized orders with a variable intertrial interval (ITI) of 5 to 7 seconds between trials. Each breath-holding period was followed by a 30-second recovery phase to ensure adequate respiratory recovery. Further details on the general procedure and startle probes are provided in the supplement.

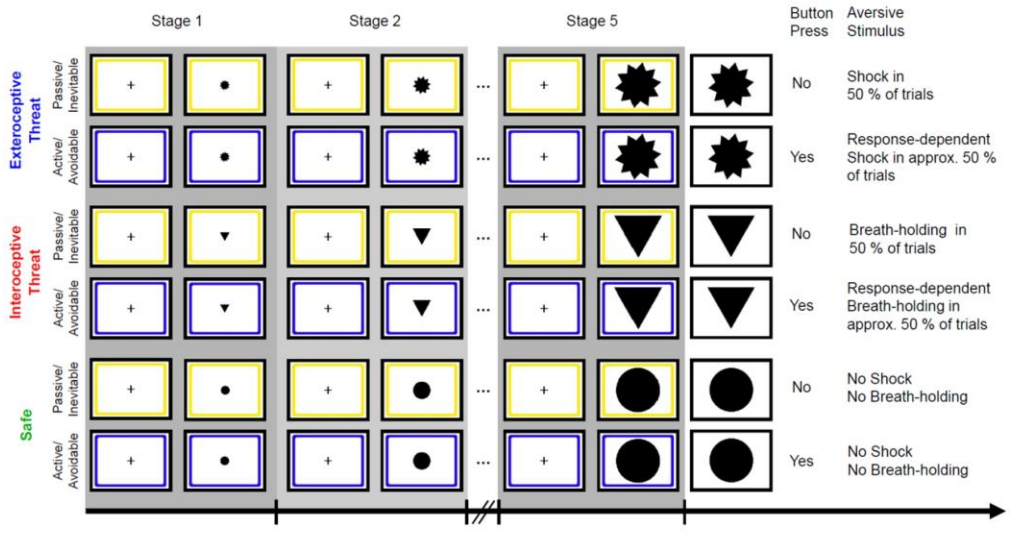

Figure 1 –Illustration of experimental design.

263 **2.3. Data Acquisition and Response Definition**

264 Please, see supplement for data acquisition and response definition.

265 **2.4. Data Analyses**

266 Physiological data were analyzed separately for inevitable and avoidable[1] threats using
267 mixed regression models, including the repeated-measures factors *threat* (forced breath-
268 holding vs. shock vs. safe) and *time* (5 data points for the startle reflex; five 2-second bins for
269 minute ventilation), and the between-subject continuous predictor *mvBHT*, as well as their
270 interactions. Fear ratings[1] were analyzed including the repeated-measures factors *threat* and
271 *time* (pre-experiment vs. 30th trial vs. 60th trial vs. 90th trial vs. post-experiment) and the
272 between-subject continuous predictor *mvBHT*, as well as their interactions. The mvBHT data
273 were transformed using the natural logarithm to ensure normal distribution. In correspondence
274 with startle data, for analyses of minute ventilation the first 10 seconds of each trial were used.

275 For all mixed regression models, the random part of the models included a person-specific
276 intercept and repeated-measures effects for threat and time with a first-order autoregressive
277 covariance structure (heterogeneous variances and correlations that decline with time). If no
278 significant main or interactive effects with *mvBHT* were found, the predictor was removed from
279 the model to increase model fit. To probe significant interactions including the continuous
280 between-subject predictor mvBHT, participants were split into two groups using median split
281 of mvBHT and analyses mentioned above were run in persons with short and long mvBHT.
282 Overall, statistical tests used a significance level of $p<.05$.

[1] Results are presented and discussed in the supplement.

3. Results

Defensive Activation to Approaching Inevitable Threats

Defensive reflex mobilization. Startle reflex magnitudes changed dynamically for any approaching inevitable threat and this pattern was differentially modulated by mvBHT, $F(8,173.13)_{\text{Threat X Time X mvBHT}} = 2.37$, $p = .019$. As expected, with approaching inevitable shock, startle reflex magnitudes continuously increased as compared to the safe condition, $F(4,130.16)_{\text{Threat X Time}} = 3.26$, $p = .014$. MvBHT did not affect this observed pattern of increasing startle potentiation, $F(4,130.16)_{\text{Threat X Time X mvBHT}} = 1.98$, $p = .101$. In contrast, startle reflex potentiation during approaching inevitable forced breath-holding was modulated by mvBHT, $F(4,180.86)_{\text{Threat X Time X mvBHT}} = 3.06$, $p = .018$.

The significant interaction with the continuous between-subject factor mvBHT was probed by testing the main and interactive effects within persons with shorter vs. longer mvBHT. As depicted in **Figure 2**, for participants with shorter mvBHT startle response magnitudes continuously increased with approaching inevitable forced breath-holding as compared to the safe condition, $F(4,82.45)_{\text{Threat X Time}} = 7.14$, $p < .001$. In contrast, participants with long mvBHT showed no potentiation of the startle reflex magnitudes for approaching forced breath-holding as compared to the safe condition, $F(4,92.41)_{\text{Threat X Time}} = 1.35$, $p = .258$, $F(1,22)_{\text{threat}} < 1$.

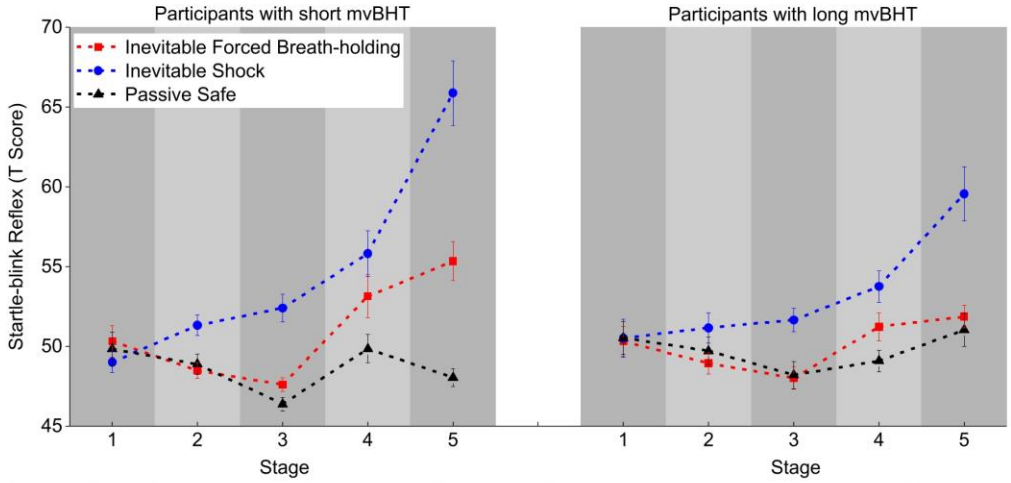

Figure 2. Defensive activation as a function of threat imminence and type of threat in participants with short (left panel) and long mvBHT (right panel). *Note*: mvBHT: Maximal voluntary breath-holding time (seconds).

Changes in respiration. Minute ventilation changed dynamically (see **Figure 3**) with increasing threat proximity depending on the type of threat as well as mvBHT, $F(8,191.84)_{\text{Threat X Time X mvBHT}} = 2.65$, $p = .009$.

With increasing proximity of expected forced breath-holding, minute ventilation initially increased compared to passive safe and then decreased towards the end of the looming sequence, $F(4,91.11)_{\text{Threat X Time}} = 17.36$, $p < .001$. This dynamic pattern of minute ventilation to approaching forced breath-holding was observed in both groups, short mvBHT: $F(4, 138.54)_{\text{Threat X Time}} = 8.6$, $p < .001$, long mvBHT: $F(4,49.69)_{\text{Threat X Time}} = 10.93$, $p < .001$.

In contrast to approaching forced breath-holding, minute ventilation only slightly increased at early stages of the looming sequence indicating approaching shock and decreased towards the anticipated shock delivery time compared to passive safe, $F(4,83.97)_{\text{Threat X Time}} = 6.38$, $p < .001$. Again, this pattern was observed in both groups, short mvBHT: $F(4, 90.06)_{\text{Threat X Time}} = 3.94$, $p = .005$, long mvBHT: $F(4,66.6)_{\text{Threat X Time}} = 4.58$, $p = .003$.

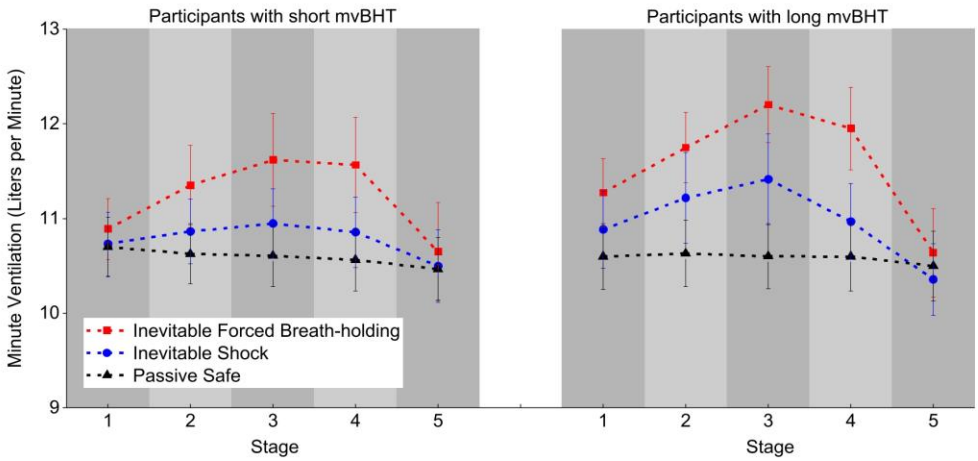

Figure 3. Respiratory mobilization as a function of threat imminence and type of threat in participants with short (left panel) and long mvBHT (right panel). *Note*: mvBHT: Maximal voluntary breath-holding time (seconds).

4. Discussion

The present study replicates previous findings (Krause et al., 2017) that defensive response mobilization changes dynamically with increasing proximity of approaching threat, irrespective of its character (shock vs. respiratory threat) and the behavioral repertoire at hand. However, the findings of the present study indicate that defensive response mobilization as indexed by the amygdala-dependent startle response potentiation to an inevitable respiratory threat but not to a threat of shock was dependent upon the voluntary breath-holding capacity of the participants. That is, those participants with shorter mvBHT, i.e., those with a low tolerance toward increasing levels of endogenous CO_2 (see Asmundson and Stein, 1994; Masdrakis et al., 2009; McNally and Eke, 1996), showed an elevated defensive response mobilization with the approaching inevitable respiratory threat. As expected, mvBHT had no effect on the dynamics of ventilatory responses to approaching threat or subjective fear ratings.

Inevitable Threat

Our data are in line with our hypothesis that persons with a more sensitive suffocation alarm system (Klein, 1993; Preter & Klein, 2008), as indicated by low tolerance to a breath-holding task, already elicit elevated defensive mobilization to cues signaling upcoming harmless respiratory distress. Interestingly, the same pattern of dysfunctional defensive mobilization has previously been demonstrated during anticipation of a respiratory threat in persons who fear body symptoms and patients with PD (Benke, Alius, Hamm, & Pané-Farré, submitted; Melzig et al., 2008). It is proposed that patients with PD have an oversensitive suffocation alarm system which is assumed to be responsible for this dysfunctional defensive mobilization to respiratory threat. Together with evidence that demonstrated that lower mvBHT is related to more anxious apprehension and avoidance behavior to actually harmless interoceptive sensations (Benke et al., 2019), the present results substantiate the assumption that lower breath-holding time might be an etiological relevant factor that might contribute the development and maintenance of panic pathologies. This needs to be further investigated using appropriate research designs.

Moreover, highlighting the specificity of the predictor mvBHT for defensive response mobilization to a respiratory threat, we observed the defensive pattern of increasing startle potentiation to an approaching inevitable electric shock irrespective of mvBHT. This is in line with previous findings (Krause et al., 2017; Löw et al., 2015; Wendt et al., 2017) and especially with our expectation, that a hypersensitive suffocation alarm monitor would specifically modulate the activation of the defensive system to a respiratory threat, but not the pattern of defensive response mobilization to an approaching mild pain threat. Moreover, we replicated previous findings (Krause et al., 2017) of threat-specific respiratory mobilization to an approaching respiratory threat. This adaptive defensive response initially overcompensate the respiratory demands in order to prepare for a suffocation situation, but might make things worse when it is maintained for a longer period as it could lead to hyperventilation and thus to elicitation of increasing body symptoms (Gardner, 1996). However, and in contrast to our expectations, the defensive respiratory pattern was not modulated by mvBHT. This might be because physiological markers can be divergent and startle responses are very sensitive for group differences (for reviews see Grillon and Baas (2003) and Vaidyanathan, Patrick, and Cuthbert (2009)). Moreover, dynamic mobilization was only analyzed during threat anticipation. Therefore, in line with Klein (1993), the effect of defensive respiratory mobilization might be small in contrast to an actual confrontation, as the oversensitive suffocation alarm monitor might not be fully triggered. Thus, our findings suggest that an oversensitive suffocation alarm monitor during anticipation is rather linked to the mobilization of defensive brainstem reflexes.

Taken together, shorter mvBHT indicates a potential hypersensitive suffocation alarm monitor and therefore may reflect a vulnerability for the development of excessive fear and behavioral disturbances as the defensive system might overreact to harmless respiratory distress or even its anticipation. Moreover, the fearful anticipation of dyspnea and a potential harmful outcome (e.g., PA, possible suffocation, critical somatic state) might increase the tendency to avoid these unpleasant respiratory sensations (Benke et al., 2019, 2018; Reiss, 1991; Simon et al., 2006). Thereby, a spiral of decline can be initiated (e.g., progressively

reducing daily-life physical activities due to safety seeking behavior; Hayen, Herigstad, and Pattinson, 2013), which increases the risk for the emergence of anxiety-related disorders.

Limitations

Our results could be affected by controllability, as participants had the opportunity to terminate each forced breath-holding at any time, and the validity of the determination of mvBHT, as it could be influenced by various variables (e.g. experimenter effects, differences in expiratory reserve volume). Moreover, our sample consisted of healthy participants and therefore the generalization of the presented findings are limited. Thus, mvBHT as a risk factor for anxiety or somatic symptom related disorders should be tested in a clinical population or in a long-term study.

Implications and conclusion

The present study replicates previous findings that defensive response mobilization to an approaching external and respiratory threat changes comparably with increasing threat proximity and the behavioral repertoire at hand. Additionally, in the present study, we identified mvBHT as a specific marker for defensive response mobilization to an approaching, inevitable respiratory threat. The present findings deliver new insights about elevated defensive activation to an anticipated respiratory threat, which may originate in a hypersensitive suffocation alarm system. Thus, the misinterpretation of respiratory distress might be associated with higher risk for the emergence of anxiety-related disorders in healthy individuals and patients suffering from different respiratory diseases.

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Hold your breath: voluntary breath-holding time predicts defensive activation to approaching internal threat

Supplementary Material

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SUPPLEMENTARY METHODS

Materials, Tasks, and Procedure

Overall study procedure. First, all sensors were attached and the face mask tightly and comfortably fitted. Afterwards, shock intensity and breath-holding time were individually determined as described above. Then, each type of looming sequence was presented and explained once, followed by a second presentation of all conditions to verify the correct comprehension of the meaning of each symbol and frame color. Before the experimental procedure started, headphones were comfortably fitted and eight startle probes were delivered with a mean ITI of 9.1 s (5.8-14 s range) to reach a stable baseline level of startle response magnitudes. Then, the experimental assessment started as explained above.

Startle probes. A 50 ms burst of white noise (95dB, rise/fall time < 1ms) was used as a startle-eliciting stimulus throughout the experiment, which was delivered via headphones (AKG K-66). One startle probe was presented per 10 s looming/threat exposure sequence, either at stage 1, 2, 3, 4, or 5 (900 – 1200 ms after the onset of the corresponding symbol). Overall, four startle probes were delivered per stage and per condition, as well as 36 startle probes during ITIs (2000 – 2200 ms after ITI onset).

Data Acquisition and Response Definition

Defensive mobilization: Startle reflex. To measure the eye-blink component of the startle response, two electrolyte-filled (Hellige electrode cream) Ag/AgCl miniature surface electrodes (Sensormedics, Yorba Linda, CA) were placed over the left orbicularis oculi muscle to record electromyographic (EMG) activity using a Coulborn V75-01 amplifier. The signal was high-pass (30 Hz) and low-pass filtered (400 Hz). Digital sampling was realized with a 12-bit A/D converter at 1000 Hz, starting 100 ms before the onset of the acoustic startle stimulus and lasting 400 ms after the startle probe. The raw EMG signal was filtered off-line with a 60 Hz high-pass filter, rectified, and integrated with a time constant of 10 ms. Then, using a computer program (Globisch, Hamm, Schneider, & Vaitl, 1993) only blinks starting 20-100 ms after delivery of the startle probe and reaching their peak amplitude within 150 ms were scored as valid startle responses. If no blinks were detected, trials were scored as zero responses. Trials

with movement artifacts or excessive baseline activity were rejected and treated as missing values. As recommended by the guidelines for human startle eye-blink studies (Blumenthal et al., 2005), all raw magnitudes were transformed to T-scores (*M*=50, *SD*=10) to remove inter-individual variability not related to the experimental manipulation.

Respiratory mobilization: Minute ventilation. A modified ZAN 600 pneumotachograph (nSpire Health, Inc., Oberthulba, Germany) was used to continuously measure respiratory flow, mouth pressure, and fractional CO_2 (FCO_2). Additionally, two respiration belts (Respiband Plus, Cardinal Health, Germany) were placed over the thorax and the abdomen and were connected to an inductance plethysmograph system (Respitrace Q.D.C., SensorMedics, NewMedics GmbH, Öhringen, Germany) to visualize in- and expiration in real-time, to be able to manually set the respiratory occlusion at the end of expiration.

Respiration cycles (beginning and end of inspirations and expirations) were automatically detected using ANSLAB (Version 2.4 Autonomic Nervous System Laboratory Software, University of Basel), and, if necessary, manually corrected (e.g., for coughing). Afterwards, minute ventilation was calculated, exported in weighted 2s means, and averaged across conditions.

Fear ratings. Fear ratings were presented on the screen at the start of the experiment and then, every 30 trials. The participants were asked to rate their fear for both threats (breath-holding, shock) and safe conditions on a scale ranging from 1 (no fear) to 6 (maximum fear).

SUPPLEMENTARY RESULTS

Modulatory Effects of Active Avoidance

Defensive reflex mobilization. Startle responses also substantially changed with increasing proximity and the type of threat, $F(8,154.76)_{\text{Threat X Time}} = 4.16$, $p < .001$, when participants had the opportunity to actively avoid delivery of the threats.

Startle responses initially increased during both approaching threats compared to the safe condition, Shock: $F(3,128.97)_{\text{Threat X Time}} = 10.56$, $p < .001$, Forced breath-holding: $F(3,152.26)_{\text{Threat X Time}} = 3.72$, $p = .013$, and were strongly inhibited right before initiation of the button press that was performed to avoid threat delivery (see **Figure S1**), Shock: $F(1,82.3)_{\text{Threat X Time}} = 70.39$, $p = .008$, Forced breath-holding: $F(1,70.62)_{\text{Threat X Time}} = 14.61$, $p < .001$. The inhibition immediately before the active avoidance of the threat delivery was similar in magnitude for both threats, $F(1,59)_{\text{threat}} < 1$.

There were no significant interactive effects with the continuous predictor mvBHT, $F(8,153.66)_{\text{Threat X Time X mvBHT}} = 1.16$, $p = .327$, $F(2,76.39)_{\text{Threat X mvBHT}} = 1.24$, $p = .295$, $F(4,127.45)_{\text{Time X mvBHT}} = 1.07$, $p = .372$.

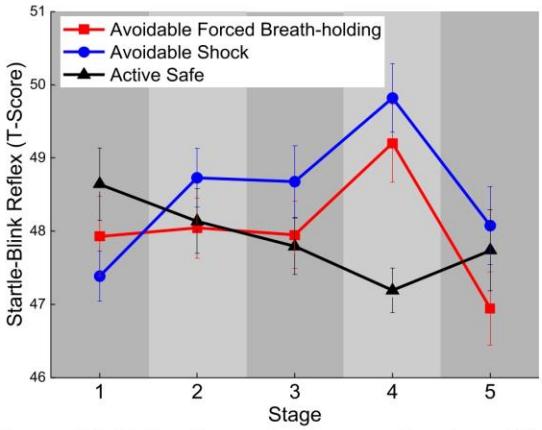

Figure S1. Defensive activation as a function of threat imminence and type of threat.

Respiratory mobilization. With the opportunity to avoid any threat delivery (see **Figure S2**), minute ventilation changed with increasing proximity and the type of threat, $F(8,339.91)_{\text{Threat X Time}} = 5.67$, $p < .001$.

Minute ventilation comparably decreased during increasing proximity of the button press performance during the avoidable shock and safe control condition, $F(4,171.1)_{time} = 30.19$, $p < .001$, $F(1,54.96)_{threat} < 1$, $F(4,197.8)_{Threat\ X\ Time} = 1.7$, $p = .152$. In contrast, there was a slight increase in minute ventilation during early stages of the avoidable forced breath-holding as compared to the active safe condition that was followed by a decrease in minute ventilation toward the timepoint of button press performance, $F(4,132.66)_{Threat\ X\ Time} = 12.24$, $p < .001$.

There were no significant interactive effects including the continuous predictor mvBHT, $F(8,150.46)_{Threat\ X\ Time\ X\ mvBHT} = 1.83$, $p = .076$.

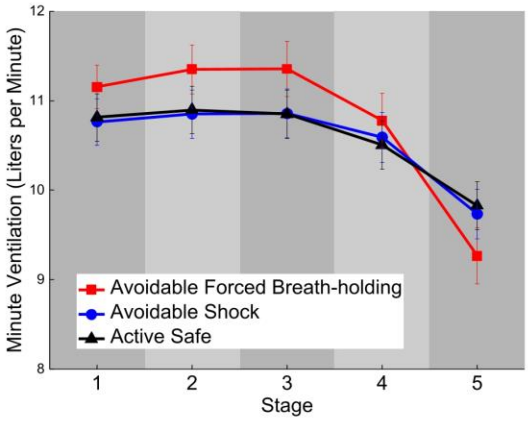

Figure S2. Respiratory mobilization as a function of threat imminence and type of threat.

Fear ratings. At the beginning of the experiment, subjective fear (see **Figure S3**) was rated higher for the breath-holding than for the shock condition and lowest for the safe condition, while there were no differences in fear ratings between both threat conditions at the end of the experiment, $F(8,240.81)_{Threat\ X\ Time} = 4.14$, $p < .001$. During the experiment, fear ratings decreased for the breath-holding condition only, $F(1,63.84)_{time} = 4.3$, $p = .004$, but not for the shock, $F(1,55.55)_{time} < 1$, or the safe condition, $F(1,554.16)_{time} < 1$. There were no significant interactive effects including the continuous predictor mvBHT, $F(8,134.99)_{Threat\ X\ Time\ X\ mvBHT} < 1$.

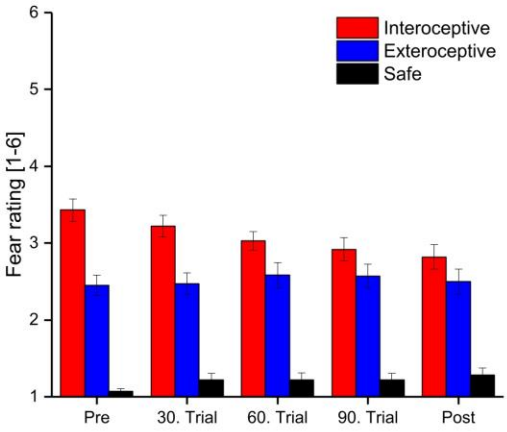

Figure S3. Fear Ratings over the course of the experiment.

SUPPLEMENTARY DISCUSSION

Active Avoidance

With the opportunity to actively avoid the threat delivery, the pattern of defensive mobilization changed substantially in both groups. Replicating and extending previous findings (Krause et al., 2017; Löw, Weymar, & Hamm, 2015; Wendt, Löw, Weymar, Lotze, & Hamm, 2017), blink reflex magnitudes were comparably inhibited when participants could avoid the respiratory or the external threat, while the defensive response pattern was not associated with mvBHT. This may have its origin in the general allocation of attentional resources to the preparation of the instructed button-press, reducing available resources for processing the auditory startle probe (Anthony & Graham, 1985; Cuthbert, Schupp, Bradley, McManis, & Lang, 1998; Filion, Dawson, & Schell, 1998). Besides, the changed pattern of defensive response mobilization might indicate a switch from attentive freezing to active avoidance – switching neural recruitment from ventrolateral to the dorsolateral part of the PAG (Benarroch, 2012; de Oca, DeCola, Maren, & Fanselow, 1998; Fanselow, 1991; Walker, Cassella, Lee, Lima, & Davis, 1997; Wendt et al., 2017). Additionally, the substantial change of defensive mobilization along with the missing association with mvBHT would be in accordance with Klein's suffocation alarm system (Klein, 1993; Preter & Klein, 2008), as the suffocation alarm monitor only triggers an alarm to a potential respiratory threat when it is inevitable in order to initiate defensive mobilization to escape. Again, this is in line with findings in patients with PD, showing an inhibition of the defensive response mobilization right before escaping entrapment (Richter et al., 2012).

Fear Ratings

In line with our assumption and our previous study (Krause et al., 2017), participants experienced more fear during the respiratory threat compared to the shock condition, while this difference in fear ratings between threats diminished with repeated confrontations with threats. In contrast to the observed effects on the low-level brainstem measure of fear, we found no modulating effects of mvBHT on subjective reports of fear, substantiating findings

during anticipation of threat in at-risk populations and PD patients (Grillon et al., 2008; Melzig, Michalowski, Holtz, & Hamm, 2008).

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Publication 4

Predictors of behavioral avoidance during respiratory symptom provocation

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CB, CFP and AOH designed the experiment. CB and EK supervised the data acquisition. CB analyzed the data and provided the first draft of the manuscript. All authors contributed to the interpretation of the data and wrote the manuscript.

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Predictors of behavioral avoidance during respiratory symptom provocation

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ABSTRACT

Excessive anxiety and avoidance during provocation of body symptoms are core features of anxiety-related disorders and might contribute to the development and maintenance of these disorders. Previous studies examined psychological (anxiety sensitivity, fear of suffocation and trait anxiety) and biobehavioral (breath-holding time) predictors of reported anxiety during symptom provocation. However, the role of these predictors on avoidance of feared body symptoms remains unclear. Therefore, the present work aimed at investigating the main and interactive effects of psychological and biobehavioral variables in predicting avoidance during provocation of dyspnea that successively increased in severity. 28 of 69 participants prematurely terminated the provocation sequence, thus preventing further progression of symptom provocation. Logistic regressions revealed that higher anxiety sensitivity and lower breath-holding time were significantly associated with avoidance during exposure. Suffocation fear and trait anxiety were not related to avoidance. Moreover, there was a significant interaction between breath-holding time and anxiety sensitivity in predicting avoidance. Participants with a lower breath-holding time showed more avoidance behavior when reporting high as compared to low anxiety sensitivity. The data suggest that anxiety sensitivity and breath-holding time increase the risk to show avoidance and thus might contribute to the development and maintenance of anxiety-related disorders.

1. Introduction

Health anxiety and various anxiety disorders including panic disorder (PD) are characterized by excessive anxiety and avoidance of feared bodily symptoms (American Psychiatric Association, 2013). Avoidance behavior as observed in these disorders is primarily aimed at alleviating feared bodily symptoms or preventing their occurrence or culmination, e.g., terminating physical activity or taking medication (Barlow, 2002). It has been demonstrated that excessive avoidance of physical activity and exertion impairs general functioning and results in decreased physical fitness and increased health problems (Broocks et al., 1997; Muotri & Bernik, 2014). While avoidance of feared body symptoms reduces the perceived risk to experience a feared event (e.g., a critical somatic state, possible suffocation or panic attack), it also prevents the disconfirmation of central concerns (e.g., possible suffocation) (Salkovskis, 1991). As such, avoidance of body symptoms is assumed to contribute to the development and maintenance of pathological anxiety of bodily symptoms. It becomes clear that avoidance of feared body symptoms should be targeted in prevention programs to reduce the risk for the emergence of anxiety-related disorders. To this end, it is crucial to - in a first step - identify those individuals from a nonclinical population who are at risk to initiate avoidance behavior when experiencing feared bodily symptoms.

It has been demonstrated that specific psychological self-report and biobehavioral variables predict inter-individual differences in anxious responding during exposure to feared bodily symptoms. In previous symptom provocation studies trait-like psychological variables such as anxiety sensitivity (AS) and fear of suffocation (SF) but not trait anxiety (TA) have been identified to specifically predict increased anxiety and symptom reports during exposure to feared bodily symptoms (Eifert, Zvolensky, Sorrell, Hopko, & Lejuez, 1999; Eke & McNally, 1996; McNally & Eke, 1996; Norton, Pidlubny, & Norton, 1999; Rapee & Medoro, 1994; Rassovsky, Kushner, Schwarze, & Wangensteen, 2000; Shipherd, Beck, & Ohtake, 2001). AS is defined as the tendency to fear body sensations driven by concerns about potentially harmful consequences of such body sensations (McNally, 2002). It has been demonstrated that AS is related to increased symptom reports and physiological arousal during provocation of body sensations and favors the development of pathological anxiety (Benke, Blumenthal, Modeβ, Hamm, & Pané-Farré, 2015; McNally, 2002; Melzig, Holtz, Michalowski, & Hamm, 2011; Schmidt, Zvolensky, & Maner, 2006). Similarly, several studies showed that SF, i.e., the tendency to fear suffocation-associated stimuli like dyspnea, accounted for elevated fear reports and physiological arousal during respiratory challenges (Alius,

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Pané-Farré, Leupoldt, & Hamm, 2013; Benke, Alius, Hamm, & Pané-Farré, 2018; Benke, Hamm, & Pané-Farré, 2017).

In addition to trait-like psychological variables, several studies incorporated voluntary breath-holding time (BHT) as a potential biobehavioral predictor of challenge-induced anxious responding (e.g., Eke & McNally, 1996; McNally & Eke, 1996; Rassovsky et al., 2000). As breath-holding leads to an accumulation of endogenous CO_2, BHT has been interpreted as a biobehavioral marker for CO_2 sensitivity, i.e., the (in)tolerance toward increasing levels of endogenous CO_2 (Masdrakis, Markianos, Vaidakis, Papakostas, & Oulis, 2009; McNally & Eke, 1996). According to Klein's false suffocation alarm theory (Klein, 1993), a higher CO_2 sensitivity reflects an increased sensitivity of a suffocation alarm monitor system which, in turn, has been discussed to be responsible for the elicitation of panic, hyperventilation, and active avoidance to prevent potential suffocation. Interestingly, it has been demonstrated that persons with PD have lower BHT than healthy controls (Asmundson & Stein, 1994; Zandbergen, Strahm, Pols, & Griez, 1992). Moreover, lower BHT in PD has been related to a higher frequency of panic attacks during related respiratory challenges (Masdrakis et al., 2009). The accumulation of CO_2 during breath holding is typically accompanied by unpleasant respiratory symptoms. Therefore, psychological factors such as the ability to withstand distressing and aversive states or body symptoms (i.e., distress tolerance) have been discussed to affect BHT (Zvolensky, Vujanovic, Bernstein, & Leyro, 2010). It is assumed that a lower BHT indexes lower capacity to tolerate respiratory distress that is associated with avoidance of aversive states as well as anxiety and panic symptoms in general (Leyro, Zvolensky, & Bernstein, 2010; Zvolensky et al., 2010).

As demonstrated above, various studies have successfully identified potential predictors of physiological arousal and experienced anxiety during provocation of feared bodily symptoms. However, it remains unclear whether these variables also relate to active avoidance when experiencing feared body symptoms, i.e., the premature termination of body symptoms to alleviate symptoms and avoid a further worsening of body symptoms (e.g., by terminating physical activity). Therefore, in the present study, we explored the impact of psychological trait variables (AS, SF, and TA) and BHT on avoidance behavior in a situation where the intensity of body symptoms (i.e., dyspnea) systematically increased. A similar increase of the intensity of body symptoms is typically observed during panic attacks. The increase in intensity and unpleasantness of dyspnea was experimentally induced by applying increasing inspiratory resistive loads followed by a complete breathing occlusion. In contrast to during breath-holding, levels of CO_2 do not significantly change during loaded breathing and thus do not physiologically limit the continuation of the task (e.g., Alius, Pané-Farré, Leupoldt, & Hamm, 2013). Importantly, during the given experimental task participants could prematurely terminate the exposure to increasing dyspnea at any time, thus alleviating symptoms and preventing a further progression of dyspnea. Whenever this avoidance behavior is performed during exposure to body symptoms, one can assume that avoidance learning takes place (Krypotos, Effting, Kindt, & Beckers, 2015). Consequently, after repeated learning trials the frequency of avoidance responses may increase that set the stage for the development of excessive and maladaptive avoidance. Therefore, in the present study, we examined whether the variables mentioned above may predict whether individuals avoid or do not avoid further progression of dyspnea, i.e., avoidance was considered as a binary outcome variable.

Based on previous studies, we considered AS, SF, TA and voluntary BHT as potential predictors of avoidance behavior. In accordance with previous evidence (e.g., Eke & McNally, 1996), it was expected that AS and SF are significant predictors of avoidance during exposure to increasing dyspnea, while TA would not be associated with avoidance. Moreover, it was hypothesized that a lower BHT predicts more frequent avoidance behavior during exposure to respiratory sensations – an assumption that is derived from the false suffocation alarm hypothesis (Klein, 1993). Given that lower BHT is related to anxious responding in persons who fear body sensations, it was expected that BHT interacts with the tendency to fear body sensations in predicting avoidance of body symptoms. Accordingly, we hypothesized an interactive effect, i.e., that a lower BHT is associated with more frequent avoidant behavior but only in those individuals who report elevated fear of body sensations.

2. Methods

2.1. Participants

Participants were recruited from a pool of 400 university students. Exclusion criteria were cardiovascular, respiratory (e.g., asthma, COPD), or neurological (e.g., epileptic or apoplectic seizures, multiple sclerosis) diseases, current or past psychotherapeutic treatment for anxiety problems, hearing impairment, or pregnancy. Overall 69 Caucasian participants (59 females; age: $M = 22.7$, $SD = 3.3$) took part in the laboratory assessment. Three participants (2 females) were excluded from analyses as they did not adhere to the experimental procedure for determining the breath-holding time. All participants provided written informed consent prior to the study and either received course credit or financial compensation for their participation. The study protocol was approved by the ethics committee of the German Psychological Society.

2.2. Apparatus and materials

2.2.1. Inspiratory resistive loads (IRL) and breathing occlusion

Participants breathed through a tightly fitting soft silicone face mask (7400 series; Hans Rudolph, Inc., Kansas City, MO) connected to a two-way y-shaped non-rebreathing valve (no. 2630; Hans Rudolph, Inc.) which enabled unrestricted expiration through the expiratory port of the valve. A plastic tube (length: 2.75 m; diameter: 35 mm) was connected to the inspiratory port of the valve and mounted to the common port of a Five-Way Gatlin-Shape™ Inflatable-Balloon-Type™ valve (2440 series, Hans Rudolph, Inc.). Closing and opening of the valves were controlled via VPM software triggering a pneumatic controller (2430 series, Hans Rudolph, Inc.). This system allowed a prompt and easy switching between different ports and thus between three different inspiratory resistive loads, i.e., nylon flow resistors of linear type (7100 series, Hans Rudolph, Inc.; range: 0.05–23.19 kPa/l/s) inducing dyspnea, and unrestricted breathing (one port without attached load). Breathing occlusions (simultaneous closure of all inspiratory ports for 15 s) were manually triggered at the end of expiration.

2.2.2. Subjective reports

Participants rated the intensity and unpleasantness of dyspnea as well as the anxiety and panic symptoms experienced during loaded breathing and breathing occlusion using a computer keyboard on the following scale: 1 (*not at all*), 2 (*slight*), 3 (*moderate*), 4 (*strong*), 5 (*very strong*), and 6 (*maximally tolerable*). Ratings were projected onto a 1.50 × 1.30 m screen in front of the participants.

2.3. Procedure

Following the attachment of the breathing mask, the experiment started with the determination of the post-expiratory maximal voluntary breath-holding time. Next, the individual detection threshold for respiratory loading as well as the unpleasantness and intensity of IRLs and the respiratory occlusion was determined (see Alius et al. (2013), for detailed information).

The main part of the experiment started with a 110 s adaptation phase. Then, three loads of increasing intensity (previously rated as producing slight [load1], strong [load2] and maximally tolerable [load3] unpleasant feelings of dyspnea) were consecutively presented

for 60 s each. Presentation of the third load was immediately followed by a post-expiratory breathing occlusion for 15 s and a 30 s recovery phase of unrestricted breathing. The described load-occlusion-recovery sequence (trial) was presented eight times.

After the experiment, the three previously selected loads and the breathing occlusion were presented again separately for 30 s (15 s for the occlusion, respectively) each, followed by a 30 s recovery phase and anxiety and symptoms were rated again. At the end of the laboratory session, participants completed a German version of the questionnaires mentioned below and were fully debriefed by the experimenter.

2.4. Measures

2.4.1. Suffocation fear subscale (SF)

SF is a subscale of the claustrophobia questionnaire (Radomsky, Rachman, Thordarson, McIsaac, & Teachman, 2001) comprising of 14 items that are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). Participants rate how anxious they would feel in specific situations associated with suffocation fear. The SF subscale of the CLQ has evidenced excellent reliability (e.g., internal consistency $\alpha = 0.85$) and validity (Radomsky et al., 2001).

2.4.2. Anxiety Sensitivity Index-3 (ASI-3)

The ASI-3 (Taylor et al., 2007) is an 18-item measure that assesses the tendency to fear anxiety-related sensations (McNally, 2002) on a 5-point Likert scale ranging from 0 (very little) to 4 (very much). The ASI-3 has demonstrated good reliability and validity (e.g., internal consistency $\alpha = 0.92$) (Taylor et al., 2007).

2.4.3. State-trait anxiety-inventory (STAI)

The trait portion of the STAI (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) measures the general proneness to experience anxiety and perceive situations as threatening with 20 items on a 4-point Likert scale. The internal consistency typically ranges from 0.86 to 0.95 (Spielberger et al., 1983).

2.4.4. Maximal voluntary breath-holding time (mvBHT)

The maximal post-expiratory breath-holding time in seconds (breath-holding at functional residual capacity as suggested by Asmundson & Stein, 1994) was determined using a standardized procedure. At the end of an expiration, the examiner signaled to the study participant via a computer screen to hold the breath as long as possible, while the breathing circuit was occluded. Hence, during this period no breathing was possible until the participants terminated the breathing occlusion by button press which automatically initiated opening of the inspiratory port.

2.4.5. Avoidance behavior during exposure to increasing dyspnea

Participants were provided with a button that could be used to terminate the sequences of increasing loads and the occlusion at any point in time to avoid any further feelings of dyspnea. Persons who prematurely terminated the exposure to increasing dyspnea were classified as avoiders (n = 26) and those who completed the whole experimental procedure as non-avoiders (n = 40).

2.5. Analysis

The intensity of IRLs as well as anxiety and panic symptom ratings were analyzed using a mixed-model analysis of variance (ANOVA) with the repeated-measures factor *load* (first vs. second vs. third load, resp., first vs. second vs. third load vs. occlusion for anxiety and panic symptom ratings) and the between-subject factor *group* (avoiders vs. non-avoiders). Second, a multiple logistic regression was used to test associations of ASI-3, SF and STAI scores as well as mvBHT as predictors for avoidance behavior as outcome (avoidance vs. non-avoidance). Third, a multiple logistic regression with an interaction term was applied to test interactions of the trait-like fear of body sensations (i.e., AS and SF) and mvBHT in predicting avoidance behavior.

3. Results

3.1. Manipulation check

As expected reported unpleasantness of felt dyspnea increased significantly with physical intensity of the selected IRLs, load F (2, 128) = 92.76, $p < .001$, with no differences between avoiders and non-avoiders, Group x Load F (2, 128) < 1, $p = .405$, group F (1, 64) < 1, $p = .796$. The same pattern of results was obtained for rated anxiety, load F (3, 192) = 50.11, $p < .001$, Group x Load F (3, 192) = 1.31, $p = .275$, and reported panic symptoms, load F (3, 192) = 55.25, $p < .001$, Group x Load F (3, 192) = 2.32, $p = .111$, except that avoiders reported overall higher anxiety (non-avoiders: $M = 2.3$, $SD = 1.1$; avoiders: $M = 3.4$, $SD = 1.1$) and symptom intensity (non-avoiders: $M = 1.6$, $SD = 0.5$; avoiders: $M = 2.2$, $SD = 0.9$) than non-avoiders, group F (1, 64) = 15.60, $p < .001$; group F (1, 64) = 11.31, $p = .001$ for anxiety and symptom ratings, respectively.

3.2. Zero-order correlations between predictors and outcome

While self-report measures were positively correlated with each other (see Table 1) they were not associated with mvBHT. Avoidance was significantly correlated with mvBHT and ASI but was not associated with STAI and SF.

3.3. Predicting avoidance during exposure

SF (OR = 0.95, $p = .271$) and STAI (OR = 0.93, $p = .086$) scores did not predict avoidance during exposure to increasing dyspnea. However, higher ASI scores (OR = 1.13, $p = .007$) and lower mvBHT (OR = 0.91, $p = .012$) were associated with avoidance behavior during the task. Moreover, ASI scores interacted with mvBHT in predicting avoidance, OR = 0.99, $p = .049$. The significant interaction effect was visualized by dichotomizing ASI scores (low vs. high) and mvBHT (short vs. long) using median split. The interaction is shown in Fig. 1, indicating that lower voluntary BHT was associated with more frequent avoidance behavior during exposure in those who reported high AS. There was no significant interaction between SF and mvBHT in predicting avoidance behavior, OR = 0.99, $p = .083$.

4. Discussion

The present study examined psychological (AS, SF, TA) and biobehavioral (BHT) predictors of avoidance behavior during increasing feelings of dyspnea. Higher AS and lower BHT were associated with more avoidance behavior, while TA and SF did not predict avoidance. The association between BHT and avoidance behavior was moderated by AS in that persons with a lower BHT only exhibited increased

Table 1
Means (SD) for predictors and zero-order correlations between predictors and outcome.

Predictors	*M* (*SD*)	ASI	SF	STAI	mvBHT	Avoidance[#] [no/yes]
ASI-3 [0–72]	21.0 (11.3)	–	.674**	.475**	.108	.293*
SF [0–46]	11.5 (8.6)	–	–	.302*	.007	.143
STAI [20–80]	39.0 (8.8)	–	–	–	.155	-.035
mvBHT (s)	20.9 (9.4)	–	–	–	–	-.327**

Note: ASI-3: Anxiety Sensitivity Index, SF: Suffocation Fear, STAI: State-Trait Anxiety Inventory, mvBHT: Maximal Voluntary Breath-holding Time; *$p < .05$, **$p < .01$; $^{\#}r_{spearman}$.

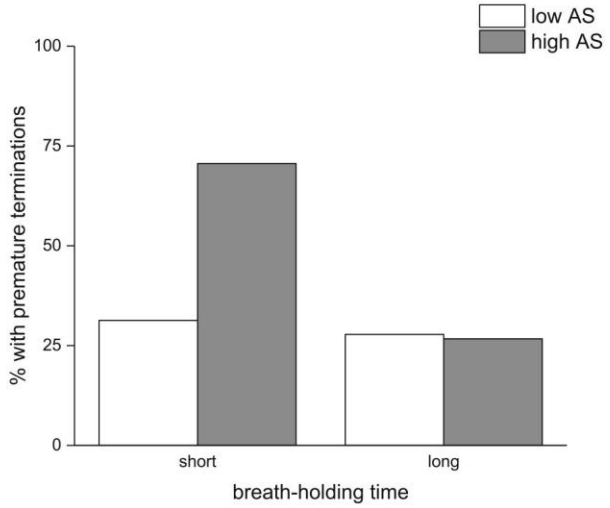

Fig. 1. Interaction between anxiety sensitivity and maximal voluntary breath-holding time in predicting premature termination of exposure.

avoidance behavior when also reporting high AS.

Several studies demonstrated that AS is a strong predictor of subjective and physiological responses to experimentally induced feared bodily symptoms (Eifert et al., 1999; Eke & McNally, 1996; McNally & Eke, 1996; Rassovsky et al., 2000; Shipherd et al., 2001). The present data extend these findings in demonstrating that AS is also related to avoidance behavior aiming to terminate unpleasant feelings of dyspnea. This corroborates findings in clinical and nonclinical populations showing that concerns about harmful consequences of body symptoms are associated with *reported* avoidance of agoraphobic situations and interoceptive sensations (e.g., dyspnea) (Simon et al., 2006; Taylor & Rachman, 1992; White, Brown, Somers, & Barlow, 2006). Our finding also corresponds to models suggesting that avoidance behavior is primarily motivated by the anticipation of expected outcomes (central concerns) (see expectancy model of fear; Reiss, 1991).

Moreover, the present data suggest that AS is a better predictor of avoidance behavior in this task than SF and TA. This corresponds to experimental evidence indicating that subjective and physiological responses to exposure to feared bodily symptoms are better explained by AS than TA (Carter, Suchday, & Gore, 2001; Eke & McNally, 1996; McNally & Eke, 1996) or SF (Shipherd et al., 2001). In contrast to this evidence are studies indicating that SF is related to subjective and physiological indicators of anxious responding to respiratory threat (Alius et al., 2013; Benke et al., 2017, 2018; Eifert et al., 1999; Eke & McNally, 1996; McNally & Eke, 1996; Rassovsky et al., 2000). In the light of previous evidence and our present results, SF is possibly associated with subjective and physiological anxious responses but not with overt anxious behavior during respiratory threat.

In the present study, we also provide first evidence that a lower BHT predicted avoidance behavior during exposure to respiratory sensations. It is assumed that a lower tolerance (i.e., a higher sensitivity) toward increasing levels of endogenous CO_2 during breath-holding may indicate a higher sensitivity of an evolved suffocation alarm monitor system (Asmundson & Stein, 1994; Eke & McNally, 1996; Masdrakis et al., 2009). Animal research revealed that this suffocation alarm monitor system might be located in the periaqueductal gray (PAG) of the brainstem that integrates physiological (brain O_2, CO_2, and lactate) as well as environmental information (Preter & Klein, 2008) to detect respiratory threat and initiate a defensive alarm reaction for effective coping, e.g., escape/avoidance (Schimitel et al., 2012). Interestingly, hypoxia-induced flight behavior in rats is potentiated by CO_2 and suppressed by lesions of the PAG (Schimitel et al., 2012). In accordance with the suffocation false alarm theory proposed by Klein (1993), it might be that persons who have a higher sensitivity of the suffocation alarm might also more readily exhibit avoidance behavior when confronted with suffocation-related stimuli such as dyspnea. Importantly, lower BHT may also signify a reduced behavioral capacity to withstand aversive sensations. Our results corroborate current findings indicating that distress tolerance is associated with avoidance and anxiety or panic symptoms (Leyro et al., 2010).

Importantly, our data also indicate that the oversensitive suffocation alarm system only triggered exaggerated avoidance in those persons who also report higher trait fears of unpleasant body sensations based on beliefs about harmful consequences of such sensations (i.e., AS). Or, put it in terms of the perspective of distress tolerance, avoidance of body symptoms is more likely initiated in individuals who show less tolerance toward unpleasant body symptoms but only when these individuals fear those body symptoms. Our results suggest that AS and BHT may act as psychological and biobehavioral vulnerability factors that *interact* to increase the risk to exhibit avoidance and thus might contribute to the etiology and maintenance of anxiety-related disorders. Current etiological model of anxiety disorders and prospective studies relating AS to later onset of panic and anxiety psychopathology (Plehn & Peterson, 2002; Schmidt et al., 2006) as well as previous studies demonstrating lower BHT in patients with PD and more panic attacks in those patients with lower BHT (Asmundson & Stein, 1994; Masdrakis et al., 2009; Zandbergen et al., 1992) corroborate this assumption.

The present study revealed effects of psychological and biobehavioral variables in predicting avoidance during provocation of body symptoms. However, limitations of the present findings need to be commented on. The sample size of the current study is relatively small and the sample is predominantly composed of young, female undergraduate students which might limit the generalizability of the results. Therefore, the present findings should be replicated in larger and more diverse samples in terms of age, gender, and educational level. Moreover, comprehensive data on diagnostic and symptom levels of participants is missing which complicates the comparison of the present results to findings in other study samples. However, the existing self-report data indicate that the characteristics of the sample are comparable to a nonclinical student sample (Radomsky et al., 2001; Spielberger et al., 1983; Taylor et al., 2007). Moreover, future studies ought to replicate and extend the current findings in patients with anxiety disorders and should use a longitudinal design to examine the exact role of BHT and AS on avoidance and its effects on the development and maintenance of anxiety disorders. As mentioned above, one might also argue that BHT is affected by psychological factors such as the disposition to fear body sensations in that participants who fear body sensations terminate breath-holding earlier due to fear and body sensations experienced during breath-holding. However, in line with previous studies (e.g., Eke & McNally, 1996; Rassovsky et al., 2000), psychological factors were not associated with BHT supporting the view that psychological factors and BHT constitute independent factors.

5. Implications and conclusion

The present study successfully identified BHT and AS as predictors of avoidance behavior during exposure to feared bodily sensations. It was demonstrated that both variables interacted in predicting avoidance. The present results suggest that BHT and AS might act as vulnerability factors that may contribute to the proliferation of avoidance as well as to the development and maintenance of anxiety and panic psychopathology. Therefore, both predictors might be used to identify persons for targeted prevention programs. These prevention programs should be aimed at reducing avoidance behavior and fear of body symptoms to prevent the progression of anxiety disorders. These prevention programs should include interoceptive exposure and techniques that aim at managing increasing levels of CO_2 and respiratory distress (e.g., underwater breath holding or hypoventilation therapy) in order to

alter both risk factors, i.e., BHT and AS (Craske & Barlow, 2014; Gardenswartz & Craske, 2001). In addition to exposure-based approaches, it might also be useful to include acceptance and mindfulness-based techniques in prevention programs to increase the tolerance toward aversive body symptoms or emotional states (distress tolerance) and thus decrease avoidance of aversive body symptoms.

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Conflicts of interest

The authors declare no conflict of interest.

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Appendix B: Liste der Publikationen und Anteile aller Autoren

Publikation 1

Krause, E., Benke, C., Koenig, J., Thayer, J. F., Hamm, A. O., & Pané-Farré, C. A. (2017). Dynamics of Defensive Response Mobilization to Approaching External Versus Interoceptive Threat. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.* Advance online publication. https://doi.org/10.1016/j.bpsc.2017.12.002

EK, CB, CPF und AOH konzipierten und designten das Experiment. EK und CB führten die Datenerhebung durch. EK verarbeitete und analysierte die Daten und schrieb den ersten Manuskriptentwurf. Alle Autoren interpretierten die Daten und wirkten an der Manuskripterstellung mit.

Publikation 2

Benke, C., **Krause, E.**, Hamm, A. O., & Pané-Farré, C. A. (2018). Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat. International journal of psychophysiology: official journal of the International Organization of Psychophysiology, 131, 44–56. https://doi.org/10.1016/j.ijpsycho.2017.09.013

CB, CFP und AOH konzipierten und designten das Experiment. CB und EK führten die Datenerhebung durch. CB verarbeitete und analysierte die Daten unter Mitarbeit von EK und CB schrieb den ersten Manuskriptentwurf. Alle Autoren interpretierten die Daten und wirkten an der Manuskripterstellung mit.

Publikation 3

Krause, E., Benke, C., Hamm, A.O., Pané-Farré C.A. (Under review). Hold your breath: voluntary breath-holding time predicts defensive activation to approaching internal threat.

EK, CB, CPF und AOH konzipierten und designten das Experiment. EK führte die Datenerhebung durch. EK verarbeitete und analysierte die Daten unter Mitarbeit von CB. EK schrieb den ersten Manuskriptentwurf. Alle Autoren interpretierten die Daten und wirkten an der Manuskripterstellung mit.

Publikation 4

Benke, C., **Krause, E.**, Hamm, A. O., & Pané-Farré, C. A. (2019). Predictors of behavioral avoidance during respiratory symptom provocation. *Behaviour Research and Therapy*, *112*, 63–67. https://doi.org/10.1016/j.brat.2018.11.012

CB, CFP und AOH konzipierten und designten das Experiment. CB und EK führten die Datenerhebung durch. CB verarbeitete und analysierte die Daten und schrieb den ersten Manuskriptentwurf. Alle Autoren interpretierten die Daten und wirkten an der Manuskripterstellung mit.

Appendix E: Publikationen und andere wissenschaftliche Leistungen

Peer-reviewed Manuskripte

Krause, E., Benke, C., Koenig, J., Thayer, J. F., Hamm, A. O., & Pané-Farré, C. A. (2017). Dynamics of Defensive Response Mobilization to Approaching External Versus Interoceptive Threat. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.* Advance online publication. https://doi.org/10.1016/j.bpsc.2017.12.002

Benke, C., **Krause, E.**, Hamm, A. O., & Pané-Farré, C. A. (2018). Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat. International journal of psychophysiology: official journal of the International Organization of Psychophysiology, 131, 44–56. https://doi.org/10.1016/j.ijpsycho.2017.09.013

Krause, E., Benke, C., Hamm, A.O., Pané-Farré C.A. (Under review). Hold your breath: voluntary breath-holding time predicts defensive activation to approaching internal threat.

Benke, C., **Krause, E.**, Hamm, A. O., & Pané-Farré, C. A. (2019). Predictors of behavioral avoidance during respiratory symptom provocation. *Behaviour Research and Therapy*, *112*, 63–67. https://doi.org/10.1016/j.brat.2018.11.012

Konferenzen und Vorträge

10.2017	Kongress der Society for Psychophysiological Research 2017, Wien, Österreich (**Posterpräsentation**: Dynamics of defensive mobilization to interoceptive vs. exteroceptive threat. Krause E., Benke C., Hamm A. & Pané-Farré C.)
09.2017	**Vortrag** bei der International Society for the Advancement of Respiratory Psychophysiology, Lille, Frankreich (Don't panic – Brain and respiratory responses to increasing dyspnea in high and low suffocation fearful individuals) **Auszeichnung Nachwuchspreis**
05.2016	Kongress Psychologie und Gehirn, Berlin (**Posterpräsentation**: Die dynamische Organisation defensiver Reaktionen – Ein Vergleich zwischen einer Bedrohung von innen und einer Bedrohung durch einen aversiven externen Reiz, Krause E., Benke C., & Pané-Farré C.)
04.2016	**Eingeladener Vortrag** am Anxiety and Depression Research Center (Prof. Dr. Craske), Los Angeles, CA, USA (*The Threat from the Inside: Dynamics of Defensive Mobilization to Feared Somatic Sensations*)

Appendix F: Danksagung

Ich möchte mich bei allen Personen bedanken, die mich bei meiner Promotion über die Jahre begleitet und unterstützt haben.

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