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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; *$p < .05$, **$p < .01$; [#]$r_{spearman}$.

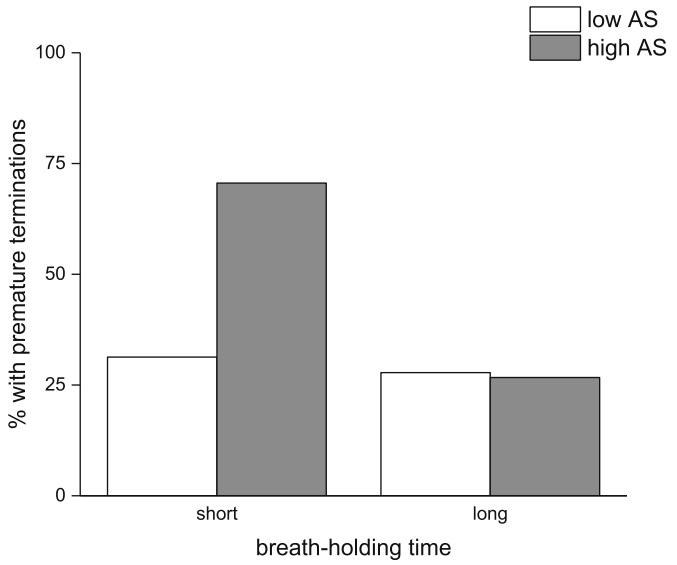

Fig. 1. Interaction between anxiety sensitivity and maximal voluntary breath-holding time in predicting premature termination of exposure.

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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