European Neuropsychopharmacology 53 (2021) 104–113

www.elsevier.com/locate/euroneuro

The cognitive anxiety sensitivity treatment (CAST) in anxiety prevention – Focus on separation anxiety and interoception

Miriam A. Schiele[a], Melanie Vietz[b], Agnieszka Gajewska[b], Stefan Unterecker[b], Michael G. Gottschalk[a], Jürgen Deckert[b], Susanne Neufang[c,d], Norman B. Schmidt[e], Katharina Domschke[a,f,*]

[a] *Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany*
[b] *Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany*
[c] *Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany,*
[d] *Comparative Psychology, Institute of Experimental Psychology, Heinrich-Heine University, Düsseldorf, Germany*
[e] *Florida State University, Department of Psychology, Tallahassee, FL, USA*
[f] *Center for Basics in Neuromodulation, Faculty of Medicine, University of Freiburg, Freiburg, Germany*

Received 1 October 2020; received in revised form 18 August 2021; accepted 24 August 2021

KEYWORDS
Targeted prevention;
Anxiety disorders;
Respiration;
Panic;
Interoceptive exposure

Abstract
Given the high prevalence and considerable clinical and societal burden of anxiety disorders, preventive measures are urgently warranted to reduce their incidence and overall healthcare impact. Anxiety sensitivity (AS) – a key element in learning theories of anxiety disorders in the context of interoceptive conditioning – constitutes a malleable risk factor of particularly panic disorder and separation anxiety, which share developmental, nosological, epidemiological and pathomechanistic characteristics.
The computer-assisted 'Cognitive Anxiety Sensitivity Treatment' (CAST) targeting interoceptive anxiety symptoms (cf. Schmidt et al., 2014) was translated, intensified and culturally adapted to German and evaluated in a sample of 105 healthy adult volunteers with elevated AS (mean

* Corresponding author at: Department of Psychiatry and Psychotherapy, University of Freiburg, Hauptstrasse 5, D-79104 Freiburg, Germany.
E-mail address: katharina.domschke@uniklinik-freiburg.de (K. Domschke).

https://doi.org/10.1016/j.euroneuro.2021.08.265

ASI-3: 29.5) applying a randomized design. Success of the intervention was measured as a function of AS and separation anxiety (ASA-27) ~6 weeks (T1) and ~6 months (T2) after the intervention.
As compared to waitlist, CAST resulted in a significant reduction of AS at both T1 and T2. Separation anxiety was not directly reduced by the intervention, but decreased mediated by a decline in AS. A composite interoceptive score capturing changes in sensitivity to respiratory symptoms during the baseline therapist-accompanied CAST session was shown to be predictive of overall response at T1.
In sum, CAST-German Version was successfully established as an effective intervention reducing AS, while at the same time indirectly decreasing separation anxiety. A composite interoceptive score predicting treatment response might aid in further delineating risk markers informing targeted preventive interventions for anxiety disorders.

1. Introduction

Anxiety disorders constitute the most common mental disorders with a 12-month prevalence of 14-21% (Kessler et al., 2012; Wittchen et al., 2011). They confer a high socioeconomic burden amounting to total annual costs of approximately 74 billion € in the European Union (Gustavsson et al., 2011). Anxiety disorders such as specific phobias, social anxiety disorder or selective mutism mostly emerge early in childhood or adolescence, while panic disorder and generalized anxiety disorder frequently initially manifest later in life with the mean age of onset of panic disorder reported at approximately 30 years (e.g., Lijster et al., 2017; Solmi et al., 2021). Separation anxiety disorder, while previously thought to first emerge relatively early in childhood, often first manifests in adulthood, i.e., over the age of 18, with adult-onset occurring in over 43% of patients (Shear et al., 2006; Silove et al., 2015). The chronicity of anxiety disorders, if untreated, is high, and 20-30% of the patients display treatment resistance (for review see Craske et al., 2017; Ströhle et al., 2018). Accordingly, the World Health Organization (WHO) reported anxiety disorders to rank sixth among all mental and somatic illnesses worldwide as a cause of 'years lived with disability' (YLD) (WHO, 2017).

Given these considerable developmental, clinical and socioeconomic implications of anxiety disorders, preventive measures are urgently warranted to reduce the incidence of this disorder group *per se* and – considering the substantial sequential comorbidity of anxiety disorders – also of depression, substance abuse disorders and possibly even dementia (e.g., Grant et al., 2015; Mah et al., 2016; Meier et al., 2015). Most available primary preventive interventions target children and young adolescents (for review see Domschke, 2021a; Fisak et al., 2011; Moreno-Peral et al., 2017), while by contrast, only few preventive programs have been developed for adults. Most preventive interventions for adults aim at modifying anxiety sensitivity (AS), the heritable cognitive inclination to interpret arousal-related bodily symptoms like shortness of breath or respiratory distress as dangerous (Reiss and McNally, 1985; for review see: Zvolensky and Schmidt, 2007). Anxiety sensitivity has been proposed as a key element in learning theories of anxiety disorders in the context of interoceptive conditioning (cf. Bouton et al., 2001; Domschke et al., 2010; Paulus, 2013), as a robust risk marker for subsequent clinical diagnosis of anxiety disorders, particularly of panic disorder and separation anxiety disorder (e.g., Eley et al., 2004; Schmidt et al., 1997, 1999; Schmidt et al., 2006; Waszczuk et al., 2013), and a strong psychological predictor of a persistent course of anxiety disorders in adults (Hovenkamp-Hermelink et al., 2021). Furthermore, anxiety sensitivity has been shown to be targetable and malleable by therapeutic interventions such as cognitive-behavioral treatment with exposure elements (Barlow et al., 1989; Boswell et al., 2013; Schmidt et al., 2000b; Telch et al., 1993; Westling and Öst, 1999).

Following earlier preventive programs focusing on anxiety sensitivity modulation (Gardenswartz and Craske, 2001; Kenardy et al., 2003; Maltby et al., 2005), Schmidt et al. have established three brief, computer-based programs to reduce anxiety sensitivity in an effort to eventually prevent anxiety disorders (for review see Schmidt et al., 2019): The Anxiety Sensitivity Amelioration Training (ASAT) provides information on the nature of stress and the effects of stress on the body and teaches participants about interoceptive conditioning along with instructions of exposure exercises to internal bodily cues delivered via an audio-visual computer presentation. In a sample of 404 participants with high anxiety sensitivity, ASAT produced greater reductions in AS levels compared with the control condition, and significantly reduced anxiety disorder incidence during a two-year follow-up period (Schmidt et al., 2007). Extending ASAT, the Anxiety Sensitivity Education and Reduction Training (ASERT) consists of a computer-based program with psychoeducative elements, a stress-reduction training as well as interoceptive exposure exercises focusing on respiratory distress (hyperventilation, breathing through a straw). Additionally, during a one-time manualized and therapist-accompanied session as well as by means of daily homework surveyed via an online schedule over the course of four weeks, participants repeat the above-mentioned symptom provocation exercises designed to correct interoceptive conditioning. Again, in a sample of 104 high AS participants the active intervention resulted in significantly greater reductions in AS at posttreatment, at 1-month and at 6-month follow-up than the control group (Keough and Schmidt, 2012). Building on ASERT, the Cognitive Anxiety Sensitivity Treatment (CAST) contains all elements comprised by ASERT, but puts specific emphasis

on AS cognitive concerns. It is based on a more sophisticated computer presentation, audio narration throughout, video instructions of repeated interoceptive hyperventilation and straw breathing exercises with rating options and four interspersed "quizzes" testing comprehension of important material. The active intervention produced significantly greater reductions in AS at posttreatment and at 1-month follow-up (Schmidt et al., 2014).

All programs mentioned above have successfully been shown to reduce anxiety sensitivity (Schmidt et al., 2007; Keough and Schmidt, 2012(Keough and Schmidt, 2012); Schmidt et al., 2014). Changes in anxiety sensitivity have furthermore been demonstrated to have a secondary effect on alleviating symptom dimensions closely intertwined with anxiety sensitivity, such as panic symptoms or suicidal ideation (see Norr et al., 2018; Schmidt et al., 2014; Schmidt et al., 2016; Schmidt et al., 2017), however, this has not yet been investigated with regard to symptoms of separation anxiety. Separation anxiety disorder has a lifetime prevalence of 4.1% for childhood onset and 6.6% for adult onset of the disorder, with onset after the age of 18 years occurring in over 43% of patients (see above; Shear et al., 2006; Silove et al., 2015). In the DSM-5 (American Psychiatric Association, 2013), separation anxiety disorder – previously classified in the section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" – has been moved to the "Anxiety Disorders" chapter reflecting the substantial proportion of first manifestations in adulthood and suggesting a developmental, nosological, epidemiological and pathomechanistic relationship between separation anxiety disorder and other anxiety disorders, particularly panic disorder (cf. Baldwin et al., 2016): On a genetic level, twin study data propose a shared genetic liability between separation anxiety disorder and panic disorder (Roberson-Nay et al., 2012) as well as between anxiety sensitivity, separation anxiety disorder and panic disorder (Waszczuk et al., 2013) suggesting the notion of a biologically founded anxiety sensitivity, separation anxiety disorder and panic disorder spectrum. Also on a clinical level, anxiety sensitivity has been reported to correlate significantly with separation anxiety scores (Muris et al., 2001), and patients with SAD displayed higher levels of anxiety sensitivity and fears of physical symptoms as patients with other anxiety disorders such as social or specific phobias (Hannesdottir et al., 2018). Given this converging evidence towards a potentially shared developmental trajectory (for review see Schiele et al., 2020a), separation anxiety constitutes a promising phenotype to potentially also be ameliorated by an intervention primarily directed at anxiety sensitivity.

Also, for targeted and thus presumably the most effective preventive interventions in anxiety, it is essential to establish valid markers of disorder risk in order to define relevant symptom dimensions and, consequently, target groups most likely to benefit from a specific intervention (cf. (Domschke, Schiele and Romanos, 2021); Domschke, 2021a; Fusar-Poli et al., 2019). Interoceptive sensitivity, particularly sensitivity towards respiratory distress (Paulus, 2013) has been suggested to be crucially linked to anxiety sensitivity and to serve as a key risk factor of anxiety disorders. Additionally, exposure to interoceptive stimuli constitutes a core component of cognitive behavioral therapy for anxiety disorders (cf. Domschke et al., 2010; Paulus and Stein, 2010). Accordingly, interoceptive exposure may facilitate the overall response to a preventive intervention targeting anxiety sensitivity as well.

Against this background, the goals of the present study were threefold, aiming 1) at establishing a culturally adapted and intensified (therapist-accompanied, repeated at follow-up appointment) German version of the Cognitive Anxiety Sensitivity Treatment (CAST) and evaluating this program with regard to its impact on AS over the time period of ~6 months, given that so far no preventive programs for anxiety disorders in adults are available in German-speaking countries, 2) at assessing the direct and indirect impact of CAST on separation anxiety for the first time, and 3) at investigating symptom changes in response to interoceptive exposure as predictors of prevention outcome.

2. Experimental procedures

2.1. Translation and cultural adaptation of the intervention

Following the 'Translation and Cultural Adaptation of Patient Reported Outcomes Measures – Principles of Good Practice' (PGP) of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) (Wild et al., 2005), a sequential forward and backward translation approach was applied: The original English version of the Cognitive Anxiety Sensitivity Treatment (CAST; Schmidt et al., 2014) was translated into German independently by two investigators fluent in both English and German. The consistency and the face validity of the translations were assessed by five psychiatrists and psychologists in a consensus meeting. This first German version was subsequently pretested in five probands resulting in a second German version, which was independently translated back into English by an investigator fluent in both German and English and subsequently validated by the author of the original English version. Finally, the authors agreed on a third, final version of the German CAST version ('Kognitives Angstsensitivitätstraining', KAST).

2.2. Sample and study design

Healthy Caucasian adult volunteers (initial N=130) aged 18-30 years, fluent in German and pre-stratified for moderate to high anxiety sensitivity (ASI-3 score ≥17; Allan et al., 2014) were recruited at the Department of Psychiatry, Psychosomatics and Psychotherapy, Centre for Mental Health, University of Würzburg, Germany, in the context of project C02 within the Collaborative Research Centre SFB-TRR58 "Fear, Anxiety, Anxiety Disorders" between 2016 and 2020 (see Fig. 1). An ASI-3 score ≥17 – suggested to be most amenable to a preventive intervention (Capron and Schmidt, 2016) – has been recommended as an optimal cut-off for differentiating moderate and high AS from the normative AS class in the general population (Allan et al., 2014). Eligibility of participants was confirmed using a standard medical examination and a structured clinical interview (SCID-I) performed by an experienced psychologist. Exclusion criteria constituted manifest or past mental disorders, current or past cardiovascular or respiratory diseases, hypertension, any other severe internal or neurological somatic illnesses, somatic medication (particularly adrenergic receptor blockers), psychotropic medication, illegal drugs including cannabis (assessed by urine toxicology), excessive smoking and pregnancy. Education, BMI, smoking/alcohol consumption status and family his-

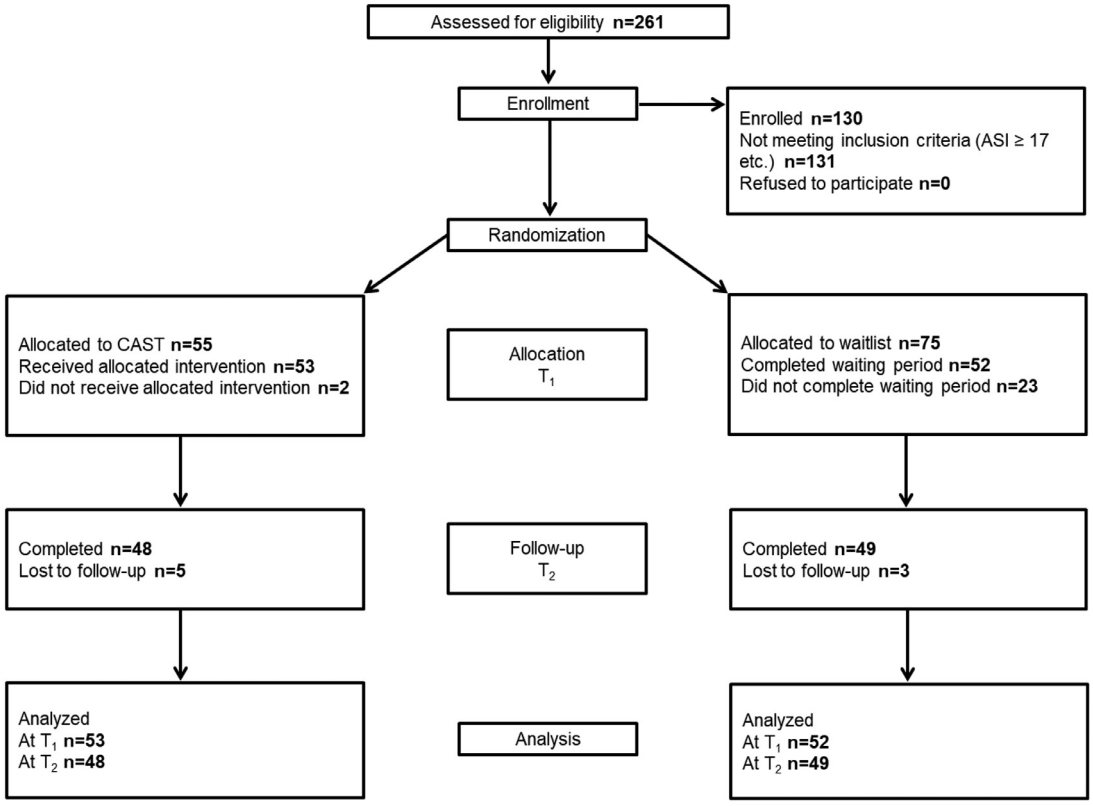

Fig. 1. CONSORT chart of participant recruitment, allocation and analysis. CONSORT: Consolidated Standards of Reporting Trials, CAST: Cognitive Anxiety Sensitivity Treatment, T1: Post-intervention (~6 weeks); T2: Follow-up (~6 months).

tory of mental disorders were recorded. Participants were randomly assigned to the intervention (see below) and wait-list group, respectively (see Fig. 1). At baseline, participants were psychometrically characterized for anxiety measures using the Anxiety Sensitivity Index (ASI-3; Taylor et al., 2007) and the Adult Separation Anxiety Questionnaire (ASA-27; Manicavasagar et al., 2003), depression (Beck Depression Inventory [BDI-II]; Beck et al., 1996) as well as childhood trauma load (Childhood Trauma Questionnaire [CTQ]; Bernstein and Fink, 1998) and recent negative life events (List of Threatening Experiences [LTE]; Brugha and Cragg, 1990) (see Table 1), given previous evidence for stressors negatively impacting on AS (Schmidt et al., 2000a). Efficacy of the prevention training after the intervention (T1; after 6.05±0.61 weeks) as well as at follow-up (T2; after 6.95±0.30 months) was measured using the ASI-3 (primary outcome) and ASA-27 (secondary outcome), respectively, in the final sample of participants completing the intervention or the waitlist condition (see Fig. 1). All psychometric measures were obtained at the beginning of the session, before the intervention was delivered. Participants received financial compensation to the amount of €50 at T0 and T1 as well as €25 at T2. Written informed consent was obtained from all participants. The study was reviewed and approved by the ethical committee of the University of Würzburg (vote no. 139/15) and was conducted in compliance with the declaration of Helsinki.

2.3. Intervention

This training intervention was developed based on cognitive-behavioral principles commonly employed in the treatment of anxiety disorders comprising psychoeducational information and interoceptive exposure exercises (Schmidt et al., 2014).

2.3.1. Psychoeducation

A therapist met individually with the participant and guided the participant through an audio-visual PowerPoint presentation. The first part focused on the nature of stress and its effect on the body and sought to dispel myths regarding the immediate dangers of stress on the body. Participants were taught that the physiological arousal associated with stress is not dangerous and that they may have developed a conditioned fear to those arousal sensations, which is reflected by their elevated AS score. Three interactive questions were posed during in the presentation in order to increase the comprehension of important input. Correct answers were reinforced, incorrect answers resulted in corrective information.

2.3.2. Interoceptive exposure exercises

In the second part of the presentation, the rationale for interoceptive exposure exercises (IE) was explained. Participants then received video-guided instructions on how to perform two exercises involving repeated exposure to feared bodily sensations (i.e., respiratory distress) in order to promote habituation. The exercises were started by the therapist whenever participants signalized they were ready and understood the instruction.

Straw breathing exercises involved breathing through a narrow straw (approximately 0.1-inch outer diameter) while holding the nose closed for 60 seconds.

Hyperventilation exercises involved repeated deep, rapid breathing through the open mouth for 60 seconds.

Table 1 Sample descriptives.

	TotalSample (N=105)	Intervention Group (N=53)	WaitlistGroup (N=52)	Statistics[a)]
Female sex	79 (75.2%)	39 (73.6%)	40 (76.9%)	χ^2=0.157, p=0.692
Age (mean±SD)	23.58±3.29	23.49±3.22	23.67±3.39	t_{103}=-0.283, p=0.778
ASI-3 (mean±SD)	29.48±8.84	29.89±9.26	29.06±8.46	t_{103}=0.479, p=0.633
ASA-27 (mean±SD)	22.17±10.71	23.15±11.16	21.17±10.25	t_{103}=0.945, p=0.347
BDI (mean±SD)	8.99±6.61	8.81±6.85	9.17±6.42	t_{103}=-0.279, p=0.781
CTQ (mean±SD)	33.00±7.33	31.98±6.77	34.04±7.79	t_{103}=1.446, p=0.151
LTE (mean±SD)	1.49±1.35	1.32±1.00	1.65±1.63	t_{103}=-1.260, p=0.211

ASI-3: Anxiety Sensitivity Index 3; ASA-27: Adult Separation Anxiety Questionnaire; BDI: Beck Depression Inventory; CTQ: Childhood Trauma Questionnaire; LTE: Modified List of Threatening Experiences (see 1.2). [a)] Comparison between Intervention Group and Waitlist Group.

Each exercise was repeated a total of ten consecutive times. The instruction video was presented during each repetition along with a countdown. After each repetition, participants rated the perceived intensity of the physical sensations (e.g., feeling lightheaded or dizzy) as well as the level of fear/distress (e.g., feelings of anxiety or unpleasantness) experienced during the exercise on two ten-point rating scales (0: not at all, 10: extremely).

At the end of the session, exemplary graphs depicting the course of the subjective ratings with regard to symptom strength and experiences distress over the ten repetitions were shown to explain the rationale behind the repeated provocation exercises.

Finally, the importance of repeated practice in order to increase the likelihood of achieving lasting effects (i.e., decreased anxiety sensitivity) was explained, and the major points discussed throughout the presentation were summarized in order to increase retention.

After completion of the presentation, participants received instructions to perform these exercises twice per week on their own as homework. Participants received a scheduled reminder summarizing the psychoeducational information presented during the therapist-accompanied session midway through the homework period. Participants completed on average 9.40±1.44 exercises as homework until T1.

In an effort to intensify the effects of the intervention, CAST presentation was repeated in full at T1. Exercises at T0 and T1 were administered therapist-accompanied. Each session lasted for approximately 90 minutes, homework exercises took about 30 minutes each. The PowerPoint presentation, interoceptive exposure exercises and homework instructions were delivered by an experienced psychologist.

2.4. Statistics

All analyses were conducted using SPSS vers. 25 (IBM Corp.). Correlation analyses (Pearson correlations) were used to test for associations between continuous variables. Differences between categorical variables in dimensional data were tested by means of t-tests.

For comparisons of changes in ASI-3 (main analysis) and ASA-27 (secondary analysis) over time, repeated-measures ANOVAs with the within-subjects factor 'time' (T0, T1, T2) and the between-subjects factor 'group' (intervention vs. waitlist control) controlled for baseline ASI-3 or ASA-27, respectively, were conducted followed by post-hoc t-tests where applicable.

To address whether ASI-3 differences from T0 to T1 as an index of intervention success impacted changes in ASA-27, mediation analysis was applied using PROCESS for SPSS (model 4; Hayes, 2018) with X=group (intervention vs. waitlist control), Y=%ΔASA-27, M=%ΔASI-3.

To assess within-session changes in symptom appraisals of interoceptive provocation exercises, a composite interoceptive score (CIS) was calculated as the mean of intra-individual change (last repetition – first repetition) in fear/distress ratings in response to straw breathing and hyperventilation exercises ([Δstraw breathing+Δhyperventilation]/2) as an index of habituating to fear/distress elicited by respiratory distress. Linear regression analysis corrected for average baseline fear/distress ratings was applied to capture changes in ASI-3 scores from T0 to T1 (%Δ) as an index of intervention success as a function of CIS in the intervention group.

For all analyses at T0/T1, data from N=53 probands in the intervention group and N=52 in the waitlist control group were available; analyses including T2 were limited to N=48 (intervention group) and N=49 (waitlist control group), respectively, due to missing data. For T0/T1/T2 analyses including ASA-27, data were available for N=87 (intervention group: N=44; waitlist control group: N=43). Greenhouse-Geisser correction (GG-ϵ) for non-sphericity was performed where indicated, though uncorrected degrees of freedom are reported. Cohen's d/partial eta square (η_p^2) are reported as measures of effect size. For all analyses, a significance level of $p<.05$ was assumed.

3. Results

3.1. Descriptives

The final analysis sample of participants consisted of 105 healthy probands. At T0, probands completing the intervention (N=53) did not differ from probands completing the waiting time period (N=52) in sex, age, anxiety sensitivity (ASI-3) and separation anxiety (ASA-27) or depression (BDI-II), childhood trauma load (CTQ) and negative recent life events (LTE) (see Table 1).

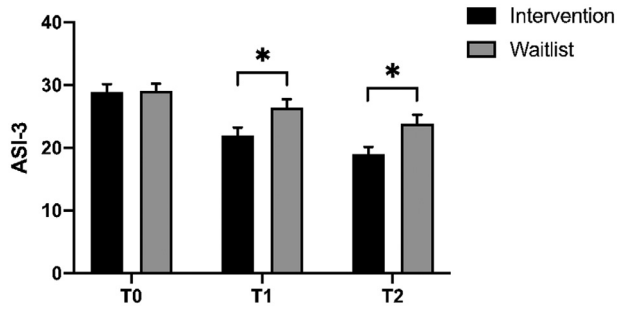

Fig. 2. Effect of CAST on anxiety sensitivity. Between-group differences at T0, T1 and T2. ASI-3: Anxiety Sensitivity Index 3; CAST: Cognitive Anxiety Sensitivity Treatment; T0: Baseline; T1: Post-intervention (~6 weeks); T2: Follow-up (~6 months). Error bars indicate standard errors. *: $p<0.05$.

3.2. Intervention effect on anxiety sensitivity

A significant interaction of time x group ($F_{2,188}$=6.967, GG- ε=.913, p=.001, η_p^2=.069) emerged, indicating significant differences in ASI-3 scores between groups at T1 (t_{103}=2.341, p=.021, Cohen's d: 0.457) and T2 (t_{97}=2.508, p=.014, Cohen's d: 0.504), with greater ASI-3 reductions in the intervention compared to the waitlist control group (see Fig. 2). Overall, CAST resulted in a 22.9% decrease in AS from T0 (mean±SD: 29.89±9.26) to T1 (mean±SD: 21.98±9.20; Cohen's d: 0.753) and a 34.4% decrease in AS from T0 to T2 (mean±SD: 18.94±8.39; Cohen's d: 1.241) as compared to the waitlist condition decreasing by only 7.6% from T0 (mean+SD: 29.06±8.46) to T1 (mean±SD: 26.37±9.98; Cohen's d: 0.342) and 18.9% from T0 to T2 (mean±SD: 23.82±10.32; Cohen's d: 0.728).

3.3. Intervention effect on separation anxiety

There was no overall effect of CAST on ASA-27 scores over time (main effect time: $F_{2,168}$=2.227, p=.111; interaction time x group: $F_{2,168}$=0.185, p=.831). However, when taking the effects of CAST on ASI-3 into account, the difference in ASI-3 score change (%ΔT1-T0) emerged as a significant mediator of the effect of CAST on changes in ASA-27 scores (%ΔT1-T0): While there was no statistically significant direct effect of CAST on ASA-27 (c=-1.912, p=.841), there was a significant indirect effect of CAST on ASA-27 changes via changes in ASI-3 (ab=-6.562, 95%CI: -13.019 to -1.272; bias-corrected bootstrap confidence intervals (based on 5,000 bootstrap samples) (see Fig. 3); that is, reductions in ASA-27 following CAST emerged only if ASI-3 scores decreased over the course of training.

3.4. Prediction of intervention effect by composite interoceptive score

Differences in ASI-3 sum scores from T0 to T1 (%Δ) were significantly predicted by the CIS as a marker of within-session changes in fear/distress ratings in response to interoceptive exposure exercises (t=2.084, β=.370, p=.042). That is, greater within-session reductions in fear/distress ratings (i.e., habituation) went along with greater differences in ASI-3 scores from T0 to T1 (see Fig. 4:.

4. Discussion

In the present study, the 'Cognitive Anxiety Sensitivity Treatment' (CAST) targeting high anxiety sensitivity as initially established in the United States (Schmidt et al., 2014) was successfully translated and culturally adapted to German. Also, as the original version by Schmidt et al. (2014) was not therapist-accompanied, took less than an hour and was not repeated at follow-up appointments, the presently applied version delivered a more potent dose of CAST. The CAST-German Version resulted in a significant reduction of anxiety sensitivity as compared to the waitlist condition. In detail, CAST was followed by a 22.9% decrease in anxiety sensitivity after ~6 weeks and a 34.4% decrease in anxiety sensitivity after ~6 months. This is comparable to decreases in total ASI scores reported in previous studies applying interventions targeting anxiety sensitivity (Schmidt et al., 2014: 32%; Schmidt et al., 2007: 30%), particularly to those reported in the study by Keough and Schmidt (2012: 28%), which was most similar to the current therapist-aided administration, while single interventions applying a cognitive bias modification intervention for interpretation biases (CBM-I) or adding a CBM-I intervention to an anxiety sensitivity psychoeducation intervention, respectively, have reported even higher decreases in anxiety sensitivity (Capron and Schmidt, 2016: 62% post-intervention, 64% at 1-month follow-up; Capron et al., 2017: 59% post-intervention, 52% at 1-month follow-up). In sum, the present data confirms the short- and long-term clinical effects of CAST and suggests its use as a resilience-increasing preventive measure for anxiety disorders *per se*, but possibly also for a variety of other conditions given evidence for a pivotal role of anxiety sensitivity in alcohol and substance abuse (Stewart et al., 1995; Stewart et al., 2001; Zvolensky and Schmidt, 2003), pain-related outcomes (Ocanez et al., 2010), posttraumatic stress symptoms (Boffa and Schmidt, 2019), suicidal ideation (Norr et al., 2018; Stanley et al., 2018) as well as mood disorders (Cox et al., 2001; Lambert et al., 2004; Taylor et al., 1996) .

While several studies have suggested a developmental, nosological, epidemiological and pathomechanistic spectrum shared by anxiety sensitivity and separation anxiety (see introduction; cf. Baldwin et al., 2016; Schiele et al., 2020a, Roberson-Nay et al., 2012; Waszczuk et al., 2013; Muris et al., 2001; Hannesdottir et al., 2018), no direct effects of CAST on separation anxiety could be discerned. However, reductions in separation anxiety symptoms occurred via declines in anxiety sensitivity as a result of the intervention. This observed indirect effect is not surprising given that CAST is not designed to primarily target separation anxiety, and similar observations have been made regarding suicidal ideation (Schmidt et al., 2017). Accordingly, it seems reasonable to expect CAST to only affect symptoms of separation anxiety to the degree to which AS is associated with separation anxiety. This notion is furthermore in line with a longitudinal study by Waszczuk et al. (2013) suggesting anxiety sensitivity to constitute the primary risk factor

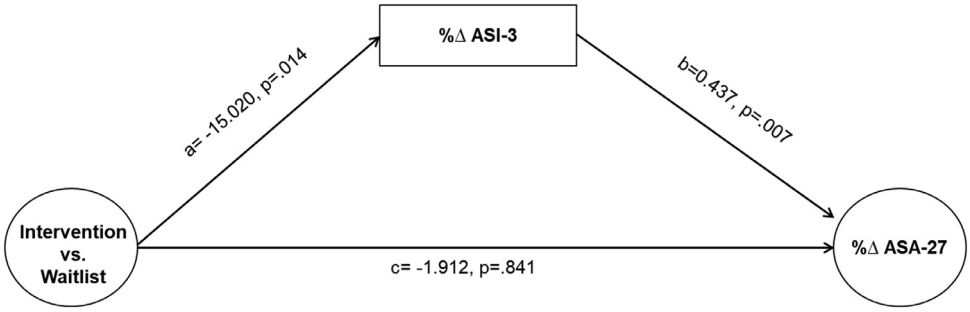

Fig. 3. Effect of CAST on changes in separation anxiety mediated by changes in anxiety sensitivity. ASI-3: Anxiety Sensitivity Index 3; ASA-27: Adult Separation Anxiety Questionnaire; %Δ: relative change from T0 to T1.

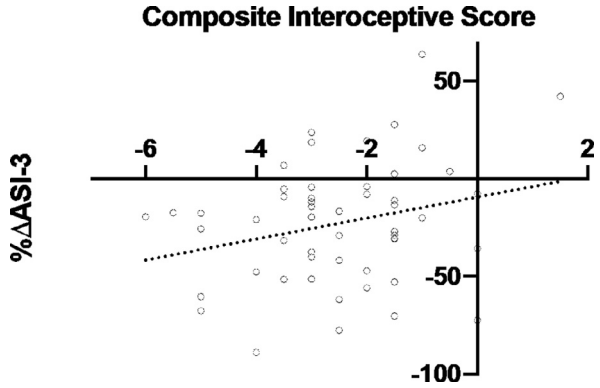

Fig. 4. Prediction of response to CAST by composite interoceptive score linear regression analysis of composite interoceptive score (see 2.4) as a marker of within-session changes in response to interoceptive exposure on ASI-3 changes from T0 to T1. Greater reductions in interoceptive ratings predicted greater ASI-3 differences. ASI-3: Anxiety Sensitivity Index 3, %Δ: relative change from T0 to T1.

for a sequentially increased risk of heightened separation anxiety. Thus, separation anxiety symptoms may be indirectly improved by preventive interventions targeting and successfully reducing anxiety sensitivity. However, for persons not responding to a preventive intervention focusing on anxiety sensitivity, a more targeted approach towards specifically modifying separation anxiety symptoms could be useful, although further research into the exact nature of the relationship between anxiety sensitivity and separation anxiety is warranted.

Furthermore, in an effort to identify early markers of response a 'composite interoceptive score' capturing habituation to respiratory symptoms elicited by instructed straw breathing and hyperventilation exercises was shown to be predictive of response to the preventive intervention. That is, the greater the habituation to the respiratory challenges during the first CAST session, the greater the decline in anxiety sensitivity after ~6 weeks. In the future, markers like the present 'composite interoceptive score' as an early indicator of prevention success might aid in an improved tailoring of preventive measures to the individual participant, e.g. by increasing session numbers, repeated explanation of the exposure rationale, increasing the number of repetitions etc. based on performance during the first session, or might inform early adaptations based on the individual appraisal of perceived bodily symptoms most associated with anxiety, e.g. by alternatively offering a broader range of exercises beyond respiratory distress (running in place, rapid shaking of the head, etc.) and thus in increasing the efficacy of such interventions. Future studies are warranted to further expand high-risk profiles indicating a particular benefit from CAST and other preventive interventions by additional (neuro)psychological or biological, e.g. physiological (e.g. response to carbon dioxide challenge; cf. Schmidt et al., 2007) and genetic and epigenetic markers of stress, resilience and (psychotherapeutic) treatment response (cf. Domschke, 2021b; Gottschalk et al., 2020; Schiele and Domschke, 2018; Schiele et al., 2020b).

The present results ought to be considered in light of the following limitations: The waitlist condition also decreased in anxiety sensitivity at both time points T1 and T2. This is in line with the initial study on ASAT efficacy, where the control group also declined by 17% in anxiety sensitivity (Schmidt et al., 2007). However, while in the latter study the control group received an intervention focused on health and nutrition, in the present study no intervention was offered. Small symptom improvements in waitlist control groups are not uncommon in psychotherapy trials (e.g. Devilly and McFarlane, 2009; Elliott and Brown, 2002; Hesser et al., 2011) which may be due to the fact that a waitlist control group is not entirely untreated in the sense that, at the very least, the diagnostic process as well as a therapeutic relationship have been initiated, and a timeline for receiving a specific intervention in the near future has been established. Additionally, although drop-out rates at the 6-month follow-up mark were low, it cannot be excluded that drop-outs in the waitlist control group occurred due to symptom deteriorations and, as a consequence, interim initiation of treatment in those individuals, which may have biased T2 assessments. Furthermore, while there is previous evidence for interventions targeting anxiety sensitivity to reduce anxiety disorder incidence within a two-year follow-up period (Schmidt et al., 2007), sample size and limited time of follow-up in the present study did not allow for evaluation of the incidence of categorical anxiety or other mental disorders, which should be addressed in future studies. Finally, the present sample was restricted to adult persons with high AS; future studies might thus want to explore effects of the preventive program – particularly

regarding separation anxiety and the role of the 'composite interoceptive score' – in cohorts of at-risk youth using an age-adapted version of CAST (ASAP-Y; Knapp et al., 2020).

In sum, CAST-German Version was successfully established as an effective intervention reducing anxiety sensitivity. Additionally, CAST may indirectly also reduce separation anxiety in high-risk individuals via decreasing anxiety sensitivity. A composite interoceptive score predicting therapeutic response might aid in further delineating risk factors informing future targeted and thus even more effective preventive interventions in an effort to reduce the high individual and socioeconomic burden of anxiety disorders Domschke, Schiele and Romanos, 2021.

Role of funding source

This work was funded by the German Research Foundation (DFG) – project number 44541416 – TRR 58, subproject C02 (to KD and SN) as well as by the German Academic Exchange Service (DAAD), project number 91534760 (to AG). The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Declaration of Competing Interest

KD is a member of the Janssen Pharmaceuticals, Inc. Steering Committee Neurosciences. All other authors declare that they have no potential conflicts of interest.

CRediT authorship contribution statement

Miriam A. Schiele: Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Melanie Vietz:** Data curation, Investigation, Writing – review & editing. **Agnieszka Gajewska:** Methodology, Software, Writing – review & editing. **Stefan Unterecker:** Supervision, Writing – review & editing. **Michael G. Gottschalk:** Methodology, Software, Writing – review & editing. **Jürgen Deckert:** Supervision, Resources, Writing – review & editing. **Susanne Neufang:** Conceptualization, Funding acquisition, Writing – review & editing. **Norman B. Schmidt:** Conceptualization, Methodology, Software, Writing – review & editing. **Katharina Domschke:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Acknowledgements

We gratefully acknowledge assistance with translation by M. Milzer. KD is a member of the ECNP Network on 'Prevention of Mental Disorders and Mental Health Promotion' (PMD-MHP); MAS and KD are members of the ECNP Anxiety Disorders Research Network (ADRN).

References

Allan, N.P., Raines, A.M., Capron, D.W., Norr, A.M., Zvolensky, M.J., Schmidt, N.B., 2014. Identification of anxiety sensitivity classes and clinical cut-scores in a sample of adult smokers: results from a factor mixture model. J. Anxiety Disord. 28, 696–703.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC.

Baldwin, D.S., Gordon, R., Abelli, M., Pini, S., 2016. The separation of adult separation anxiety disorder. CNS Spectr. 21, 289–294.

Barlow, D.H., Craske, M.G., Cerny, J.A., Klosko, J.S., 1989. Behavioral treatment of panic disorder. Behav. Ther. 20, 261–282.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II.. Psychological Corporation, San Antonio, TX.

Bernstein, D.P., Fink, L., 1998. Childhood Trauma Questionnaire: A retrospective self-report manual.. The Psychological Corporation, San Antonio, TX.

Boffa, J.W., Schmidt, N.B., 2019. Reductions in anxiety sensitivity cognitive concerns prospectively mitigate trauma symptom development. Behav. Res. Ther. 113, 39–47.

Boswell, J.F., Farchione, T.J., Sauer-Zavala, S., Murray, H.W., Fortune, M.R., Barlow, D.H., 2013. Anxiety sensitivity and interoceptive exposure: a transdiagnostic construct and change strategy. Behav. Ther. 44, 417–431.

Bouton, M.E., Mineka, S., Barlow, D.H., 2001. A modern learning theory perspective on the etiology of panic disorder. Psychol. Rev. 108, 4–32.

Brugha, T.S., Cragg, D., 1990. The list of threatening experiences: the reliability and validity of a brief life events questionnaire. Acta Psychiatr. Scand. 82, 77–81.

Capron, D.W., Norr, A.M., Allan, N.P., Schmidt, N.B., 2017. Combined "top-down" and "bottom-up" intervention for anxiety sensitivity: pilot randomized trial testing the additive effect of interpretation bias modification. J. Psychiatr. Res. 85, 75–82.

Capron, D.W., Schmidt, N.B., 2016. Development and randomized trial evaluation of a novel computer-delivered anxiety sensitivity intervention. Behav. Res. Ther. 81, 47–55.

Cox, B.J., Enns, M.W., Freeman, P., Walker, J.R., 2001. Anxiety sensitivity and major depression: examination of affective state dependence. Behav. Res. Ther. 39, 1349–1356.

Craske, M.G., Stein, M.B., Eley, T.C., Milad, M.R., Holmes, A., Rapee, R.M., Wittchen, H.U., 2017. Anxiety disorders. Nat. Rev. Dis. Primers 3, 17024.

Devilly, G.J., McFarlane, A.C., 2009. When wait lists are not feasible, nothing is a thing that does not need to be done. J. Consult. Clin. Psychol. 77, 1159–1168.

Domschke, K., 2021b. Prevention in psychiatry: a role for epigenetics? World Psychiatry 20, 227–228.

Domschke, K., 2021a. Targeted prevention of anxiety disorders. Eur. Neuropsychopharmacol. 46, 49–51.

Domschke, K., Schiele, M.A., Romanos, M., 2021. Prevention of anxiety disorders. Nervenarzt 92, 450–456.

Domschke, K., Stevens, S., Pfleiderer, B., Gerlach, A.L., 2010. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin. Psychol. Rev. 30, 1–11.

Eley, T.C., Stirling, L., Ehlers, A., Gregory, A.M., Clark, D.M., 2004. Heart-beat perception, panic/somatic symptoms and anxiety sensitivity in children. Behav. Res. Ther. 42, 439–448.

Elliott, S.A., Brown, J.S.L., 2002. What are we doing to waiting list controls? Behav. Res. Ther. 40, 1047–1052.

Fisak Jr., B.J., Richard, D., Mann, A., 2011. The prevention of child and adolescent anxiety: a meta-analytic review. Prev. Sci. 12, 255–268.

Fusar-Poli, P., Bauer, M., Borgwardt, S., Bechdolf, A., Correll, C.U., Do, K.Q., Domschke, K., Galderisi, S., Kessing, L.V., Koutsouleris, N., Krebs, M.-O., Lennox, B., McGuire, P., Meyer-Lin-

denberg, A., Millan, M.J., Nieman, D., Pfennig, A., Sand, M., Whenert, A., van Amelsvoort, T., Arango, C., 2019. European college of neuropsychopharmacology network on the prevention of mental disorders and mental health promotion (ECNP PMD-MHP). Eur. Neuropsychopharmacol. 29, 1301–1311.

Gardenswartz, C.A., Craske, M.G., 2001. Prevention of panic disorder. Behav. Ther. 32, 725–737.

Gottschalk, M.G., Domschke, K., Schiele, M.A., 2020. Epigenetics underlying susceptibility and resilience relating to daily life stress, work stress, and socioeconomic status. Front. Psychiatry 11, 163.

Grant, B.F., Goldstein, R.B., Saha, T.D., Chou, S.P., Jung, J., Zhang, H., Pickering, R.P., Ruan, W.J., Smith, S.M., Huang, B., Hasin, D.S., 2015. Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. JAMA Psychiatry 72, 757–766.

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E., Dodel, R., Ekman, M., Faravelli, C., Fratiglioni, L., Gannon, B., Jones, D.H., Jennum, P., Jordanova, A., Jonsson, L., Karampampa, K., Knapp, M., Kobelt, G., Kurth, T., Lieb, R., Linde, M., Ljungcrantz, C., Maercker, A., Melin, B., Moscarelli, M., Musayev, A., Norwood, F., Preisig, M., Pugliatti, M., Rehm, J., Salvador-Carulla, L., Schlehofer, B., Simon, R., Steinhausen, H.C., Stovner, L.J., Vallat, J.M., Van den Bergh, P., van Os, J., Vos, P., Xu, W., Wittchen, H.U., Jonsson, B., Olesen, J., 2011.. Cost of disorders of the brain in Europe 2010.. Eur. Neuropsychopharmacol. 21, 718–779.

Hannesdottir, D.K., Sigurjonsdottir, S.B., Njardvik, U., Ollendick, T.H., 2018. Do youth with separation anxiety disorder differ in anxiety sensitivity from youth with other anxiety disorders? Child Psychiatry Hum. Dev. 49, 888–896.

Hayes, A.F., 2018. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach, 2nd ed. Guilford Press, New York.

Hesser, H., Weise, C., Rief, W., Andersson, G., 2011. The effect of waiting: a meta-analysis of wait-list control groups in trials for tinnitus distress. J. Psychosom. Res. 70, 378–384.

Hovenkamp-Hermelink, J., Jeronimus, B.F., Myroniuk, S., Riese, H., Schoevers, R.A., 2021. Predictors of persistence of anxiety disorders across the lifespan: a systematic review. Lancet Psychiatry 8, 428–443.

Kenardy, J., McCafferty, K., Rosa, V., 2003. Internet-delivered indicated prevention for anxiety disorders: a randomized controlled trial. Behav. Cogn. Psychother. 31, 279–289.

Keough, M.E., Schmidt, N.B., 2012. Refinement of a brief anxiety sensitivity reduction intervention. J. Consult. Clin. Psychol. 80, 766–772.

Kessler, R.C., Petukhova, M., Sampson, N.A., Zaslavsky, A.M., Wittchen, H.U., 2012. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int. J. Methods Psychiatr. Res. 21, 169–184.

Knapp, A.A., Feldner, M., Allan, N.P., Schmidt, N.B., Keough, M.E., Leen-Feldner, E.W., 2020. Test of an anxiety sensitivity amelioration program for at-risk youth (ASAP-Y). Behav. Res. Ther. 126, 103544.

Lambert, S.F., McCreary, B.T., Preston, J.L., Schmidt, N.B., Joiner, T.E., Ialongo, N.S., 2004. Anxiety sensitivity in African-American adolescents: evidence of symptom specificity of anxiety sensitivity components. J. Am. Acad. Child Adolesc. Psychiatry 43, 887–895.

Lijster, J.M., Dierckx, B., Utens, E.M., Verhulst, F.C., Zieldorff, C., Dieleman, G.C., Legerstee, J.S., 2017. The age of onset of anxiety disorders. Can. J. Psychiatry 62, 237–246.

Mah, L., Szabuniewicz, C., Fiocco, A.J., 2016. Can anxiety damage the brain? Curr. Opin. Psychiatry 29, 56–63.

Maltby, N., Mayers, M.F., Allen, G.J., Tolin, D.F., 2005. Anxiety sensitivity: stability in prospective research. J. Anxiety Disord. 19, 708–716.

Manicavasagar, V., Silove, D., Wagner, R., Drobny, J., 2003. A self-report questionnaire for measuring separation anxiety in adulthood. Compr. Psychiatry 44, 146–153.

Meier, S.M., Petersen, L., Mattheisen, M., Mors, O., Mortensen, P.B., Laursen, T.M., 2015. Secondary depression in severe anxiety disorders: a population-based cohort study in Denmark. Lancet Psychiatry 2, 515–523.

Moreno-Peral, P., Conejo-Ceron, S., Rubio-Valera, M., Fernandez, A., Navas-Campana, D., Rodriguez-Morejon, A., Motrico, E., Rigabert, A., Luna, J.D., Martin-Perez, C., Rodriguez-Bayon, A., Ballesta-Rodriguez, M.I., Luciano, J.V., Bellon, J.A., 2017. Effectiveness of psychological and/or educational interventions in the prevention of anxiety: a systematic review, meta-analysis, and meta-regression. JAMA Psychiatry 74, 1021–1029.

Muris, P., Schmidt, H., Merckelbach, H., Schouten, E., 2001. Anxiety sensitivity in adolescents: factor structure and relationships to trait anxiety and symptoms of anxiety disorders and depression. Behav. Res. Ther. 39, 89–100.

Norr, A.M., Allan, N.P., Reger, G.M., Schmidt, N.B., 2018. Exploring the pathway from anxiety sensitivity intervention to suicide risk reduction: chained mediation through anxiety and depressive symptoms. J. Affect. Disord. 231, 27–31.

Ocanez, K.L., McHugh, R.K., Otto, M.W., 2010. A meta-analytic review of the association between anxiety sensitivity and pain. Depress. Anxiety 27, 760–767.

Paulus, M.P., 2013. The breathing conundrum-interoceptive sensitivity and anxiety. Depress. Anxiety 30, 315–320.

Paulus, M.P., Stein, M.B., 2010. Interoception in anxiety and depression. Brain. Struct. Funct. 214, 451–463.

Reiss, S., McNally, R., 1985. Expectancy model of fear. In: Reiss, S., Bootzin, R. (Eds.), Theoretical Issues in Behavior Therapy Inside. Academic Press, San Diego, CA.

Roberson-Nay, R., Eaves, L.J., Hettema, J.M., Kendler, K.S., Silberg, J.L., 2012. Childhood separation anxiety disorder and adult onset panic attacks share a common genetic diathesis. Depress. Anxiety 29, 320–327.

Schiele, M.A., Bandelow, B., Baldwin, D.S., Pini, S., Domschke, K., 2020a. A neurobiological framework of separation anxiety and related phenotypes. Eur. Neuropsychopharmacol. 33, 45–57.

Schiele, M.A., Domschke, K., 2018. Epigenetics at the crossroads between genes, environment and resilience in anxiety disorders. Genes Brain Behav. 17, e12423.

Schiele, M.A., Gottschalk, M.G., Domschke, K., 2020b. The applied implications of epigenetics in anxiety, affective and stress-related disorders - a review and synthesis on psychosocial stress, psychotherapy and prevention. Clin. Psychol. Rev. 77, 101830.

Schmidt, N.B., Allan, N.P., Knapp, A.A., Capron, D., 2019. Targeting anxiety sensitivity as a prevention strategy. In: Smits, J.A.J., Otto, M.W., Powers, M.B., Baird, S.O. (Eds.), The Clinician's Guide to Anxiety Sensitivity Treatment and Assessment. Academic Press, pp. 145–178.

Schmidt, N.B., Capron, D.W., Raines, A.M., Allan, N.P., 2014. Randomized clinical trial evaluating the efficacy of a brief intervention targeting anxiety sensitivity cognitive concerns. J. Consult. Clin. Psychol. 82, 1023–1033.

Schmidt, N.B., Eggleston, A.M., Woolaway-Bickel, K., Fitzpatrick, K.K., Vasey, M.W., Richey, J.A., 2007. Anxiety sensitivity amelioration training (ASAT): a longitudinal primary prevention program targeting cognitive vulnerability. J. Anxiety Disord. 21, 302–319.

Schmidt, N.B., Lerew, D.R., Jackson, R.J., 1997. The role of anxiety sensitivity in the pathogenesis of panic: prospective evaluation of spontaneous panic attacks during acute stress. J. Abnorm. Psychol. 106, 355–364.

Schmidt, N.B., Lerew, D.R., Jackson, R.J., 1999. Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: replication and extension. J. Abnorm. Psychol. 108, 532–537.

Schmidt, N.B., Lerew, D.R., Joiner, T.E., 2000a. Prospective evaluation of the etiology of anxiety sensitivity: test of a scar model. Behav. Res. Ther. 38, 1083–1095.

Schmidt, N.B., Norr, A.M., Allan, N.P., Raines, A.M., Capron, D.W., 2017. A randomized clinical trial targeting anxiety sensitivity for patients with suicidal ideation. J. Consult. Clin. Psychol. 85, 596–610.

Schmidt, N.B., Raines, A.M., Allan, N.P., Zvolensky, M.J., 2016. Anxiety sensitivity risk reduction in smokers: a randomized control trial examining effects on panic. Behav. Res. Ther. 77, 138–146.

Schmidt, N.B., Woolaway-Bickel, K., Trakowski, J., Santiago, H., Storey, J., Koselka, M., Cook, J., 2000b. Dismantling cognitive-behavioral treatment for panic disorder: questioning the utility of breathing retraining. J. Consult. Clin. Psychol. 68, 417.

Schmidt, N.B., Zvolensky, M.J., Maner, J.K., 2006. Anxiety sensitivity: prospective prediction of panic attacks and Axis I pathology. J. Psychiatr. Res. 40, 691–699.

Shear, K., Jin, R., Ruscio, A.M., Walters, E.E., Kessler, R.C., 2006. Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication. Am. J. Psychiatry 163, 1074–1083.

Silove, D., Alonso, J., Bromet, E., Gruber, M., Sampson, N., Scott, K., Andrade, L., Benjet, C., Caldas de Almeida, J.M., De Girolamo, G., de Jonge, P., Demyttenaere, K., Fiestas, F., Florescu, S., Gureje, O., He, Y., Karam, E., Lepine, J.P., Murphy, S., Villa-Posada, J., Zarkov, Z., Kessler, R.C., 2015. Pediatric-onset and adult-onset separation anxiety disorder across countries in the world mental health survey. Am. J. Psychiatry 17, 647–656.

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de, Pablo G., Il, Shin J., Kirkbride, J.B., Jones, P., Kim, J.H., Kim, J.Y., Carvalho, A.F., Seeman, M.V., Correll, C.U, Fusar-Poli, P., 2021. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol. Psychiatry.

Stanley, I.H., Boffa, J.W., Rogers, M.L., Hom, M.A., Albanese, B.J., Chu, C., Capron, D.W., Schmidt, N.B., Joiner, T.E., 2018. Anxiety sensitivity and suicidal ideation/suicide risk: a meta-analysis. J. Consult. Clin. Psychol. 86, 946–960.

Stewart, S.H., Peterson, J.B., Pihl, R.O., 1995. Anxiety sensitivity and self-reported alcohol consumption rates in university women. J. Anxiety Disord. 9, 283–292.

Stewart, S.H., Zvolensky, M.J., Eifert, G.H., 2001. Negative-reinforcement drinking motives mediate the relation between anxiety sensitivity and increased drinking behavior. Pers. Individ. Dif. 31, 157–171.

Ströhle, A., Gensichen, J., Domschke, K., 2018. The diagnosis and treatment of anxiety disorders. Dtsch. Arztebl. Int. 155, 611–620.

Taylor, S., Koch, W.J., Woody, S., McLean, P., 1996. Anxiety sensitivity and depression: how are they related? J. Abnorm. Psychol. 105, 474.

Taylor, S., Zvolensky, M.J., Cox, B.J., Deacon, B., Heimberg, R.G., Ledley, D.R., Abramowitz, J.S., Holaway, R.M., Sandin, B., Stewart, S.H., Coles, M., Eng, W., Daly, E.S., Arrindell, W.A., Bouvard, M., Cardenas, S.J., 2007. Robust dimensions of anxiety sensitivity: development and initial validation of the Anxiety Sensitivity Index-3. Psychol. Assess. 19, 176–188.

Telch, M.J., Lucas, J.A., Schmidt, N.B., Hanna, H.H., Jaimez, T.L., Lucas, R.A., 1993. Group cognitive-behavioral treatment of panic disorder. Behav. Res. Ther. 31, 279–287.

Waszczuk, M.A., Zavos, H.M., Eley, T.C., 2013. Genetic and environmental influences on relationship between anxiety sensitivity and anxiety subscales in children. J. Anxiety Disord. 27, 475–484.

Westling, B.E., Öst, L.-G., 1999. Brief cognitive behaviour therapy of panic disorder. Scand. J. Behav. Ther. 28, 49–57.

WHO, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization, Geneva Licence: CC BY-NC-SA 3.0 IGO.

Wild, D., Grove, A., Martin, M., Eremenco, S., McElroy, S., Verjee-Lorenz, A., Erikson, P., 2005. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Heal 8, 94–104.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010.. Eur. Neuropsychopharmacol. 21, 655–679.

Zvolensky, M.J., Schmidt, N.B., 2003. Panic disorder and smoking. Clin. Psychol. 10, 29–51.

Zvolensky, M.J., Schmidt, N.B., 2007. Introduction to anxiety sensitivity: recent findings and new directions. Behav. Modif. 31, 139–144.