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Subjective and physiological reactivity to flight in people with fear of flying

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Chapter 8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

The main aim of the empirical studies in this thesis was to increase the available knowledge on individual differences in subjective and physiological reactivity to flight (related) stimuli in people with serious fear of flying. A second objective was to elucidate the added value of psychophysiological measures for diagnosis of aviophobia and for prognosis of treatment outcome. This final chapter summarizes and discusses the findings of the empirical studies.

SUMMARY OF RESULTS

Chapter 2

The question addressed in chapter two was whether aviophobics have an exaggerated physiological arousal that leads to an exaggerated subjective arousal during exposure to anxiety-related stimuli, or whether the exaggerated subjective arousal is caused by misinterpretation of normal bodily sensations as is often the case with individuals high on anxiety sensitivity. We found that aviophobic participants reported significantly higher levels of subjective fear than did control participants when exposed to a video with flight-related stimuli. In contrast, on average the three physiological variables (heart rate (HR), respiratory sinus arrhythmia (RSA), and pre-ejection period (PEP)) did not differ between the two groups, although the phobic participants showed a much stronger variation in cardiac parasympathetic reactivity. Anxiety sensitivity did not moderate the relationship between self-reported anxiety and recorded physiological arousal. These results emphasize the heterogeneous nature of aviophobia, with large inter-individual differences in reactivity to stimuli of low ecological validity (Bornas et al. 2004, 2005, 2006).

Chapter 3

Graded in-vivo exposure with aviophobics is challenging, and especially the last step. To board, or not to board, that is the question. A little boarding does not exist. Cognitive interventions prior to in-vivo exposure increase confidence in the ability to handle the last step. Another helpful tool to ease anxiety associated with the last step is graded exposure by means of Virtual Reality. This technique enables cost-effective often-repeated exposures, as well as exposure graded according to a fear hierarchy (Powers and Emmelkamp 2008). Therapists monitor the anxiety levels, and patients accordingly progress through their fear hierarchy. Basal to this approach are reliable and valid

indicators of anxiety and arousal, preferably with a baseline measurement in a neutral virtual world. Chapter 3 describes two studies on baseline measurements in Virtual Reality. In the first study both phobic and non-phobic participants showed higher heart rates during exposure in a neutral virtual world than in a virtual world with phobic stressors, and in the recovery phase after the VR exposure. This led to the conclusion that the previously used neutral world (Schuemie 2003) was probably not truly neutral after all. In the second study, we presented a new neutral world that closely replicated the actual room where the individual was situated, so that participants would see the same environment when they put on or removed the head mounted display. Both subjective accounts of anxiety and physiological indicators of arousal indicated that it is indeed possible to design a truly neutral VR world that can be used for baseline measurements in therapy and research. Furthermore, despite reports in the literature, we did not find indications that the novelty of the virtual environment caused arousal (Wiederhold et al. 1998; Jang et al. 2002; Wiederhold and Wiederhold 2005) or that a virtual world would by definition generate arousal and anxiety (Wiederhold and Wiederhold 2005; Parsons and Rizzo 2008; Powers and Emmelkamp 2008).

Chapter 4

The research question in chapter 4 was whether anxiety sensitivity (AS) moderated the effects of somatic sensations and autonomic nervous system (ANS) reactivity on flight anxiety induced by actual flight. Results indicated no moderating effect of AS on the relationship between self-reported somatic sensations and flight anxiety. However, physiological reactivity did interact with AS: changes over flights in HR and parasympathetic activity were associated more strongly with flight anxiety changes from pre-treatment to post-flight for participants with high AS, and less strongly for participants with low AS. This seems to contradict results from chapter 2, in which aviophobic participants who scored high on anxiety sensitivity did not report more distress than phobics who scored low on this trait, even when showing stronger physiological responses to a video with flight-related material. Differences in outcome may be due to the low ecological validity of the video stimulus that generated only mild physiological reactivity (chapter 2), whereas participants in chapter 4 showed great physiological reactivity to actual flight. The absence of a moderating effect of AS on somatic sensations in both studies could be due to a ceiling effect. Aviophobics generally score high on reporting somatic sensations related to flight, as was also the case in these studies.

Chapter 5

The focus of the study in chapter 5 was on (changes in) cognitive coping in relation to long-term treatment outcomes. Results indicated that the pre-treatment use of cognitive coping strategies was not predictive of therapy outcome. However, participants were in a long-term process of change that, even in cases of maladaptive cognitive coping strategies, continued positively after therapy. Aviophobic participants showed clinically significant improvement in cognitive coping strategies, from pre-treatment scores matching those of dysfunctional populations to post-treatment responses matching those of a normal population. A greater increase in the use of adaptive coping strategies, and more importantly, a greater decrease in the use of maladaptive coping strategies during therapy were indicative of less long-term relapse of flight anxiety and more flights flown within three years after treatment. To our knowledge this is the first study to report the predictive value of changes in coping strategies during treatment for subsequent clinical change within the anxiety domain.

Chapter 6

This study examined the notion that fear activation and habituation during exposure to flight (related) stimuli are indicators of successful emotional processing and therefore predictive of treatment outcome. Participants showed strong fear activation during simulated and actual flight, combined with diminishing physiological and subjective responses. However, results only partially corroborated the EPT expectations. HR habituation during the first exposure flight, and increase in parasympathetic activity over the second exposure flight, were predictive of less flight anxiety on the short-term, but not of flight anxiety three years after finishing therapy, or of long-term flying behaviour. Within-session and between-session habituation of self-reported distress was not associated with treatment outcome. These results correspond to findings of a recent systematic quantitative review of the association of the three EPT process variables (IFA, WSH and BSH) and indicators of treatment outcome after exposure therapy for people diagnosed with an anxiety disorder (Rupp et al. 2016); BSH and WSH were (not significantly) positively related to treatment outcome, while IFA was not associated with outcome. Physiological process measurements led to higher correlations with treatment outcome than did self-report measurements and were regarded to be more valid indicators of fear network activation. Positive treatment outcome in this review was defined as any improvement in pre-post difference scores. No details were provided on the timing of post-treatment measurements.

Chapter 7

The research question in chapter 7 was whether synchronous change in subjective and physiological reactivity over repeated exposures increased with the intensity of emotional stimuli, and whether the magnitude of synchronous change during treatment predicted short- and long-term treatment outcome. Very few studies have reported evidence of synchrony, despite the recent growth of interest in the relationship between emotional expression and patterns of ANS activity (Hollenstein and Lanteigne 2014; Levenson 2014a; Benoit Allen et al. 2015). It was thought that this was caused by the generally low intensity and low ecological validity of the stimuli used. Results in the present study, despite the broad range from low intensity video-stimuli to intense phobic fear provocation during actual flight, did not show a relationship between the intensity of the phobic stimuli and the magnitude of synchronous change in subjective and physiological reactivity. Furthermore, results provided no support for the functionalistic view that successful treatment of anxiety disorders is indicated by synchronous change across emotional response systems. Participants showed marked subjective and physiological reactivity, and marked changes across repeated exposures, especially in the actual flight condition. Nevertheless, at group level, these intense and ecologically very valid stimuli did not evoke synchronous change in self-reported and physiological reactivity. Within-subject synchronous change in the two systems was not indicative of short-term and long-term treatment results.

DISCUSSION OF RESULTS

People with aviophobia do not form a homogeneous group. Aviophobia is a heterogeneous phenomenon with large individual differences in the onset and acquisition of the phobia, severity of symptoms and above all comorbidity with other phobias and other anxiety disorders. The empirical research in this thesis focused on individual differences in subjective- and physiological reactivity to flight (related) stimuli. Results of these studies are mixed and difficult to fit into existing theoretical models. As often the case, results from empirical studies add complexity to attractive theoretical perspectives. Our results did not corroborate the expectations derived from emotional processing theory. Neither did results support the evolutionary and functionalistic view that the magnitude of synchrony between emotional response systems is an indication of successful treatment outcome.

Aviophobic participants showed large subjective fear reactivity to videos with flight related material, simulated flight and actual flight, and large within-session and between-session habituation of subjective fear reactivity during simulated flight and actual flight. However, only individual subjective fear reactivity shortly before actual flight exposure, and subjective fear reactivity during actual flight, were related to post-flight and long-term treatment outcome.

Aviophobic participants showed a much stronger variation in the direction of heart rate reactivity and parasympathetic reactivity to the video stimuli than did control participants without aviophobia. This led to the conclusion that before the start of treatment some participants reacted with a typical flight-fight response, while others reacted with a prototypical passive coping response (freeze). Psychophysiological reactivity to the video stimuli was not predictive of treatment outcome. Participants showed strong physiological fear activation during simulated and actual flight, and significant within-session and between-session habituation of physiological reactivity during simulated and actual flight. Heart rate habituation during simulated and actual flight, and increase of parasympathetic activity over actual flight, were associated with less flight anxiety on the short-term, but not with flight anxiety three years after finishing therapy, or with long-term flying behaviour. Heart rate reactivity at the end of in-vivo exposure was the only physiological variable that was associated with long-term treatment outcome.

Anxiety sensitivity did not moderate the relation of self-reported somatic sensations with flight anxiety during flight, however the relation of HR and parasympathetic reactivity with flight anxiety was stronger in participants with higher levels of anxiety sensitivity. The addition of physiological markers of arousal strengthened the model of cognitive misinterpretation of bodily sensations (chapter 4). Furthermore, the addition of physiological markers of arousal led to the conclusion that a supposedly neutral VR world was not neutral after all (chapter 3), an inference that had not been possible only with subjective indications of anxiety.

Sympathetic reactivity, as measured by pre-ejection period, showed no relationship with short- or long-term treatment outcomes. This could indeed indicate that changes in sympathetic activity are not related to outcomes of therapeutic interventions. Or it could indicate that in the present research we did not effectively capture sympathetic activity. Although the PEP is currently the measure of choice for psychophysiological stress research in real life settings (Goedhart et al. 2006; Neijts et al. 2015), it has several disadvantages. Scoring requires identification of the onset of the Q wave, which can be

ambiguous. In about 20% of all recordings the Q wave is not clear, or even visible (Lien et al. 2015). Recently, research on two alternatives for the PEP has emerged. Lien et al. (2015) reported on the ECG-T wave amplitude (TWA) as an alternative ambulatory sympathetic measure. The TWA requires only an ECG signal, making it even less cumbersome for participants than a PEP measurement that requires a combination of ECG and ICG. Furthermore, the TWA requires less laborious visual scoring and seems more open to automation than PEP scoring. TWA could be reliably extracted in over 90% of a group of 564 healthy adults being followed for 24 hours. However, within-participant changes in TWA and PEP correlated significantly in only 75% of the participants. A second, more promising, alternative might be to use the R peak instead of Q-onset to calculate PEP. The R peak is the clearest component of the ECG and is easily and precisely identifiable (Sherwood et al. 1990). Like TWA, the R peak is also more amenable to automated identification than is the onset of Q. In several laboratory experiments with a total of 408 healthy young adults, Seery et al. (2016) examined the relationship between PEP based on Q identification and PEP based on R identification. Absolute levels of R-peak defined PEP accounted for nearly 90% of the variance in absolute levels of traditionally defined PEP. More importantly, within-person reactivity R-peak defined PEP accounted for over 98% of the variance in traditionally Q-defined PEP. However, responses were measured during resting or minimally metabolically demanding tasks, thereby limiting generalization. Future research under naturalistic and ambulatory conditions seems warranted. Sympathetic activity in the present dissertation was assessed by a traditional scoring method using the onset of the Q wave.

Higher vagal tone and greater vagal withdrawal during challenge have been associated with a better ability to engage with and disengage from environmental demands, and reduced HRV and reduced vagal tone have been associated with anxiety (Friedman 2007; Chalmers et al. 2014). Lower vagal control has been linked to less adaptive emotion regulation. Mathewson et al. (2013) report that greater RSA reactivity (appropriate parasympathetic withdrawal to manageable stress) was associated with greater reduction of self-reported social anxiety. High levels of adaptive variability, as e.g. indicated by respiratory arrhythmia, characterize a healthy autonomic nervous system, although Beauchaine (2015) reports that excessive RSA reactivity (i.e. withdrawal) to emotional challenge is associated with symptoms of psychopathology. There is increasing evidence that non-specific vulnerability to psychopathology is reflected by low resting RSA and excessive reduction in RSA during emotion evocation, through prefrontal cortex feed-forward and feedback connections with the amygdala (Beauchaine 2015). RSA could be a transdiagnostic biomarker of emotional dysregulation, consistent with the

Research Domain Criteria (RDoC), that classifies psychopathology based on dimensions of observable behaviour and biological measures instead of traditional categorical and symptom-oriented diagnostic criteria (Lang 2014; Beauchaine 2015; Nees et al. 2015). Aviophobic participants in the present study showed a much stronger variation in the direction of cardiac parasympathetic reactivity than controls when exposed to a video with flight-related stimuli (chapter 2). Increased parasympathetic habituation over actual flight was associated with less reported flight anxiety after flight (chapter 6), while results from chapter 4 indicate that lower RSA reactivity over actual flights was associated with a stronger decrease in flight anxiety from beginning to end of therapy. In view of these mixed outcomes it seems that RSA reactivity is neither a valid and reliable diagnostic instrument to classify aviophobia, nor a reliable indicator of progress of therapy and therapy outcome for people with severe fear of flying. Further research seems warranted to examine whether HRV can supplement standard outcome measures in the treatment of aviophobia. Additionally, HRV could also be the target of intervention, based on the idea that improved HRV parameters are associated with less distress (Friedman 2007; Lehrer and Gevirtz 2014). Future research on HRV targeted intervention with people with aviophobia also seems warranted.

Heart rate is the resultant of sympathetic and parasympathetic control on the intrinsic rate of the cardiac pacemaker. HR itself does not reveal the sympathetic and parasympathetic ANS cardiac activity. Nevertheless, HR turned out to be a better predictor of treatment outcome than RSA and PEP. Higher HR habituation over actual flight predicted stronger decrease in flight anxiety from beginning to end of therapy (chapter 4 and chapter 7) and less flight anxiety after the exposure flight (chapter 4, and chapter 6). Furthermore, participants with a greater decrease in HR over simulated flight reported a greater decrease in flight anxiety from beginning to end of therapy than participants with less diminution of HR over the simulated flights (chapter 7). Finally, HR turned out to be the only physiological variable associated with long-term treatment outcome; lower HR reactivity at the end of the exposure flights was associated with less flight anxiety three years after treatment. The combination of HR reactivity still present after in-vivo exposure with SUD reactivity just before in-vivo exposure explained 29% of the variance in reported flight anxiety three years after treatment (chapter 6). Interestingly, these prognostic variables for long-term treatment outcome were all centred around in-vivo exposure. Although Seligman's (1971) proposition that phobias are highly resistant to extinction has been proven wrong (e.g. Ost et al. 1997), he correctly noted that phobias seem quite resistant to change by "cognitive means" alone (McNally 2016).

Cognitive changes during therapy proved highly influential for therapy outcome (chapter 5). Participants showed clinically significant improvement in cognitive coping strategies, from pre-treatment scores matching those of dysfunctional populations to post-treatment responses matching those of a normal population. Individual differences in changes in coping style during treatment until short-term follow-up were predictive of changes in flight anxiety from short-term follow-up to 3 years later. The additional explained variance in flight anxiety by changes in primarily maladaptive coping style over and above changes in flight anxiety during treatment was 21%. The additional explained variance of flights taken by changes in adaptive and maladaptive coping style over changes in flight anxiety was 12% (chapter 5). Participants in this study followed CBT, with cognitive therapy preceding behavioural components, including exposure in vivo. Studies on the additive value of cognitive interventions report mixed results; some studies reported enhanced treatment outcomes when cognitive interventions were added to behavioural treatment, whereas others reported no effects (for details see Raes et al. 2011 page 965; Ramnero 2012; Wolitzky-Taylor et al. 2008). For example, one of the few studies that investigated the ancillary support of cognitive interventions during CBT for specific phobias randomly assigned 31 spider phobic participants to graded exposure with or without cognitive interventions (Raes et al. 2011). Both groups benefited equally from treatment, and both groups showed a nearly equal decrease in phobia-related cognitions. Attrition rates seem to benefit from a combination that includes cognitive interventions (Ramnero 2012).

Delineating the effect of individual treatment components of CBT has been proven difficult. It is conceivable that fear extinction might take place by different pathways or mechanisms: either by behavioural pathways through exposure, or via cognitive pathways through cognitive restructuring. Another conceivable pathway is a combination of both mechanisms, in which each mechanism strengthens the other. Cognitive interventions facilitate exposure; subsequent exposure facilitates cognitive change, diminishing avoidance and lowering the threshold for further exposure that in turn will lead to additional cognitive change, and so on in a self-reinforcing process.

We did not relate changes in coping to psychophysiological arousal. Luck and Lipp (2015), in a study on instructed extinction with 80 healthy undergraduate students, reports that negative valence acquired during fear conditioning might be less responsive to cognitive interventions, while physiological indices of fear learning responded well to the same cognitive intervention. If residual negative valence persists after extinction, relapse of fear is plausible when the person is put in a high arousal situation (Kerkhof et al. 2011;

Zbozinek et al. 2015). Future research on the association of physiological markers of fear and changes in coping style over therapy could shed light on the differential time paths of fear extinction, as well as the possible use of biomarkers as indicators of cognitive treatment gains and predictors of relapse.

Interestingly, in our study higher levels of self-reported fear pre-exposure, but not physiological indicators of fear pre-exposure, were related to poorer long-term treatment outcome (chapter 6). High levels of anticipatory self-reported fear pre-exposure could indicate that participants are not yet ready to face their phobic fear; this may lead to (cognitive) avoidance. Avoidance is a maladaptive coping style that is strongly associated with negative treatment outcome and may constitute an important maintaining process in phobias (Hendriks et al. 2013; Boettcher et al. 2016; Spinhoven et al. 2016). If participants are no longer able to tolerate their phobic anxiety during exposure, extinction learning will not take place (Bouton 2004; Craske et al. 2008). The association of higher self-reported distress activation during the first exposure flight with higher levels of flight anxiety after exposure, and fewer flights flown in the three years after therapy, might as well be an indication of experiential avoidance impeding successful emotional processing.

STRENGTHS AND LIMITATIONS

A major strength of the studies described in this thesis is the use of a relatively large clinical sample of participants seeking treatment, in combination with in-vitro and in-vivo exposure and concurrent physiological measurement. Very few studies have been published with comparable numbers of clinical aviophobic patients undergoing real life exposure, and if so, mostly are without psychophysiological assessment. Chapter 4 gives a comprehensive overview. Oakes and Bor (2010) also provide an extensive review of fear of flying intervention studies with and without physiological assessment. Another positive feature of the studies is the use of two entirely different clinically relevant long-term outcome measures: a self-report measure indicating flight anxiety and a behavioural measure indicating flight behaviour.

All studies in this thesis were conducted at a treatment facility, not at a research facility. Participants were highly anxious aviophobics who applied for treatment, and all participants paid for their treatment. Although this setting considerably limited the research options, at the same time it produced ecologically highly valid results. Stress

induced in a laboratory setting is by definition artificial. However, laboratory-based research facilitates multimodal assessment that makes it possible to capture variations that might not be apparent when using a limited number of measures in ambulatory conditions. We used the VU-AMS (www.vu-ams.nl) to record ECG and ICG unobtrusively and continuously during all phases of the treatment process, including actual flight. All questionnaire data were collected before or after therapeutic interventions and experimental conditions; only during flight was there a perfect overlap between physiological recording and the verbally administered SUDs. New technological developments enable Ecological Momentary Assessment (EMA) procedures that assess emotional state by means of tablets and smartphones to overcome the retrospective reporting bias when emotional state is assessed retrospectively (Conner and Barrett 2012). Furthermore, EMA provides possibilities to study emotion regulation in the complex context of everyday life. Most laboratory-based studies have focused on regulation of specific emotions in isolation (Aldao and Tull 2015; Sims et al. 2015). Emerging technologies, however, allow for concurrent multimodal psychophysiological, subjective, and behavioural assessments in ambulatory, naturalistic settings (Seeley et al. 2015). We analysed physiological data off-line after the therapeutic intervention or experimental condition. The VU-AMS has an event marker and an integrated accelerometer. Both the therapist and the accompanying pilot kept a detailed log during both exposure flights. All these resources were used to select movement-free and artefact-free periods that lasted at least 5 minutes each as close as possible around the times when the SUDs were collected. Still, some HR, RSA and PEP changes could have been caused by metabolic needs, although during flight, when patients sit quietly, physiological activation is mainly caused by perceived stress and not physical activity (Roth 2005). Promising new ambulatory technologies and new algorithms allow for assessment of changes in cardiac parameters that are not due to metabolic needs. Verkuil et al. (2016) provided a proof of principle in a healthy sample of 51 young students. After a short person-specific calibration procedure (including sitting, standing, lying down, cycling and climbing stairs, totalling 15 minutes) participants provided cardiac measures by wearing a chestbelt for 24 hours, and self-report data that were collected hourly with the use of a smartphone. With the help of an automated algorithm the researchers were able to distinguish between prolonged metabolic and non-metabolic HRV reductions in daily life. These and other new techniques would allow for higher sample rates without causing too much of a nuisance for the patients. In our study both exposure flights lasted approximately one hour. The cruise portions of these flights were not long enough to furnish multiple movement-free measurements in the physiological domain in combination with a SUD measurement, without interfering the therapeutic process. Multiple measurements

during flight might have provided better indications of within-session habituation.

Reported success rates of treatment of aviophobia are generally higher than those reported for other anxiety disorders (Van Gerwen et al. 2004; Oakes and Bor 2010). Phobic participants are typically highly motivated and expect the therapy to be effective. Even when not cured of their fear, most of them would report improvement after investing so much in terms of time, money and emotions. This is reflected in outcomes reported by many programmes. Tests of effectiveness based on measures like number of participants taking a “graduation” flight or scores on the severity of anxiety directly after therapy are bound to be overly positive. One could argue that the reported high success rates do not adequately represent effectiveness, but merely indicate motivation and stamina to complete the program. In the current studies, we used self-reports of flight-anxiety and measurements of actual behaviour three years after finishing therapy. Ideally, positive outcome should be reported as clinically significant improvement, defined as pre-treatment scores matching those of dysfunctional populations to post-treatment responses matching those of a normal population (with an additional margin to compensate for individual subjects’ measurement error (Jacobson and Truax 1991; Hinton-Bayre and Kwapil 2017)). Additional assessment before, during and after treatment would have enhanced the research and analytic possibilities and could have provided more indications of clinically significant improvement. However, as noted before, the research setting considerably limited the options. Although we were able to add a few paper-and-pencil questionnaires to the regular battery of questionnaires used in the diagnostic phase, our effort to include the MINI or other structured diagnostic interviews was not honoured. The semi-structured interview during the diagnostic phase yielded information on the present situation and personal history of the participants; it also included questions about other phobic complaints and present emotional state. Moreover, additional questions were included to assess life events during the onset of the flying phobia, information on flying behaviour, flying history, and the phenomenology and determinants of the subjects’ fear of flying. Future research on the relationship between these dimensional variables and long-term outcomes of therapy seem warranted.

Adding extra questionnaires or procedural steps during treatment was not a viable option, and we did not want to burden the participants unnecessarily afterwards. Furthermore, for the 3-year follow-up we had to make a trade-off between probability of response and completeness of data. A 1-year follow-up using written questionnaires with participants from the same treatment facility had previously yielded response rates

of only 50%. In order to increase the probability of response in the present studies, we decided to use a very limited number of questions for the 3-year follow-up. As it is, we are satisfied with the high response rate of 85%. Nevertheless, additional assessment could have provided data for cross-legged panel design analyses. It would be very interesting to conduct a 10-year follow-up with the same group of participants. A comprehensive assessment would definitely ameliorate the analytic possibilities.

Another limitation is that we did not assess additional treatment or the use of alcohol, drugs, and medication between end of treatment and 3-year follow-up. During individual treatment and during the 2-day group therapy, participants received information on the use of alcohol, drugs and medication in relation to anxiety. Participants were made well aware that avoidance behaviour and cognitive avoidance are detrimental for maintenance of their treatment gains, and they were well informed that the use of these substances is equal to avoidance. At the end of treatment participants were urged to make a flight within three months. At the short-term follow-up (three months after end of treatment), 98% of the participants reported that they had indeed made a flight, without the use of alcohol, drugs or medication. However, at the 3-year follow-up we did not explicitly ask participants whether they had sought additional treatment or made use of medication, drugs or alcohol during the flights they self-reported. We left space for comments on the reply form. None of the responders reported additional treatment or the use of medication, drugs or alcohol during the flights. A future follow-up study would do well to include these topics.

Individual behaviour is influenced by the presence of others, and group dynamics is part of cognitive-behaviour group therapy. Group-based treatment has consequences for how individuals respond to treatment within many settings. Participants in the present studies started group-based treatment after the phase of individualized treatment. Group treatment, apart from its beneficial financial aspect, aids the participants in imparting information, gaining self-understanding, and sharing emotions. Additionally, cohesiveness helps them to minimize avoidance behaviour, especially shortly before the in-vivo exposure flights at the end of CBGT. These dynamics could partly explain the high percentage of participants boarding the exposure flights, and might be one of the reasons for the high success rate reported by many other studies on aviophobia. However, it seems unlikely that being part of a group did critically influence the independent and dependent measures used in the studies included in this thesis. SUD-scores were collected privately; members of the group were not aware of each other's scores on this questionnaire. Nevertheless, group-dynamics could have influenced these scores. We

therefore quantified the individual differences in fear activation during exposure to the phobic stimuli as the changes in subjective distress scores and physiological arousal over an appropriate baseline. Short-term effect of therapy outcome was operationalized as the flight anxiety score taken just after the second exposure flight, and again taken privately. Long-term effect of therapy outcome was operationalized as the flight anxiety scores three years after treatment, and number of flights taken in this three-year period. Email was used to gather these data. It is difficult to conceive how group-dynamics could have influenced these data. However, it could be argued from a statistical point of view that we collected repeated measurements on individuals who are nested (or clustered) within (treatment) groups, while we used statistical models (such as ANOVA and linear regression) that assume independent observations. However, given our relatively limited sample size, we refrained from performing statistical analyses such as multilevel models or hierarchical linear models that do not assume independence of observations.

The studies described in chapters 2 and 3 included participants with and without aviophobia; no other studies included control groups or control conditions. Repeating the experiments on non-phobic “regular” flyers would be very problematic, as these experiments place a substantial burden on participants (airport security, in-flight measurement, additional visits to a simulator and sessions for video exposure). In addition, including a no-treatment control condition is not feasible as most participants with aviophobia in a no-treatment control condition will not be able or willing to take a test flight resulting in unacceptable high attrition rates. The specific nature of the treatment in combination with a focus on prediction of long-term outcome based on individual differences in reactivity justifies a within-person design. Furthermore, the considerable changes in flight anxiety, flight behaviour, and cognitive coping (chapter 4) during treatment make it unlikely that these changes in a sample with protracted complaints are merely the results of passage of time or repeated testing. Nevertheless, the study design made it difficult to delineate the effect of individual treatment components. Other limitations to mention are the high attrition rate and missing data. As already described in the separate chapters, we performed extensive missing value analyses on all available physiological variables, as well as on all available questionnaire data and sociodemographic characteristics. Furthermore, when possible, analysing strategies were used that proved robust in dealing with missing cells in repeated-measures data.

CLINICAL IMPLICATIONS

In-vivo exposure is clearly the most important aspect in the treatment of aviophobia. Nevertheless, ancillary therapies could effectively optimize exposure-based interventions and will ultimately result in better short-term and long-term treatment outcomes (Pittig et al. 2016). Flanking enhancement strategies that support preparation and post-exposure processing might facilitate exposure and boost the effect of exposure treatment. Procedural enhancement strategies implemented during actual exposure focus on optimizing fear extinction by maximizing the identification of the mismatch between threat expectancies and actual outcome.

The clinical efficacy of interoceptive exposure for anxiety disorders has been well established (Khalsa and Lapidus 2016), and cognitive restructuring in combination with interoceptive exposure exercises is known to be efficacious in reducing AS (Smits et al. 2008; Boettcher et al. 2016). As problematic interpretation of physiological sensations is profoundly common in many anxiety disorders, interoceptive exposure (IE) could be a helpful transdiagnostic intervention (Boettcher et al. 2016). The processing of disconfirmatory evidence offers patients the opportunity to learn that bodily sensations are not in themselves danger signals. Maximizing opportunities to learn that feared outcomes are less severe than expected, or less likely than expected, and that fear itself is tolerable, requires intense delivery of IE, without arousal-reduction strategies and no between-trial rest periods (Deacon et al. 2013). However, despite the overwhelming evidence of the efficacy of exposure-based treatment, many self-described cognitive-behavioural therapists make infrequent use of therapist-assisted exposure, or even totally omit this most important ingredient (Hipol and Deacon 2013; Powers and Deacon 2013). Hipol and Deacon (2013) report that psychotherapists in the state of Wyoming use IE only sparingly (3% - 12%), although psychotherapists who advertise themselves as specialists in the treatment of anxiety disorders use interoceptive exposure significantly more often (25% - 40%). Although its value is evidence-based, IE is a vastly untapped resource for treatment (Boettcher et al. 2016).

Pre-exposure cognitive interventions aimed at disconfirming maladaptive beliefs and reducing fear may lower the threshold for subsequent exposure, and may prevent cognitive avoidance and disengagement during exposure (Blakey and Abramowitz 2016). Exposure to a feared object or situation without catastrophic consequences provides the phobic individual with an opportunity for corrective experiences and inhibitory learning. Pre-exposure cognitive interventions may boost this effect during exposure by focusing

attention on the discrepancy between maladaptive cognitions and the actual outcome.

The relationship between emotional response systems (chapter 7) is likely affected by many intervening variables, including higher order cognitive processes. We judge and feel emotions about our emotions. Perceiving an emotion as unacceptable, problematic, or aversive instead of normal, can influence the way a person regulates the emotional state itself (Schaefer et al. 2014; Couyoumdjian et al. 2016). A conflict between uncontrollable, automatic phobic reactions and the recognition that the phobic fear response is irrational and even embarrassing may lead to an increased attempt at emotion regulation, in an effort to suppress or control the fear reaction (Schaefer et al. 2014). The time course of emotion subsystems may vary greatly (Hollenstein and Lanteigne 2014; Levenson 2014b), and may vary even more owing to this additional cognitive regulation. Higher order cognitive processes may therefore intervene with the supposititious temporal associations between responses (Mauss et al. 2005; Schaefer et al. 2014). If a side effect of pre-exposure cognitive therapy is a reduction of automatic and coherent responses between domains, then this might lead to a lagged or reduced physiological fear response (Schaefer et al. 2014). Blunted physiological fear responses might diminish the effectiveness of (in-vivo) exposure therapy, as according to emotional processing theory, fear activation is a prerequisite of fear-extinction (Foa and Kozak 1986). Cognitive interventions, aimed at alleviating fear or at promoting regulating strategies that dampen automatic and coherent responses, might therefore better be postponed to after the exposure component of the treatment (Craske et al. 2014b).

Pre-exposure flanking strategies aimed at fear tolerance may aid in reducing avoidance behaviour and may promote extended confrontation with the feared object or situation during exposure. For example, Acceptance and Commitment Therapy (ACT) has shown promising results in facilitating engagement in subsequent exposure, thereby maximizing the mismatch effect when expected aversive events do not happen (Meuret et al. 2012; Roemer et al. 2013; Craske et al. 2014b). Several meta-analyses provide cumulative evidence for the efficacy of this transdiagnostic approach in the treatment of anxiety, with comparable outcomes for CBT and ACT (Craske et al. 2014a; Ost 2014; Landy et al. 2015; Hacker et al. 2016). Distress tolerance might be a moderator in exposure therapy (Asnaani et al. 2016). However, ATC as a stand-alone therapy is liable to high dropout rates (Arch et al. 2012; Dahlin et al. 2016). Emerging technologies allow for pre-exposure flanking therapy at home, with minimal therapist interaction. ATC can be delivered by means of interactive online modules and smartphone assisted guidance (Dahlin et al. 2016; Ivanova et al. 2016). A specialized treatment facility in the Netherlands

developed a mobile phone Flight App with functionalities that diminish pre-flight distress and reduce avoidance tendencies (VALK Fear of Flying App; <https://itunes.apple.com/nl/app/fear-of-flying-app/id501475441>). The app is available in several languages and has been downloaded over 17.000 times. Hartanto et al. (2015) developed a new home-based VRET system that could be used as pre-in-vivo-exposure aid. The system includes HMD, HR sensor, microphone, laptop, and a system manual that guides patients through various steps of therapy. Therapists can monitor progress remotely and can amend their treatment plan. SUD's and HR are available to determine anxiety level.

Several procedural enhancement strategies are available. First of all, most anxiolytics like benzodiazepines are known to impair fear extinction and should, as far as possible, be banned during the therapeutic process (Wilhelm and Roth 1997; Singewald et al. 2015). Benzodiazepines provide short-term relief but significantly diminish the effects of treatment for anxiety and hinder long-term effects of extinction (Graham et al. 2014). Pharmacological agents that work as cognitive enhancers (d-cycloserine, oxytocin, yohimbine et cetera) have gained considerable attention lately (see Hofmann et al. 2015a for a concise review, and; Singewald et al. 2015 for a more extensive review). D-cycloserine has shown promising results during CBT, although the optimal dosing and dose timing proved difficult (Hofmann et al. 2015b; Otto et al. 2016). The agent enhances cognitive processes not only during extinction learning but also augments fear memory reconsolidation (Hofmann 2014 “making good exposures better and bad exposures worse”).

Non-pharmacological procedural strategies are mostly aimed at increasing threat expectancies to augment their violation. For example, removal of safety signals and safety behaviours will increase threat expectancies and augment extinction learning because the mismatch between expected catastrophic outcome and actual outcome is not associated with the safety signals and behaviours (Craske et al. 2014b). Increasing the variability and context of extinction training facilitates maintenance of treatment gains and supports relapse prevention (Laborda et al. 2011; Swan et al. 2016). External functional mediators may facilitate treatment gains and generalization of gains. For example, a telephone app designed to be used during in-vivo exposure might prompt users to use the skills learned in treatment (Swan et al. 2016).

While exposure therapy generally advocates the removal of safety behaviours, recent publications focus on the beneficial effects of incorporating safety behaviours during exposure (Goetz et al. 2016; Meulders et al. 2016). For one, safety behaviours aid in

engaging and enduring exposures that without safety behaviour would not be tolerated, thereby giving the opportunity to generate non-threat associations (Goetz et al. 2016). The use of safety behaviours during exposure enhances the acceptability and tolerability of the intervention, and promotes greater distress tolerance (Blakey and Abramowitz 2016). A solution for dropout and refusal to undergo exposure therapy may involve the judicious use of safety behaviours (e.g. cell phones or the presence of other persons: social conversation is a safety behaviour) to enhance the acceptability of exposure-based interventions (Levy and Radomsky 2014; Goetz et al. 2016). The already mentioned mobile VALK Flight App features functionalities like relaxation exercises and a “panic button” that activates an audio message aimed at decreasing tension levels. Meulders et al. (2016), in a meta-analytic review, did not find compelling evidence to support either the removal or addition of safety behaviours during exposure. However, Goetz et al. (2016) in their review conclude that (restorative) safety behaviours that augment confrontation with a core threat do not interfere, whereas (preventive) safety behaviours that hinder engagement during exposure effectively blunt emotional processing and weaken the outcome of exposure interventions. However, most of the reviewed studies measured outcome during or directly after treatment or intervention; long-term treatment successes have not been reported (Goetz et al. 2016; Meulders et al. 2016). Safety behaviours performed in the absence of real threat do not increase survival and paradoxically could give rise to and maintain anxiety (Blakey and Abramowitz 2016). Safety behaviours and safety aids may infer imminent threat, increase perception of threatening stimuli, and direct attentional resources away from disconfirmatory information; “*if a safety aid is present, there must be danger*” (Blakey and Deacon 2015, page 264). To summarize, the use of safety behaviours at the beginning of exposure therapy might aid patients in engaging in exposure and enduring the temporary distress that is an inherent part of exposure treatment. Mobile technology might serve as a mechanism delivering safety signals that enhance willingness to endure the exposure. These technologies would allow for judicious use of safety behaviours, fading through consecutive exposures (Goetz et al. 2016). Balancing the opposing effects of safety behaviours and safety aids requires individualized tailored intervention strategies prior to, during, and after exposure (Pittig et al. 2016). Ultimately these safety behaviours should be eliminated to maximize the effect of exposure therapy (Craske et al. 2014b; Pittig et al. 2016).

Post-exposure coping interventions may be beneficial for reinforcing extinction learning and consolidating treatment gains (Vervliet et al. 2013; Craske et al. 2014b). Verbally going through the exposure experience after the actual exposure, and emphasizing the contrast between the anticipated outcome and the actual experience, can reinforce

extinction learning. This will strengthen the perceived ability to handle frightening situations, diminish avoidance, and consolidate treatment progress (Craske et al. 2014b; Clark and Rock 2016). Research on the therapeutic efficacy of post-exposure coping interventions is still in its infancy.

SUGGESTIONS FOR FUTURE RESEARCH

Most suggestions for future research have already been mentioned above, the most important are here recapitulated. To start with the most obvious one, a 10-year follow-up with the same group of participants would be very informative. This should involve a comprehensive assessment, also of additional treatment and the use of alcohol, drugs and medication before and during flight.

Integral to science are replication, expansion of existing work and refutation of previous findings. Emerging technologies and developments in software will facilitate ecological momentary assessment along with continuous physiological measurement in therapeutic settings without interfering with the therapeutic process. Hopefully these innovations will stimulate replication and expansion of the present research. Moving beyond cardiac parameters may provide additional information. Our results would suggest simplifying cardiac measurement to simply HR and HRV, thereby reducing complexity without losing content. Future research is needed to support (or refute) this proposition. HR and HRV can be measured easily and non-intrusively with modern smart watches. These devices would even allow for telemetric data transmission and real time physiological feedback. Research on HRV targeted interventions with aviophobic subjects seems warranted.

To deal with a multitude of underlying phenomena, treatment programs often use a combination of providing information, cognitive restructuring, relaxation training and graded in-vitro exposure, before moving on to in-vivo exposure. The content, timing and quantity of these ancillary therapeutic components definitely need attention. For example, although pre-exposure cognitive interventions lower the threshold for subsequent exposure, they may at the same time diminish the effectiveness of in-vivo exposure therapy by promoting regulating strategies that dampen automatic and coherent responses. On the other hand, pre-exposure acceptance and commitment therapy may help to facilitate engagement in exposure exercises without diminishing in-vivo exposure efficacy. Likewise, virtual reality exposure therapy (VRET) may assuage anxiety associated with upcoming in-vivo exposure. However, little is known about how

VRET affects efficacy of consecutive in-vivo exposure. Post-exposure cognitive therapy may help to consolidate treatment gains. Research is needed to optimise these flanking strategies.

Several available mobile phone apps claim to ease stress associated with flight. The “Am I going down” app is a risk calculator that provides the likelihood of a flight going down, the “ANA Takeoff Mode” app provides distraction through immersive gameplay, and the “Turbcast” app allow passengers to view a turbulence forecast along their flight route. However, these apps may increase rather than decrease anxiety before and during flight. More beneficial thoughts have been put into the “Flight Without Fear” and “SOAR” apps; both primarily offer information on take-off procedures, turbulence and aircraft maintenance. Nevertheless, only systematic assessment can provide data on the positive and negative aspects of these aids. Regrettably, the only available app based on scientific research has never undergone a scientific assessment; research on the VALK Fear of Flying App is long overdue. This app may promote and facilitate exposure, and diminish avoidance. On the other hand, it could be seen as a mechanism that delivers safety signals, thereby creating dependency. Future research would do well to assess these different attributes.

Very few passengers are completely comfortable during all phases of flight. A sudden jolt of turbulence alarms everyone. Very few people enjoy an approach in gusty wind conditions (though most pilots do!). Unexpected or “inexplicable” events during flight are quite common; some apprehension is an intrinsic part of flying for most passengers. After treatment the fearful flyer should be able to cope with these situations and the feelings associated with these situations. Clinically significant improvement means being able to deal with flight and all aspects associated with flight, not being perfectly comfortable all the time. Future research on efficacy of treatment would benefit from a wide array of normative data and better definitions of clinically significant improvement.

Disorder-specific treatments focus on differences rather than similarities in the treatment of disorders; transdiagnostic treatments focus on the similarities in etiology and common underlying factors of various anxiety disorders. Transdiagnostic CBT may have practical advantages over traditional CBT when group therapy participants are diagnostically heterogeneous; this is the case with aviophobics who have a multitude of underlying pathologies. Determining which combination of disorder-specific interventions and transdiagnostic interventions is most effective in this clinical setting is a great challenge, and requires continuous research. Such research would benefit

from the use of psychophysiological measures, as assessment of self-report disrupts whatever is going on; moreover, retrospective assessment of patients' own verbal report is notoriously unreliable. However, interpretation of physiological data is not clear-cut and also warrants additional research.

CONCLUSION

Pre-treatment individual differences in subjective distress reactivity and physiological reactivity to flight related stimuli, and pre-treatment use of cognitive coping strategies were not prognostic of short- and long-term post-treatment clinical course. In the course of therapy, individual reactivity became more strongly related to treatment outcome. The magnitude of change in the use of maladaptive coping strategies during therapy was indicative of long-term persistence of flight anxiety and number of flights flown within three years after treatment. Subjective distress reactivity, pre-exposure and during actual flight, was prognostic for short- and long-term treatment outcomes. Adding measurements of physiological reactivity improved the prediction of treatment outcome. The magnitude of synchronous change in subjective and physiological reactivity did not increase with higher intensity of phobic stimuli, and was not related to outcome. Subjective and physiological measurements of fear activation provided partly independent information. Prognosis for clinical course of aviophobia therefore could benefit from including physiological reactivity measurements.

REFERENCES

- Aldao, A., Tull, M.T., 2015. Putting emotion regulation in context. *Current Opinion in Psychology* 3, 100–107.
- Arch, J.J., Eifert, G.H., Davies, C., Vilardaga, J.C.P., Rose, R.D., Craske, M.G., 2012. Randomized clinical trial of cognitive behavioral therapy (CBT) versus acceptance and commitment therapy (ACT) for mixed anxiety disorders. *Journal of Consulting and Clinical Psychology* 80, 750–765.
- Asnaani, A., McLean, C.P., Foa, E.B., 2016. Updating Watson & Marks (1971): How Has Our Understanding of the Mechanisms of Extinction Learning Evolved and Where Is Our Field Going Next. *Behavior Therapy* 47, 654–668.
- Beauchaine, T.P., 2015. Respiratory sinus arrhythmia: a transdiagnostic biomarker of emotion dysregulation and psychopathology. *Current Opinion in Psychology* 3, 43–47.
- Benoit Allen, K., Allen, B., Austin, K.E., Waldron, J.C., Ollendick, T.H., 2015. Synchrony-Desynchrony in the Tripartite Model of Fear: Predicting Treatment Outcome in Clinically Phobic Children. *Behaviour Research and Therapy* 71, 54–64.
- Blakey, S., Deacon, B., 2015. If a safety aid is present, there must be danger: The paradoxical effects of hand sanitizer during a contamination exposure task. *Journal of experimental psychopathology* 6, 264 – 277.
- Blakey, S.M., Abramowitz, J.S., 2016. The effects of safety behaviors during exposure therapy for anxiety: Critical analysis from an inhibitory learning perspective. *Clinical Psychology Review* 49, 1–15.
- Boettcher, H., Brake, C.A., Barlow, D.H., 2016. Origins and outlook of interoceptive exposure. *Journal of Behavior Therapy and Experimental Psychiatry* 53, 41–51.
- Bornas, X., Llabres, J., Noguera, M., Lopez, A.M., Barcelo, F., Tortella-Feliu, M., Fullana, M.A., 2004. Self-implication and heart rate variability during simulated exposure to flight-related stimuli. *Anxiety Stress and Coping* 17, 331–339.
- Bornas, X., Llabres, J., Noguera, M., Lopez, A.M., Barcelo, F., Tortella-Feliu, M., Fullana, M.A., 2005. Looking at the heart of low and high heart rate variability fearful flyers: self-reported anxiety when confronting feared stimuli. *Biological Psychology* 70, 182–187.
- Bornas, X., Llabres, J., Noguera, M., Lopez, A.M., Tortella-Feliu, M., Fullana, M.A., Montoya, P., Gelabert, J.M., Vila, I., 2006. Changes in heart rate variability of flight phobics during a paced breathing task and exposure to fearful stimuli. *International Journal of Clinical and Health Psychology* 6, 549–563.
- Bouton, M.E., 2004. Context and behavioral processes in extinction. *Learning & memory* 11, 485–494.
- Chalmers, J.A., Quintana, D.S., Abbott, M.J., Kemp, A.H., 2014. Anxiety disorders are

- associated with reduced heart rate variability: a meta-analysis. *Frontiers in Psychiatry* 5, 1–11.
- Clark, G.I., Rock, A.J., 2016. Processes Contributing to the Maintenance of Flying Phobia: A Narrative Review. *Frontiers in Psychology* 7, 754.
- Conner, T.S., Barrett, L.F., 2012. Trends in Ambulatory Self-Report: The Role of Momentary Experience in Psychosomatic Medicine. *Psychosomatic Medicine* 74, 327–337.
- Couyoumdjian, A., Ottaviani, C., Petrocchi, N., Trincas, R., Tenore, K., Buonanno, C., Mancini, F., 2016. Reducing the Meta-Emotional Problem Decreases Physiological Fear Response during Exposure in Phobics. *Frontiers in Psychology* 7, 1–10.
- Craske, M.G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., Baker, A., 2008. Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy* 46, 5–27.
- Craske, M.G., Niles, A.N., Burklund, L.J., Wolitzky-Taylor, K.B., Vilaridaga, J.C.P., Arch, J.J., Saxbe, D.E., Lieberman, M.D., 2014a. Randomized controlled trial of cognitive behavioral therapy and acceptance and commitment therapy for social phobia: outcomes and moderators. *Journal of consulting and clinical psychology* 82, 1034–1048.
- Craske, M.G., Treanor, M., Conway, C.C., Zbozinek, T., Vervliet, B., 2014b. Maximizing exposure therapy: An inhibitory learning approach. *Behaviour Research and Therapy* 58, 10–23.
- Dahlin, M., Andersson, G., Magnusson, K., Johansson, T., Sjogren, J., Hakansson, A., Pettersson, M., Kadowaki, A., Cuijpers, P., Carlbring, P., 2016. Internet-delivered acceptance-based behaviour therapy for generalized anxiety disorder: A randomized controlled trial. *Behaviour Research and Therapy* 77, 86–95.
- Deacon, B., Kemp, J.J., Dixon, L.J., Sy, J.T., Farrell, N.R., Zhang, A.R., 2013. Maximizing the efficacy of interoceptive exposure by optimizing inhibitory learning: A randomized controlled trial. *Behaviour Research and Therapy* 51, 588–596.
- Foa, E.B., Kozak, M.J., 1986. Emotional processing of fear: exposure to corrective information. *Psychological bulletin* 99, 20.
- Friedman, B.H., 2007. An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. *Biological psychology* 74, 185–199.
- Goedhart, A.D., Kupper, N., Willemsen, G., Boomsma, D.I., de Geus, E.J., 2006. Temporal stability of ambulatory stroke volume and cardiac output measured by impedance cardiography. *Biological Psychology* 72, 110–117.
- Goetz, A.R., Davine, T.P., Siwiew, S.G., Lee, H.-J., 2016. The functional value of preventive and restorative safety behaviors: A systematic review of the literature. *Clinical Psychology Review* 44, 112–124.
- Graham, B.M., Callaghan, B.L., Richardson, R., 2014. Bridging the gap: Lessons we have learnt from the merging of psychology and psychiatry for the optimisation of

- treatments for emotional disorders. *Behaviour Research and Therapy* 62, 3–16.
- Hacker, T., Stone, P., MacBeth, A., 2016. Acceptance and commitment therapy - Do we know enough? Cumulative and sequential meta-analyses of randomized controlled trials. *Journal of Affective Disorders* 190, 551–565.
- Hartanto, D., Brinkman, W.-P., Kampmann, I.L., Morina, N., Emmelkamp, P.G.M., Neerincx, M.A. 2015. Design and Implementation of Home-Based Virtual Reality Exposure Therapy System with a Virtual eCoach. In: Brinkman, W.-P., Broekens, J., Heylen, D., editors, *Intelligent Virtual Agents*. Cham: Springer International Publishing. p. 287–291.
- Hendriks, S.M., Spijker, J., Licht, C.M.M., Beekman, A.T.F., Penninx, B.W.J.H., 2013. Two-year course of anxiety disorders: different across disorders or dimensions. *Acta Psychiatrica Scandinavica* 128, 212–221.
- Hinton-Bayre, A.D., Kwapil, K.J. 2017. Best Practice Approaches for Evaluating Significant Change for Individuals. In: Bowden, S.C., editor. *Neuropsychological Assessment in the Age of Evidence-Based Practice*. Oxford University Press. p. 121 – 154.
- Hipol, L.J., Deacon, B.J., 2013. Dissemination of Evidence-Based Practices for Anxiety Disorders in Wyoming A Survey of Practicing Psychotherapists. *Behavior Modification* 37, 170–188.
- Hofmann, S.G., 2014. D-cycloserine for Treating Anxiety Disorders: Making Good Exposures Better and Bad Exposures Worse. *Depression and anxiety* 31, 175–177.
- Hofmann, S.G., Mundy, E.A., Curtiss, J., 2015a. Neuroenhancement of Exposure Therapy in Anxiety Disorders. *AIMS neuroscience* 2, 123–138.
- Hofmann, S.G., Otto, M.W., Pollack, M.H., Smits, J.A., 2015b. D-cycloserine augmentation of cognitive behavioral therapy for anxiety disorders: an update. *Current psychiatry reports* 17, 1–5.
- Hollenstein, T., Lanteigne, D., 2014. Models and methods of emotional concordance. *Biological Psychology* 98, 1–5.
- Ivanova, E., Lindner, P., Ly, K.H., Dahlin, M., Vernmark, K., Andersson, G., Carlbring, P., 2016. Guided and unguided Acceptance and Commitment Therapy for social anxiety disorder and/or panic disorder provided via the Internet and a smartphone application: A randomized controlled trial. *Journal of Anxiety Disorders* 44, 27–35.
- Jacobson, N.S., Truax, P., 1991. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of consulting and clinical psychology* 59, 12.
- Jang, D.P., Kim, I.Y., Nam, S.W., Wiederhold, B.K., Wiederhold, M.D., Kim, S.I., 2002. Analysis of physiological response to two virtual environments: driving and flying simulation. *CyberPsychology & Behavior* 5, 11–18.
- Kerkhof, I., Vansteenwegen, D., Beckers, T., Dirikx, T., Baeyens, F., D’Hooge, R., Hermans, D.

2011. The role of negative affective valence in return of fear. In: Gervaise, A.D., editor. *Psychology of Fear : New Research*. New York: Nova Science Publishers, Inc. p. 153–170.
- Khalsa, S.S., Lapidus, R.C., 2016. Can Interoception Improve the Pragmatic Search for Biomarkers in Psychiatry. *Frontiers in Psychiatry* 7:121, 1–19.
- Laborda, M.A., McConnell, B.L., Miller, R.R. 2011. Behavioral Techniques to Reduce Relapse After Exposure Therapy. In: Schachtman, T.R., Reilly, S.S., editors. *Associative Learning and Conditioning Theory: Human and Non-Human Applications*, Oxford university press, NY, USA.
- Landy, L.N., Schneider, R.L., Arch, J.J., 2015. Acceptance and commitment therapy for the treatment of anxiety disorders: a concise review. *Current Opinion in Psychology* 2, 70–74.
- Lang, P.J., 2014. Emotion's Response Patterns: The Brain and the Autonomic Nervous System. *Emotion Review* 6, 93–99.
- Lehrer, P.M., Gevirtz, R., 2014. Heart rate variability biofeedback: how and why does it work. *Frontiers in Psychology* 5, 1–9.
- Levenson, R.W., 2014a. Emotion and the Autonomic Nervous System: Introduction to the Special Section. *Emotion Review* 6, 91–92.
- Levenson, R.W., 2014b. The autonomic nervous system and emotion. *Emotion Review* 6, 100–112.
- Levy, H.C., Radomsky, A.S., 2014. Safety Behaviour Enhances the Acceptability of Exposure. *Cognitive Behaviour Therapy* 43, 83–92.
- Lien, R., Neijts, M., Willemsen, G., de Geus, E.J.C., 2015. Ambulatory measurement of the ECG T-wave amplitude. *Psychophysiology* 52, 225–237.
- Luck, C.C., Lipp, O.V., 2015. A potential pathway to the relapse of fear? Conditioned negative stimulus evaluation (but not physiological responding) resists instructed extinction. *Behaviour Research and Therapy* 66, 18–31.
- Mathewson, K.J., Schmidt, L.A., Miskovic, V., Santesso, D.L., Duku, E., McCabe, R.E., Antony, M.M., Moscovitch, D.A., 2013. Does respiratory sinus arrhythmia (RSA) predict anxiety reduction during cognitive behavioral therapy (CBT) for social anxiety disorder (SAD)? *International Journal of Psychophysiology* 88, 171–181.
- Mauss, I.B., Levenson, R.W., McCarter, L., Wilhelm, F.H., Gross, J.J., 2005. The Tie That Binds? Coherence Among Emotion Experience, Behavior, and Physiology. *Emotion* 5, 175–190.
- McNally, R.J., 2016. The Legacy of Seligman's "Phobias and Preparedness" (1971). *Behavior Therapy* 47, 585–594.
- Meulders, A., Van Daele, T., Volders, S., Vlaeyen, J.W.S., 2016. The use of safety-seeking behavior in exposure-based treatments for fear and anxiety: Benefit or burden? A meta-analytic review. *Clinical Psychology Review* 45, 144–156.

- Meuret, A.E., Twohig, M.P., Rosenfield, D., Hayes, S.C., Craske, M.G., 2012. Brief acceptance and commitment therapy and exposure for panic disorder: A pilot study. *Cognitive and Behavioral Practice* 19, 606–618.
- Nees, F., Heinrich, A., Flor, H., 2015. A mechanism-oriented approach to psychopathology: the role of pavlovian conditioning. *International Journal of Psychophysiology* 351–364.
- Neijts, M., van Lien, R., Kupper, N., Boomsma, D., Willemsen, G., de Geus, E.J.C., 2015. Heritability and Temporal Stability of Ambulatory Autonomic Stress Reactivity in Unstructured 24-Hour Recordings. *Psychosomatic Medicine* 77.
- Oakes, M., Bor, R., 2010. The psychology of fear of flying (part II): A critical evaluation of current perspectives on approaches to treatment. *Travel Medicine and Infectious Disease* 8, 339–363.
- Ost, L.G., Ferebee, I., Furmark, T., 1997. One-session group therapy of spider phobia: Direct versus indirect treatments. *Behaviour Research and Therapy* 35, 721–732.
- Ost, L.G., 2014. The efficacy of Acceptance and Commitment Therapy: An updated systematic review and meta-analysis. *Behaviour Research and Therapy* 61, 105–121.
- Otto, M.W., Kredlow, M.A., Smits, J.A.J., Hofmann, S.G., Tolin, D.F., de Kleine, R.A., van Minnen, A., Evins, A.E., Pollack, M.H., 2016. Enhancement of Psychosocial Treatment With D-Cycloserine: Models, Moderators, and Future Directions. *Biological Psychiatry* 80, 274–283.
- Parsons, T.D., Rizzo, A.A., 2008. Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: a meta-analysis. *Journal of Behavior Therapy and Experimental Psychiatry* 39, 250–261.
- Pittig, A., Van Den Berg, L., Vervliet, B., 2016. The key role of extinction learning in anxiety disorders: behavioral strategies to enhance exposure-based treatments. *Current Opinion in Psychiatry* 29, 39–47.
- Powers, M.B., Deacon, B.J., 2013. Dissemination of empirically supported treatments for anxiety disorders: Introduction to the special issue. *Journal of Anxiety Disorders* 27, 743–744.
- Powers, M.B., Emmelkamp, P.M., 2008. Virtual reality exposure therapy for anxiety disorders: A meta-analysis. *Journal of Anxiety Disorders* 22, 561–569.
- Raes, A.K., Koster, E.H.W., Loeys, T., De Raedt, R., 2011. Pathways to change in one-session exposure with and without cognitive intervention: An exploratory study in spider phobia. *Journal of Anxiety Disorders* 25, 964–971.
- Ramnero, J. 2012. Exposure Therapy for Anxiety Disorders: Is There Room for Cognitive Interventions. In: Neudeck, P., Wittchen, H.-U., editors. New York, NY: Springer New York. p. 275–297.
- Roemer, L., Williston, S.K., Eustis, E.H., Orsillo, S.M., 2013. Mindfulness and Acceptance-

- Based Behavioral Therapies for Anxiety Disorders. *Current Psychiatry Reports* 15, 410.
- Roth, W., T., 2005. Physiological markers for anxiety: Panic disorder and phobias. *International Journal of Psychophysiology* 58, 190–198.
- Rupp, C., Doebler, P., Ehring, T., Vossbeck-Elsebusch, A.N., 2016. Emotional Processing Theory Put to Test: A Meta-Analysis on the Association Between Process and Outcome Measures in Exposure Therapy. *Clinical Psychology & Psychotherapy* n/a.
- Schaefer, H.S., Larson, C.L., Davidson, R.J., Coan, J.A., 2014. Brain, body, and cognition: Neural, physiological and self-report correlates of phobic and normative fear. *Biological Psychology* 98, 59–69.
- Schuemie, M.J. 2003. Human-Computer Interaction and Presence in Virtual Reality Exposure Therapy [dissertation]. Delft University of Technology.
- Seeley, S.H., Garcia, E., Mennin, D.S., 2015. Recent advances in laboratory assessment of emotion regulation. *Current Opinion in Psychology* 3, 58–63.
- Seery, M.D., Kondrak, C.L., Streamer, L., Saltsman, T., Lamarche, V.M., 2016. Preejection period can be calculated using R peak instead of Q. *Psychophysiology* 53, 1232–1240.
- Seligman, M.E.P., 1971. Phobias and preparedness. *Behavior Therapy* 2, 307–320.
- Sherwood, A., Allen, M., Fahrenberg, J., Kelsey, R., Lovallo, W., Van Doornen, L.J., 1990. Methodological guidelines for impedance cardiography. *Psychophysiology* 27, 1–23.
- Sims, T., Hogan, C.L., Carstensen, L.L., 2015. Selectivity as an emotion regulation strategy: lessons from older adults. *Current Opinion in Psychology* 3, 80–84.
- Singewald, N., Schmuckermair, C., Whittle, N., Holmes, A., Ressler, K.J., 2015. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacology & therapeutics* 149, 150–190.
- Smits, J., A.J., Berry, A., C., Tart, C., D., Powers, M., B., 2008. The efficacy of cognitive-behavioral interventions for reducing anxiety sensitivity: A meta-analytic review. *Behaviour Research and Therapy* 46, 1047–1054.
- Spinhoven, P., Batelaan, N., Rhebergen, D., van Balkom, A., Schoevers, R., Penninx, B.W., 2016. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. *Journal of Anxiety Disorders* 44, 92–101.
- Swan, A.J., Carper, M.M., Kendall, P.C., 2016. In Pursuit of Generalization: An Updated Review. *Behavior Therapy* 47, 733–746.
- Van Gerwen, L.J., Diekstra, R.F.W., Arondeus, J.M., Wolfger, R., 2004. Fear of flying treatment programs for passengers: an international update. *Travel Medicine and Infectious Disease* 2, 27–35.
- Verkuil, B., Brosschot, J.F., Tollenaar, M.S., Lane, R.D., Thayer, J.F., 2016. Prolonged Non-metabolic Heart Rate Variability Reduction as a Physiological Marker of Psychological Stress in Daily Life. *Annals of Behavioral Medicine* 50, 704–714.

- Vervliet, B., Craske, M.G., Hermans, D., 2013. Fear extinction and relapse: state of the art. *Annual review of clinical psychology* 9, 215–248.
- Wiederhold, B.K., Davis, R., Wiederhold, M.D., 1998. The effect of immersiveness on physiology. *Studies in Health Technology and Informatics* 58, 52–60.
- Wiederhold, B.K., Wiederhold, M.D. 2005. *Virtual reality therapy for anxiety disorders: Advances in evaluation and treatment*. Washington, D.C.: American Psychological Association.
- Wilhelm, F.H., Roth, W.T., 1997. Acute and delayed effects of alprazolam on flight phobics during exposure. *Behaviour Research and Therapy* 35, 831–841.
- Wolitzky-Taylor, K.B., Horowitz, J.D., Powers, M.B., Telch, M.J., 2008. Psychological approaches in the treatment of specific phobias: A meta-analysis. *Clinical Psychology Review* 28, 1021–1037.
- Zbozinek, T.D., Hermans, D., Prenoveau, J.M., Liao, B., Craske, M.G., 2015. Post-extinction conditional stimulus valence predicts reinstatement fear: Relevance for long-term outcomes of exposure therapy. *Cognition and Emotion* 29, 654–667.



