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Psychophsyiological reactivity during uncertainty and ambiguity processing in high and low worriers

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ABSTRACT

Background and objectives: Intolerance of uncertainty (IU) has been linked to Generalized Anxiety Disorder (GAD), but studies experimentally manipulating uncertainty have mostly failed to find differences between GAD patients and controls, possible due to a lack of distinction between uncertainty and ambiguity. This study therefore investigated reactivity to ambiguity in addition to uncertainty in high worriers (HW) and low worriers (LW). We hypothesized an interpretation bias between the groups during ambiguity tasks, while uncertainty would facilitate threat processing of subsequent aversive stimuli.
Methods: HW (N = 23) and LW (N = 23) completed a paradigm comprising the anticipation and perception of pictures with dangerous, safe, or ambiguous content. Anticipatory cues were certain (always correct information about the following picture) or uncertain (no information). Subjective ratings, reaction times and skin conductance responses (SCRs) were recorded.
Results: HW rated particularly ambiguous pictures as more aversive and showed longer reaction times to all picture conditions compared to LW. SCRs were also larger in HW compared to LW, particularly during uncertain but also safe anticipation. No group differences were observed during perception of stimuli.
Limitations: All participants were female. HW was used as subclinical phenotype of GAD.
Conclusions: Intolerance of ambiguity seems to be related to individual differences in worry and possibly to the development of GAD. Threat-related interpretations differentiating HW and LW occurred particularly for ambiguous pictures but were not accompanied by increased autonomic arousal during the picture viewing. This disparity between subjective rating and arousal may be the result of worrying in response to intolerance of uncertainty, restraining physiological responses.

1. Introduction

Generalized Anxiety Disorder (GAD) is a common anxiety disorder with a lifetime prevalence of 4–6% (Beesdo, Pine, Lieb, & Wittchen, 2010; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). However GAD pathophysiology has been relatively understudied in comparison to other anxiety conditions, possibly due to the lack of a specific anxiety inducing stimulus or event for GAD sufferers, making experimental studies more difficult to design. Current theories of GAD propose that the anticipation of negative experiences relates to the high levels of worry observed in those with GAD. The intolerance of uncertainty model of GAD (Dugas, Gagnon, Ladouceur, & Freeston, 1998) states that patients tend to overestimate the risk and negative consequences of situations and that this overestimation of risk is especially evident in uncertain situations (i.e., those lacking explicit information about the further course of events). It has therefore been proposed that intolerance of uncertainty (IU) underpins the relationship between

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uncertainty and excessive worry in GAD. IU is suggested to arise from a combination of enhanced activation of internal representations of uncertain information and the threat-related interpretations of such information (Dugas et al., 2005). This model is supported by empirical data showing positive associations between IU and worry (Buhr & Dugas, 2006).

Several studies indicated that biased information processing occurs during uncertainty. Studies in healthy individuals have shown negatively biased expectancies of aversion following uncertain anticipation cues (Sarinopoulos et al., 2010) and subsequent increased negative mood ratings towards aversive pictures (Grupe & Nitschke, 2011). Healthy individuals also showed increased response times and decreased response accuracy with increasing uncertainty (Krain et al., 2006). On a psychophysiological level, uncertainty during anticipation has also been associated with increased skin conductance responses (SCRs) during perception of aversive stimuli (Grupe & Nitschke, 2011). On a neural level, recent findings suggest the processing of uncertain anticipation is modulated by prefrontal areas (Clauss et al., 2014; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014) and is executed in distinct neural processes and brain regions (Grupe & Nitschke, 2013; Grupe, Oathes, & Nitschke, 2013). For example, areas implicated in emotion regulation such as the anterior cingulate cortex (AAC) and orbitofrontal cortex (OFC) have been reported to show increased activation during anticipation (Critchley, Mathias, & Dolan, 2001). In contrast, the insula has been reported to show decreased activation (Sarinopoulos et al., 2010). Higher insula and amygdala responses to aversive pictures were also found when their presentation followed an uncertain cue and ACC activity during the anticipatory phase was inversely associated with these responses (Sarinopoulos et al., 2010).

However, similar investigations on biased processing during uncertainty have not found differences between high worriers or GAD patients and healthy controls. In these studies, patient and control groups did not differ on a behavioral (Krain et al., 2008; Yassa, Hazlett, Stark, & Hoehn-Saric, 2012) or psychophysiological level (Grillon et al., 2009; Yassa et al., 2012). Differential functional brain activations between GAD patients and controls were reported by Yassa et al. (2012) but have not been observed in other investigations (Krain et al., 2008; Mochcoyitch, da Rocha Freire, Garcia, & Nardi, 2014). Given this data, one urgent research question is why these studies failed to find differential group effects as predicted by current models.

We propose that IU should be carefully distinguished from intolerance of ambiguity (IA), a closely related concept that has been confused with IU in the past (Grenier, Barrette, & Ladouceur, 2005). According to Grenier et al. (2005) and more recently Carleton (2012), both concepts share a biased interpretation of situations or stimuli as threatening. For IU, the causes of threat are in or are referring to the future, whereas for IA the causes of threat are in or referring to the present. With these temporal differences between both concepts in mind, some authors argue that IA is the part of IU pertaining to possible current threat (Carleton, 2012) whereas IU is related to a possible imminent future threat. As such situations containing uncertainty or ambiguity have been described in different terms regarding the source of subjective insecurity experienced in both cases. For instance, uncertainty has been described as “unknowable” (Carleton, 2012, p. 940) in this respect, while ambiguity has been described as “characterized by equivocal or ambiguous features” (Grenier et al., 2005, p. 596). Based on such differences, there appears to be potential for a delineation of both concepts besides just temporal differences which can be experimentally tested. In our experimental conceptualization, based on the above literature, uncertainty is characterized by an absence of available information on the outcome of the situation. In contrast, ambiguity is characterized by contradictory or ambivalent information available on the situation. We propose that the combined effects of uncertainty and ambiguity in a given situation compose the marked information processing bias that differentiates GAD patients from healthy controls. Studies of threat biases in children and adolescents (Lau et al., 2012) and in adults with GAD (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007) consistently revealed biases in various stages of information processing. These stages included reactions towards stimuli of possible threat as well as threatening interpretations of ambiguous situations. However, only one experimentally based study (Simmons, Matthews, Paulus, & Stein, 2008) investigated ambiguity, using a ‘wall of faces’ task. The authors reported longer response times as well as increased neural activation in the insula during ambiguity, which was also found to be correlated with IU. This study used a non-clinical sample. For other samples, levels of processing, or tasks, no experimental studies were available so far. The need for further research on that topic was also demanded by a recent review which described an unpublished study on the temporal order in the association between IA and IU (Rosen, Ivanova, & Knaeuper, 2014).

The current study aimed to examine reactivity to more distal and to more proximal potential threat, i.e. uncertainty (during anticipation) and ambiguity (during perception), in high worriers (HW) as a subclinical phenotype of GAD compared to low worriers (LW). Skin conductance responses (SCR) were examined as psychophysiological correlates, as they are considered a useful autonomic marker of anticipatory anxiety (Boucsein, 1992) and information processing activity (Spinks & Siddle, 1985). By integrating work from related research (Aikins & Craske, 2001; Dugas et al., 2005; Nitschke et al., 2009; Sarinopoulos et al., 2010; Schienle, Kochel, Ebner, Reishofer, & Schafer, 2010; Schwerdtfeger, 2006), we developed a paradigm that involved presentation of certain and uncertain anticipation cues, subsequently followed by pictures showing scenes of positive, aversive or ambiguous valence. On a behavioral level, we hypothesized that HW compared to LW would rate ambiguous scenes as more aversive and show slower reaction times (RTs) for negative scenes following uncertain cues compared to scenes following certain cues. On a psychophysiological level, we expected HW compared to LW to show increased tonic and phasic SCRs during ambiguity but not during uncertainty, as well as during danger/ambiguity perception after uncertain cues compared to danger perception after certain cues.

2. Methods

2.1. Development of the picture set for the paradigm

The pictures used in the study (safe, danger or ambiguous) were either chosen from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) on the basis of their valence and arousal ratings or were generated by our research group. Pictures with ambiguous content related to typical worry topics (e.g., health or finances). A preliminary set of 196 pictures were evaluated online by student volunteers (n = 53, 21% male) ranging in age from 18 to 36 years (M = 23.47; SD = 4.2). Each picture was rated for valence (from 0 = “most pleasant” to 8 = “most unpleasant”) and arousal (from 0 = “not arousing” to 8 = “most arousing”) using a modified version of the Self-Assessment Manikin Scale (Bradley & Lang, 1994), in which the five original ratings were supplemented with four intermediate ratings. Participants also rated how anxious the picture scene made them (from 0 = “not at all” to 8 = “extremely”), how dangerous they judged the scene (from 0 = “safe” to 4 = “ambiguous” to 8 = “danger”), and how difficult it

was to tolerate the picture scene (from 0 = "not at all" to 8 = "extremely").

Based on these ratings, a final set of pictures was chosen to be used in the paradigm for the current study by sorting the pictures into three categories. Pictures rated as most unpleasant, frightening, dangerous, difficult to tolerate and arousing (identified by a score ≥ 7 on all these scales) comprised the danger picture set (i.e., attack scenes).

Pictures rated as most pleasant, safe, easy to tolerate and with low arousal and anxiety ratings (identified by a score ≤ 2 on all these scales) comprised the safe picture set e.g., men talking to each other). Pictures rated as slightly unpleasant, frightening, difficult to tolerate (identified by a score between 5 and 7 on all of these scales) and with ambiguous ratings regarding the judgment-about- dangerosity -scale (identified by a between 3 and 5 on this scale) comprised the ambiguous picture set (e.g., a man climbing a wall). The selected pictures were matched between conditions with regard to color, complexity and luminance. In total 44 safe pictures, 44 danger pictures and 44 ambiguous pictures were selected for the final paradigm.

2.2. Participants

Flyer and advertisements were used to recruit 128 university student volunteers who were screened for level of worry using the German version of the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990), demographic characteristics (gender, education and handedness) and exclusion criteria (current pharmacological treatment or participation in the online picture evaluation). To designate individuals to the HW or LW group, we applied cut-off scores introduced by Fisher (2006; for a detailed description see pp. 366–368). Individuals were classified as HW if their PSWQ score was equal to or higher than 47, while those who scored below 47 on the PSWQ were designated as LW. All participants were matched for age, education and handedness. The final sample included forty-six female student volunteers: 23 HW (age: M = 20.5, SD = 1.6; PSWQ: M = 58.2, SD = 7.5) and 23 LW (age: M = 20.7, SD = 2.0; PSWQ: M = 31.7, SD = 6.0). None of the participants fulfilled the DSM-IV-TR criteria for a GAD diagnosis. For a detailed description of the sample characteristics see Table 1. All participants provided written informed consent and received course credit or a free cinema ticket for participation. The study protocol was approved by the local Ethics Committee.

2.3. Experimental design

As shown in Fig. 1, each trial consisted of an anticipatory cue presented for 3 s, followed by a black screen presented for 3, 6 or 9 s. This was followed by either a danger, a safe, or an ambiguous picture for 3 s and then by another black screen for 3, 6 or 9 s. For the danger trials, the cue was a "−", which was always followed by a danger picture. For the safe trials, the cue was a "+", which was always followed by a safe picture. For the uncertain trials, the cue was a "?", which was followed by a danger, a safe or an ambiguous picture. Of the 44 danger pictures, 22 were presented on danger trials and the remaining 22 on uncertain trials. Similarly, 22 of the safe pictures were presented on safe trials and 22 on uncertain trials. The 44 ambiguous pictures were only presented during the uncertain trials. In total the participants performed 132 trials and the total presentation time was 40 min. Trial order was pseudo randomized, with the stipulation that no trial type (danger, safe, or uncertain) was presented more than twice in a row. In addition, no picture type (safe, danger, ambiguous) in the uncertain trials was presented more than twice in a row. The duration of the interstimulus interval (3, 6 or 9 s) following the anticipatory cue and picture presentation was randomized across trials. Participants were informed about all cue parings and were familiarized with the paradigm by completing a test run with 12 additional trials before beginning the experiment. Participants were instructed to promptly press a button whenever they saw a picture. The paradigm was programmed using Presentation 11.3 (Neurobehavioral Systems, Albany, CA, USA).

2.4. Procedure and materials

Following the screening procedure, participants were directly referred to the psychophysiology laboratory located at the Neuroimaging Center of the Department of Psychology, Technische Universität Dresden, Germany. After obtaining their written informed consent, participants underwent a GAD screening according to the DSM-IV-TR criteria (APA., 2000) based on questions of the standardized DIA-X/M-CIDI (Wittchen & Pfister, 1997). Participants also completed assessments of trait anxiety (STAI-T; Spielberger, Gorssuch, Lushene, Vagg, & Jacobs, 1983), depressive symptoms (BDI-II; Beck, Steer, & Brown, 1996), worry tendencies (PSWQ; Meyer et al., 1990) and intolerance of uncertainty (IUS; Carleton, Norton, & Asmundson, 2007), all in their respective German translations. Following this participants were seated in a comfortable chair in front of a monitor, with their non-dominant forearm placed on a soft armrest. In order to guarantee equal distance between monitor and participants (approximately 60 cm) across all participants, we used a chin-rest with a stop for the forehead. SC electrodes were attached and participants were asked to find a comfortable position and to avoid any unnecessary movement during the experiment. After completing the paradigm, participants completed a 10 min baseline period where they were instructed to relax. Finally, all participants completed several

Table 1
Sample characteristics.

	Low worriers	High worriers	U-test/t-test (df)	*p*-value	Effect-size (*r*)
N	23	23			
Age, *M* (SD)	20.7 (2.0)	20.5 (1.6)	254.5	.825	.03
PSWQ, *M* (SD)	31.7 (6.0)	58.2 (7.5)	13.2 (44)	<.001	.89
BDI-II, *M* (SD)	4.3 (3.8)	14 (6.8)	51.5	<.001	.69
STAI-T, *M* (SD)	31 (5.1)	50.3 (9.8)	8.4 (33.3)	<.001	.82
IUS-12-D, *M* (SD)	22 (4.3)	34.3 (6.5)	7.5 (37.8)	<.001	.77
SCL, *M* (SD)[a]	0.4 (0.1)	0.5 (0.1)	1.1 (41)	.860	.17
SCR, *M* (SD)[a]	0.5 (0.1)	0.5 (0.1)	0.4 (41)	.222	.06

M, Mean; SD, standard deviation; *PSWQ* Penn State Worry Questionnaire; *BDI-II* Beck Depression Inventory II; *STAI-T* Sate-Trait Anxiety Inventory; *IUS-12-D* Intolerance of Uncertainty Scale; *SCL* tonic electrodermal activity during baseline (sqrt μS); *SCR* non-stimulus-specific phasic electrodermal activity (average Amplitude; sqrt μS) during baseline.

[a] Available for n = 21 High worriers and n = 22 Low worriers.

Fig. 1. Experimental procedure for the safe, danger and uncertain trials. Each trial consisted of an anticipatory cue, followed by a black screen. This was followed by either a danger, safe or ambiguous picture followed by another black screen. For the danger trials, the cue was a "−", which was always followed by a danger picture (n = 22). For the safe trials, the cue was a "+", which was always followed by a safe picture (n = 22). For the uncertain trials, the cue was an "?", which was followed by either a danger (n = 22), safe (n = 22) or ambiguous picture (n = 44). In total the participants performed 132 trials.

questionnaires and rated the paradigm pictures using the web-based procedure described above.

2.5. Physiological data acquisition and parameterization

Throughout the experiment the temperature was kept as constant as possible (temperature range 20–24C). Skin conductance (SC) was recorded from the second phalanx of the index and middle finger of the subject's non-dominant hand, using Ag/AgCl electrodes (MES Medizintechnik, Munich, Germany) and isotonic electrode paste as the contact medium (Synapse; Kustomer Kinetics, Arcadia, CA, USA). Psychophysiological recordings were carried out using Brain Vision hardware and software (Brain Vision ExG Amplifier and Brain Vision Recorder; Brain Products, Munich, Germany). All data were filtered using low cut −off (10 s) and high cut-off (250 Hz) filters. The initial sampling rate was 1000 Hz and SC data was subsequently downsampled to 10 Hz. SC data were exported using the Brain Vision Analyzer. SC data were analyzed using a Matlab (MathWorks, Natick, MA, USA)-based application (Ledalab Version V3.2.9) from which we used the Continuous Decomposition Analysis (Benedek & Kaernbach, 2010). Phasic electrodermal responses (SCRs), were characterized using an amplitude criterion of 0.02 μS and a latency window of 1–5 s after stimulus onset for both anticipation cue and picture. Trials with a duration of 3s were omitted in these analyses. As a parameter for the stimulus-specific electrodermal response we used the average phasic driver within the response window, which were computed by averaging responses across each anticipation phase and picture

condition. In order to investigate baseline differences between the HW and LW groups, mean SCRs amplitude and tonic electrodermal activity (SCL) scores during the baseline period were calculated for each group separately. All SC parameters were range-corrected according to the method introduced by Lykken (1972). Skin conductance data were normalized using a square root transformation and explored using the Shapiro–Wilk test of normality (Shapiro & Wilk, 1965) to determine distribution (all $p > .05$).

2.6. Statistical analyses

All data analyses were conducted with the statistic software SPSS 17 (SPSS Inc, Chicago, Illinois) with all effects reported as significant at $p < .05$. The data distribution was explored using the Shapiro–Wilk test of normality. Age and BDI-II scores were not normally distributed and were therefore analyzed using Mann Whitney U tests. All other variables (including skin conductance) did not differ significantly from a normal distribution. Boxplots were used to identify outliers with regard to each of the outcome parameters. Cases were deemed outliers if they were over 3 standard deviations away from the mean. Questionnaire scores and baseline electrodermal activity were compared between groups using Independent Samples *t* tests. Mean ratings, reaction times and SCRs values were calculated for each participant during the following conditions: safe pictures following a safe cue, danger pictures following a danger cue, safe pictures following an uncertain cue, danger pictures following an uncertain cue and ambiguous pictures following an uncertain cue. These conditions were compared using repeated measures analyses of variance (ANOVAs), with group as the between-subjects factor and condition as within-subjects factor. To minimize type I errors, the Greenhouse-Geisser correction (Geisser & Greenhouse, 1958) was applied in all ANOVAs. Partial eta squared (η_p^2) and Pearson's correlation coefficient (r) were calculated as measures of effect size to discover if an effect was substantive. Post hoc tests were conducted using t-tests.

3. Results

3.1. Sample characteristics

Sample characteristics are shown in Table 1. HW and LW were comparable in terms of age ($U = 254.5$, $p = .825$), handedness (all right handed), tonic electrodermal activity (SCL; $t\ (41) = -1.14$, $p = .860$) and non-stimulus-specific phasic electrodermal activity (SCR; $t\ (41) = -0.44$, $p = .222$) during the baseline. The two groups were different in terms of worry tendencies (PSWQ; $t\ (44) = -13.16$, $p < .001$), current depressive symptoms (BDI II; $U = 51.5$, $p < .001$), trait anxiety (STAI-T; $t\ (33.3) = -8.39$, $p < .001$) and intolerance of uncertainty (IUS-12-D; $t\ (37.76) = -7.53$, $p < .001$) with higher mean scores in the HW group.

3.2. Behavioral data

Ratings for the different picture conditions are depicted in Fig. 2a–e. Significant main effects of picture condition were detected for all dimensions (*valence*: $F(2, 88) = 553.40$, $p < .001$, $\eta_p^2 = .93$; *arousal*: $F(2, 88) = 117.86$, $p < .001$, $\eta_p^2 = .73$; *anxiety*: $F(2, 88) = 173.68$, $p < .001$, $\eta_p^2 = .80$; *judgment about dangerosity*: $F(2, 88) = 297.12$, $p < .001$, $\eta_p^2 = .87$; *difficulty to tolerate*: $F(2, 88) = 1856.03$, $p < .001$, $\eta_p^2 = .98$). Planned pairwise comparisons revealed that dangerous pictures were rated as more unpleasant ($p < .001$, $r = .95$), arousing ($p < .001$, $r = .88$), anxiety provoking ($p < .001$, $r = .88$), dangerous ($p < .001$, $r = .93$) and difficult to tolerate ($p < .001$, $r = .98$) than ambiguous pictures. Ambiguous pictures were rated as more unpleasant ($p < .001$, $r = .95$), arousing ($p < .001$, $r = .77$), anxiety provoking ($p < .001$, $r = .83$), ambiguous ($p < .001$, $r = .86$) and difficult to tolerate ($p < .001$, $r = .96$) than safe pictures. Significant main effects of group were detected for the dimensions *arousal* ($F(1, 44) = 8.10$, $p = .007$, $\eta_p^2 = .16$), *anxiety* ($F(1, 44) = 6.14$, $p = .017$, $\eta_p^2 = .12$), *judgment about dangerosity* ($F(1, 44) = 11.97$, $p = .001$, $\eta_p^2 = .21$) and *difficulty to tolerate* ($F(1, 44) = 7.03$, $p = .011$, $\eta_p^2 = .14$), with HW showing higher ratings than LW. There was no significant main effect of worry group for *valence* ($F(1, 44) = 3.85$, $p = .056$, $\eta_p^2 = .08$). Significant picture condition × group interactions emerged for *anxiety* ($F(2,88) = 4.44$, $p = .031$, $\eta_p^2 = .09$), *judgment about dangerosity* ($F(2, 88) = 8.79$, $p = .002$, $\eta_p^2 = .17$), and *difficulty to tolerate* ($F(2,88) = 4.39$, $p = .019$, $\eta_p^2 = .09$), but not for *valence* ($F(2, 88) = 0.52$, $p = .512$, $\eta_p^2 = .01$) and *arousal* ($F(2, 88) = 1.74$, $p = .193$, $\eta_p^2 = .04$). Planned pairwise comparisons revealed that anxiety ratings were higher in the HW group than the LW group for the ambiguous picture condition ($p = .004$, $r = .42$). For *judgment about dangerosity*, groups differed on ratings for the ambiguous ($p < .001$, $r = .51$) and danger picture conditions ($p = .006$, $r = .44$), with HW judging these pictures as more dangerous as compared to LW. For *difficulty to tolerate*, groups differed on ratings for the ambiguous ($p = .007$, $r = .41$) and safe picture conditions ($p = .007$, $r = .41$) with higher difficulty tolerating these scenes in the HW group.

As intolerance of uncertainty was strongly correlated with PSWQ scores ($r = .82$, $p < .01$), additional analyses revealed significant correlations between IUS and picture rating dimensions. For ambiguous pictures, correlations of IUS (all $p < .05$) were positive for ratings of *arousal* ($r = .38$), *anxiety* ($r = .39$), *judgment about dangerosity* ($r = .44$) and *tolerance* ($r = .42$) but negative for ratings of *valence* ($r = -.30$). For danger pictures only *judgment about dangerosity* ($p < .05$, $r = .31$) was associated with IUS. No significant correlations emerged for IUS and ratings of safe pictures. In multiple regression analyses with a backward approach, PSWQ scores remained as significant predictor of picture rating dimensions while IUS was removed (results not shown but available upon request).

Mean reaction times for each group for the different picture conditions are depicted in Fig. 3. No main effect of picture condition ($F(3.44, 137.7) = 1.39$, $p = .240$, $\eta_p^2 = .03$) emerged. There was a main effect of group ($F(1, 40) = 4.73$, $p = .036$, $\eta_p^2 = .31$), indicating that HW showed longer reaction times to all picture conditions compared to LW. No significant interaction between worry group and picture condition ($F(3.44, 137.7) < 1$, $p = .550$, $\eta_p^2 = .02$) was found. In addition, there was no significant correlation between IUS and reaction times (all $p > .05$, all $r < .1$).

3.3. Physiological data

Anticipation Phase: SCRs to the different anticipation cues are depicted in Fig. 4a. There was a significant main effect of the anticipation cue ($F(1.63, 66.94) = 4.55$, $p = .020$, $\eta_p^2 = .100$), with planned pairwise comparisons indicating that uncertain anticipation cues were accompanied by stronger SCRs than were safe anticipation cues ($p < .001$, $r = .51$). SCRs did not differ between uncertain and danger anticipation cues ($p = .303$. $r = .15$) or between safe and danger anticipation cues ($p = .111$, $r = .24$). No significant main effect of group on SCRs ($F(1, 41) = 2.94$, $p = .094$, $\eta_p^2 = .067$) emerged, though there was a trend for an interaction between worry group and anticipation cue ($F(1.63, 66.94) = 3.24$, $p = .055$, $\eta_p^2 = .073$). Further exploration showed that HW exhibited elevated SCRs during all three anticipation conditions while LW showed elevated SCRs only during the danger anticipation, (i.e., group differences were significant for the safe ($p = .017$, $r = .36$) and uncertain ($p = .043$, $r = .32$) anticipation but not for the danger anticipation ($p = .715$, $r = .06$)).

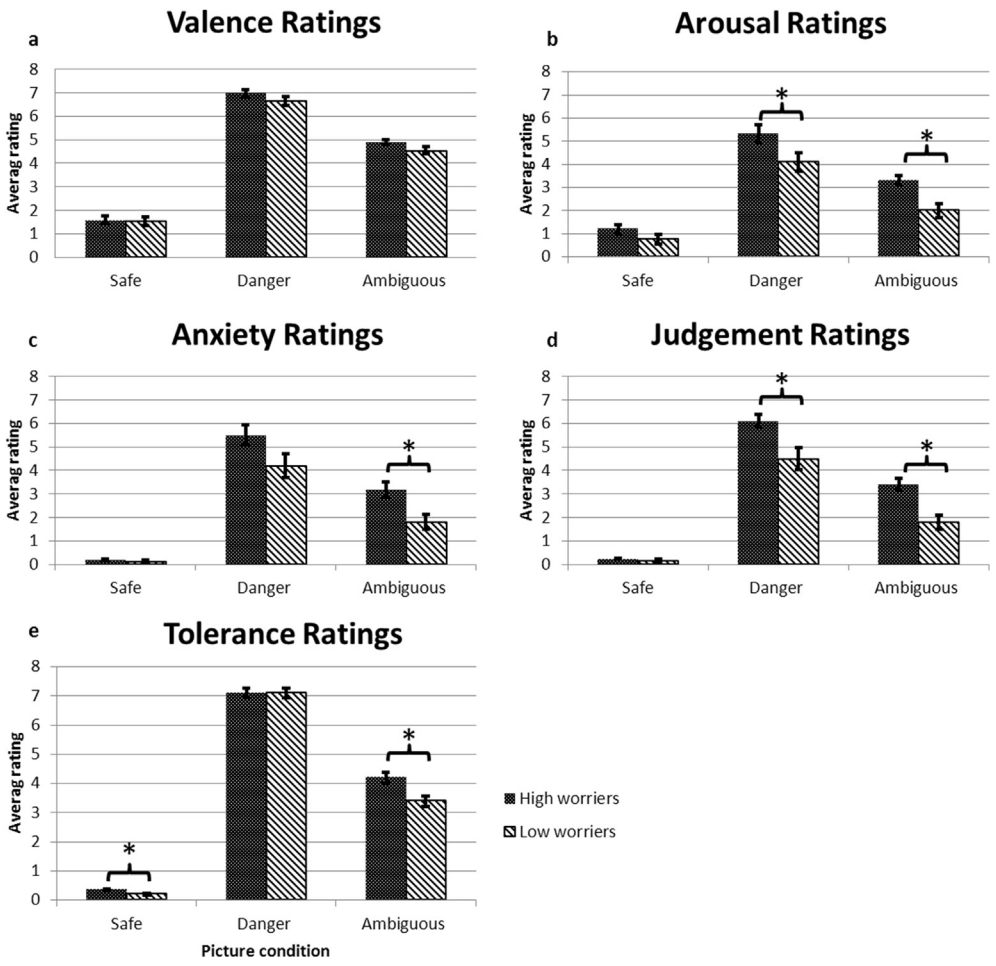

Fig. 2. a–e: Average ratings and standard error of the different picture conditions for both groups. Valence ratings ranged from 0 = most pleasant to 8 = most unpleasant; arousal ratings ranged from 0 = not arousing to 8 = most arousing; anxiety ratings ranged from 0 = not freighting to 8 = most freighting; judgment about dangerosity ratings ranged from 0 = safe to 8 = danger; ratings how difficult it is to tolerate the picture ranged from 0 = not at all to 8 = extremely. Danger pictures received the highest scores and safe pictures the lowest scores. *Note.* $^{*}p < .05$.

Perception Phase: SCRs to the different picture conditions for HW and LW are depicted in Fig. 4b separated by the different anticipation cues. The main effect of picture condition was significant ($F(3.43, 140.52) = 4.712$ $p = .001$, $\eta_p^2 = .10$). Planned pairwise comparisons revealed that ambiguous pictures viewed after an uncertain cue were accompanied by stronger SCRs than safe pictures following a safe ($p = .019, r = .36$) or uncertain anticipation cue ($p = .001, r = .53$), and danger pictures following a danger anticipation cue ($p = .004$, $r = .44$). Danger pictures viewed after an uncertain cue were accompanied by stronger SCRs than safe pictures following an uncertain cue ($p = .002, r = .43$). There was no significant difference in SCRs between ambiguous pictures after an uncertain cue and danger pictures viewed after an uncertain cue ($p = .562$, $r = .10$), danger pictures after a danger cue and danger pictures viewed after an uncertain cue ($p = .099, r = .25$), and danger pictures viewed after an uncertain cue and safe pictures viewed after a safe cue (p = .066, $r = .28$). There was no significant main effect of group ($F(1, 40) = .03$, $p = .863$, $\eta_p^2 = .001$) and no significant interaction between worry group and picture condition ($F(3.42, 140.52) = .99$, $p = .411$, $\eta_p^2 = .02$).Additional correlation analyses between IUS and SCRs revealed no significant correlation (all $p > .05$).

4. Discussion

According to the intolerance of uncertainty model of GAD (Dugas et al., 1998), intolerance of uncertainty (IU) and related threatening interpretations play a prominent role in the etiology and maintenance of anxiety disorders (Beck & Clark, 1997). Intolerance of ambiguity (IA) may be relevant for such biases as well and help to explain the lack of differences between anxious and healthy groups in previous research, via the combined effects of uncertainty and ambiguity. Therefore, the aim of the current study was to investigate both anticipatory uncertainty and perceptual ambiguity in a tailored paradigm and to examine more specifically the pathophysiology involved in worrying - the hallmark feature of GAD. The main results of this study are: a) ambiguous pictures were experienced differently by each group (more aversive in HW compared to LW), b) HW showed longer response latencies irrespective of the stimulus, and c) group differences in autonomic responding were only found during anticipation, with stronger SCRs for the HW group during uncertain but also safe cues.

This study revealed select differences between HW and LW in subjective picture processing. While the HW group rated all pictures as more arousing, anxiety inducing, dangerous and difficult to tolerate than the LW group, this effect was most pronounced for the ambiguous pictures. As hypothesized, ratings of anxiety, arousal, perception of danger and difficulty to tolerate ambiguous pictures were higher for HW than for LW. Group differences found for the safe and danger picture conditions were unexpected and might relate to higher levels of vigilance for emotional stimuli, an observation that has been noted in patients with anxiety and anxiety related disorders (Brosschot, Gerin, & Thayer, 2006). However, it

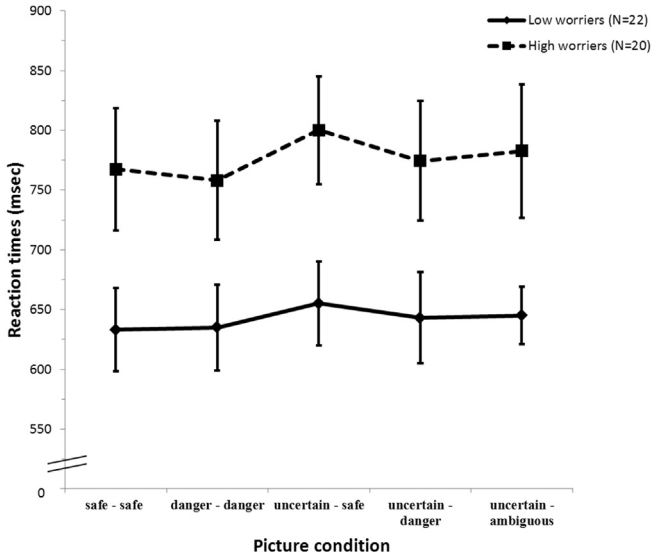

Fig. 3. Reaction times and standard errors for the five picture conditions among high and low worriers. Reaction times to safe pictures that followed a safe cue are depicted in the safe condition. Reaction times to danger pictures that followed a danger cue are depicted in the danger condition. Reaction times to safe pictures that followed an uncertain cue are depicted in the uncertain-safe condition. Reaction times to danger pictures that followed an uncertain cue are depicted in the uncertain-danger condition. Reaction times to ambiguous pictures that followed an uncertain cue are depicted in the uncertain-ambiguous condition. *Note.* From the high worry group one behavioral data set and from the low worry group three data sets were excluded from the analyses because they were detected as outliers.

should be noted from the interaction effects between group and picture condition, as well as from effect sizes and descriptive data, that group differences for the safe and danger pictures were not as substantial as those for the ambiguous pictures. Findings for the ambiguous condition are in line with the suggested threat-related interpretation of ambiguous stimuli in GAD (Aikins & Craske, 2001). Additionally, we infer from the data that ambiguity, as outlined above, is experienced in a threatening way comparable to uncertainty by anxious participants and may indeed complement uncertainty. This is substantiated by our finding that although intolerance of uncertainty was highly correlated with PSWQ scores and various ambiguous picture rating dimensions, group differences could not be merely attributed to IUS. The use of ambiguous pictures might therefore be useful for further exploration of the specific characteristics of information processing in GAD in future studies.

Regarding reaction times a statistically significant main effect of worry group was found, with HW having longer reaction times to all picture conditions compared to LW. A possible explanation is that HW had increased cognitive evaluative processing when confronted with the stimulus material, resulting in longer reaction times. While earlier studies of uncertainty found no group differences for reaction time (Krain et al., 2008; Yassa et al., 2012) these data suggest that ambiguity may be an important part of uncertainty in a broader sense which has been largely neglected so far. The absence of a picture condition effect and interaction effect was not expected but might also be explained by higher levels of vigilance for emotional stimuli observed in patients with anxiety (e.g. Brosschot et al., 2006) as well.

For the phasic electrodermal responses to different anticipation cues, an interaction between worry group and anticipation cue emerged, with stronger SCRs for the HW group in the uncertain but also safe condition. The finding of stronger SCRs in the uncertain anticipation condition for the HW group is contrary to earlier studies investigating psychophysiological responses to uncertainty (Grillon et al., 2009), although Grillon et al. (2009) used the startle response as an index of autonomic arousal and not SCRs. Comparable to the findings presented here Greco and Roger (2003) reported increased peripheral autonomic responses during anticipation in high IU compared to low IU. These results support the intolerance of uncertainty model of GAD (Dugas et al., 1998) and suggest increased arousal in HW during the anticipation of unknown yet possibly aversive stimuli. In addition, HW also responded stronger in the safe condition. In a startle fear conditioning study Gazendam and Kindt (2012) found that induced worrying resulted in increased fear responses to a conditioned feared but also an originally safe stimulus. Thus, worrying could impair the acquisition of safe contingencies and thus lead to increased autonomic arousal even in the anticipation of safe cues.

Regarding the phasic electrodermal responses to different picture conditions, a significant main effect of picture condition was found, but no group differences were observed. Higher levels of autonomic arousal were observed for ambiguous compared to all other conditions and for danger pictures preceded by an uncertain cue compared to all safe pictures. The lack of a significant interaction between worry group and picture condition (specifically during danger and ambiguous pictures following an uncertain cue) was

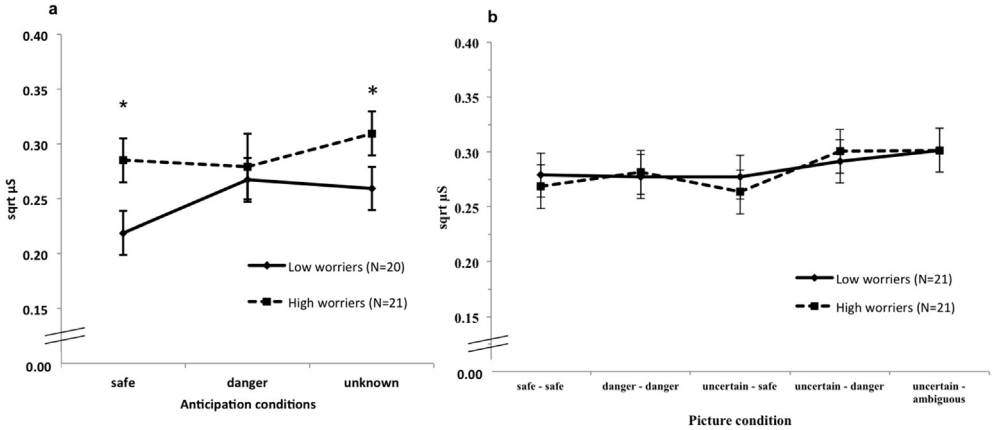

Fig. 4. a–b. Electrodermal responses and standard errors towards the three different anticipation cues (4a) and the five picture conditions (4b) among high and low worriers. *Sqrt µS*, square root transformed mean amplitude of stimulus-specific skin-conductance reactions. *Note.* Data from four participants were missing in the analysis (4a: hardware failure: n = 2 high worrier; n = 1 low worrier; rated as outlier n = 2 low worrier 4b: hardware failure: n = 2 high worrier; n = 1 low worrier; rated as outlier: n = 1 low worrier). *$p < .05$.

contrary to our expectation. However, a recent study reported similar results when comparing GAD patients and healthy controls, albeit only during conditions of uncertainty (Yassa et al., 2012). Yassa et al. (2012) reported a diminished autonomic flexibility in skin conductance data, results that have also been found in earlier studies as well (Hoehn-Saric, McLeod, Funderburk, & Kowalski, 2004). These results seem to suggest an effect of uncertainty on arousal which is only present during anticipation, but not during perception. In other words, intolerance of uncertainty is related to future stimuli but not to present ones. This is in keeping with the differentiation of uncertainty and ambiguity as proposed by Grenier and others (Buhr & Dugas, 2006; Grenier et al., 2005; Rosen et al., 2014).

The lack of group differences between HW and LW during perception might also be explained by the avoidance theory of worry (Borkovec, Alcaine, & Behar, 2004) suggesting that worry acts as a restraint for physiological responses and general arousal. This theoretical approach proposes that HW would be assumed to show increased autonomic arousal in the anticipation phase due to both uncertainty and the anticipation of aversive stimuli. This increased arousal would then subsequently be suppressed by increased worrying, which results from the inability to tolerate high arousal levels in this group. Therefore, in the perception phase of the task a dissociation between subjective feelings and autonomic arousal may have emerged in the HW, suggesting a temporal dynamic of the effect of worry. However, as we investigated event-related autonomic reactivity, but not tonic levels of autonomic arousal it is possible from a methodological viewpoint that the result discussed here are caused by the response intervals being too short to detect group differences and not the absence of such differences.

The findings presented here must be interpreted in light of the limitations of this study. Sample size was moderate and study participants were all female. Replication of this study would benefit from inclusion of male s and an enlarged sample. HW and LW were used as a subclinical phenotype of GAD. Thus future studies should investigate whether these findings can be replicated in GAD patients and generalized to this clinical sample. Besides group differences in intolerance of uncertainty, there were also group differences in current depressive symptoms and trait anxiety. Trait anxiety, intolerance of uncertainty and worry tendencies are suggested to be closely related to GAD (Borkovec & Inz, 1990; Dugas et al., 1998), while worrying and depressive rumination are overlapping constructs and GAD and depressive disorders are commonly found as comorbid conditions. The group differences found on these questionnaires were therefore expected, and current depressive symptoms were only of a low to moderate degree. This does not rule out the possibility that depressive symptoms had an influence of the outcome of this study. Finally, as we wanted to test the combined effect of uncertainty and ambiguity, all ambiguous pictures were presented after uncertain anticipation cues, inevitably confounding both variables. Given that the findings of this current study show the capability of ambiguous stimuli to differentiate HW and LW, it might be worthwhile to investigate the effects of ambiguity alone in future studies.

4.1. Conclusion

Reactivity to uncertainty and ambiguous stimuli is a potentially important area for future research on information processing in worriers and GAD patients. It was recently proposed that IU might be more of a trans-diagnostic factor which underlies a range of psychiatric disorders (Carleton, 2012; Carleton et al., 2012; Einstein, 2014; Fetzner et al., 2014) but its combination with IA might be a specific feature of GAD. The use of ambiguous pictures could provide a useful addition in future studies investigating anticipatory anxiety and uncertainty. Although the results were more pronounced for the subjective than for the autonomic data, information processing biases were investigated satisfactory by the paradigm. These processes are important for etiology and maintenance of anxiety disorders like GAD (Aikins & Craske, 2001). Future studies should investigate the effects of ambiguity further. For example by inspecting whether IA predicts GAD status or treatment response, whether it is treatment sensitive and or what neural correlates are related to ambiguity.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jbtep.2015.06.001.

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