The relation between anxious personality traits and fear generalization in healthy subjects: A systematic review and meta-analysis

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ABSTRACT

Background: Anxious personality characteristics form a risk factor for anxiety disorders. A proposed mechanistic pathway is that anxious personality could lead to greater vulnerability by increasing fear generalization. Here, we investigate if there is evidence for this relationship before the onset of pathological anxiety, with a meta-analysis in healthy subjects.
Methods: Our search (anxious personality & fear generalization) was performed in PubMed, PsychInfo, and Embase and via snowballing.
Results: In total, 4892 studies were screened and 19 studies (1348 participants) were included in the current review (meta-analysis: 18 studies, 1310 participants). The meta-analysis showed a significant, small, positive relationship between anxious personality and fear generalization (r = .19, 95%CI [.126, .260], p < .001). No moderators of the relationship were identified.
Conclusions: The identified robust relation suggests that people who score high on anxious personality have a somewhat stronger tendency to generalize fear to safe or novel situations. This might explain their vulnerability to anxiety disorders mechanistically, yet future (prospective) studies are warranted to confirm the hypothesized directionality of this effect.

1. Introduction

Anxiety disorders are associated with high health care costs and therefore pose an economic burden to western governments (Bandelow and Michaelis, 2015). Moreover, anxiety disorders cause great distress and suffering in those affected (Bandelow and Michaelis, 2015). After years of research, evidence-based treatment of anxiety disorders still seems to be insufficient, as 48% of patients who undergo cognitive behavioral therapy remain symptomatic after 2–14 years of follow-up (Bandelow et al., 2017). A better understanding of the processes that lead to pathological anxiety could foster the development of more effective treatments in the future.

Risk factors can provide important insights in disease pathology (World Health Organization, 2018). Over the last decades, many predisposing traits and environmental factors that increase the vulnerability to develop anxiety disorders have been identified (Mineka and Oehlberg, 2008; Sharma et al., 2016). Amongst others, well described

vulnerability factors are avoidant and anxious personality traits, such as neuroticism, trait anxiety and harm avoidance (Chambers et al., 2004; Kok et al., 2016; Mundy et al., 2015; Sandi and Richter-Levin, 2009; Weger and Sandi, 2018). However, central mechanisms in the pathology of anxiety disorders have not been identified using a single risk factor approach (Uher and Zwicker, 2017). Due to the complexity of psychological and biological traits and the heterogeneity of psychiatric disorders, it is most likely that mental disorders arise from the interplay between multiple risk factors (Uher and Zwicker, 2017). Therefore, it is relevant to investigate the relation between anxiety-related traits and other mechanisms contributing to vulnerability for anxiety disorders.

One proposed mechanism, that may explain why trait anxiety leads to increased risk for developing an anxiety disorder, is fear generalization (Dymond et al., 2015; Haddad et al., 2012; Raymond et al., 2017). Fear generalization can be defined as the expression of fear to stimuli with perceptual or conceptual similarities to a feared stimulus (Dymond et al., 2015; Lopresto et al., 2016; Mertens et al., 2019). Fear

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generalization and personality traits have been discussed in previous meta-analyses in patients with anxiety disorders (Duits et al., 2015; Lissek et al., 2005). Interestingly, patients indeed show increased fear generalization, that is: they show increased fear responses to safe stimuli (CS-) and to novel stimuli (GS) that have similarities to the conditioned stimuli (CS +), compared to healthy people (Duits et al., 2015; Lissek et al., 2005). For example, a patient suffering from posttraumatic stress disorder may interpret the sound of firework as the firing of explosives, which will make the patient relive the incurred trauma and the accompanying feelings of anxiety and fear reactions. Moreover, patients with anxiety disorders *and* high anxious personality characteristics show more fear generalization than patients with low anxious personality traits (Duits et al., 2015). This implies that there may be a relation between anxious personality characteristics, fear generalization and (vulnerability to) anxiety disorders.

The question remains whether this relation already exists before the onset of anxiety disorders, or that it arises as part of disease pathology. If increased anxious personality characteristics are also related to increased fear generalization in healthy subjects, it can be carefully assumed that fear generalization is indeed a mechanism that leads to the development of anxiety disorders (Schiele et al., 2016). A recent review of empirical evidence for computational models on the relation between trait anxiety and vulnerability for pathological anxiety, describes the role for fear generalization (Raymond et al., 2017). Accumulating evidence suggest that biological predispositions (like reinforcement sensitivity and sensory uncertainty) alter learning and behavior (via generalized aversive learning to generalized avoidance and heightened threat detection), which subsequently affect experienced anxiety (by the frequency of anxious states) (Raymond et al., 2017). According to this model (Raymond et al., 2017), people with a more anxious predisposition (e.g. trait anxiety) will experience more general anxiety *because* their ability to discriminate between dangerous and safe situations is hampered (fear generalization). As a consequence, general anxiety would rise after each (stressful) experience, thereby increasing vulnerable to an anxiety disorder. If trait anxiety indeed increases the risk for pathological anxiety by increasing fear generalization before the onset of a disorder, the relationship between these factors should at least already be present in the absence of pathology. Therefore, as a next step in unraveling the relationship between trait anxiety and fear generalization in the etiology of pathological anxiety, an overview needs to be created of all scientific studies investigating the relationship between anxious personality characteristics and fear generalization in healthy subjects.

Hence, the primary aim of the current systematic review and meta-analysis is to thoroughly examine the evidence for the relation between anxious personality characteristics and fear generalization in healthy subjects. We expect that healthy subjects with higher levels of anxious personality characteristics display more fear generalization, than individuals with lower levels of anxious traits. The secondary aim is to evaluate which subject-related and methodological factors have a robust influence on the interaction between anxious personality characteristics and fear generalization. Investigation of moderators can help to identify which crucial elements of anxious personality characteristics and fear generalization drive the relationship. For example, it is known that (conditioned) fear can be generalized to both stimuli (cues) and environments (contexts) with similarities to the original learning experience (Lopresto et al., 2016). These cues and contexts can be novel (i.e. generalization stimulus (GS) or context (G-CTX)), or previously associated with safety (i.e. safety stimulus (CS-) or context (CTX-)). Identified moderators can provide insight in the most likely mechanistic relation between the studied processes and be useful to determine which paradigm is most informative to study risk factors for anxiety disorders before the onset of pathological anxiety in the future.

2. Method

The documents and datasets used during literature search, screening, data extraction, and analyses are available via Open Science

Framework (https://osf.io/kzjmw/).

2.1. Search strategy

This study was conducted according to the PRISMA guidelines, see *Appendix A* (Liberati et al., 2009) and pre-registered in PROSPERO (CRD42018090886; Steenmeijer et al., 2018). The search strategy was developed to retrieve all publications that investigated the relation between anxious personality traits and fear generalization, and performed in three computerized reference databases (PubMed, Embase and Psychinfo). The search was based on a combination of keywords that could to be present in all fields of the article: (*fear generalization* OR *fear consolidation* OR *context** OR *fear conditioning* OR *generalization of fear*) AND (*trait anxiety* OR *avoidance* OR *neuroticism* OR *BIS* OR *behavioral inhibition system* OR *negative affect* OR *negative affectivity* OR *shyness* OR *type D*) AND *Human* AND *NOT review*. The final search was performed on the 31 st of July 2017 (*see* Appendix B). To update the search and check for any additional articles, reference lists of included articles were screened for relevant articles. Furthermore, articles referring to the included papers were screened for eligibility. This additional search was performed in September and October 2018.

2.2. Screening

The retrieved articles were screened on *a priori* defined inclusion and exclusion criteria. Inclusion criteria used were: (1) original studies that include avoidant/anxious personality traits, fear generalization and report the relation between the former two subjects, (2) healthy participants (not diagnosed with a mental health disorder), (3) participants had to be 12 years or older (4) English or Dutch language. The initial screening was performed by three researchers (AS, AM, AB) and based on abstract and title according to the established selection criteria. Articles were eligible for full-text screening if they included a form of fear generalization or fear conditioning and anxious personality characteristics in the title and/or abstract, used healthy adults as participants and English or Dutch language. Second, the full-text articles were screened by one member of our research team, and independently checked by another. All included articles were checked by two researchers (MS, AS). Furthermore, ambiguous articles regarding inclusion and/or exclusion criteria were discussed with a third researcher (MK).

2.3. Data extraction and quality assessment

Extracted data included: (1) Publication details (authors, publication year); (2) Sample details (sample size, mean age/range); (3) Methodological details (personality scale, fear measure fear generalization paradigm); (4) Effect sizes (i.e. fear generalization performance in relation to anxious personality traits). Fear measures comprised physiological readouts (e.g. skin conductance response, startle response) and self-report (e.g. questionnaires on arousal or expectancy ratings). Details on the generalization paradigm included information on the unconditioned stimulus (US), conditioned stimulus (CS +), and generalization stimuli (e.g. safety-associated stimulus after conditioning (CS-), safety-associated context (CTX-), novel generalization stimulus (GS), and novel generalization context (G-CTX)). For later subgroup analysis (*see statistical analysis)*, fear generalization paradigms were classified as either 1) cued generalization (cue), 2) cue-context generalization (cue in context) or 3) contextual generalization (context). Paradigms were classified as 'cue in context' if the association between a cue and context stimuli predicted US in the fear conditioning paradigm (in other words: if cue and context served as CS together). Generalization stimuli were grouped in novel (GS, G-CTX) and safety-associated stimuli (CS-, CTX-). Note, only fear responses to CS- or CTX-stimuli *after* fear conditioning were included as generalization responses in this meta-analysis. Finally, effect sizes were extracted, including correlations (Pearson's *r* and Spearman's ρ*)* and group

Table 1

Overview of selected studies, both in systematic review and meta-analysis. F = Female; NS = not shown; VAS = visual analogue scale; SCR = skin conductance response; FPS = fear potential startle; VEMFs = vector electromagnetic fields; UCS = unconditioned stimulus; CS + = threat cue; CS- = safe cue; GS = generalization cue; CTX + = threat context; CTX- = safe context; G-CTX = generalization context. *Articles included in systematic review, not in meta-analysis.

| Reference	Number of participants (sex)	Age (mean / range)	Personality scale	Fear measure (continuously / once)	UCS	Stimuli + / - / new	Fear generalization paradigm	Physiological/ Self-report	Pearson's r reported / calculated with
1. (Andreatta et al., 2015)	32 (53% F)	23.8	STAI	VAS (C) / SCR (C) / FPS (C)	Shock	Room	G-CTX	S P P	r reported
2. (Baas, 2013)	22 (73% F)	21.4	STAI	VAS (C) / FPS (C)	Shock	Lights	CS- in CTX- | CS- in CTX +	S / P	r reported
3. (Baas and Heitland, 2015)	150 (60% F)	21.6	STAI	VAS (C) / FPS (C)	Shock	Lights	CS- in CTX +	S P	r reported
4. (Baumann et al., 2017)	62 (55% F)	23.1	STAI	Arousal Ratings (O) / UCS Expectancy (O) / Valance Ratings (O) / SCR (C)	Scream	Face	GS	S S S / P	r reported
5. (Boddez et al., 2012)	46 (83% F)	18.9	STAI	SCR (C)	Shock	Geometrical	GS	P	r reported
6. (Davey and Matchett, 1994)	40 (55% F)	18-37	STAI	SCR (C)	Noise	Words	CS-	P	r calculated
7. (Dunsmoor et al., 2011)	29 (33% F)	19.1	STAI	SCR (C)	Shock	Animal	GS	P	r reported
8. (Garcia and Zoelner, 2016)	129 (60% F)	19.1	EPQ-RN	Online Risk Rating	Scream	Face	GS	S	r calculated
9. (Gazendam et al., 2013)	42 (69% F)	20	STAI	UCS Expectancy (C) / Self-reported Distress (C)	Shock	Face	CS-	S S	r reported
10. (Glotzbach-Schoon et al., 2013)	49 (63% F)	21.8	STAI	Arousal ratings (C) / SCR (C) / UCS Expectancy (C) / Fear Ratings (C)	Shock	Room	CTX-	S P / S / S	r reported
11. (Haaker et al., 2015)	377 (69% F)	24.6	STAI	UCS Expectancy (O) / Fear Ratings (O)	Shock	Geometrical	CS- in CTX + & CS + in CTX- & CS- in CTX-	S S	r reported
12. (Joos et al., 2012)	43 (NS)	18.2	STAI	Fear Ratings (C)	Scream	Face	CS-	S	r reported
13. (Lee et al., 2009)	32 (50% F)	22.9	STAI	Stroop Interference Score (C)	Shock	Face	CS-	S	r reported
14. (Lommen et al., 2010)	48 (52% F)	21.7	EPQ-RN	UCS Expectancy (O) / SCR (C)	Shock	Color	GS	S	r reported
15. (Morriss et al., 2016b)	54 (91% F)	19.5	STAI	SCR (C) / Uneasiness rating (C)	Scream	Geometrical	GS	P S	r calculated
16. (Morriss et al., 2016a) *	38 (84% F)	18-25	IU	SCR (C) / UCS Expectancy (C) / Fear Ratings (C)	Scream	Geometrical	CS-	P	N/A
17. (Rehbein et al., 2015)	47 (100% F)	24	STAI	VEMFs (C)	Noise	Face	CS-	P	r reported
18. (Staples-Bradley et al., 2018)	29 (79% F)	19.3	BIS	UCS Expectancy (C) / Fear ratings (C)	Scream	Face	CS- in G-CTX CS + in G-CTX	S / S	r reported
19. (Torrents-Rodas et al., 2013)	79 (72% F)	22.5	STAI	Fear ratings (C) / SCR (C) / FPS (C)	Shock	Geometrical	GS	S / P / P	r reported
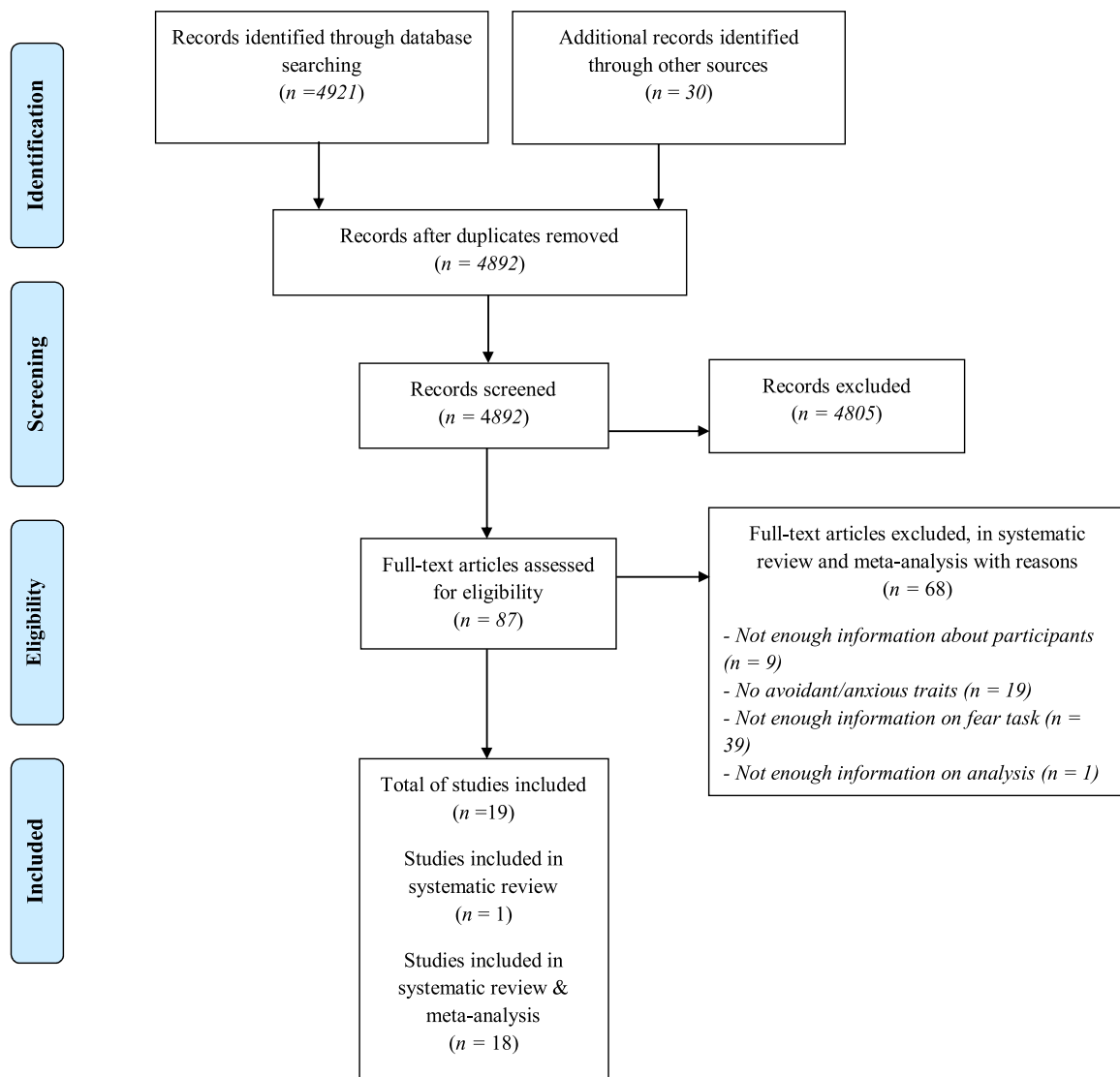
Fig. 1. Flow-diagram.

differences or statistics (high vs low anxious personality). Suitable data presented in supplementary tables was also extracted.

Since no preexisting quality assessment (QA) tool was available, a QA tool with eligibility criteria was specifically developed for this meta-analysis according to quality measures also applied in meta-analysis on anxiety disorders (Duits et al., 2015; Lissek et al., 2005), see *Appendix C* including Table 1 for QA Score or PROSPERO (ID: CRD42018090886; Steenmeijer et al., 2018). Extracted data included: (1) selection bias, (2) participant drop-out, (3) quality of personality measurement, and (4) fear acquisition score. Points were given for each reported criterion. Potential scores ranged from 0 to 8, with higher scores rating greater methodological quality. Two authors independently assessed the quality of the included papers and conflicts were resolved by discussion with all authors until consensus is reached.

2.4. Statistical analysis

The statistical analysis was performed using Comprehensive Meta-Analysis (CMA) (Borenstein, 2005). The majority of the studies reported Pearson's *r* correlations (*r* reported). For the studies that reported Spearman's ρ correlations, group differences and group statistics, Pearson's *r* correlations were calculated with the CMA software (*r* calculated).

To assess the main hypothesis if higher levels of anxiety personality characteristics are related to more fear generalization, an overall pooled mean effect size (in Pearson's *r*) was calculated based on the Pearson's *r* correlations of individual studies weighted by study variance (Borenstein et al., 2009). Note, both physiological and self-report measures from cued and contextual fear generalization paradigms were included, as this analysis is performed under the assumption that they all capture aspects of fear conditioning (and generalization) (Lonsdorf et al., 2017). As heterogeneity in the data was expected, a nested random effects model was used to calculate the overall effect size (Borenstein et al., 2009). A correlation of .10 represents a small correlation; .30 represents a medium correlation and .50 represents a large correlation (Cohen, 1988). A sensitivity analyses was performed only on studies that reported Pearson's *r* directly, to check if the overall effect size was influenced by the Pearson's *r* calculations in CMA.

To investigate the secondary objectives, three subgroup analyses were performed to investigate if the relation between anxious personality and fear generalization was different when 1) fear was measured with physiological readouts versus self-report, 2) cued, cue-context or contextual generalization was assessed and 3) new (GS or G-CTX) or safety-associated (CS- or CTX-) stimuli served as generalization stimuli. Next to the subgroup analyses, meta-regression analyses with a mixed effects model, were used to investigate if age, quality assessment and

sex moderated the relationship between anxious personality characteristics and fear generalization. Note, the available data in the included studies determined which secondary follow-up analyses were possible to conduct. The I² statistic was used to assess heterogeneity of effect sizes. According to Higgins et al. (2003) values of 25, 50 and 75% are indicative of low, moderate and high heterogeneity, respectively. Rosenthal's fail-safe *N* was used to assess the robustness of effect sizes. Fail-safe *N* determines the number of studies with effect size 0 that would be necessary to cancel out significant effect sizes. Effect sizes were considered robust when *N* values > 5k + 10, where k refers to the number of studies used in the meta-analysis (Rosenthal, 1995). The possibility of publication bias was also assessed by Egger Funnel plot asymmetry (Egger et al., 1997) and all reported significance tests were two tailed with α = .05.

3. Results

3.1. Selection of studies

In total, 4892 studies were screened based on title and abstract and 87 studies were included for full-text screening (Fig. 1). Of these, a total of 19 studies fulfilled the inclusion criteria. In these 19 studies a total of 1348 participants were included (age range: 18–37; sex range: 33–100 % female). Most studies measured cued fear generalization (*n*=13), four papers measured generalization to cue's in context and two measured generalization to context alone. Fear generalization was equally measured to new and safe stimuli in the included studies (new *n*=9; safe *n*=10), as was the use of physiological and self-report measures (physiological alone: *n*=5; self-report alone: *n*=7; both: *n*=7). Interestingly, the majority of the studies used the same personality scale (*n*=15): Spielberger's State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). Only Garcia and Zoellner (2016); Lommen et al. (2010); Morriss et al. (2016a) and Staples-Bradley et al. (2018) used different personality scales: the neuroticism scale of Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975) (*n*=2), the Intolerance of Uncertainty scale (Buhr and Dugas, 2002) (*n*=1) and the Behavioral Inhibition System scale from the BIS/BAS questionnaire (Carver and White, 1994) (*n*=1), respectively. One study provided insufficient information to be included in the meta-analysis and will therefore narratively reviewed below the results of the meta-analysis (Morriss et al., 2016a). In the 18 papers included the meta-analysis, 1310 participants were used.

3.2. Relation between anxious traits and fear generalization: meta-analysis

Overall, results of the primary analysis show that there is a significant, small, positive correlation between anxious personality traits and fear generalization (*n*=18, *r* = .19, 95%CI [.126, .260], *p* < .001). The results are presented in Fig. 2 and Table 2. The effect remained similar when excluding studies of which the correlation (*r*) was calculated, or when excluding outliers. The I²-test showed low heterogeneity in effect sizes between studies (21.61%, *p* = .197). With respect to the secondary aim, the subgroup analyses revealed no significant differences, and no moderating factors were identified in the meta-regression (see Table 2). Subjective measures of fear generalization only have a marginally stronger correlation with trait anxiety than physiological measurements (*p* = 0.058). Rosenthal's fail-safe *N* and Egger funnel plot showed no evidence for publication bias, see *Appendix D*.

3.3. Relation between anxious traits and fear generalization: narrative review

The study of Morriss et al. (2016a) confirms the relation between anxious personality characteristics and heightened fear generalization (*see* Table 1). In this study, Intolerance of Uncertainty (IU), a tendency that affects the interpretation and perception of uncertain situations,

was positively correlated with fear generalization.

4. Discussion

This systematic review and meta-analysis provide a comprehensive overview of the current literature on the relation between anxious personality characteristics and fear generalization in healthy subjects. More specifically, this study aimed to determine if higher levels of anxious personality traits are already related to greater fear generalization in the absence of pathology, which may provide mechanistic insights in the development of anxiety disorders. In line with our hypothesis, the meta-analysis showed that healthy individuals with high levels of anxious personality characteristics show significant greater generalization of fear (small-medium positive correlation) to safe and novel cues and contexts, as measured with self-report and physiological measures.

4.1. Anxious traits increase fear generalization

The results may imply that anxious personality traits increase vulnerability to anxiety disorders, via fear generalization. Although statistical conclusions about causation cannot be made based on an identified correlation (Aldrich, 1995), we can speculate about the direction of the effect based on theoretical frameworks on trait anxiety, anxiety disorders and fear generalization. A neurocognitive model (Sandi and Richter-Levin, 2009) and recent literature overviews (Raymond et al., 2017; Weger and Sandi, 2018) discuss how high trait anxiety increases vulnerability to stress and stress-induced psychopathology, like anxiety disorders and depression. It has been suggested that anxious personality traits increase the frequency of experienced anxious states, via fear generalization (Raymond et al., 2017). As the distinction between safe and unsafe situations becomes more ambiguous, more situations elicit a fear response (Raymond et al., 2017). As a consequence, the amount of threats experienced in the environment increases, thereby triggering a state of anxiety more frequently (Raymond et al., 2017). The increased frequency of anxious states can subsequently predispose to anxiety and depressive disorders (Raymond et al., 2017; Sandi and Richter-Levin, 2009), which might partially explain the comorbidity between pathological anxiety and depression (Sandi and Richter-Levin, 2009; Weger and Sandi, 2018). More specifically, the characteristic cognitive style of high anxious individuals that focusses on fear and threat (together with distinct neuro and neuroendocrine patterns) can lead to ineffective responses to stressful situations (Sandi and Richter-Levin, 2009). This can trigger worrying, avoidance, and increase fear when confronted with similar situations thereby increasing vulnerability to anxiety disorders (Raymond et al., 2017). In parallel, this inadequacy can trigger loss of motivation and negative feelings like hopelessness, helplessness and worthlessness (Sandi and Richter-Levin, 2009). Subsequent behavioral withdrawal in multiple life domains can lead to loss of (positive) reinforcements (Sandi and Richter-Levin, 2009). Upon repeated exposure to stressful events, this cascade can turn into a spiral towards a depressive episode, that later develops into a depressive disorder (Sandi and Richter-Levin, 2009; Weger and Sandi, 2018). As no patient data was included is this meta-analysis, the prognostic value of the identified relation for pathological anxiety and / or depression could not be tested directly. Interestingly, however, it has also been shown in a prospective design that fear generalization predicted subclinical levels on anxiety (or 'anxious states') in healthy participants (Lenaert et al., 2014). Additional prospective studies, also including anxious personality traits, are needed to determine the directionality of the effect and elucidate on the proposed mechanism.

As the overall pooled correlation between anxious personality characteristics and fear generalization is small, caution is necessary with drawing definitive conclusions from the current study (Greco et al., 2013). Although we found a small effect indicating that
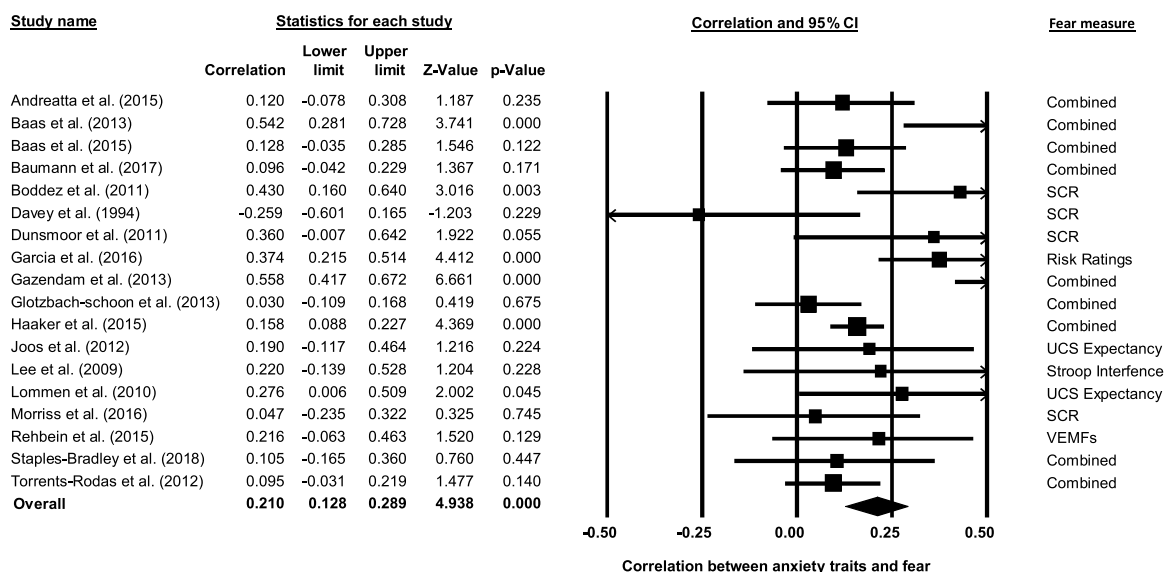
Study name	Statistics for each study					Correlation and 95% CI	Fear measure
	Correlation	Lower limit	Upper limit	Z-Value	p-Value		
Andreatta et al. (2015)	0.120	-0.078	0.308	1.187	0.235		Combined
Baas et al. (2013)	0.542	0.281	0.728	3.741	0.000		Combined
Baas et al. (2015)	0.128	-0.035	0.285	1.546	0.122		Combined
Baumann et al. (2017)	0.096	-0.042	0.229	1.367	0.171		Combined
Boddez et al. (2011)	0.430	0.160	0.640	3.016	0.003		SCR
Davey et al. (1994)	-0.259	-0.601	0.165	-1.203	0.229		SCR
Dunsmoor et al. (2011)	0.360	-0.007	0.642	1.922	0.055		SCR
Garcia et al. (2016)	0.374	0.215	0.514	4.412	0.000		Risk Ratings
Gazendam et al. (2013)	0.558	0.417	0.672	6.661	0.000		Combined
Glotzbach-schoon et al. (2013)	0.030	-0.109	0.168	0.419	0.675		Combined
Haaker et al. (2015)	0.158	0.088	0.227	4.369	0.000		Combined
Joos et al. (2012)	0.190	-0.117	0.464	1.216	0.224		UCS Expectancy
Lee et al. (2009)	0.220	-0.139	0.528	1.204	0.228		Stroop Interference
Lommen et al. (2010)	0.276	0.006	0.509	2.002	0.045		UCS Expectancy
Morriss et al. (2016)	0.047	-0.235	0.322	0.325	0.745		SCR
Rehbein et al. (2015)	0.216	-0.063	0.463	1.520	0.129		VEMFs
Staples-Bradley et al. (2018)	0.105	-0.165	0.360	0.760	0.447		Combined
Torrents-Rodas et al. (2012)	0.095	-0.031	0.219	1.477	0.140		Combined
Overall	**0.210**	**0.128**	**0.289**	**4.938**	**0.000**		

-0.50   -0.25   0.00   0.25   0.50

Correlation between anxiety traits and fear

Fig. 2. Forest plot visualizing effects per study and the overall effect size (*r*). Combined outcome means multiple measures were included in that study (see Table 1). SCR = skin conductance response, VEMFs = vector electromagnetic fields, UCS = unconditioned stimulus.

heightened vulnerability of trait anxiety may arise via increased fear generalization, it must be noted that we did not investigate other processes (e.g. fear inhibition, extinction, etc.). Also, no conclusions about interactions with other risk factors for anxiety disorders can be drawn from the current meta-analysis. Further interactions with other risk factors like (stressful) life events may be necessary to actually develop an anxiety or depressive disorder (Kok et al., 2016; Ruscio et al., 2015; Sandi and Richter-Levin, 2009; Weger and Sandi, 2018). Future meta-analytic and experimental longitudinal studies could take these risk factors into account, to cover the broader spectrum of potential mechanisms and their interactions in the development of anxiety disorders. Nevertheless, effect sizes in psychological research are mostly small or medium, matching the complexity of psychopathology in general (Szucs and Ioannidis, 2017). Therefore, even though the effect is small, it is important to note that our results shed some light on the complexity of anxiety vulnerability and can be a starting point for future, more complex, meta-analytic projects such as network meta-analysis (Tonin et al., 2017).

4.2. No robust influence of methodological factors

In contrast to our expectations, the relation between anxious personality traits and fear generalization was not differentially affected by stimulus type (neither cue versus context, nor new versus safe). More specifically, the current results show that fear generalization towards both cue and context stimuli, as well as new and safe information is positively correlated with anxious personality characteristics. The absence of these differential effects to stimulus type in health subjects point towards a more generic role of the relation between anxious personality traits and fear generalization that increases one's vulnerability for pathological fear (Raymond et al., 2017). This might indicate that the investigated mechanism interacts with other factors like temperament, environmental factors, genetic pre-dispositions, life-events, attitudes and additional individual differences to determine which anxiety disorder will be developed (Gallagher et al., 2014; Hong and Cheung, 2015). For example, it has been shown that these additional processes influence the development of Social Anxiety Disorder

Table 2
Meta-analytic results of the primary and secondary (subgroup and meta-regression) analysis * Studies that measure 2 conditions (e.g. both physiological and self-report) are included in both conditions. Thus, this may be an overestimation of the effect. Caution should be taken with interpreting the results.

	Number of studies (k)	Pooled Pearson's *r*	Lower limit	Upper limit	Significance of the pooled correlation (*p*)	I²	Significance of I², subgroup difference or meta-regressor (*p*)
Primary analysis: overall correlation between anxiety and fear generalization	18	0.194	0.126	0.260	< 0.001	21.610	0.197
Secondary subgroup analyses							
Physiology vs self-report ratings*							0.058
P	12	0.093	−0.044	0.227	0.181		
S	14	0.249	0.160	0.335	< 0.001		
Context vs cue							0.442
Context	2	0.065	−0.150	0.275	0.554		
Cue	12	0.216	0.125	0.303	< 0.001		
Cue in context	4	0.185	0.046	0.316	0.009		
Safe vs new							0.676
Safe	7	0.174	0.070	0.274	0.001		
New	11	0.204	0.108	0.296	< 0.001		
Pearson's *r* reported vs CMA calculated							0.651
CMA calculated	3	0.098	−0.261	0.434	0.597		
Reported	15	0.182	0.122	0.241	< 0.001		
Secondary meta-regression analyses							
Quality Assessment score	18	−0.034	−0.109	0.041	0.075		0.212
Percentage female	15	−0.001	−0.006	0.004	0.679		0.250
Age	15	−0.027	−0.054	−0.001	0.046		0.504

(Raymond et al., 2017).

In addition, the current results show that physiological measurements and self-report ratings can both be used to measure the relation between anxious personality characteristics and fear generalization as both are positively correlated to anxious personality traits (Of note, it seems that subjective measures of fear generalization ($r = 0.249$) have a stronger correlation with trait anxiety than physiological measurements ($r = 0.093$), yet this difference is not significant ($p = 0.058$)). This provides support for the relevance of using both self-report and physiological measures as (bio) feedback for patients undergoing diagnostic testing and/or therapy for anxiety disorders. Physiological measures might improve treatment for patients with less introspective and/or verbal abilities. These measurements can be provided as wearables measuring physiological stress through for example heart rate, sweat analysis, sleep patterns and changes in cognitive functions, which make patients aware of the connection between their physiology and behavior (Peake et al., 2018). Furthermore, measuring physiological responses provides better insight in experienced sensations and complaints during the actual treatment or homework assignments, like exposure exercises. On the other hand, self-report ratings can be helpful in helping the patient to establish a healthy lifestyle or rationalize certain negative cognitions.

4.3. Limitations

Although this meta-analysis provides a comprehensive overview of the literature, it is subject to some limitations. First, for analyses-purposes various different self-report or physiological measurement methods (i.e. startle reflex and skin conductance) are grouped together under the same label. Although all methods are commonly used measures of fear (Lonsdorf et al., 2017), bundling these different measurements could have increased the heterogeneity in the analyses. Due to the limited number of studies per measurement type, it was not possible to analyze the differences between measurement types. More primary studies or more advanced meta-analytic methods might be needed to reveal differences between measurement types. However, the overall low heterogeneity in the current analyses indicates limited variation in effect size's between studies, suggesting a limited influence of measurement type, amongst others. Second, in contrast to our expectations, almost all studies included in this meta-analysis and systematic review used trait anxiety as a personality scale. This uniformity was not expected beforehand as the search terms were not limited to trait anxiety, but covered many different anxious personality characteristics. Although this reduced the variance in the analyses, it might limit the generalizability of the meta-analytic results. Finally, no observable behavioral measures of personality were included in the analyses, since we choose to focus on anxious personality questionnaires. Future studies can also include behavioral tests to study avoidance/anxiety.

4.4. Implications for clinical practice

Our results show that there is a relationship between anxious personality characteristics and fear generalization already before the onset of pathological anxiety, that may lead to the development of anxiety disorders (Schiele et al., 2016) and also of depression (Sandi and Richter-Levin, 2009; Weger and Sandi, 2018). This implies that perhaps people who experienced a stressful or traumatic event and score high on anxious personality characteristics should be closely monitored in the weeks, months or even years after the event as they are possibly more likely to generalize the experienced fear during trauma to other non-threatening situations. Besides, people who actually develop an anxiety-related disorder and score high on anxious personality characteristics could have a tailored treatment plan in which the clinician focuses more on the learned and generalized fear component of the disorder. For example, by incorporating exposure therapy in the treatment plan, as this is a type of behavioral therapy in which extinction of the conditioned fear (the trauma) is the main goal (Beck et al., 2015; Hofmann, 2008). Reducing

behavioral withdrawal via exposure therapy might not only help to threat pathological anxiety, but could also reduce the vulnerability to depression in high anxious individuals (Sandi and Richter-Levin, 2009). In addition, clinicians could perhaps use physiological measurement methods during treatment as biofeedback if a patient's introspection is limited.

4.5. Conclusion

To conclude, our meta-analysis established a small relation between anxious traits and fear generalization over 18 independent studies, implying that trait anxiety may increase vulnerability via increasing fear generalization. In addition, in contrast to our expectations, no moderating effects were established. This implicates that different types of measurements are sensitive to pick up this small effect. Perhaps both physiological as well as self-report methods can be applied in the future to measure and reduce fear generalization in clinical settings. This valuable information and mechanistic insights may be used in the future for identifying persons at risk or improving treatment strategies. Future studies should investigate the complex relations between vulnerability factors to establish useful models for studying and treatment of anxiety disorders. In addition, prospective studies investigating the relation between anxiety and fear generalization as predictors of the development of anxiety disorders are necessary to confirm the proposed directionality of the relation and the potential causality of this mechanism.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2019.09.029.

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