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Review

A review and meta-analysis of the heritability of specific phobia subtypes and corresponding fears

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ABSTRACT

Evidence from twin studies suggests that genetic factors contribute to the risk of developing a fear or a phobia. The aim of the present study was to review the current literature regarding twin studies describing the genetic basis of specific phobias and their corresponding fears. The analysis included five twin studies on fears and ten twin studies on specific phobias. Heritability estimates of fear subtypes and specific phobia subtypes both varied widely, even within the subtypes. A meta-analysis performed on the twin study results indicated that fears and specific phobias are moderately heritable. The highest mean heritability (±SEM) among fear subtypes was found for animal fear (45% ± 0.004), and among specific phobias for the blood–injury–injection phobia (33% ± 0.06). For most phenotypes, variance could be explained solely by additive genetic and unique environmental effects. Given the dearth of independent data on the heritability of specific phobias and fears, additional research is needed.

Contents

1. Introduction

It is estimated that more than 40% of the general population suffers from one or more fears of a specific object or situation at some times in their lives (Curtis, Magee, Eaton, Wittchen, & Kessler, 1998; Depla, ten Have, van Balkom, & de Graaf, 2008; Oosterink, De Jongh, & Hoogstraten, 2009). If a fear becomes excessive or unreasonable it is termed a phobia (American Psychiatric Association, 2000). Specific phobia is an anxiety disorder that is defined as an unreasonable or irrational fear which has a significant negative impact on daily living (APA, 2000). With life-time prevalence rates of over 10% (Kessler, Berglund, et al., 2005; LeBeau et al., 2010), specific phobias are the most prevalent group of mental disorders.

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A specific phobia is a common, long lasting, often chronic anxiety disorder (Depla et al., 2008; Goisman et al., 1998), associated with serious impairment (Alonso et al., 2004; Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996; Oosterink, De Jongh, & Aartman, 2009) that represents a serious public health problem with a substantial economic burden (Alonso et al., 2004; Greenberg et al., 1999; Robins et al., 1984).

The DSM-IV-TR (APA, 2000) distinguishes five main categories or subtypes of specific phobia: *animal type*, *natural environment type*, *situational type*, *blood–injury–injection type*, and *other type*. The subtypes of specific phobia differ in terms of prevalence, sex distribution and age of onset. Women appear to have higher prevalence rates of fears and specific phobias in general than men (Fredrikson, Annas, Fischer, & Wik, 1996; Lipsitz, Fyer, Paterniti, & Klein, 2001; McNally, 1994; Oosterink et al., 2009b). In the natural environment, animal, blood–injury subtype and other type (i.e., emetophobia ("vomiting phobia"); Czajkowski, Kendler, Tambs, Røysamb, & Reichborn-Kjennerud, 2011; Depla et al., 2008; Lipsitz et al., 2001) the age of onset varies between 8 and 13 years, while in the situational subtype this appears to be higher (14–15 years; Depla et al., 2008).

There is a common theory that the development of fears and specific phobias can best be understood by application of the behavioral paradigm or classical conditioning model; that is, the pairing of a indifferent stimulus, conditioned stimulus (CS) with an unconditioned stimulus (US) which automatically evokes a fear response (e.g., Davey, 1997). Conditioning theories state that objects and situations which are irrationally feared resemble previous distressing experiences (e.g., pain). Yet, not all phobia subtypes develop according to the principle of classical conditioning alone. For example, animal phobias (e.g., spiders, mice, bats, etc.), and phobias of the natural environment type (e.g., water phobia), have not been found to be the result from experiences associated with pain or terror (Menzies & Clarke, 1993). An influential model concerning the development of fears and phobias states that specific phobias are not only acquired through traumatic conditioning experiences, but also through transmission of information and observational learning (Rachman, 1977). For some fear and specific phobia subtypes the contribution of these pathways does not appear to be substantial or is even lacking (e.g., King, Gullone, & Ollendick, 1998). A study that aimed to maximize the prediction of a current specific phobia diagnosis by using combinations of distressing experiences, including those based on modeling and negative information, show that these accounted for less than 50% of the variance (Oosterink, De Jongh, & Aartman, 2009). Such findings cast doubt on the validity of conditioning, modeling, and information pathways as the sole explanation of how specific phobias develop, and have inspired others to develop a so-called non-associative account of phobic etiology (Poulton & Menzies, 2002). This theory assumes that a number of fears have an evolutionary background and pertain to stimuli that once posed a challenge to the survival of mankind.

The observation that conditioning processes are not always necessary for the acquisition of a fear and thus for a number of specific phobias implies that other innate factors, including genetic susceptibility, may play a role in the development of specific phobias (see Hettema, Neale, & Kendler, 2001). The model that describes this combination of genetic and environmental influences is the diathesis-stress model of illness (Monroe & Simons, 1991). This model attempts to explain behaviors or psychological disorders as a result of the interaction of genetic vulnerability or predisposition (diathesis) with the environment and life events (stressors). According to this classical model, there is an inverse relationship between the level of genetic liability and the level of onset-related environmental stressors (Jang, 2005).

To determine whether there is a familial component to fears and phobias, studies have been conducted that showed aggregation within families (Depla et al., 2008; Fyer, Manuzza, Chapman, Martin, & Klein, 1995; Hettema et al., 2001). Once familial aggregation is observed, twin or adoption studies test to what extent familiarity is explained by shared genetic factors or shared family environment. In twin studies the resemblance of monozygotic (MZ) and dizygotic (DZ) twin pairs is compared. Identical or monozygotic (MZ) twins, being male–male (MM) or female–female (FF) pairs, share (nearly) 100% of their genes, while non-identical or dizygotic (DZ) twins, which can be MM, FF or MF (male–female or opposite sex, OS) share on average 50% of their segregating genes. The variation in liability to a disorder or trait can be described to four potential sets of effects: additive genetic effects (A), non-additive or dominant genetic effects (D), family or common environmental effects (C; e.g., events, conditions or experiences that are common to all members of a household) and individual specific or unique environmental effects (E; e.g., individual events). A, D and C all contribute to resemblance of MZ and DZ twins, whereas E does not. Since MZ twins are (nearly) genetically identical, any differences between them will be the result of non-shared environmental factors. If the correlation in MZ twins exceeds the correlation in DZ twins this indicates additive genetic effects on this trait or disorder, and if the correlation in MZ twins is more than twice the correlation in DZ twins there is also evidence for non-additive genetic influences (D). Shared environmental factors, on the other hand, will cause the same degree of resemblance in MZ and DZ twins, because both types of twins share these environmental factors to the same extent. Based on these principles, it is possible to disentangle the effects of non-shared environmental, shared environmental and genetic factors on a trait.

A meta-analysis conducted more than 10 years ago suggested that phobias are moderately heritable with an estimated heritability ranging from 20% to 40% (Hettema et al., 2001). However, in this study within each of the individual categories, specific phobias were grouped together with the other main categories of phobias (i.e., social phobia, generalized social phobia, and agoraphobia), making it difficult to estimate the variance explained by genetic factors for specific phobia per se (Hettema et al., 2001). To provide an overview and update of the current knowledge regarding the heritability of specific phobias and their corresponding fears, the aims of this study are (1) to review the current literature of twin studies regarding the genetic basis of specific phobias and their corresponding fears, and (2) to conduct a meta-analysis of published twin studies in order to provide an estimate of the genetic and environmental influences of the different subtypes of specific phobias and fears.

2. Methods

A systematic search of the published literature (MEDLINE-PubMED) was conducted for all studies published between 1967 and April 2012 to select relevant twin studies describing the heritability of specific phobias and their corresponding fears. Combinations of the following search themes were used: "fear, genetic(s)"; "phobia, genetic(s)"; "fear, heritability" and "phobia, heritability". Abstracts of these search results were examined and relevant full text articles were retrieved for review. The reference lists and citations were examined to identify any eligible report not previously located through the database search.

Criteria for inclusion and exclusion of relevant articles were determined a priori and assessed. Articles were included when they described a twin study in an adult population and contained information on estimated heritability of any fear or specific phobia subtype. Studies reporting on other anxiety disorders (e.g., panic disorder with/without agoraphobia) were included only when a fear or specific phobia was reported as a comorbid anxiety disorder and when data on estimated heritability were available

for inclusion. Articles that aimed to describe specific phobias, but which used a fear measure, such as the Fear Questionnaire (Fredrikson et al., 1996) rather than a psychological assessment procedure, like the Structured Clinical Interview for DSM Disorders (SCID; First, Spitzer, Gibbon, & Williams, 2002) or Composite International Diagnostic Interview (CIDI; Robins et al., 1988), are described separately. We excluded studies that depended on electrodermal skin conductance (i.e., Hettema, Annas, Neale, Kendler, & Fredrikson, 2003) or other non-specific diagnostic tools without additional psychological assessment. Literature reviews were excluded. Studies including only social phobia or agoraphobia without co-morbid specific phobias were excluded as these phobias do not belong to the category of specific phobias according to DSM-IV-TR (APA, 2000). Furthermore, studies measuring the stable component of heritability across assessment times (Kendler, Karkowski, & Prescott, 1999) were excluded since these stand apart from the single assessment studies, and already represents a type of 'meta-analysis' obtained by structural equation analysis as applied to a measurement model. Studies using a rater-bias model (Kendler, Gardner, Annas, Neale, et al., 2008) were also excluded, since the heritability obtained thereby is not comparable to those obtained from standard twin studies. Candidate gene studies and genetic association studies (regarding the effects of specific genes on a trait, rather than estimates of heritability) were beyond the scope of this review and were therefore excluded.

From each included study, whenever possible, the lead author, year of publication, demographics, sample size, fear or specific phobia subtype, assessment instrument, correlation in MZ and DZ twins, heritability estimates and best fit model were extracted.

A meta-analysis was conducted for different fears and specific phobia subtypes (i.e., animal, situational, blood–injury–injection and miscellaneous) by averaging the estimates of the additive genetic (A), dominant genetic (D), common environmental (C), and unique environmental (E) variance components estimates weighted by the sample size according to Sutton (Sutton, Abrams, Jones, Sheldon, & Song, 2000; see also Li, Cheng, Ma, & Swan, 2003; Verweij et al., 2010) in order to give more powerful studies greater influence. Calculations were conducted in Microsoft Office Excel 2007. Estimates were made separately for each phenotype (fear or specific phobia subtype) when at least two independent studies estimated a variance component for that phenotype. Forest plots could not be created since only a limited number of studies (i.e., for fear Vassend, Røysamb, & Nielsen, 2011; i.e., for specific phobia subtypes Kendler, Myers, Prescott, & Neale, 2001; Kendler, Jacobsen, Myers, & Prescott, 2002) reported the necessary information. If studies were based on the same cohort and also reported heritability estimates of the same specific phobia subtype (i.e., Hettema, Prescott, Meyers, Neale, & Kendler, 2005; Hettema, Neale, Myers, Prescott, & Kendler, 2006; Kendler, Prescott, Myers, & Neale, 2003) the study with a focus being most in line with the scope of our review was selected and included in the meta-analysis (i.e., Hettema et al., 2005). Reported estimated heritabilities of the non-specified "any phobia" category were excluded. One study was excluded, because the phobia subtypes investigated did not relate to any official specific phobia subtype (i.e., blood–needle–hospital and blood–needle–hospital–illness; Neale et al., 1994). Due to the scarcity of studies on fear and phobia subtypes for which the male–female ratio was reported, it was not possible to conduct separate meta-analyses for the heritability in both sexes.

3. Results

3.1. General

The search themes "fear, genetic" identified a total of 1356 manuscripts, "fear, genetics" identified 2255 hits, "phobia, genetic" identified a total of 308 hits, and "phobia, genetics" identified to 424 hits. "Fear, heritability" produced 29 hits and "phobia, heritability" 31 hits. The search strategy resulted in 4403 titles. After screening 15 articles were included. Ten of them were included in the meta-analysis. The study selection process is detailed in Fig. 1.

Five articles met our inclusion criteria for a fear study. Table 1 summarizes the characteristics of the eligible studies on fears. Ten articles fulfilled the criteria for a specific phobia study. In Table 2 the characteristics of the eligible studies on specific phobias are characterized. No adoption studies on fears and phobias were found. No additional articles were found by consulting publications cited by other articles and reference lists of other articles.

3.2. Twin studies of fears

Table 1 summarizes results from the five twin studies on fears. All of the studies included both genders. Two studies tested for qualitative sex effects (i.e., genetic factors that influence a trait are at least partially distinct in males and females), and quantitative sex effects (i.e., the same genetic factors impact to different degrees in males and females) (Distel et al., 2008; Kendler, Gardner, Annas, & Lichtenstein, 2008). A total of four studies used a population-based sample; one study was based on a clinical sample (Skre et al., 2000).

Page and Martin (1998) investigated the relative genetic and environmental contributions of three sets of variables to blood–injury–injection fears. Univariate analyses showed that with respect to blood fears nearly one third (29%) of the variance could be explained by unique environmental factors, and that the remaining part was associated with factors shared by family members.

In 2000, Skre et al. published a study using a relatively small clinical sample to examine the genetic and environmental contribution to common fears. For all the fear subtypes, except the combination of natural environment and situational fears, the correlations in MZ twins exceeded the correlations in DZ twins, suggesting the influence of genetic factors. It is difficult to evaluate the significance of these findings due to the low number of twin pairs and the absence of a comparison group from the general population.

Using a longitudinal study, Kendler, Gardner, Annas, and Lichtenstein (2008) assessed the development of fears from adolescence to adulthood. Genetic and environmental risk factors for individual fears were found to be partly mediated through a common fear factor. With increasing age, total heritability for all four specific fears declined, but genetic influences on fears tended to be more specific in their effect. The best fit models had no quantitative or qualitative sex effects.

In a study of the Netherlands Twin Registry, Distel et al. (2008) examined the genetic and environmental influences in a large sample of Dutch twins on blood–injury, social and agoraphobic fears and assessed their interaction with gender and age. No sex differences were found in the influence of genetic effects. Genetic effects contributed to individual differences in blood–injury fears, with a broad-sense heritability estimate (i.e., additive plus non-additive genetic factors) of 36%. For all fears, there was support for a contribution of non-additive genetic influences. There was no evidence for genotype x sex interactions.

Vassend et al. (2011) examined dental anxiety in relation to neuroticism and pain sensitivity in a relatively small sample. Dental anxiety proved moderately heritable. A considerable overlap between the factors that influence individual variation in neuroticism, and those that affect liability to dental anxiety was found. Because of the low statistical power it is difficult to evaluate the significance of these findings.

Table 1
Twin studies on fears.

Study	Population and sample	Mean age (years ± SD)	Gender	Number of twins (cases and controls)	Subtype fear	Assessment instrument	*R*mz	*R*dz	A	D	C	E	Genetic model
Page and Martin (1998)	Australian Population based	45.2 (±11.2)	M, F	659 twin pairs	Blood	Three questions about blood–injections injury fears	–	–	.71	–	–	.29	AE
Skre et al. (2000)	Norwegian Clinical based	41 (±9)	M, F	61 twin pairs (cases)	Any	Fear questionnaire[a]	.46	.25	.16	–	–	.84	AE
					Animal		.55	.14	.47	–	–	.53	AE
					Natural environment/situational		.37	.56	–	–	.21	.79	CE
					Blood–injection-injury		.19	−.08	.02	–	.00	.98	ACE[f]
Kendler, Gardner, Annas, and Lichtenstein (2008)	Swedish Population based	19–20	M, F	1705	Animal	Fear questionnaire[b]	.55 M .52 F	.39 M .30 F .09 OS	.45	–	–	.55	AE
					Blood–injury	Fear questionnaire[b]	.36 M .36 F	.16 M .12 F .23 OS	.39	–	–	.61	AE
					Situational	Fear questionnaire[b]	.50 M .36 F	.40 M .13 F .16 OS	.41	–	–	.59	AE
Distel et al. (2008)	Dutch Population based	14–65 26–65	M, F	7089 2814	Blood–injury	Dutch version FQ[c]	Age 14–25 .33 Age 26–65 .39	Age 14–25 .13 Age 26–65 .09	.099	.26	–	.64	ADE
Vassend et al. (2011)	Norwegian Population based	23–35	M, F	188	Dental	NEO-PI-R[d] DAS[e]	.47	.23	.41	–	–	.59	AE

Notes: *R*mz: MZ twin correlation; *R*dz: DZ twin correlation; A: additive genetic effects; C: common environmental effects; D: non-additive genetic effects; E: unique environmental effects; MM: male–male; FF: female–female; MF: male–female; OS, opposite–sex.

[a] Fear questionnaire (Torgersen, 1979).
[b] Fear questionnaire developed byFredrikson et al. (1996).
[c] FQ, Fear Questionnaire (Marks & Mathews, 1979).
[d] NEO Personality Inventory Revised (Costa & McCrae, 1992).
[e] Corah's Dental Anxiety Scale (Corah, 1969).
[f] Violation of the assumption of equal variances in MZ and DZ twins.

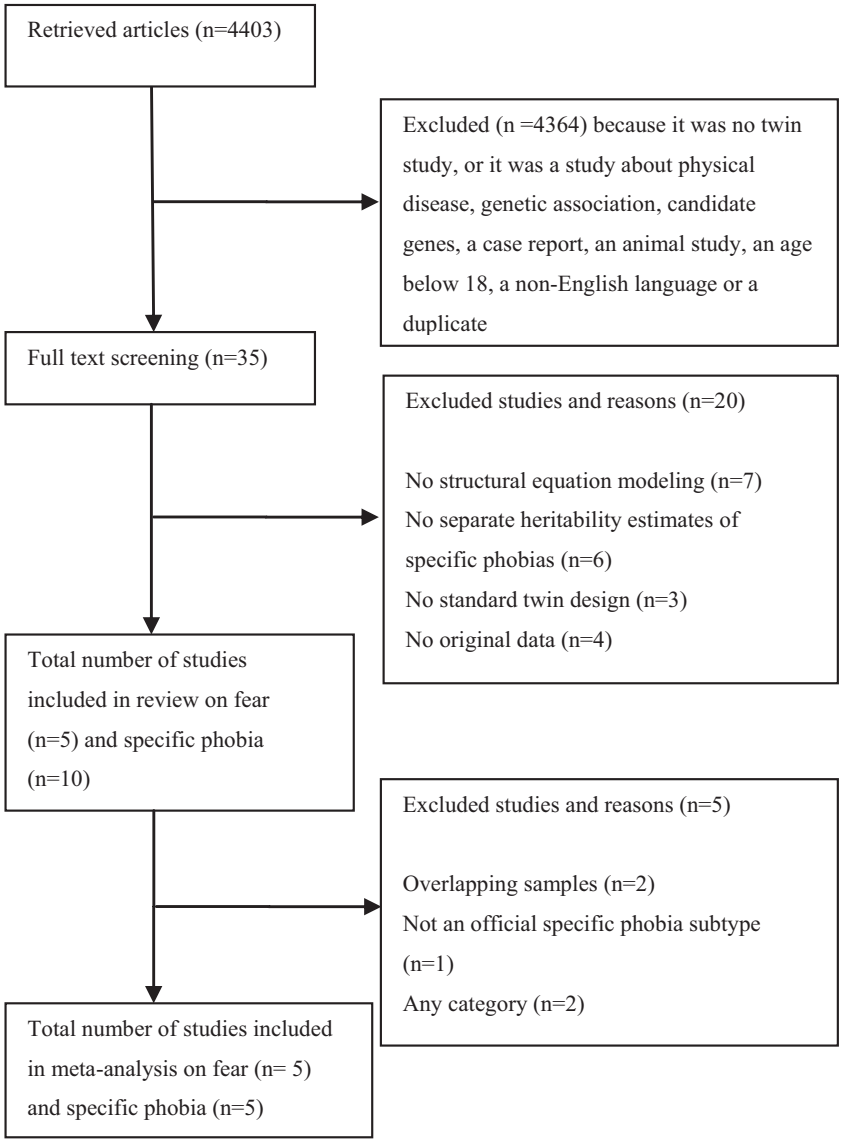

Fig. 1. Flowchart of studies included in review and meta-analysis.

3.3. *Twin studies of specific phobias*

Table 2 summarizes the results from ten twin studies on specific phobias that met the inclusion criteria. Of these studies, five included only women in their sample; one included only men and four were based on data from both males and females. All of the studies were population-based. The studies of Kendler, Neale, Kessler, Heath, and Eaves (1992), Kendler, Neale, Kessler, Heath, and Eaves (1993b), Neale et al., 1994 and Kendler et al. (1995) were based on the same sample of female twin pairs from the Virginia Twin Registry. The studies of Kendler et al. (2003), Hettema et al. (2005) and Hettema et al. (2006) reported on the same sample of male and female twins from the Virginia Twin Registry. Note that while these studies report heritability estimates for partly the same traits, based on the same or overlapping samples, the estimates differ slightly between studies because of differences in the models from which these were derived.

A large study examined the genetic epidemiology of phobias in female twins (Kendler et al., 1992). The results of the multivariate genetic analyses showed strong evidence supporting the presence of genetic and environmental risk factors unique to each phobia subtype, but also of genetic and environmental risk factors that would influence all phobia subtypes.

Kendler et al. (1993b) published another study based on the same sample with a similar design as in the study described above (Kendler et al., 1992). Their purpose was to test the equal environment assumption (i.e., the assumption that MZ and DZ twins are equally correlated for their exposure to environmental influences that are of etiologic relevance of a certain trait) in five common psychiatric disorders. The results in this study supported the equal environment assumption in these conditions.

Using a telephone interview, Neale and his colleagues investigated a condition termed “blood, needles, hospitals and illness (BNHI) phobia”. Unfortunately, it was not possible to choose a best fitting model, due to small differences in fit. The only model that was rejected was that of only unique environmental factors.

Kendler et al. (1995) examined the interrelationship between genetic and environmental risk factors for six psychiatric disorders (for study design, see Kendler et al., 1992). For specific phobia, the role of familial environment appeared to be of little importance.

Another population based study examined the sources of individual differences in risk of developing phobia subtypes in male

Table 2
Twin studies on specific phobias.

Study	Population and sample	Mean age (years± SD)	Gender	Number of twins (cases and controls)	Subtype phobia	Assessment instrument	*R*mz	*R*dz	A	D	C	E	Genetic model
Kendler et al. (1992)	American Population based	30.1 (± 7.1)	F	2163	Any	Phobic disorders section DIS-III-A[a]	.32	.15	.32	–	–	.68	AE
					Animal	Phobic disorders section DIS-III-A[a]	.38	.04	.32	–	–	.68	AE
					Situational	Phobic disorders section DIS-III-A[a]	.27	.27	–	–	.27	.73	CE
Kendler et al. (1993b)	American Population based	30.1 (± 7.1)	F	2163	Any	Phobic disorders section DIS-III-A[a]	–	–	.28	–	–	.72	AE
Neale et al. (1994)	American Population based	30.1 (± 7.1) years + 17.8 (±3.8) months	F	1858	Blood Needle Hospital Illness	Phobic disorders section DIS-III-A[a]	.33	.33	.057	–	.28	.66	ACE[d]
					Blood Needle Hospital	Phobic disorders section DIS-III-A[a]	.30	.29	.049	–	.26	.69	ACE[d]
Kendler et al. (1995)	American Population based	30.1 (± 7.1)	F	2163	Any	Phobic disorders section DIS-III-A[a]	–	–	.35	–	.02	.63	ACE
Kendler et al. (2001)	American Population based	36.8 (±9.1) (age range 20–58)	M	1198 twin pairs and 544 individual twins	Animal	Phobic disorders section DIS-III-A[a]	–	–	.35	–	–	.65	AE
					Situational	Phobic disorders section DIS-III-A[a]	–	–	.25	–	–	.75	AE
					Blood–injury	Phobic disorders section DIS-III-A[a]	–	–	.28	–	–	.72	AE
					Any	Phobic disorders section DIS-III-A[a]	–	–	.22	–	–	.78	AE
Kendler et al. (2002)	American Population based	36.3 (±8.2) (FF) 37.0 (±9.1) (MF/MM)	M, F	7569	Animal	Phobic disorders section DIS-III-A[a]	.40 M .37 F	.0.03 M .12 F .14 OS	.35	–	–	.65	AE
					Situational	Phobic disorders section DIS-III-A[a]	.35 M .38 F	.06 M .14 F .07 OS	.33	–	–	.67	AE
					Blood–injury	Phobic disorders section DIS-III-A[a]	.31 M .33 F	.13 M .05 F .05 OS	.30	–	–	.70	AE
Kendler et al. (2003)	American Population based	36.6 (±8.1) (FF) 36.8 (±9.1) (MM/MF)	M, F	>5600	Phobia	Phobic disorders section DIS-III-A[a]	–	–	.16	–	.11	.73	ACE
					Situational	Phobic disorders section DIS-III-A[a]	–	–	.33	–	.01	.66	ACE
					Animal	Phobic disorders section DIS-III-A[a]	–	–	.22	–	.06	.71	ACE
Hettema et al. (2005)	American Population based	36.6 (±8.1) (FF) 36.8 (±9.1) (MM/MF)	M, F	>5000	Animal	DSM-III[b]	–	–	.24	–	.07	.69	ACE
					Situational	DSM-III[b]	–	–	.24	–	.02	.74	ACE
Hettema et al. (2006)	American Population based	36.6 (±8.1) (FF) 36.8 (±9.1) (MM/MF)	M, F	9270	Animal	DSM-III[b]	–	–	.20	–	0.09	.71	ACE
					Situational	DSM-III[b]	–	–	.16	–	.10	.73	ACE
Czajkowski et al. (2011)	Norwegian Population based	28.1	F	1430	Any	CIDI[c]	–	–	–	–	–	–	–
					Animal		–	–	.44	–	–	.56	AE
					Natural environment/situational				.43	–	–	.57	AE
					Blood–injection				.63	–	–	.37	AE

Notes: *R*mz: MZ twin correlation; *R*dz: DZ twin correlation; A: additive genetic effects; C: common environmental effects; E: unique environmental effects; MM: male–male; FF: female–female; MF: male–female; OS, opposite-sex.

[a] Modified. See for modifications (Kendler et al., 1992).
[b] Adaptation of the DSM-III criteria.
[c] CIDI (Haro, Arbabzadeh-Bouchez, & Brugha, 2006).
[d] Small difference in fit between models, not possible to choose between the different models.

twins (Kendler, Myers, Prescott, & Neale, 2001). Multivariate analyses suggested the presence of genetic and individual-specific environmental etiologic factors common to all phobia subtypes. Additionally, for each phobia subtype evidence was found for the presence of genetic and unique environmental factors specific to that phobia.

A similar study from the same research group examined sex differences in fears and phobias (Kendler et al., 2002). The low DZ-OS

correlations (Table 2) suggested sex differences in these specific phobia subtypes. Although no support was found for the presence of quantitative and qualitative sex effects for animal phobia, the authors suggested for situational and blood/injury phobia the presence of qualitative sex effects.

Another study of Kendler et al. (2003) investigated lifetime diagnosis for 10 psychiatric syndromes in more than 5600 MZ en DZ male and female twins. No sex differences were found in the underlying structure of genetic and environmental risk factors.

Hettema et al. (2005) studied the liability of two subcategories of specific phobias: animal and situational. The pattern of genetic and environmental risk factors did not appear to differ significantly between both sexes.

In another study by Hettema and his colleagues the relationship between neuroticism and internalizing was examined (Hettema et al., 2006). The results of the multivariate analyses showed that in specific phobia condition-specific genetic and condition-specific unique environmental factors were substantial. The genetic correlation between neuroticism and animal phobia and situational phobia was 0.58 and 0.74, respectively. Effects were roughly the same in men and women.

Czajkowski et al. (2011) published a population-based study about the structure of genetic and environmental risk factors for phobias in women. Co-occurrence between phobia subtypes could be explained by two common liability factors. Genetic risk factors for complex phobias and animal phobias were largely distinct.

3.4. Meta-analyses of twin studies

Table 3 shows the results of the meta-analyses. Results for fears in the meta-analyses of parameters of h^2 (heritability), c^2 (common environment) and e^2 (unique environment) were derived from five independent studies (Distel et al., 2008; Kendler, Gardner, Annas, & Lichtenstein, 2008; Page & Martin, 1998; Skre et al., 2000; Vassend et al., 2011). For specific phobias results were included from five independent studies (Czajkowski et al., 2011; Hettema et al., 2005; Kendler et al., 1992, 2001, 2002). For fears estimated heritabilities were calculated for the animal, blood–injury–injection and miscellaneous categories. For specific phobias estimated heritabilities were determined for the animal, situational and blood–injury–injection subtypes. As none of the studies contained data about the natural-environment and the 'other' specific phobia subtypes, these categories are absent in Table 3. The highest mean heritability (±SEM) for fear subtypes was found for animal fear (45% ± 0.004), and the highest mean heritability for the specific phobia subtypes that was identified was for the blood–injury–injection subtype (33% ± 0.06).

4. Discussion

The present study sought to go beyond the limitations of a prior review and meta-analysis that did not distinguish specific phobias from other types of phobias (Hettema et al., 2001), and attempted to derive a current estimate of the heritability of fears and specific phobia subtypes. Since the study of Hettema et al. (2001) only five publications reporting heritability estimates on specific phobias, and three reporting heritability estimates on fears were published. As far as we know, no review pertained to heritability estimates of fears alone.

The results of our study suggest that specific phobias and their corresponding fears are moderately heritable with rates that vary across subtypes. The estimated heritability of fears and specific phobias falls within the range of 0–71% with the lowest estimate for the miscellaneous fear subtype (0%), and the highest estimates for the category of blood–injury–injection fears (71%) and phobias (63%; Table 3). The data converge on the conclusion that there is familial vulnerability to the phenotypic expression of particular types of fears and specific phobias. Other than additive genetic effects, unique environmental effects appear to explain most of the variance, whereas the influence of common environmental effects seems to be relatively modest. In this respect it is important to note that the data on estimated heritability of fears are not to be much different from those on phobias. This is on par with findings of research aimed at delineating the multidimensional structure of fears suggesting that the structure of subclinical fears can be inferred from the DSM classification of phobia subtypes and that fears and phobias are two observable manifestations of a fear response along a single continuum (De Jongh, Oosterink-Wubbe, Hoogstraten, Kieffer, & Aartman, 2011).

Findings of this meta-analysis are largely in line with those derived by Hettema et al. (2001), albeit they found somewhat more variation with regard to the influence of additive genetic effects compared to the present study. One possible explanation for the differences between the heritability estimates of both meta-analyses relates to sample characteristics of the studies being reviewed. For example, the present review included "pure" samples of individuals who met DSM criteria for specific phobias, in contrast to samples of specific phobia that were grouped together with social phobia and/or agoraphobia (e.g., Tambs et al., 2009). A second explanation for the differences with the previous review relates to the fact that many studies used diagnostic instruments that are incapable of assessing the diagnostic features of specific phobia. For this reason relatively stringent criteria for distinguishing between fears and specific phobias were applied in the present study.

The results of the present study suggest that unique environments, such as conditioning events, personal life events and other personal psychosocial stress factors, can have robust influences on the development of phobias. This mirrors earlier findings (Gregory, Lau & Eley, 2008; Hettema et al., 2001), and investigations on the concept of neuroticism (Eysenck & Eysenck, 1975), and the presence of a human fear conditioning trait (Hettema et al., 2003). These views predict that there are individual differences in the tendency to respond to exposure to a certain event (Andrews, Crino, Hunt, Lampe, & Page, 1994; Carey, 1990). According to this line of reasoning, the underlying genetics of specific phobias would explain why one individual reacts with more worry and catastrophic expectations and associated arousal during a conditioning experience than another, and how this makes some individuals more vulnerable to acquire a fear or specific phobia than others. Thus, genetic factors may moderate the effect of individuals' confrontations with a phobic stimulus by influencing the extent to which fear associations are acquired, a process that may depend on the type of fear or specific phobia involved. This view is supported by the results of a study among 173 same sex twin pairs (90 MZ and 83 DZ) using a fear conditioning paradigm during which pictures of spiders and snakes as well as of triangles and circles were paired with mild electric shocks (Hettema et al., 2003). The fear conditioning process was found to be moderately heritable, accounting for 35–45% of the variability in electrodermal skin conduction. Further, the authors found some support for the notion that the heritability of the fear response to evolutionary fear-relevant stimuli spiders and snakes is higher than to geometric shapes. This would be in line with evolutionary theories predicting that people are primed to automatically and selectively attend to specific stimuli that are important to survival, thereby making these fears easily conditioned and relatively difficult to extinguish (LoBue, Rakinson, & DeLoache, 2010; Menzies & Clarke, 1995; Menzies, Kirkby, & Harris, 1998). According to Menzies and Clarke's non-associative model of fear acquisition, fears of long-standing natural dangers to the species (e.g., height phobia) can be acquired without any direct conditioning, whereas direct conditioning would play a prominent role in fears of relatively

Table 3
Summary of findings included in the meta-analysis.

Phenotype	Fear studies included in analyses	Phobia studies included in analyses	Range heritability fear	Range heritability specific phobia	Mean heritability fear % (±SEM)	Mean heritability specific phobia % (±SEM)	Genetic model
Animal	Skre et al. (2000) Kendler, Gardner, Annas, and Lichtenstein (2008)	Kendler et al. (1992) Kendler et al. (2001) Kendler et al. (2002) Hettema et al. (2005) Czajkowski et al. (2011)	45–47	22–44	45 (0.004)	32 (0.03)	AE/ACE
Situational	–	Kendler et al. (1992) Kendler et al. (2001) Kendler et al. (2002) Hettema et al. (2005)	–	0–33	–	25 (0.05)	AE/ACE/CE
Blood–injury–injection	Page and Martin (1998) Skre et al. (2000) Kendler, Gardner, Annas, and Lichtenstein (2008) Distel et al. (2008)	Kendler et al. (2001) Kendler et al. (2002) Czajkowski et al. (2011)	2–71	28–63	41 (0.06)	33 (0.06)	AE/ACE/ADE
Miscellaneous[a]	Skre et al. (2000) Vassend et al. (2011)	–	0–41	–	25 (0.14)	–	AE/CE

Notes: A: additive genetic effects; C: common environmental effects; D: non-additive genetic effects; E: unique environmental effects; SEM: standard error of mean.
[a] Other fears (i.e., dental and a combination of natural environment/situational).

recent stimuli, such as motor cars (in the case of driving phobia), dental drills (in the case of dental phobia), airplanes (in the case of flight phobia) and hypodermic needles (in case of injection phobia), for which evolution has not yet have directly protected the species. According to this model, the latter stimuli should have the highest conditioning rates according to this model (Menzies & Clarke, 1995). Unfortunately, the present data are insufficiently detailed and to scarce to provide support for this hypothesis.

In general, women report higher prevalence rates of fears and specific phobias than men (Lipsitz et al., 2001; McNally, 1994; Oosterink, De Jongh, & Hoogstraten, 2009; Oosterink, De Jongh, & Aartman, 2009). However, no support was found for the presence of sex differences in genetic contribution to fears and specific phobias. The failure to detect sex differences for anxiety disorders may be due to limited statistical power of the studies (Kendler et al., 2002), but may also be considered as evidence for the contention that the same genes affect fear in men and women (Distel et al., 2008).

Several potential limitations of this study should be noted. First, the lack of power in some studies threatened their internal and external validity. For instance, in the study of Neale et al. (1994) only 124 subjects suffered from a specific phobia and only 11 of them reported an 'illness phobia'. Second, the DSM category of specific phobias is a diagnostically heterogeneous class of conditions, even within the subtypes. This is particularly relevant when one considers how fears have been grouped in previous genetic studies (e.g., Kendler et al., 1999). For example, when evolutionarily-relevant (e.g., blood–injury) and evolutionarily neutral (e.g., dental) fears are collapsed it becomes potentially difficult to assess heritability differences among these fears in case these would exist. Even more obscuring is the fact that some fears are in themselves a repository of fears that each may differ in terms of genetic and environmental variability. An example of such heterogeneity within the fears domain is the wide array of fears that pertain to the dental treatment setting, such as fear of pain experience, gagging or suffocating, drilling in or extractions of teeth, receiving a dental injection, having a root canal treatment, and 60 other potential fear-evoking objects and situations (see Oosterink, De Jongh, & Aartman, 2008, for an overview). Thus, like many other fears, fear of dental treatment might actually be the expression of a series of other underlying fears which possess features that distinguish them from each other. Third, the heritable part of specific phobia should be considered polygenetic (see also Broekman, Olff, & Boer, 2007; Stewart & Pauls, 2010 for similar arguments in relation to other types of anxiety disorders). Related to this is the fact that specific phobia subtypes are highly comorbid with other anxiety disorders (Curtis et al., 1998; Depla et al., 2008; Kendler, Neale, Kessler, Heath, & Eaves, 1993a; Kessler, Chui, Demler, Merikangas, & Walters, 2005; Magee et al., 1996; Tambs et al., 2009; Trumpf, Margraf, Vriends, Meyer, & Becker, 2010), suggesting a shared genetic vulnerability (Middeldorp, Cath, van Dyck, & Boomsma, 2005).

5. Conclusions

The present paper provides a state-of-the-art overview of the available evidence on the heritability of specific phobias and fears. It is a dissatisfying observation to find that data on the genetic contribution to fears and specific phobias are still scarce. Since many of the studies appear to represent data from the same subject populations, the meta-analysis represents results of only few studies. In addition, only five twin studies pertained to specific phobia, whereas the other five studies focused on the heritability of specific phobia as a comorbid anxiety disorder. Because of these limitations it is difficult to draw definitive conclusions on the basis of the meta-analysis. Therefore, perhaps the most notable conclusion of the present review is the need for additional research, examining a wider array of fear and phobia subtypes, using proper diagnostic

assessment instruments, a clear sex distribution and large sample sizes.

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