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The Genetic Covariation between Fear Conditioning and Self-Report Fears

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Abstract

Background—Fear conditioning is a traditional model for the acquisition of phobias, while behavioral therapies utilize processes underlying extinction to treat phobic and other anxiety disorders. Furthermore, fear conditioning has been proposed as an endophenotype for genetic studies of anxiety disorders. While prior studies have demonstrated that fear conditioning and self-report fears are heritable, no studies have determined whether they share a common genetic basis.

Methods—We obtained fear conditioning data from 173 twin pairs from the Swedish Twin Registry who also provided self-report ratings of 16 common fears. Using multivariate structural equation modeling, we analyzed factor-derived scores for the subjective fear ratings together with the electrophysiologic skin conductance responses during habituation, acquisition, and extinction to determine the extent of their genetic covariation.

Results—Phenotypic correlations between experimental and self-report fear measures were modest and, counter-intuitively, negative; that is, subjects who reported themselves as more fearful had smaller electrophysiologic responses. Best-fit models estimated a significant (negative) genetic correlation between them, although genetic factors underlying fear conditioning accounted for only 9% of individual differences in self-report fears.

Conclusions—Experimentally-derived fear conditioning measures share only a small portion of the genetic factors underlying individual differences in subjective fears, cautioning against relying too heavily on the former as an endophenotype for genetic studies of phobic disorders.

Keywords

twin study; psychophysiology; fears; phobias; endophenotype; fear conditioning

Introduction

Anxiety disorders in general, and phobias in particular, are highly prevalent in the general population (1). Phobias have been shown to be familial (2–5), and results of several small twin studies have suggested that genetic factors play an important role in a wide range of self-report

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phobic fears (6–9). The only large twin sample that has comprehensively examined the genetics of phobias in adults is the Virginia Twin Registry. Analyses from that sample have found that genetics is largely responsible for twin resemblance in females (10) and males (11), with reliability-corrected estimates of heritability that ranged from 0.46 for situational phobia to 0.67 for agoraphobia (12). Two other broad findings emerged from these analyses. First, it is likely that self-report fears and clinically-derived phobia diagnoses fall along the same liability continuum. That is, it is likely that there is substantial overlap in the genetic factors that underlie susceptibility to normal fears and pathological phobias. Second, multivariate modeling found evidence for a common genetic factor for “phobia proneness” that increased liability across classes of phobic fears, although this is somewhat at odds with the results of family studies (13).

Fear conditioning, a basic form of associative learning, is a traditional model for the acquisition of fears and phobias (14). Also, fear conditioning has long been an important experimental method for the study of etiological processes related to fear and anxiety (15). Behavioral treatment paradigms for anxiety disorders, such as exposure and response prevention, are based on the related processes of habituation and extinction. Habituation allows individuals to ignore innocuous events by producing a progressive decline in response to repeated presentations of a neutral stimulus via non-associative learning. Fear conditioning occurs when fear is associated with a neutral (conditioned) stimulus (CS) after pairing with a fear-provoking (unconditioned) stimulus (UCS) such as electric shock. The CS acquires the fear-provoking response attributes of the UCS. Extinction is the decremental response to further presentations of the CS when it is no longer paired with the UCS. A recent review and meta-analysis of fear conditioning in anxiety disorders reported significant differences between patients and control subjects for electrophysiologic responses during fear conditioning paradigms (16).

In a prior analysis, we demonstrated that the electrodermal skin conductance response (SCR) amplitudes seen in response to the habituation, acquisition, and extinction components of the classical fear conditioning paradigm are moderately heritable and share a substantial proportion of their underlying genetic factors (17). Similarly, Crider et al. showed that nonspecific electrodermal response (EDR) lability and speed of habituation exhibited genetic covariation, with heritability similar to our estimate for SCR (40–50%). The finding that experimental measures of fear conditioning are heritable and possess heritability estimates that are in the same range as those found in twin studies of anxiety disorders (5) has potentially important implications. There have been suggestions that clinical phenotypes may not reflect the underlying pathophysiological processes involved in the etiology of psychiatric disorders in general (18) and for anxiety disorders in particular (19), and, therefore, may not provide optimum targets for gene-finding strategies. One approach to overcome this limitation is to investigate potential endophenotypes that more robustly reflect processes more proximal to gene expression and are involved in the development of pathological anxiety states. In their 2003 review of the subject, Gottesman and Gould suggested a set of criteria that a putative endophenotypic measure must satisfy, including association with illness, heritability, and co-segregation with the illness in families (20). As summarized above, fear conditioning, as a potential anxiety disorder endophenotype, is both associated with anxiety pathology and is heritable. No studies have examined whether there is a genetic association (“co-segregation”) between fear conditioning and anxiety-related phenotypes. To this end, the present study attempts to elucidate the potential genetic covariation between experimentally-derived electrophysiologic measures of fear conditioning and self-report phobic fears.

Methods and Materials

Subjects

Subjects were twin pairs recruited by mailed inquiry from the Swedish Twin Registry after approval from the Swedish Twin Board. The Ethical Committee of Karolinska Hospital approved this study. The sample consisted of 90 monozygotic (MZ) and 83 dizygotic (DZ) same-sex twin pairs aged 25–38, comprised of 62 male-male and 111 female-female pairs. Zygosity determination was based upon questionnaires of physical similarity that were validated by serological measures in 96% of cases (21).

Electrophysiologic Measures

Details of the fear conditioning paradigm were presented previously (17). The outcome measures were electrodermal skin conductance response (SCR) amplitudes recorded at discrete intervals during the presentation sequences. Subjects were seated in an armchair two meters from a projection screen on which sequences of pictorial stimuli serving as CS were shown for 8-second intervals in habituation, acquisition, and extinction phases. For the habituation phase, two slides were displayed two times each. During the acquisition phase, there were eight presentations of each slide, where one (CS+) but not the other (CS–) was paired with the UCS. A mild 18 Hz AC electric current applied to each subject's right index and middle fingers for duration of 0.5 second, individually adjusted to be "uncomfortable but not painful", served as the UCS. This was followed by the extinction phase, in which both slides were presented again eight times each, but without pairing with the UCS. The maximum SCR measured in microsiemens starting 1–4 seconds after the stimulus onset was recorded (22;23), as this measure has been shown to provide the best internal consistency and stability to assess individual differences in conditioning (24).

Self-report Fear Measures

The main self-report fear measures included in our study were based on a questionnaire developed by us (25). Subjects were asked to rate the intensity of their fears of 16 different objects and situations on a Visual Analogue Scales (VAS) scale from 0 (no fear) to 100 (maximal fears). Treated as a quantitative variable in our analyses, such an ordinal scale provides more power for examining the relationship between fears and conditioning than a categorical variable like having a phobia or not. And, as discussed in the introduction, self report fear symptoms appear to lie on the same liability continuum as phobias. We did, however, perform exploratory analyses at the level of phobia diagnoses. For each of the 16 fear items, we rated a subject as meeting criteria for a phobia according to the standard DSM-IV subtype categorizations (animal, situational, social, etc.) (26) if (1) their VAS score was in the upper 90th percentile, (2) they perceived their fear to be excessive, and (3) they avoided the feared object or situation. In addition to these phobic fears, we asked the subjects to rate their long-term propensity towards anxiety using the Trait portion of the State-Trait Anxiety Inventory (STAI) (27).

Statistical Analyses

SCR measures, averaged over the separate presentations for each of the five phase-pairing conditions (habituation, acquisition CS–, acquisition CS+, extinction CS–, and extinction CS+), were the main electrophysiological variables included in our analyses. Several preliminary steps were undertaken to suitably process the data before entering it into the main analyses (see Supplement for details). In addition to using these averaged SCR variables, we also examined the slope of each of the five measures as they varied across the sequence of presentation trials (4 for habituation and 8 each for the other four measures). The slopes contain information on the decremental rates of response with repeated presentations of the same stimulus, and thus,

relate to speed of habituation. The slopes were extracted from linear regressions performed by subject in the SAS PROC GENMOD routine (28) and substituted for the averaged SCR amplitudes in correlation analyses with the self-report measures.

Due to rightward skew of their distributions, we applied a square-root transformation to the VAS self-report fear ratings and the STAI. Each of the 16 fear items was significantly correlated with the others ($\sim .2-.4$), suggesting that they may make up a higher order fear factor within each subject that we denote “self-report fearfulness (SRF)”. This is consistent with twin studies reviewed above that found evidence for a common genetic factor for “phobia proneness” that increases liability across classes of phobic fears. Therefore, in order to explore the effects of this composite SRF as well as to reduce the number of individual tests, we performed a factor analysis on the 16 fear items using SAS PROC FACTOR to extract the first principal component corresponding to this SRF for use in analyses with the electrophysiologic measures.

Within-subject (phenotypic) product moment correlations between electrophysiologic and self-report fear measures were calculated. We used Huber-White corrected significance tests to account for dependency of the observations due to the twin pairs. Twin resemblance within and between measures was estimated by the polychoric correlation separately by zygosity. For those electrophysiologic-fear variable combinations with significant correlations, we performed structural equation modeling to estimate the sources of the correlation (genetic and environmental) (29). Under the basic twin model, individual differences in liability for the phenotype of interest are assumed to arise from four sources: additive genes (A), genetic dominance (D), common or familial environment (C) (e.g., social class or rearing), and individual-specific environment (E) (e.g., marital discord). Also, because we had already determined that only A and E significantly contributed to individual differences in SCR (17), and fear symptoms and phobias have similarly been shown to depend primarily on A and E in adults (5), we began our analyses with AE baseline models. We fit the models with maximum likelihood estimation of the contributions of A and E using the raw data option of the Mx statistical modeling program (30). These are expressed in terms of each factor’s proportion of total variance in liability as a^2 and e^2 , respectively, where a and e represent the factor loadings (path coefficients) onto the phenotype.

Multivariate structural equation modeling was used to assess genetic and environmental liabilities shared between the measures. We chose a reduced (unsaturated) Cholesky to allow us to test a particular hypothesis about the covariation between electrophysiologic and self-report fear measures. (See Supplement for background on Cholesky models.) Our hypothesis is that there are only three genetic factors needed to explain the six phenotypes in the data. The first (A_1) corresponds to genes that may be common to all of the measures, i.e., A_1 underlies the fear conditioning electrophysiologic responses seen during habituation, acquisition, and extinction that may be shared with SRF. The second (A_2) models associative learning that takes place during the fear conditioning process in the acquisition and extinction phases, which may also be shared with SRF. These two reflect our prior finding that two genetic factors are sufficient to account for individual differences in the five electrophysiologic response variables (17). Finally, we postulated a third factor (A_6 – corresponding to the sixth measured variable, SRF) that accounts for individual variation in self-report fears not accounted for by the factors explaining the electrophysiologic responses. Note that it is the correlations derived from loadings of the first two factors on the self-report fears that, if significant, suggest a common genetic basis between fear conditioning and SRF. Also, we need to include six E factors in the model, as these subsume measurement error for each variable. Model parameters and indices that characterize the fit of this model are calculated, and this model is compared with sub-models created by eliminating or constraining parameters in a step-wise fashion, testing specific hypotheses about the data. Twice the difference in log-likelihood between a higher-order and sub-model yields a statistic that is asymptotically distributed as χ^2 with degrees of

freedom equal to the difference in their number of parameters. This permits one to use a χ^2 difference test to determine if a statistically significant difference exists between models. We used Akaike's information criterion (AIC) (31) for model selection. The *lower* its value, the better is the balance between explanatory power and parsimony.

Results

Factor analysis of the VAS ratings for the 16 fear items produced three significant factors with (eigenvalues, proportions of variance) of (4.91, 31%), (1.65, 10%), and (1.22, 8%), respectively. The principal components output from the FACTOR procedure are listed in Table 1. We selected the first factor, which we designated as SRF for "self-report fearfulness", for further analysis, as it possessed substantial loadings (> 0.5) on most of the individual fear items. Table 2 shows within-subject (phenotypic) Pearson product moment correlations between the self-report fear measures and the five electrophysiologic SCR measures. Note that almost all of the correlations are negative, significantly so for 25 out of the 80 pairings. Phenotypic correlations between SRF and each electrophysiologic measure were modest but significant, prompting us to use this measure in the modeling portion of the analyses.

The numbers (and proportions) of subjects who met our criteria for phobias are (by subtype): animal – 17 (4.91%), natural environment – 22 (6.36%), situational – 12 (3.47%), agoraphobia – 8 (2.31%), blood/injection/dental – 28 (8.09%), and social 10 (2.89%). Only 3 (all negative) of 36 correlations between dichotomous phobia diagnoses and electrophysiologic measures were significantly different from zero, so we excluded these from further analyses. Similarly, all of the correlations between STAI and the electrophysiologic measures were negative but not significantly different from zero, so these were not pursued further.

Table 3 lists, separately by zygosity, the twin polychoric correlations between SRF and the five electrophysiologic measures, with values for monozygotic (MZ) pairs above the diagonal (shaded) and dizygotic (DZ) below the diagonal (unshaded). The upper left and lower right blocks contain the within-twin (twin1-twin1, twin2-twin2) correlations between any of the six measures while the lower left and upper right contain the cross-twin (twin1-twin2, twin2-twin1) correlations. It is the latter ("twin similarity") that determines the proportion of genetic variance. The magnitude of each of the MZ cross-twin, within-trait correlations exceeds that of the corresponding DZ correlation, suggesting that each of the six measures is heritable, as has been found before. For example, the MZ T1SRF-T2SRF correlation is 0.55, while its DZ correlation is 0.20. Each of the five electrophysiologic measures is positively correlated with the others and negatively correlated with SRF, again with MZ correlations exceeding DZ, suggesting genetic covariance between the measures. For example, the MZ T1HAB-T2ACQ + correlation is 0.37 and its DZ correlation is 0.24, while the MZ T1SRF-T2EXT- correlation is -0.23 and its DZ correlation is -0.09.

Table 4 provides results from the multivariate modeling of the six measures. Again, these are restricted to contain only additive genetic (A) and individual specific environmental (E) sources of variance as indicated by prior analyses. Model I is a saturated 6-factor Cholesky constructed for model fit comparison. Model II is a reduced Cholesky with only three additive genetic factors (A_1 , A_2 , A_6). It fits the data almost as well as the saturated Cholesky ($\Delta \chi^2=4.28$, $\Delta df=9$, $p=.89$) with lower AIC, making it the model we used for further comparisons. Model III differs from model II in that the third genetic factor (A_6) was removed (constrained to zero), testing whether all of the genetic variation underlying SRF can be explained by the genetic factors for electrophysiologic responding (A_1 and A_2). We could definitively reject model III by a chi-squared difference test ($p=.00004$). Models IV and V test whether there is significant genetic correlation between SRF and A_1 and A_2 , respectively (i.e., do either A_1 or A_2 explain any of the genetic variance of SRF). While we could again reject model IV by a chi-squared

difference test ($p=.0092$), we just barely lacked the statistical power to discriminate between model II and model V ($\Delta\chi^2=3.22$, $\Delta df=1$, $p=.073$). However, model II possessed the lowest AIC, making it best fitting by that criterion.

We present the parameter estimates for model II in Figure 1. The proportions of variance for the six variables due to the three genetic factors included in this model are shown in Table 5. Looking at the “Total” column in Table 5, additive genetics accounts for about 50% of the total variance for each of the measures. A_1 and A_2 account for only 6% and 3%, respectively, of the total variance, or about 11% and 5%, respectively, of the genetic variance of SRF. Note that all of the genetic correlations between SRF and the electrophysiologic measures are negative, in the range -0.3 and -0.4 (corresponding to the negative loadings of A_1 and A_2 on SRF).

When we examined the relationship between the regression slope of each of the five electrophysiologic measures with the 16 self-report fear items, we found only three correlations significant at the $P<0.05$ level (two positive and one negative). Furthermore, none of the correlations between the slopes and SRF was significantly different from zero, so we performed no further analysis using the slopes.

Discussion

The goal of this study was to investigate the potential genetic covariation between experimentally-derived electrophysiologic measures of fear conditioning and self-report fear measures using the twin method. We used the skin conductance response (SCR) amplitude averaged over the five phase-pairing conditions as the primary indicator variable for fear conditioning and a self-report fear (SRF) factor derived from a factor analysis of the VAS ratings of 16 fear items to indicate a subject’s general level of fearfulness. Correlation analyses and multivariate structural equation modeling were used to analyze the data.

As indicated in Table 2, modest negative phenotypic correlations were found between the majority of the VAS fear items (and the SRF derived from them) and the SCR measures. Breaking these correlations down by zygosity in Table 3, the larger cross-twin, cross trait negative correlations in MZ (upper triangle) versus DZ (lower triangle) indicates that these negative phenotypic correlations are likely derived from negative genetic correlations. This was substantiated in the modeling results (Table 4), where significant genetic covariation is seen between SRF and the five electrophysiological measures. The fact that the magnitudes of genetic correlations exceed that of the phenotypic correlations can be explained by the fact that smaller, positive environmental correlations (range 0.1-0.2) between them offset the negative genetic correlations to produce the smaller phenotypic correlations. Thus, small phenotypic correlations do not necessarily imply small genetic correlations.

Despite the existence of significant genetic correlations between SRF and the SCR measures (about -0.4), Table 5 indicates that only about 9% ($0.06+0.03$) of the total phenotypic variation for SRF is explained by the genetic factors A_1 and A_2 underlying the SCR measures, while, in total, genetic factors account for about 55% of individual variation in SRF. Thus, at least according to our data, the majority of the genetic factors underlying self-report fearfulness are *not* shared with SCR. Emotions have often been postulated as consisting of a subjective, a behavioral, and a neuro-physiological component (e.g. (32)). These are loosely coupled and do not always substantially correlate. If replicated, the present data suggest that electrophysiologic response during fear conditioning may be unsuitable as an endophenotypic marker for genetic investigations of pathologic fear states.

The finding of negative phenotypic and genetic correlations between self-report fears and electrophysiologic measures is, at face value, counterintuitive. That is, the more fearful a subject reported him/herself to be, the less reactive they were in the fear conditioning protocol.

This is not an isolated finding among non-clinical samples. In their study of stress and fear conditioning, Jackson et al. reported large ($>.43$), negative correlations between trait anger, trait depression, trait anxiety, and neuroticism and differential fear conditioning responses in their female control (non-stressed) subjects (33). Similarly, Wilken et al. reported that subjects with low trait anxiety (as measured by the Trait portion of the STAI) exhibited greater electrodermal activity in response to stressful stimuli than those with high trait anxiety (34; 35). “Non-intuitive” relationships with trait anxiety are not limited to peripheral autonomic measures. A recent functional imaging study examining the relationship between NEO personality measures and brain activity reported a highly significant negative correlation between NEO neuroticism and resting regional cerebral glucose metabolism in the left insular cortex, a region implicated in anxiety disorders (36).

In the only study identified examining a physiologic measure and a range of self-report phobic fears, Kawachi et al. observed decreased heart rate variability in subjects with higher levels of phobic fears (37). This finding is similar to those from a series of studies by Hoehn-Saric and colleagues in clinical samples, who report decreased autonomic flexibility in patients with several different anxiety disorders (38;39). This reduced flexibility was primarily indicated by decreased heart rate variability in patients compared with controls, but one study reported relatively weaker SCR and narrower range of both SCR and heart rate in women with generalized anxiety disorder during a psychological stress task (40). Interestingly, a recent review and meta-analysis of fear conditioning in anxiety disorders reported overall modest *increases* in patient compared with control subject electrophysiologic responses (16). This meta-analysis, however, is predominantly composed of studies of anxiety disorders other than phobias, and only social phobia is represented among them. It is unclear how to reconcile these diverse findings, although one may speculate that there may be qualitative differences in measures of autonomic response between highly fearful “normal” individuals and patients with anxiety disorders.

Our finding of significant association between electrophysiologic measures and self-report fear ratings was limited to the fear items, although there was a trend for a similarly negative correlation with subject trait anxiety via the STAI. In addition, few of the correlations between dichotomous phobia diagnoses and the electrophysiologic SCR measures were significantly different from zero, although those that were also were negative. In general, dichotomous measures possess lower power to detect deviations from the null hypothesis than continuous measures, and, although a fair proportion of subjects qualified for a phobic diagnosis of some kind by our definition, the absolute numbers were small. It is also somewhat surprising that we found no association between self-report fears and rates of response decrement for any of the electrophysiologic measures. There is a genetic component to habituation (41), and patients with anxiety disorders tend to show retarded habituation, particularly to anxiogenic but also to neutral stimuli (42;43). Here again, there may be qualitative differences between normal individuals with high trait anxiety and patients who suffer from anxiety disorders. Well-powered studies that directly compare electrophysiologic measures in a sample of normal subjects with a sufficiently wide range of self-reported anxiety measures as well as patients with anxiety disorders may resolve these differences.

Limitations

The results of this study are subject to several potential limitations. First, due to the immense effort and expense required for this experimental protocol, the sample size is relatively small compared to recent epidemiological twin studies, limiting the power to significantly distinguish potential sources of variance. Second, the maximum likelihood method used by Mx in the twin models assumes that the variables follow a multivariate normal distribution, which we were only able to approximate via transformation procedures. Third, the validity of interpreting

increased similarity of MZ over DZ twins as representing genetic effects is predicated upon the equal environment assumption, which states that MZ and DZ twins are equally correlated for environmental experiences of relevance to the trait under study (reviewed in (44)). Although there have been several twin studies designed to detect such violations with negative findings (45) (46), we do not have any direct means of establishing the assumption's validity in this sample. Fourth, for analyses involving dichotomous phobias, we constructed diagnoses from several self-report items involving excessiveness and avoidance rather than performing a clinical interview. Finally, the sample is limited to Swedish Caucasian subjects, and as such, the results may not generalize to other ethnic groups.

Conclusions

We found evidence for modest-sized, negative phenotypic and genetic correlations between electrophysiologic fear conditioning measures and self-report fears. While correlations with trait anxiety and phobia diagnoses were also generally negative, they were statistically non-significant. Future family or twin studies in larger samples are needed to confirm the magnitude and direction of the familial co-aggregation of fear conditioning and anxiety disorders before the former can be reliably proposed as an endophenotype for genetic studies of the latter.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Best-fit three genetic factor model (model II from Table 4). Only additive genetic (A) sources of variance and parameter estimates are shown for simplicity. A_1 represents a general set of genetic factors that underlie individual differences in all of the electrophysiologic measures shared with the self-report fear (SRF) factor. A_2 represents a second set that models associative learning that occurs during acquisition and extinction phases of the fear conditioning process that also is shared with the self-report fear factor. A_6 represents any genetic factors specific to the SRF factor not accounted for by genetic factors for the electrophysiologic measures.

Table 1**Principal Components Analysis on 16 Fear Items**

Fear Item	Factor 1	Factor 2	Factor 3
Snakes	0.504	0.372	-0.030
Spiders	0.433	0.337	-0.378
Heights	0.525	0.262	-0.062
Dark	0.599	0.269	-0.385
Thunder	0.582	0.229	-0.317
Closed Space	0.615	0.196	0.003
Open Places	0.588	-0.592	-0.127
Flying	0.530	0.051	-0.101
Being Alone	0.597	-0.125	-0.208
Crowds	0.639	-0.565	-0.022
Being Observed	0.575	-0.112	0.418
Public Speaking	0.525	0.087	0.356
Public Eating	0.580	-0.597	-0.117
Blood	0.585	0.313	0.344
Injections	0.489	0.110	0.553
Dental Procedures	0.452	-0.003	0.136

Table 2
Within-Subject (Phenotypic) Pearson Product Moment Correlations between Self-Report Fears and Five Electrophysiologic Measures

Fear Item	Habituation	Acquisition CS-	Acquisition CS+	Extinction CS-	Extinction CS+
SRF	-.120 *	-.140 *	-.152 **	-.117 *	-.121 *
Snakes	-.099	-.114 *	-.154 **	-.078	-.080
Spiders	-.131 *	-.138 *	-.151 **	-.142 **	-.121 *
Heights	-.061	-.030	-.057	-.069	-.034
Dark	-.174 **	-.124 *	-.166 **	-.134 *	-.143 *
Thunder	-.129 *	-.044	-.118 *	-.058	-.106
Closed Space	-.082	-.062	-.062	-.025	-.002
Open Places	-.043	-.141 **	-.130 *	-.121 *	-.132 *
Flying	-.012	.003	-.055	-.085	-.076
Being Alone	-.055	.005	.005	-.033	-.011
Crowds	-.051	-.096	-.086	-.044	-.040
Being Observed	-.008	-.128 *	-.030	-.023	-.045
Public Speaking	-.107	-.082	-.095	-.058	-.015
Public Eating	-.104 *	-.178 **	-.179 **	-.129 **	-.165 **
Blood	-.091	-.066	-.072	-.084	-.124 *
Injectons	-.004	-.083	-.028	.012	.001
Dental Procedures	.061	.024	-.014	.027	.009

Bolded (significant):

* $P < 0.05$;

** $P < 0.01$

Abbreviations: CS- and CS+ - conditioned stimuli either unpaired (-) or paired (+) with the unconditioned stimulus (shock); SRF (self-report fear factor) - first principal component extracted from factor analysis of 16 individual self-report fear items

Table 3

Twin Correlations by Zygosity between Self-Report Fear Factor and Five Electrophysiologic Measures (MZ upper/shaded; DZ lower/unshaded)

	T1SRF	T1HAB	T1ACO-	T1ACO+	T1EXT-	T1EXT+	T2SRF	T2HAB	T2ACO-	T2ACO+	T2EXT-	T2EXT+
T1SRF	1.0	-.15	-.22	-.16	-.15	-.15	.55	-.13	-.25	-.22	-.23	-.23
T1HAB	-.27	1.0	.77	.79	.61	.56	-.16	.52	.33	.37	.28	.34
T1ACO-	-.18	.66	1.0	.78	.77	.77	-.20	.38	.52	.49	.46	.48
T1ACO+	-.26	.72	.79	1.0	.72	.71	-.20	.53	.49	.56	.45	.51
T1EXT-	-.19	.43	.60	.67	1.0	.87	-.24	.28	.47	.42	.51	.54
T1EXT+	-.20	.53	.72	.78	.77	1.0	-.22	.23	.41	.42	.49	.56
T2SRF	.20	-.22	.07	-.06	-.05	-.03	1.0	.01	-.01	-.07	-.13	-.06
T2HAB	-.002	.18	.11	.29	.31	.23	-.08	1.0	.62	.74	.41	.49
T2ACO-	-.14	.19	.16	.29	.39	.27	-.02	.74	1.0	.85	.73	.74
T2ACO+	-.06	.24	.10	.26	.37	.18	-.06	.74	.86	1.0	.64	.74
T2EXT-	-.09	.27	.21	.31	.32	.18	.03	.58	.83	.78	1.0	.91
T2EXT+	-.18	.32	.27	.33	.43	.24	.02	.60	.79	.86	.88	1.0

Bolded denotes within trait, cross-twin (MZ or DZ) correlations

Abbreviations: T1/T2 – Twin 1/Twin 2; SRF – self-report fear factor; HAB – habituation; ACQ+/- – Acquisition CS+/-; EXT+/- – Extinction CS+/-

Goodness-of-Fit Statistics for Multivariate Analysis of Five Electrophysiologic Measures plus Self-Report Fear Factor (SRF)

Model	Description	Sources of Variance	Model Fit			Difference in Fit from Higher Order Model	
			-2LL	df	AIC	$\Delta(-2LL)$	p
I	Six-Factor AE Cholesky	A_1E_1 through A_6E_6	4303.73	1987	329.74		
II*	Three-Factor AE Cholesky	A_1E_1 - A_2E_2 - E_3 - E_4 - E_5 - A_6E_6	4308.01	1996	316.01	4.28	0.89
III	Model II - Constrain A_6 to zero	A_1E_1 - A_2E_2 - E_3 - E_4 - E_5 - E_6	4325.07	1997	331.07	17.06	0.00004
IV	Model II - Constrain $r_{E_1E_2}$ to zero	A_1E_1 - A_2E_2 - E_3 - E_4 - E_5 - A_6E_6	4314.80	1997	320.80	6.79	0.0092
V	Model II - Constrain $r_{E_1E_2}$ to zero	A_1E_1 - A_2E_2 - E_3 - E_4 - E_5 - A_6E_6	4311.23	1997	317.23	3.22	0.073

* Model II is the best-fit model by AIC. See Figure 1 for its depiction as a path diagram.

Abbreviations: A - additive latent genetic factor; E - individual specific environmental latent factor; -2LL – negative two times the log-likelihood; df – degrees of freedom; AIC - Akaike’s information criterion; Δ - change from higher order model.

Notes: Model I is a saturated six-factor Cholesky constructed for model fit comparison. Model II is a reduced Cholesky with three additive genetic factors (A_1 , A_2 , A_6). Model III differs from model II in that the third genetic factor (A_6) was constrained to zero, testing whether all of the genetic variation underlying SRF can be explained by the genetic factors A_1 and A_2 . Models IV and V test whether there is significant genetic correlation between SRF and A_1 and A_2 , respectively.

Table 5
Proportion of Variance Accounted for by Additive Genetic Factors

Measure	Proportion of Total Variance			Total	Genetic Correlation with SRF
	A ₁	A ₂	A ₆		
Habituation	0.44	-	-	0.44	-0.32
Acquisition CS-	0.22	0.24	-	0.46	-0.40
Acquisition CS+	0.40	0.12	-	0.52	-0.40
Extinction CS-	0.19	0.25	-	0.44	-0.39
Extinction CS+	0.22	0.25	-	0.47	-0.40
SRF	0.06	0.03	0.46	0.55	1.0