Evidence for distinct genetic and environmental influences on fear acquisition and extinction

K. L. Purves[1,2] [iD], G. Krebs[1,3] [iD], T. McGregor[1] [iD], E. Constantinou[1] [iD], K. J. Lester[4], T. J. Barry[5], M. G. Craske[6] [iD], K. S. Young[1] [iD], G. Breen[1,2] [iD] and T. C. Eley[1] [iD]

[1]King's College London, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, London, UK; [2]NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Trust, London, UK; [3]National and Specialist OCD and Related Disorders Clinic for Young People, South London and Maudsley, London, UK; [4]School of Psychology, University of Sussex, Brighton, Sussex, UK; [5]Experimental Psychopathology Lab, Department of Psychology, The University of Hong Kong, Pok Fu Lam, Hong Kong and [6]Department of Psychology, University of California, Los Angeles, California, USA

Abstract

Background. Anxiety disorders are highly prevalent with an early age of onset. Understanding the aetiology of disorder emergence and recovery is important for establishing preventative measures and optimising treatment. Experimental approaches can serve as a useful model for disorder and recovery relevant processes. One such model is fear conditioning. We conducted a remote fear conditioning paradigm in monozygotic and dizygotic twins to determine the degree and extent of overlap between genetic and environmental influences on fear acquisition and extinction.

Methods. In total, 1937 twins aged 22–25 years, including 538 complete pairs from the Twins Early Development Study took part in a fear conditioning experiment delivered remotely via the Fear Learning and Anxiety Response (FLARe) smartphone app. In the fear acquisition phase, participants were exposed to two neutral shape stimuli, one of which was repeatedly paired with a loud aversive noise, while the other was never paired with anything aversive. In the extinction phase, the shapes were repeatedly presented again, this time without the aversive noise. Outcomes were participant ratings of how much they expected the aversive noise to occur when they saw either shape, throughout each phase.

Results. Twin analyses indicated a significant contribution of genetic effects to the initial acquisition and consolidation of fear, and the extinction of fear (15, 30 and 15%, respectively) with the remainder of variance due to the non-shared environment. Multivariate analyses revealed that the development of fear and fear extinction show moderate genetic overlap (genetic correlations 0.4–0.5).

Conclusions. Fear acquisition and extinction are heritable, and share some, but not all of the same genetic influences.

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Introduction

Anxiety disorders affect over 20% of individuals during their lifetime (Kessler et al., 2012), have an early age of onset (Kessler et al., 2005) and are currently increasing sharply in prevalence (Baker, 2020; O'Connor, Downs, Shetty, & McNicholas, 2020). Both genetic and environmental influences are implicated in the development of anxiety, with twin heritability estimates ranging from 20% to 60% (Ask, Torgersen, Seglem, & Waaktaar, 2014; Meier et al., 2019; Polderman et al., 2015), and estimates of heritability derived from genome-wide association studies (GWASs) ranging from 1.7% in childhood and adolescence to 31% in adulthood (for a review see Ask et al., 2021). Notably, the upper range of heritability estimated from common genetic variants indexed by genome-wide analyses of anxiety [single-nucleotide polymorphism (SNP) heritability] overlaps with the lower end of estimates from twin studies. This is unusual, with SNP heritability substantially less than half that of twin heritability observed for most psychiatric disorders (Yang, Zeng, Goddard, Wray, & Visscher, 2017). This might suggest a larger role for common genetic variants in anxiety in particular. Effectively, evidence-based treatments exist for anxiety disorders, notably pharmacological approaches such as antidepressants and benzodiazepines (Baldwin et al., 2014), and psychological approaches such as cognitive behavioural therapy (CBT) (Carpenter et al., 2018; Hofmann & Smits, 2008). However, only ~50% of individuals respond regardless of treatment type (Clark et al., 2009; Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016; Loerinc et al., 2015; Rush et al., 2006). Individual differences in treatment response are likely to be heritable,

given known genetic influences on response to many aspects of the environment, such as life events and parenting (Kendler & Baker, 2007). Although there is evidence for familial clustering (Franchini, Serretti, Gasperini, & Smeraldi, 1998; O'Reilly, Bogue, & Singh, 1994) and influence of common genetic variants (Tansey et al., 2013) in response to antidepressant treatment for depression, the heritability of psychological treatment response is currently unknown. The largest studies in this field to date, both of which are genome-wide analyses, were insufficiently powered to draw strong conclusions (Coleman et al., 2016; Rayner et al., 2019).

Crucially, we do not yet know the specific mechanisms through which anxiety develops or recovery occurs, or how genetic influences contribute to these. Furthermore, using an experimental model of specific processes underlying disordered anxiety and treatment response has the advantage of a likely reduction in heterogeneity in the dataset (Scheveneels, Boddez, Vervliet, & Hermans, 2016). One possible set of experimental mechanisms is the acquisition and subsequent extinction of fears through direct learning experiences. These processes can be measured using fear conditioning paradigms. During the fear acquisition phase, participants are exposed to two neutral stimuli, known as conditional stimuli (CS), one of which is repeatedly paired with an aversive (e.g. a loud noise) or unconditional stimulus (US). The stimulus paired with the US is referred to as the CS+. The other stimulus is never paired with anything aversive and is referred to as the CS−. Over repeated trials, participants learn that the CS+ is associated with the aversive stimulus and typically demonstrate a 'fear' or 'anxiety' response to the CS+. This initial phase models processes implicated in anxiety development. Following acquisition, participants undergo an extinction phase where both CS+ and CS− are repeatedly presented without the aversive noise. The extinction phase models exposure-based treatment of fear and anxiety disorders used in CBT (Hofmann, 2008), which developed out of the fear extinction literature (Eelen & Vervliet, 2006).

A common way of measuring conditioning is to require participants to rate how much they expected the aversive outcome to occur with the CS+ and CS− throughout the task (Lonsdorf et al., 2017). These assessments can be thought of as risk-estimates. In order to measure task-related learning while controlling for general interindividual differences in responsivity, a differential metric (risk-estimates for the CS− subtracted from the risk-estimates for the CS+) is often calculated (Lonsdorf et al., 2017). In order to investigate the underlying contributions of genes and environment to these mechanisms, sample sizes are needed far in excess of those typically included in laboratory administered studies of fear conditioning. Notably, only one study in the largest meta-analysis of fear conditioning to date contained over 100 participants (Duits et al., 2015). One prior twin study obtained preliminary estimates of heritability of skin conductance responses during fear acquisition and extinction (0.20–0.46), and genetic overlap between them (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003). However, although large in terms of fear conditioning, the sample size (173 twin pairs) was small for genetic analyses, as evidenced by large confidence intervals (CIs). Furthermore, the sample was split into two groups, each of which received a different stimuli set. Thus, although this provides preliminary evidence for the heritability of fear acquisition, extinction and their overlap, a larger, more heterogeneously administered study is required to consider this question.

The current study aimed to answer two important questions: (1) to what extent are fear acquisition and extinction influenced by genetic and environmental factors; and (2) are the genetic and environmental influences on the acquisition and extinction of fear shared between all processes, or are there distinct influences on each phase? We used the recently developed Fear Learning and Anxiety Response (FLARe) smartphone app (Purves et al., 2019) to remotely administer a differential fear conditioning and extinction paradigm to a subset of twins from the Twins Early Development Study (TEDS) (Rimfeld et al., 2019). We assessed participant discrimination between the CS+ and CS− during early and late acquisition and extinction.

Methods

Sample

Participants were recruited by email invitation sent to 5934 twins enrolled in the TEDS (Rimfeld et al., 2019), a longitudinal birth cohort study of twins born in England and Wales between 1994 and 1996. Twins who agreed downloaded the FLARe app (Purves et al., 2019) via the iTunes or Google Play Stores. The experiment was completed by 2554 individuals of whom 1937 were included in the analyses after excluding those who removed their headphones, reduced phone volume <50% or exited the app during the task. See Online Supplementary Fig. S1 for a detailed illustration of participant drop-out at each stage. We explored the characteristics of twins who chose to participate in the study ($n = 2554$) compared to those who did not ($n = 3380$). Our participant groups were more likely to be older [$d = 0.07$; $t(5909.9) = 2.78$, $p = 0.006$], female (odds ratio 1.67; 95% CI 1.50–1.86, $p < 0.001$) and to have lower socioeconomic status ($d = 0.08$; $U = 866\ 163$, $p = 0.036$) than those who chose not to take part. However, there were no statistically significant differences in anxiety scores between respondents and non-respondents ($d = 0.05$; $U = 1\ 065\ 914.5$, $p = 0.191$).

Twin zygosity was determined by parental responses to a twin similarity questionnaire. This has 95% concordance with genotyped zygosity (Price et al., 2000). The sample consisted of 250 complete monozygotic pairs (MZF = 180, MZM = 70), 288 dizygotic pairs (DZF = 131, DZM = 50, DZopp = 107) and 860 singletons (F = 549, M = 312). See Online Supplementary Table S1 for a description of the total sample including age, gender and self-reported clinician-provided diagnoses of any anxiety or depressive disorder.

Experimental procedure

Participants were given instructions designed to maintain optimal experimental conditions, ensure headphone usage and maximum phone volume (see online Supplementary Figs S2 and S3). They were asked to complete the task in a single, undisturbed session. The fear conditioning procedure began with a fear acquisition phase during which 12 presentations each of a large and small circle (CS) were shown in a pseudo-randomised sequence on a background image of an outdoor scene. One of these (CS+) was paired with the aversive 'unconditional stimulus' (US; a loud scream sound) during the final 500 ms of the trial on nine out of 12 presentations (75% reinforcement). The other was never paired with the US (CS−). The use of the large v. small circle as the CS+ was counterbalanced across participants. See online Supplementary material for trial presentation rules. Participants then had a break of at least 10-min, during which they were unable to continue with the task due to a built-in time-based restriction within
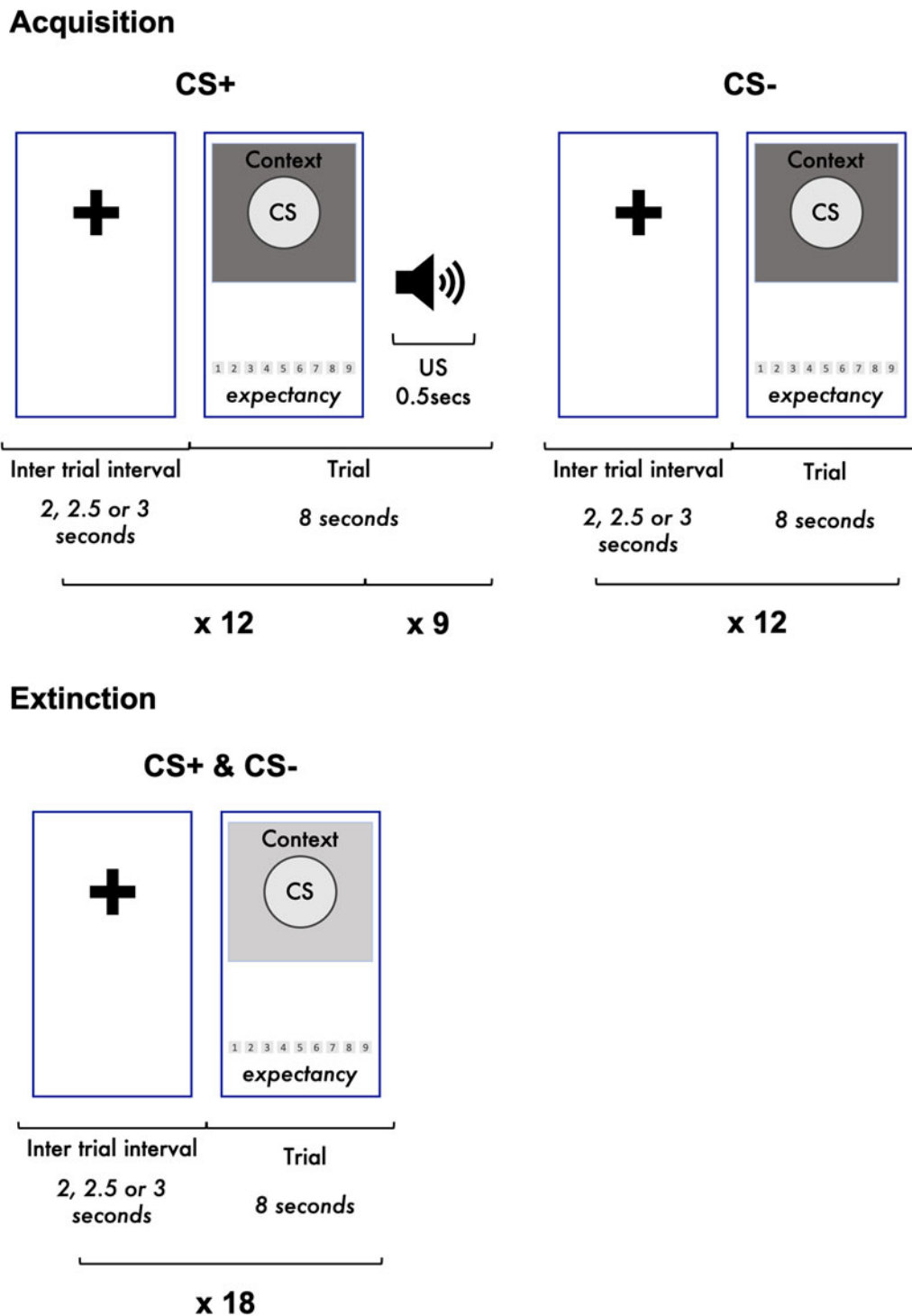
Acquisition

Extinction

Fig. 1. Schematic diagram of fear conditioning procedures as implemented in the FLARe app. This figure shows trial and overall task structure of the fear conditioning task as implemented in the Fear Learning and Anxiety Response (FLARe) app. CS: conditional stimuli. Context: background image of an outdoor garden scene (acquisition) or indoor living room scene (extinction) displayed behind CS during each trial. US: unconditional stimulus, a loud human scream played at maximum phone volume.

the app and completed a series of online questionnaires. This was followed by a fear extinction phase. This break was enforced in order to ensure a clear temporal distinction between the acquisition and extinction phases. The same large and small circles were shown 18-times each on the background of an indoor living room scene. Neither shape was paired with the aversive stimulus. We

used 18 trials in the extinction phase to ensure full extinction prior to the end of the task, given the remote delivery. After the extinction phase, participants were redirected to an external website (Qualtrics, 2019) to answer questions including whether or not they removed their headphones during the task. See Fig. 1 for a schematic diagram of the experimental procedure.
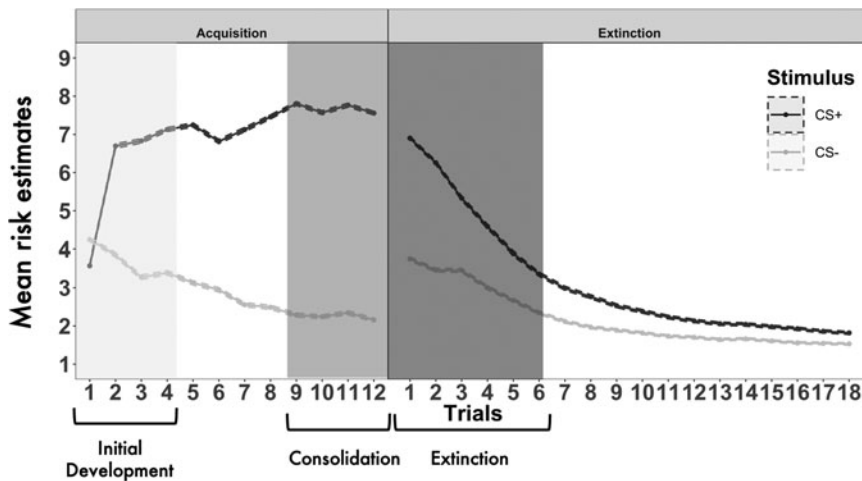
Fig. 2. Average risk-estimates per trial across all participants during fear conditioning task. Average risk-estimate per stimulus, per trial, averaged across all participants. Dashed lines indicate standard error of the mean (note, these intervals are narrow). CS+, conditional stimulus paired with the aversive scream; CS−, conditional stimulus never paired with the aversive scream.

Outcome measures

During each trial, participants were asked to rate how much they expected to hear the aversive stimulus on a scale ranging from 1 (completely certain NO scream will occur) to 9 (completely certain a scream WILL occur). Risk-estimates (sometimes known as expectancy ratings) for the CS− were subtracted from those of the CS+ to obtain differential scores, an index of how well participants were able to differentiate between the two experimental cues. Repetition is a core component of memory and learning (Hintzman, 1976), and evidence from neuroimaging paradigms demonstrates that the association between fear conditioning and brain regions varies across time within phase (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). Thus, in order to assess rapid acquisition of fear learning relative to later, consolidated fear learning after several repetitions, the post hoc decision was taken to consider fear acquisition and extinction in early and late stages. Differential scores created from risk-estimates made during the first and final thirds of the acquisition phase and the first third of the extinction phase were retained to assess the initial development, consolidation and extinction of fear learning respectively (see Fig. 2). Differential scores for the last third of the extinction trials (late extinction) were not analysed in twin modelling as by this stage nearly all participants had reduced their risk-estimates for both stimuli to ~1 (see Table 1).

Statistical analyses

Data preparation

Outcome variables (initial development, consolidation and fear extinction) were age and sex regressed to avoid artificial inflation of twin correlations (McGue & Bouchard, 1984), and the residuals were normalised using square-root transformation in R.

Multivariate twin modelling

Monozygotic (MZ) twins share 100% of their segregating genes, dizygotic (DZ) twins share ~50%, while both MZ and DZ twins share their rearing environments (Rijsdijk & Sham, 2002). Monozygotic and dizygotic twin similarity can be compared to estimate genetic and environmental influences on a trait. The degree to which MZ twins are more similar than DZ twins reflects approximately half (100–50%) of the genetic influence (labelled A; additive genetic influence). Twin resemblance not due to genetic factors is attributed to environmental factors that make twins

more similar (common environmental factors, labelled C). Finally, the extent to which the MZ twin correlation differs from 1 reflects the non-shared environment and residual/error variance (labelled E).

A trivariate *correlated factors solution* of the Cholesky decomposition model was applied (see Fig. 3). This estimates the relative influence of latent factors A, C and E on each of the fear conditioning variables as well as the correlations between the genetic and environmental influences on each (Loehlin, 1996). These parameters are then used to estimate the degree to which phenotypic correlations are attributable to genetic and environmental influences.

Genetic modelling was undertaken in R using the OpenMx package (Boker et al., 2011). OpenMx used full information maximum likelihood to estimate structural equation parameters, an effective method to deal with missing data (Boker et al., 2016; Jelicić, Phelps, & Lerner, 2009). Model fit was assessed using χ^2 and Akaike's information criterion.

Results

Differential fear conditioning

As shown in Fig. 2, the difference between the CS+ and CS− was largest during the last four trials of acquisition, the phase we refer to as consolidation. The difference was smallest during late fear extinction when reinforcement of either stimulus had ceased. During the first four trials of acquisition (initial development), participants already showed a greater expectation of the scream occurring to the CS+ than the CS−, see first row, first section of Table 1 (mean$_{CS+}$ = 6.05, S.D.$_{CS+}$ = 1.63, mean$_{CS−}$ = 3.70, S.D.$_{CS−}$ = 1.56). By the consolidation phase (second row), risk-estimates had further increased for the CS+ and decreased for the CS−. Average risk-estimates reduced for both stimuli over the course of extinction. During the first third of extinction trials, ratings were similar to average risk estimates during the initial development of fear. By the end of extinction, almost all participants had ceased to report any expectation of a scream occurring for either stimulus.

Trivariate twin modelling

See Table 1 middle section for monozygotic and dizygotic twin correlations for each fear conditioning variable and Table 2 for
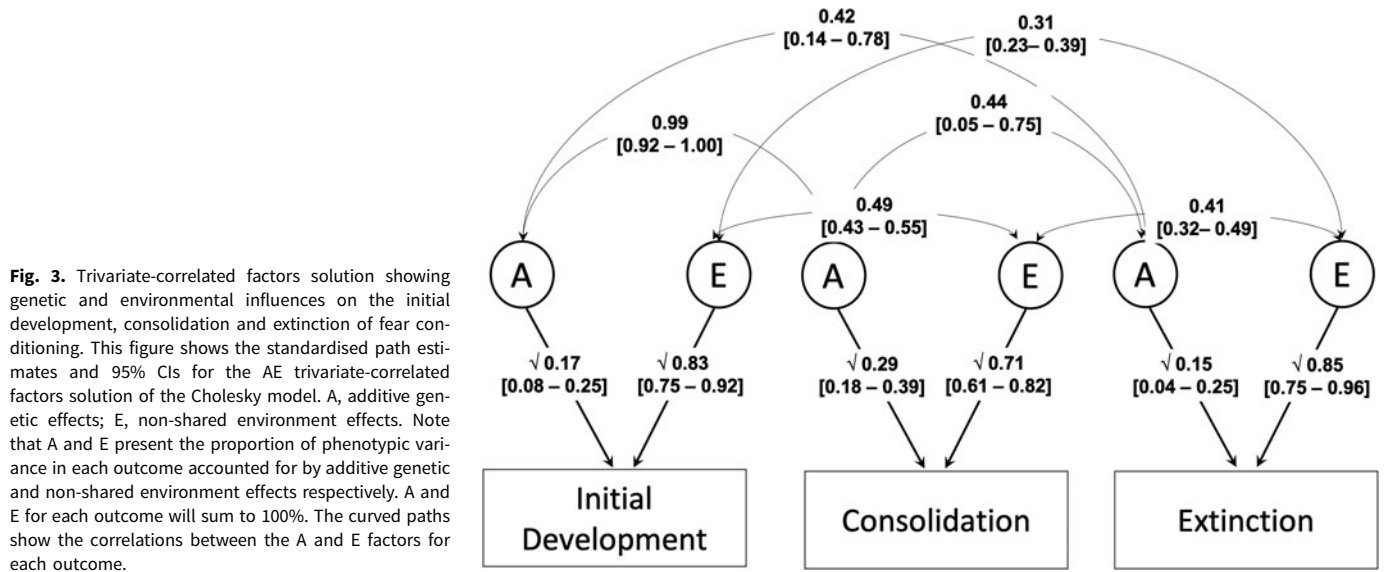
Fig. 3. Trivariate-correlated factors solution showing genetic and environmental influences on the initial development, consolidation and extinction of fear conditioning. This figure shows the standardised path estimates and 95% CIs for the AE trivariate-correlated factors solution of the Cholesky model. A, additive genetic effects; E, non-shared environment effects. Note that A and E present the proportion of phenotypic variance in each outcome accounted for by additive genetic and non-shared environment effects respectively. A and E for each outcome will sum to 100%. The curved paths show the correlations between the A and E factors for each outcome.

Table 1. Descriptive statistics and twin pair intraclass correlations for fear conditioning risk estimates

	Average risk estimates[a]			Twin pair intraclass correlations for CS differential[b]		CS+/CS− comparison[c]		
	CS+ mean (s.d.)	CS− mean (s.d.)	CS differential mean (s.d.)	MZ (95% CI)	DZ (95% CI)	t	df	p
Initial development	6.05 (*1.63*)	3.70 (*1.56*)	2.35 (*2.39*)	0.14 (0.07–0.20)	0.08 (−0.01–0.17)	34.26	1936	<2.2 × 10⁻¹⁶
Consolidation	7.67 (*1.74*)	2.28 (*1.79*)	5.39 (*3.16*)	0.24 (0.14–0.33)	0.12 (0.03–0.20)	70.53	1936	<2.2 × 10⁻¹⁶
Extinction	5.06 (*1.85*)	3.11 (*1.69*)	1.95 (2.12)	0.18 (0.06–0.27)	0.04 (−0.05–0.13)	25.28	1936	<2.2 × 10⁻¹⁶
Late extinction	1.96 (*1.68*)	1.6 (*1.3*)	0.36 (*1.23*)	–	–	6.01	1936	2.2 × 10⁻⁹

This table compares [a]mean and standard deviation (s.d.) for the average risk-estimate per stimulus (CS+ or CS−) during the first third of acquisition trials (initial development), last third of acquisition trials (consolidation), first third of extinction trials (extinction) and the last third of extinction trials (late extinction), with [b]intraclass correlations (bootstrapped 95% CIs) between the members of twin pairs for the [c]average difference in risk-estimates between the CS+ and CS− for each experimental phase (initial development, consolidation and extinction). MZ, monozygotic twins; DZ, dizygotic twins; CS+, the conditional stimulus paired with the aversive scream; CS−, the conditional stimulus that is never paired with the aversive scream; CS differential, difference between CS+ and CS−.

Table 2. Cross-twin cross-trait (lower) and phenotypic (upper) correlations with proportion of variance explained by A and E

	Initial development	Consolidation	Extinction
Initial development	**0.32** (0.08–0.25)	**0.59** (0.55–0.64) **A** 37% | 63% **E**	**0.32** (0.28–0.38) **A** 19% | 81% **E**
Consolidation	**0.21** (0.13–0.29) **0.12** (0.05–0.20)	**0.29** (0.18–0.39)	**0.38** (0.34–0.43) **A** 22% | 78% **E**
Extinction	**0.05** (−0.05 to 0.15) **0.04** (−0.05 to 0.15)	**0.08** (0.00–0.17) **0.03** (−0.04 to 0.13)	**0.15** (0.04–0.25)

This table shows cross-twin cross-trait correlations (95% CI) for MZ (top) and DZ (bottom) twin pairs (below diagonal) and phenotypic correlations (95% CI) with the standardised proportion of phenotypic association accounted for by A/E (above diagonal). Estimate of heritability from multivariate twin analyses (95% CI) shown on the diagonal. CIs are obtained by bootstrapping over 100 iterations.

cross-twin cross-trait genetic and phenotypic correlations. We only report results from multivariate modelling, as these are better powered compared to univariate models. The ACE model produced C estimates that were zero and non-significant (see online Supplementary Fig. S4), and we therefore tested a more parsimonious AE model. This did not result in loss of fit and was therefore selected as the final model (see online Supplementary Table S2 for model fit information).

Estimates from this model are shown in Fig. 3. Initial development, consolidation and extinction of fear were all significantly influenced by additive genetic factors (A). For example, the estimate of heritability (a^2) for consolidation was 0.29 (0.18–0.39). In addition, there were significant shared genetic effects (r_a) between all variables, with genetic correlations being highest between initial development and consolidation of fear [rG = 0.99 (0.97–1.00)]. In comparison, genetic correlation were significantly lower between each of the acquisition phases and extinction of fear [initial development and extinction: rG = 0.42 (0.14–0.78); consolidation and extinction: rG = 0.44 (0.05–0.75)]. The effect of non-shared environment (E) was also significant for all variables (range e^2 = 0.71–0.83), with significant non-shared environmental correlations (0.31–0.49) between all variables. See Table 2 for the standardised proportion of the phenotypic variance between variables accounted for by A and E respectively.

Discussion

We present the largest twin study of fear conditioning to date, providing evidence for genetic and non-shared environmental influences. Discriminative fear learning is significantly heritable during the initial development, consolidation and extinction of fear conditioning. We demonstrated significant contributions from non-shared environmental influences (which includes measurement error), but no evidence for the contribution of common environment. Shared genetic effects between initial development and the consolidation of fear approached unity. This indicates that the genetic variants involved in the initial development of fear learning are virtually the same as those involved in the later consolidation of fear learning. The genetic correlations between both stages of fear acquisition and extinction were moderate and significant, indicating either that some of the genetic variants implicated in fear learning also play a role in the extinction of these learned associations. However, these genetic correlations were around 0.5, indicating that roughly half the genetic factors on extinction of fear are different from those on fear learning. Although a previous study provided preliminary evidence for complete genetic overlap between acquisition and extinction of fear, these results were difficult to interpret as CIs were not included for estimates from the multivariate model (Hettema et al., 2003). Our study provides further support for significant shared genetic influences on acquisition and extinction. The prior study also found that both acquisition and extinction of fear were robustly heritable, with heritability estimates for fear extinction substantially greater than we find (h^2: 0.34–0.36). This may be due to differences in our paradigm (in lab *v.* remotely administered) and resultant measurement error, or due to differences in outcome variables (absolute *v.* differential expectancy ratings). However, taken together, the results from present and prior studies provide strong support for the role of genetic influences in the acquisition and extinction of fear.

Findings should be considered in light of some limitations. First, the remote delivery of the experiment necessitates lower experimental control compared to laboratory delivery. This is particularly reflected in the number of individuals who removed their headphones during the task, and thus excluded from analyses. Second, the sample was drawn from a population-based twin cohort. In future studies, it will be important to test whether there are differences in the genetic and environmental contributors to fear conditioning between individuals with anxiety disorders compared to healthy individuals.

Genetic influences on fear acquisition

We explored genetic influences on two stages of fear acquisition. Initial fear development was calculated using risk-estimate differences for the CS+ and CS− during the first third of acquisition trials. Fear consolidation was indexed by the risk-estimates differences during the final third of trials. Although initial development and consolidation shared all of the same genetic influences, genetic factors accounted for more variance in fear consolidation. A persistent reduced capacity to distinguish between cues paired and never paired with threat is similar to the tendency to interpret neutral stimuli as threatening (negative interpretation bias). This cognitive bias is a core feature of anxiety in adults and children (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Dudeney, Sharpe, & Hunt, 2015; Lau & Waters, 2017; Lester, Lisk, Carr, Patrick, & Eley, 2019). Generalised anxiety disorder (GAD), in particular, is associated with interpretation biases (Eysenck, MacLeod, & Mathews, 1987; Eysenck, Mogg, May, Richards, & Mathews, 1991; Hayes, Hirsch, Krebs, & Mathews, 2010; Mathews, Richards, & Eysenck, 1989; Mogg et al., 1994), which we have previously shown to be heritable (Brown et al., 2014; Eley et al., 2008; Lau, Belli, Gregory, & Eley, 2014). In sum, the consolidation of fear learning is probably more relevant than initial fear learning to understanding anxiety disorders. Notably, the heritability of fear consolidation (29%) is similar to estimates of GAD from previous twin studies (Hettema, Neale, & Kendler, 2001). This supports the possibility that the consolidation of fear conditioning is a relevant mechanism underlying disordered anxiety.

Genetic and environmental influences on fear extinction

The modest but significant heritability of fear extinction (15%) suggests that a relatively small degree of variation in fear extinction in healthy individuals is influenced by genetic factors. The only prior twin study of fear conditioning to date (Hettema et al., 2003) estimated the heritability of fear extinction of the CS+ specifically to be 36% (95% CI 18–52), and the CS− 34% (95% CI 16–50). The CIs for the current study include estimates up to 25% (95% CI 4–25). It is possible that the range of overlap between CIs from the prior and current study (16–25) may represent the 'true' range of heritability. There have been no twin studies of treatment response for anxiety, and two genome-wide meta analyses of CBT treatment response have failed to derive significant heritability estimates despite having statistical power to detect heritability of 30% or greater (Coleman et al., 2016; Rayner et al., 2019). This study thus adds to our limited knowledge about the relative role for genes and the environment in fear extinction, a mechanism underpinning exposure-based treatment, a core component of CBT for anxiety disorders.

The high estimate of the non-shared environment (e^2 = 85%) influencing fear extinction in this study partially reflects high measurement error given our task (Purves et al., 2019). Furthermore, the use of difference scores as an outcome, which, while reducing the total number of variables examined, aggregates the error variance of each individual stimuli, and thus inflates the overall non-shared environmental estimate.

There are several plausible contributors to variable treatment response over and above direct genetic influences. These include specific life experiences, and individual characteristics such as unemployment, low educational attainment and poor interpersonal relationships that are also known to reduce treatment

efficacy (DeRubeis et al., 2014; Mojtabai, 2017; Newman, Llera, Erickson, Przeworski, & Castonguay, 2013; Renaud, Russell, & Myhr, 2014). Specific disorder profiles, including greater symptom severity, comorbidity with other mental health disorders and poor treatment adherence are associated with poor treatment response in anxious adults and children (Hudson et al., 2013, 2015; Rayner et al., 2019; Wergeland et al., 2016). Understanding modifiable personal risk factors may help identify areas for intervention that could serve as a precursor or adjunct to therapy to further enhance the effect of exposure within a personalised medicine framework.

Genetic and environmental overlap between fear acquisition and extinction

There were moderate genetic ($r_a = 0.41$–0.44) and non-shared environment ($r_e = 0.31$–0.41) correlations between fear acquisition and extinction. If fear extinction is considered a credible marker underlying treatment response (Craske, Hermans, & Vervliet, 2018), then at least some of the genetic markers underlying treatment response are the same as those underlying anxiety development, and approximately half the genes relevant to extinction should be identified in GWAS of anxiety. This 'cause informs cure' (Uher, 2008) perspective would mean that findings from the rapidly growing anxiety genetics field would be relevant to understanding genetic influences on psychological treatment response.

We note genetic correlations between fear acquisition and extinction were below 0.5, indicating that distinct influences exist. Crucially, this indicates understanding the genetics of anxiety disorder is not sufficient to fully understand the genetics of psychological treatment response. It continues to be important to find ways of investigating treatment response as a distinct phenotype in large samples of individuals with sufficient depth of phenotyping to explore the role of variance in a range of environmental and individual factors within genetically informed designs.

Conclusions

We presented robust evidence for genetic influences on fear acquisition and extinction, shedding light on possible mechanisms underlying known genetic influences on anxiety. We have also shown moderate genetic overlap between fear acquisition and extinction. This indicates that genetic susceptibility to developing fears is likely to have a moderate influence on reducing learned fears, for example through exposure-based treatment. Future studies using genotyped samples with fear conditioning or treatment outcome data will enable more detailed investigation of the genetics of the development and treatment of anxiety.

In conclusion, these findings represent a significant advance in the genetics of fear acquisition and extinction, two key processes underlying the development and exposure-based treatment of anxiety disorders.

References

Ask, H., Cheesman, R., Jami, E., Levey, D., Purves, K., & Weber, H. (2021). Genetic contributions to anxiety disorders: Where we are and where we are heading. *Psychological Medicine*, 1–16. doi:10.1017/S0033291720005486

Ask, H., Torgersen, S., Seglem, K. B., & Waaktaar, T. (2014). Genetic and environmental causes of variation in adolescent anxiety symptoms: A multiple-rater twin study. *Journal of Anxiety Disorders*, 28(4), 363–371. doi:10.1016/j.janxdis.2014.04.003

Baker, C. (2020). Mental health statistics for England: prevalence, services and funding (Briefing Paper No. 6988). House of Commons Library.

Baldwin, D. S., Anderson, I. M., Nutt, D. J., Allgulander, C., Bandelow, B., den Boer, J. A., … Wittchen, H.-U. (2014). Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British association for psychopharmacology. *Journal of Psychopharmacology*, 28(5), 403–439. doi:10.1177/0269881114525674

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychological Bulletin*, 133 (1), 1–24. doi:10.1037/0033-2909.133.1.1

Boker, S. M., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., … Fox, J. (2011). Openmx: An open source extended structural equation modeling framework. *Psychometrika*, 76(2), 306–317. doi:10.1007/s11336-010-9200-6

Boker, S. M., Neale, M. C., Maes, H. H., Wilde, M. J., Spiegel, M., Brick, T. R., … Kirkpatrick, R. M. (2016). OpenMx 2.3.1 User Guide (2.3.1). Computer manual, OpenMX.

Brown, H. M., Waszczuk, M. A., Zavos, H. M. S., Trzaskowski, M., Gregory, A. M., & Eley, T. C. (2014). Cognitive content specificity in anxiety and depressive disorder symptoms: A twin study of cross-sectional associations with anxiety sensitivity dimensions across development. *Psychological Medicine*, 44(16), 3469–3480. doi:10.1017/S0033291714000828

Carpenter, J. K., Andrews, L. A., Witcraft, S. M., Powers, M. B., Smits, J. A. J., & Hofmann, S. G. (2018). Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. *Depression and Anxiety*, 35(6), 502–514. doi:10.1002/da.22728

Clark, D. M., Layard, R., Smithies, R., Richards, D. A., Suckling, R., & Wright, B. (2009). Improving access to psychological therapy: Initial evaluation of two UK demonstration sites. *Behaviour Research and Therapy*, 47(11), 910–920. doi:10.1016/j.brat.2009.07.010

Coleman, J. R. I., Lester, K. J., Keers, R., Roberts, S., Curtis, C., Arendt, K., … Eley, T. C. (2016). Genome-wide association study of response to cognitive-behavioural therapy in children with anxiety disorders. *The British Journal of Psychiatry*, 209(3), 236–243. doi:10.1192/bjp.bp.115.168229

Craske, M. G., Hermans, D., & Vervliet, B. (2018). State-of-the-art and future directions for extinction as a translational model for fear and anxiety. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 373(1742). doi:10.1098/rstb.2017.0025

Cuijpers, P., Cristea, I. A., Karyotaki, E., Reijnders, M., & Huibers, M. J. H. (2016). How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry*, 15(3), 245–258. doi:10.1002/wps.20346

DeRubeis, R. J., Cohen, Z. D., Forand, N. R., Fournier, J. C., Gelfand, L. A., & Lorenzo-Luaces, L. (2014). The personalized advantage index: Translating research on prediction into individualized treatment recommendations. A demonstration. *PLoS ONE*, 9(1), e83875. doi:10.1371/journal.pone.0083875

Dudeney, J., Sharpe, L., & Hunt, C. (2015). Attentional bias towards threatening stimuli in children with anxiety: A meta-analysis. *Clinical Psychology Review*, 40, 66–75. doi:10.1016/j.cpr.2015.05.007

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., … Baas, J. M. P. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety*, 32(4), 239–253. doi:10.1002/da.22353

Eelen, P., & Vervliet, B. (2006). Fear conditioning and clinical implications: What can we learn from the past? In M. G. Craske, D. Hermans & D. Vansteenwegen (Eds.), *Fear and learning: From basic processes to clinical implications* (pp. 17–35). Washington: American Psychological Association. doi:10.1037/11474-001

Eley, T. C., Gregory, A. M., Lau, J. Y. F., McGuffin, P., Napolitano, M., Rijsdijk, F. V., & Clark, D. M. (2008). In the face of uncertainty: A twin study of ambiguous information, anxiety and depression in children. *Journal of Abnormal Child Psychology*, 36(1), 55–65. doi:10.1007/s10802-007-9159-7

Eysenck, M W, MacLeod, C., & Mathews, A. (1987). Cognitive functioning and anxiety. *Psychological Research*, 49(2–3), 189–195. doi:10.1007/BF00308686

Eysenck, M. W., Mogg, K., May, J., Richards, A., & Mathews, A. (1991). Bias in interpretation of ambiguous sentences related to threat in anxiety. *Journal of Abnormal Psychology*, 100(2), 144–150. doi:10.1037/0021-843X.100.2.144

Franchini, L., Serretti, A., Gasperini, M., & Smeraldi, E. (1998). Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. *Journal of Psychiatric Research*, 32(5), 255–259. doi:10.1016/S0022-3956(98)00004-1

Hayes, S., Hirsch, C. R., Krebs, G., & Mathews, A. (2010). The effects of modifying interpretation bias on worry in generalized anxiety disorder. *Behaviour Research and Therapy*, 48(3), 171–178. doi:10.1016/j.brat.2009.10.006

Hettema, J. M., Annas, P., Neale, M. C., Kendler, K. S., & Fredrikson, M. (2003). A twin study of the genetics of fear conditioning. *Archives of General Psychiatry*, 60(7), 702–708. doi:10.1001/archpsyc.60.7.702

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *The American Journal of Psychiatry*, 158(10), 1568–1578. doi:10.1176/appi.ajp.158.10.1568

Hintzman, D. L. (1976). Repetition and memory. In Kara D. Federmeier (Ed.), *Psychology of Learning and Motivation* (Vol. 10, pp. 47–91). Elsevier. doi:10.1016/S0079-7421(08)60464-8.

Hofmann, S. G. (2008). Cognitive processes during fear acquisition and extinction in animals and humans: Implications for exposure therapy of anxiety disorders. *Clinical Psychology Review*, 28(2), 199–210. doi:10.1016/j.cpr.2007.04.009

Hofmann, S. G., & Smits, J. A. J. (2008). Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. *The Journal of Clinical Psychiatry*, 69(4), 621–632. doi:10.4088/jcp.v69n0415

Hudson, J. L., Lester, K. J., Lewis, C. M., Tropeano, M., Creswell, C., Collier, D. A., … Eley, T. C. (2013). Predicting outcomes following cognitive behaviour therapy in child anxiety disorders: The influence of genetic, demographic and clinical information. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 54(10), 1086–1094. doi:10.1111/jcpp.12092

Hudson, J. L., Rapee, R. M., Lyneham, H. J., McLellan, L. F., Wuthrich, V. M., & Schniering, C. A. (2015). Comparing outcomes for children with different anxiety disorders following cognitive behavioural therapy. *Behaviour Research and Therapy*, 72, 30–37. doi:10.1016/j.brat.2015.06.007

Jelicić, H., Phelps, E., & Lerner, R. M. (2009). Use of missing data methods in longitudinal studies: The persistence of bad practices in developmental psychology. *Developmental Psychology*, 45(4), 1195–1199. doi:10.1037/a0015665

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: A systematic review. *Psychological Medicine*, 37(5), 615–626. doi:10.1017/S0033291706009524

Kessler, R. C., Avenevoli, S., Costello, E. J., Georgiades, K., Green, J. G., Gruber, M. J., … Merikangas, K. R. (2012). Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the national comorbidity survey replication adolescent supplement. *Archives of General Psychiatry*, 69(4), 372–380. doi:10.1001/archgenpsychiatry.2011.160

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry*, 62(6), 593–602. doi:10.1001/archpsyc.62.6.593

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron*, 20(5), 937–945. doi:10.1016/S0896-6273(00)80475-4

Lau, J. Y. F., Belli, S. R., Gregory, A. M., & Eley, T. C. (2014). Interpersonal cognitive biases as genetic markers for pediatric depressive symptoms: Twin data from the emotions, cognitions, heredity and outcome (ECHO) study. *Development and Psychopathology*, 26(4 Pt 2), 1267–1276. doi:10.1017/S0954579414001011

Lau, J. Y. F., & Waters, A. M. (2017). Annual research review: An expanded account of information-processing mechanisms in risk for child and adolescent anxiety and depression. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 58(4), 387–407. doi:10.1111/jcpp.12653

Lester, K. J., Lisk, S. C., Carr, E., Patrick, F., & Eley, T. C. (2019). Associations between attentional bias and interpretation bias and change in school concerns and anxiety symptoms during the transition from primary to secondary school. *Journal of Abnormal Child Psychology*, 47, 1521–1532. 10.1007/s10802-019-00528-3.

Loehlin, J. C. (1996). The Cholesky approach: A cautionary note. *Behavior Genetics*, 26(1), 65–69. doi:10.1007/BF02361160

Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske, M. G. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clinical Psychology Review*, 42, 72–82. doi:10.1016/j.cpr.2015.08.004

Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J., … Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neuroscience and Biobehavioral Reviews*, 77, 247–285. doi:10.1016/j.neubiorev.2017.02.026

Mathews, A., Richards, A., & Eysenck, M. (1989). Interpretation of homophones related to threat in anxiety states. *Journal of Abnormal Psychology*, 98(1), 31–34. doi:10.1037/0021-843X.98.1.31

McGue, M., & Bouchard, T. J. (1984). Adjustment of twin data for the effects of age and sex. *Behavior Genetics*, 14(4), 325–343. doi:10.1007/BF01080045

Meier, S. M., Trontti, K., Purves, K. L., Als, T. D., Grove, J., Laine, M., … Mors, O. (2019). Genetic variants associated With anxiety and stress-related disorders: A genome-wide association study and mouse-model study. *JAMA Psychiatry*, 76(9), 924–932. 10.1001/jamapsychiatry.2019.1119.

Mogg, K., Bradley, B. P., Miller, T., Potts, H., Glenwright, J., & Kentish, J. (1994). Interpretation of homophones related to threat: Anxiety or response bias effects? *Cognitive Therapy and Research*, 18(5), 461–477. doi:10.1007/BF02357754

Mojtabai, R. (2017). Nonremission and time to remission among remitters in major depressive disorder: Revisiting STAR*D. *Depression and Anxiety*, 34(12), 1123–1133. doi:10.1002/da.22677

Newman, M. G., Llera, S. J., Erickson, T. M., Przeworski, A., & Castonguay, L. G. (2013). Worry and generalized anxiety disorder: A review and theoretical synthesis of evidence on nature, etiology, mechanisms, and treatment. *Annual Review of Clinical Psychology*, 9, 275–297. doi:10.1146/annurev-clinpsy-050212-185544

O'Connor, C., Downs, J., Shetty, H., & McNicholas, F. (2020). Diagnostic trajectories in child and adolescent mental health services: Exploring the prevalence and patterns of diagnostic adjustments in an electronic mental health case register. *European Child & Adolescent Psychiatry*, 29(8), 1111–1123. doi:10.1007/s00787-019-01428-z

O'Reilly, R. L., Bogue, L., & Singh, S. M. (1994). Pharmacogenetic response to antidepressants in a multicase family with affective disorder. *Biological Psychiatry*, 36(7), 467–471. doi:10.1016/0006-3223(94)90642-4

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics*, 47(7), 702–709. doi:10.1038/ng.3285

Price, T. S., Freeman, B., Craig, I., Petrill, S. A., Ebersole, L., & Plomin, R. (2000). Infant zygosity can be assigned by parental report questionnaire data. *Twin Research*, 3(3), 129–133. doi:10.1375/twin.3.3.129

Purves, K. L., Constantinou, E., McGregor, T., Lester, K. J., Barry, T. J., Treanor, M., … Eley, T. C. (2019). Validating the use of a smartphone

app for remote administration of a fear conditioning paradigm. *Behaviour Research and Therapy*, *123*, 103475. doi:10.1016/j.brat.2019.103475

Qualtrics. (2019). Qualtrics (January 2019). Computer software, Provo: Qualtrics. Retrieved from https://www.qualtrics.com.

Rayner, C., Coleman, J. R. I., Purves, K. L., Hodsoll, J., Goldsmith, K., Alpers, G. W., … Eley, T. C. (2019). A genome-wide association meta-analysis of prognostic outcomes following cognitive behavioural therapy in individuals with anxiety and depressive disorders. *Translational Psychiatry*, *9*(1), 150. doi:10.1038/s41398-019-0481-y

Renaud, J., Russell, J. J., & Myhr, G. (2014). Predicting who benefits most from cognitive-behavioral therapy for anxiety and depression. *Journal of Clinical Psychology*, *70*(10), 924–932. doi:10.1002/jclp.22099

Rijsdijk, F. V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation models. *Briefings in Bioinformatics*, *3*(2), 119–133. doi:10.1093/bib/3.2.119

Rimfeld, K., Malanchini, M., Spargo, T., Spickernell, G., Selzam, S., McMillan, A., … Plomin, R. (2019). Twins early development study: A genetically sensitive investigation into behavioral and cognitive development from infancy to emerging adulthood. *Twin Research and Human Genetics*, *22*(6), 508–513. doi:10.1017/thg.2019.56

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *The American Journal of Psychiatry*, *163*(11), 1905–1917. doi:10.1176/ajp.2006.163.11.1905

Scheveneels, S., Boddez, Y., Vervliet, B., & Hermans, D. (2016). The validity of laboratory-based treatment research: Bridging the gap between fear extinction and exposure treatment. *Behaviour Research and Therapy*, *86*, 87–94. doi:10.1016/j.brat.2016.08.015

Tansey, K. E., Guipponi, M., Hu, X., Domenici, E., Lewis, G., Malafosse, A., … Uher, R. (2013). Contribution of common genetic variants to antidepressant response. *Biological Psychiatry*, *73*(7), 679–682. doi:10.1016/j.biopsych.2012.10.030

Uher, R. (2008). The implications of gene–environment interactions in depression: Will cause inform cure? *Molecular Psychiatry*, *13*(12), 1070–1078. doi:10.1038/mp.2008.92

Wergeland, G. J. H., Fjermestad, K. W., Marin, C. E., Bjelland, I., Haugland, B. S. M., Silverman, W. K., … Heiervang, E. R. (2016). Predictors of treatment outcome in an effectiveness trial of cognitive behavioral therapy for children with anxiety disorders. *Behaviour Research and Therapy*, *76*, 1–12. doi:10.1016/j.brat.2015.11.001

Yang, J., Zeng, J., Goddard, M. E., Wray, N. R., & Visscher, P. M. (2017). Concepts, estimation and interpretation of SNP-based heritability. *Nature Genetics*, *49*(9), 1304–1310. doi:10.1038/ng.3941