Citation: Transl Psychiatry (2011) 1, e41, doi:10.1038/tp.2011.36
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www.nature.com/tp

REVIEW

A review on experimental and clinical genetic associations studies on fear conditioning, extinction and cognitive-behavioral treatment

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Fear conditioning and extinction represent basic forms of associative learning with considerable clinical relevance and have been implicated in the pathogenesis of anxiety disorders. There is considerable inter-individual variation in the ability to acquire and extinguish conditioned fear reactions and the study of genetic variants has recently become a focus of research. In this review, we give an overview of the existing genetic association studies on human fear conditioning and extinction in healthy individuals and of related studies on cognitive-behavioral treatment (CBT) and exposure, as well as pathology development after trauma. Variation in the serotonin transporter (*5HTT*) and the catechol-o-methyltransferase (*COMT*) genes has consistently been associated with effects in pre-clinical and clinical studies. Interesting new findings, which however require further replication, have been reported for genetic variation in the dopamine transporter (*DAT1*) and the pituitary adenylate cyclase 1 receptor (*ADCYAP1R1*) genes, whereas the current picture is inconsistent for variation in the brain-derived neurotrophic factor (*BDNF*) gene. We end with a discussion of the findings and their limitations, as well as future directions that we hope will aid the field to develop further.
Translational Psychiatry (2011) **1,** e41; doi:10.1038/tp.2011.36; published online 20 September 2011

Introduction

Learning to predict danger from previous experience is critical to an organism's survival. In fear conditioning, an environmental stimulus (conditioned stimulus, CS) comes to predict a naturally aversive stimulus (unconditioned stimulus, UCS) and thereby to induce a conditioned fear response (CR).[1] After conditioning has occurred, the repeated presentation of the CS in the absence of UCS (exposure) leads to a gradual weakening of the CR, a process referred to as *extinction*.

Fear conditioning and extinction represent basic forms of associative learning with considerable clinical relevance and have been implicated in the pathogenesis of anxiety disorders.[2] Deficits in the *extinction* of learned fear associations have been observed in patients suffering from anxiety disorders like post-traumatic stress disorder (PTSD), phobias and panic disorder (PD).[3,4] Further, extinction has inspired the clinical use of exposure to fear stimuli[5] in cognitive-behavioral therapy (CBT), which is used to treat many forms of pathological anxiety.[6,7] CBT represents a learning process leading to symptom relief and long-term changes in behavior that have measurable correlates in neural activation patterns, synaptic connectivity and gene expression patterns.[8,9]

Understanding the molecular pathways that mediate conditioning and extinction might therefore make an important contribution to the study of anxiety pathophysiology, resilience and treatment mechanisms, and open up new perspectives for pharmacological interventions. One promising, although by far not the only, strategy to identify molecular pathways in humans is genetic association studies.

Genetic association studies optimally investigate simple behavioral paradigms with sufficient inter-individual variability and clear heritability that elicit robust behavioral responses, which are easy to measure and quantify and rely on a well-defined underlying neural circuitry. Fear conditioning and extinction fulfill these criteria.

First, both human[10,11] and animal studies[12] show that there is considerable inter-individual variability in the ability to acquire and extinguish conditioned fear as well as in profiting from CBT, and that genetic factors represent a significant source of this variation. Specifically, one-third of the variance in human fear conditioning[10] and in the vulnerability for anxiety disorders[13] is attributed to genetic factors.

Second, conditioned fear can be easily and reliably measured using, for example, skin conductance responses (SCRs) and/or fear potentiated startle (FPS) responses (see Table 1 for explanation of technical terms). Importantly, twin studies have proven the reliability of both SCRs[10] and FPS[11] for heritability studies.

Third, the neural network underlying fear conditioning and extinction has been studied intensively in both animals[14,15] and humans.[16] A well-delineated neural network is not only advantageous for genetic imaging studies, but may also guide selection of candidate genes.

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Keywords: anxiety; cognitive-behavioral treatment; conditioning; extinction; exposure; genetics
Received 16 May 2011; revised 29 June 2011; accepted 30 July 2011

Table 1 Explanation of technical terms and abbreviations

Term	*Explanation*
Fear potentiated startle (FPS)	Augmentation of the startle reflex by a fearful state, for example, induced by a certain stimulus
Dark-enhanced startle	Augmentation of the startle reflex by darkness
Skin conductance response (SCR)	The alteration in the electrical resistance of the skin associated with psychological or physiological arousal
Unconditioned stimulus (UCS)	In experimental human studies often an aversive electrotactile stimulation or an air puff to the eye
CS+	Stimulus that predicts the UCS
CS−	Stimulus that does not predict the UCS
CS+ potentiation	Augmentation of a reaction (e.g., FPS) elicited by/during the CS+ as compared to a reaction elicited by/during the ITI
CS− potentiation	Augmentation of a reaction (e.g., FPS) elicited by/during the CS− as compared to a reaction elicited by/during the ITI
CS+/CS− discrimination	Augmentation of a reaction (e.g., FPS) elicited by/during the CS+ as compared to a reaction elicited by/during the CS−
Inter-trial interval (ITI)	Time between two stimulus presentations; here: time between two CS's

In this review, we summarize existing findings, sorted by molecular pathways, covering conditioning and extinction in healthy individuals, CBT and exposure outcome in clinical populations, as well as PTSD development after trauma. We try to propose mechanistic interpretations, critically discuss limitations and pitfalls, and show up interesting new directions for future research.

Serotonin

Although the serotonin (5-HT) system presents with a multitude of promising candidate genes, only polymorphisms in the serotonin transporter (*5-HTT)* gene, which is responsible for presynaptic 5-HT reuptake (for a review, see ref. 17), and the monoamine oxidase A (*MAO-A*) gene, which degrades 5-HT (for a review, see ref. 18), have been studied with respect to fear conditioning and extinction processes.

***5-HTT*LPR.** *5-HTT* presents with a 43 bp insertion/deletion polymorphism in its promoter region, which is referred to as *5-HTT* linked polymorphic region (*5-HTT*LPR) and most commonly comprises a short (s) and a long (l) variant. The s-allele is associated with ~50% reduced transcriptional activity *in vitro*,[19] but human *in vivo* or post-mortem studies failed to reveal consistent functional effects,[20–22] probably because the polymorphism exerts its effect during early neurodevelopment (for example, ref. 23).

The G-allele of a functional A/G single-nucleotide polymorphism (SNP, rs25531) upstream of the *5-HTT*LPR[24] is almost always in phase with the *5-HTT*LPR l-allele[25] and is associated with reduced 5-HTT transcriptional efficacy.[24,26] *5-HTT*LPR and rs25531 are often combined as a functional mini-haplotype ('tri-allelic *5-HTT*LPR'). The l-allele of the *5-HTT*LPR is thereby further subdivided into L_A and L_G. Functionally, the L_G-allele is equivalent to the low expressing *5-HTT*LPR s-allele,[26] and grouping of individuals based on the triallelic *5-HTT*LPR is based on inferred 5-HTT expression levels.[26]

Three experimental and five clinical studies have to date investigated an association of the bi- and/or triallelic *5-HTT*LPR with fear conditioning- and/or extinction-related processes.

Garpenstrand and co-workers[27] selected 20 good and 20 bad performers from a cohort of 346 fear-conditioned subjects, on the basis of their SCR discrimination, during conditioning, between a CS paired with the UCS (CS+), and a control stimulus never paired with the UCS (CS−) (see Tables 2 and 3 for details on design and sample). Testing for CS+/CS− discrimination is an appropriate means to control for general sensitization and stimulus responsivity effects. The authors observed an over-representation of the *5-HTT*LPR s-allele in the good performers and, accordingly, significantly more SCR discrimination (CS+ > CS−) in s-allele carriers than in non-carriers. This effect was maintained during (immediate) extinction on a descriptive level ($P = 0.11$).

Lonsdorf and co-workers[28] replicated and extended the above findings in a sample of 48 volunteers, partly selected *a priori* for their *5-HTT*LPR and *COMT*val158met (see below) genotypes. Eyeblink startle responses were induced by presenting auditory (startle probe) probes during both types of CSs and during the inter-trial interval (ITI, see Table 1 for explanations of technical terms). S-carriers displayed significantly more FPS CS+ potentiation (CS+ > ITI) during acquisition than non-carriers, in the absence of significant differences in CS+/CS− discrimination, CS− potentiation (CS− > ITI) or ITI raw startle (untransformed ITI scores elicited during the ITI). In addition, while s-carriers showed the expected conditioning-related effects (significant CS+ and CS− potentiation, CS+/CS− discrimination), these effects were absent in non-carriers. During the 24 h delayed extinction phase, s-carriers again showed significantly more CS+ potentiation, but also less CS− inhibition (CS− < ITI, an effect that is taken to reflect the learned safety of the CS−), in the absence of group differences in CS+/CS− discrimination or ITI raw startle. However, using SCR, no learning-related group differences were observed, whether during conditioning or extinction (see below for a discussion of the different measurements).

Finally, Crisan and co-workers[29] reported an association between the *5-HTT*LPR s-allele and enhanced *observational* fear learning[30] in 32 participants. In this paradigm, s-carriers displayed marginally higher SCRs when observing a model (that is, another person) being presented with the CS+ or the UCS, but not when the model was presented with the CS−. During subsequent testing, s-carriers displayed significantly higher SCRs to CS+s, but not to CS−s, presented to

Table 2 Overview of important design specifications of the experimental studies

Author [ref.]	Polymorphism	Stimuli	UCS	Number of trials	Reinforcement ratio (%)	EXT[a]	CS duration	ITI duration	Peak detection window	Data processing	Instructed acquisition	Awareness reported	Time taken into account[b]
Garpenstrand *et al.*[27]	*5-HTT*LPR *MAO-A* *DRD4*	Circle, triangle	Shock	H: 8 each A: 8 each E: 8 each	100	I	8 s	20–40 s	1–4 s post-onset	Range correction (*X*/max. response) SCRs summarized over stimuli and trials	?	No	No
Lonsdorf *et al.*[36,37]	*5-HTT*LPR *COMT*v158m *BDNF*v66m	KDEF faces (angry male) 95 dB startle probe	Shock	H: 6 whereof 1 each to be CS A: 9 each E: 18 each	100	D	6 s	10–18 s	SCR: 0.9–4 s post-onset FPS: 20–100 ms post-onset with peak within 150 ms	SCR: Log and range correction (1+(*X*/max. response)) FPS: rectified, *z*-scores to *T*-scores	No	Yes[c]	No (2009) Yes (2010)
Crisan *et al.*[29]	*5-HTT*LPR	Two colored squares (movie)	Shock	Obs.: 5 each Test: 5 each	60	—	10 s	10–14 s	0.5–4.5 s post-onset	Area under the curve extracted	No	No	No
Hajcak *et al.*[72]	*BDNF* val66met	Rectangles differing in size	Shock	H: 4 trials A: 12 CS+ 8 each CS−	100	—	8 s	10–12 s	150 ms window relative to average of 50 ms pre-probe	Rectified in a 200 ms window starting 50 ms before startle probe, smoothed using six-point running average Amplitude converted to *T*-scores	Yes	N/A (instructed)	No
Soliman *et al.*[74]	*BDNF* val66met	Two colored squares	95 dB aversive sound	A: 24 each[d] Rev: 24 each[d] E: 24 each	50	I	3 s	13 s	1–8 s post-onset	Smoothed (kernel ?) square root transformed		No	No
Huertas *et al.*[79]	*DRD2* C957T	Eckman faces (neutral male, neutral female)	Shock A: 200 ms AP: 180 ms	H: 10 faces A: 11 each[e] E: 2 each[f]	72.7	I	H: 8 s A: 8 s E: max 3 s	H: 4 s A: 16–20 s E: 19–21 s	1–4 s post-onset minimum amplitude: 0.01 μS	Range correction ((*X*/mean of the three max) × 100) Square-root transform (1+range corrected SCR)	Yes[g]	No	No
Raczka *et al.*[75]	*NPSR1* $A^{107}T$	Circle, triangle	Shock	H: 4 each A: 18 each E: 18 each Re-A: 18 each	80	I	5 s	9–14 s	0–5 s post-onset	Peak SCR–SCL at the time of CS onset	No	No	Yes
Ressler *et al.*[87]	*ADCYAP1R1* rs2267735	Two different colored shapes 108 dB startle probe	250 ms air blast (intensity 140 psi)	H: 6 startle alone A: 12 each	100	—	C: 6 s	9–22 s	20–200 ms post-onset (startle probe)	Filtered, rectified, smoothed	?	No	Yes/no

Abbreviations: A, acquisition; ADCYAP1R1, pituitary adenylate cyclase 1 receptor; AP, aversive priming; BDNF, brain-derived neurotrophic factor; CS, conditioned stimulus; E, extinction; FPS, fear potentiated startle; 5-HTTLPR, 5-HTT linked polymorphic region; H, habituation; ITI, Inter-trial interval; KDEF, Karolinska directed emotional faces; NPS, neuropeptide; Obs, observation; Re-A, reacquisition; Rev, reversal; S; SCR, skin conductance response; UCS, unconditioned stimulus.
?, Not specified in the respective publication.
[a]Extinction timing: I = immediate extinction; D = delayed extinction.
[b]Time taken into account by providing additional analyses, for example, by comparing first and second half of the experiment or by providing learning rates to quantify response changes over time.
[c]Participants classified as unaware were excluded from primary analyses in both publications. Of note, BDNF met-carriers failed more often to report correctly the conditioning contingencies as compared with homozygote val-carriers, as assessed by a standardized interview performed right after the acquisition.[99]
[d]Reinforced CS+ trials were analyzed separately; thus, in principle 24 CS− and 12 CS+ trials.
[e]Plus 4 presentations of two additional faces (data not reported); during conditioning, the CS+ was paired with an aversive shock, whereas the CS− was paired with a neutral tone (both events occurring 3 s after picture onset). Although SCRs to eight paired trials each were not analyzed, only SCRs to three presentations each, which were not paired with either shock or tone respectively, were used for statistical analyses. In addition, two additional faces were each presented four times, but SCRs to these faces were not reported.
[f]Both the CS+ and CS− were presented two times in total, with the last presentation of each of them (which was used for statistical analyses) not being preceded by either a tone or a shock. During the phase preceding the two extinction test trials (the aversive priming experiment), there was one presentation of each CS+ and CS− (possibly preceded by a shock), seven presentations of the additional faces from the acquisition, 10 presentations of distracters (these were the 10 faces presented during habituation). During the AP phase, participants were presented with a set of new and old faces and had to indicate by button presses, whether the face presented was one of the four faces presented during conditioning or not. Reactions had to be made within 3 s and the face disappeared after the reactions. Any of the faces could during this AP phase been preceded by the shock or the tone.
[g]Participants were informed that one of the faces would be paired with the shock and the other one with a tone.

Table 3 Overview of important specifications of the sample for the experimental and clinical studies

Author[ref.]	Polymorphism	Ethnicity	Screening	Study	N	F/M	Genotypes	HWE	Age	Genotyping	Measure	Results
Garpenstrand *et al.*[27]	*5-HTT*LPR	Swedish Caucasian	No	E	40	14/26	24s+/16ll	?	29.7	Post	SCR	● Participants good in acquisition had a higher frequency of the s-allele as compared to those with bad acquisition performance ● No differences during (immediate) extinction
Lonsdorf *et al.*[36]	*5-HTT*LPR	German Caucasian	Yes[a]	E	48	25/23	30s+/18ll	N/Aa	23.9	Pre and post	FPS SCR	● CS+ potentiation s-carriers >l/l (FPS) during acquisition and (delayed) extinction ● CS− inhibition s-carriers <l/l (FPS) during extinction
Crisan *et al.*[29]	*5-HTT*LPR	Probably Romanian Caucasian	Yes[a]	E	32	6/26	18s+/14ll	Yes	26.8	Post	SCR	● *Observational* fear learning s-carrier >l/l ● SCR reactivity during observation s-carrier >l/l
Bryant *et al.*[35]	*5-HTT*LPR[b]	Australian Caucasian	N/A	C	42[c]	30/15[d]	29s+/13ll[e]	Yes	~42	Post	CAPS	● More s-carriers than l/l fulfill criteria for PTSD diagnosis 6 months after CBT, despite no differences right after treatment
Lonsdorf *et al.*[73]	*5-HTT*LPR	Swedish Caucasian	N/A	C	73	26/43	51s+/22ll 60s+/13ll[e]	Yes	35.4	Post	HADS	● No differences in response to exposure-based CBT after treatment or at 6 months follow-up ● Main effect of symptom severity over time (s-carrier >l/l)
Kilpatrick *et al.*[32]	*5-HTT*LPR[b]	Mainly Caucasian	N/A	C	Total:589 PTSD:19	36.5%/63/5%	ss: 120/sl: 315/ll:154	?	?	Post	PTSD risk	● An association of the s/s genotype with PTSD in highly exposed adults with low social support
Koenen *et al.*[33]	*5-HTT*LPR	Mainly Caucasian	N/A	C	Total:590 PTSD:19	375 female	ss: 120/sl: 316/ll:154	?	?	Post	PTSD risk	● The s/s genotype to be associated with PTSD in high-risk environments (e.g., crime, unemployment), whereas the opposite was found for low-risk environments
Kolassa *et al.*[34]	*5-HTT*LPR	African	N/A	C	Total:408	190/218	ss:16/sl: 109/ll:283 (whereof 8 ultra-l/l)	Yes	34.7	Post	PTSD risk	● s-carriers exhibited an enhanced risk for lifetime PTSD irrespective of trauma load, whereas non-carriers exhibited a dose–response relationship
Lonsdorf *et al.*[36]	*COMT*v158met	German Caucasian	Yes[a]	E	48	25/23	39val+/9mm	N/A	23.9	Pre and post	FPS, SCR	● No differences during acquisition ● CS+ potentiation met/met >val-carrier during extinction (FPS)
Kolassa *et al.*[48]	*COMT*v158met	African	N/A	C	424	198/226	188vv/ 190vm/46mm	?	34.8	Post	PTSD risk	● met/met higher risk for lifetime PTSD even at low trauma load
Lonsdorf *et al.*[73]	*COMT*v158met	Swedish Caucasian	N/A	C	69	26/43	40val+/29mm	No	35.4	Post	HADS	● met/met less reactive to exposure-based CBT as compared to val-carrier
Valente *et al.*[50]	*COMT*v158met	Brazilian	Yes[f]	C	99 PTSD 335 CS[g]	50/59 ?/?	20mm 42vm/37vv 26mm/185vm/ 124vv	Yes/No[h] Yes	18–60	Post	CAPS	● Significantly higher frequency of the COMT met-allele in Brazilians that had developed PTSD as compared to those that had not developed PTSD after being exposed to a single urban trauma, as well as compared to a general community sample
Hajcak *et al.*[72]	*BDNF*v66met	?	No	E	57	26/31	44vv/13m+	?	?	Post	FPS Shock likelihood	● FPS to the CS+ only in val/val- not in met-carriers
Lonsdorf *et al.*[37]	*BDNF*v66met	German Caucasian	Yes[a]	E	48	25/23	43vv/14m+	Yes	23.9	Post	FPS, SCR	● CS+ potentiation and CS discrimination val/val >met-carrier during late acquisition (FPS) ● CS+ potentiation val/val >met-carriers during early extinction (FPS)

Table 3 *(Continued)*

Author[ref.]	Polymorphism	Ethnicity	Screening	Study	N	F/M	Genotypes	HWE	Age	Genotyping	Measure	Results
Soliman *et al.*[74]	*BDNF*v66met	Mixed	Yes[d]	E	70/−72[i]	34/36 33/39	35vv/35m+ 36vv/36m+	?	25.9 25.6	Post?[j]	SCR, fMRI	● Resistance to extinction in met/met (fMRI, SCR see text for severe problems interpreting these results due to methodological shortcomings)
Garpenstrand *et al.*[27]	*DRD4* exon III	Swedish Caucasian	No	E	40°	14/26	29 Short/ 11 long+	?	29.7	Post	SCR	● No differences during acquisition ● CS discrimination during extinction long allele <short/short
Garpenstrand *et al.*[27]	*MAO-A* VNTR	Swedish Caucasian	No	E	40°	14/26	15 low/25 high	?	29.7	Post	SCR	● Differences during either acquisition or extinction
Huertas *et al.*[79]	*DRD2* C957T	Spanish Caucasian	No	E	63	31/32	51T+/9CC	?	19–27	Post	SCR	● Differential conditioning during acquisition CC > T-carriers ● NS for extinction
Huertas *et al.*[79]	*DRD2 Taq*1A/ *ANKK1 Taq*1A	Spanish Caucasian	No	E	63	31/32	18A1−/42A1+	?	19–27	Post	SCR	● Differences during either acquisition or extinction
Domschke *et al.*[83]	*NPSR1* A/T	German Caucasian	?	E/C	205	151/54	25AA/150T+	?	35.4	Post	Subjective anxiety	● Symptom reports during exposure (but not anticipation and recovery) T-carrier > AA
Raczka *et al.*[75]	*NPSR1* A/T	German Caucasian	Yes[k,l]	E	66	0/66	28AA/38T+ (13TT)	?	27.8	Post	SCR, fear ratings, fMRI	● Fear ratings to the CSs T-carrier > AA ● CS− evoked brain activity in the rdmPFC T-carrier > AA
Ressler *et al.*[87]	*ADCYAP1R1* rs2267735	?	?	E	?	?	?	?	?	?	FPS	● CS+/CS− discrimination in female CC < G-carriers ● No differences in men

Abbreviations: ADCYAP1R1, pituitary adenylate cyclase 1 receptor; ANKK1, ankyrin repeat and kinase domain containing; BDNF, brain-derived neurotrophic factor; CAPS, Clinician-Administered PTSD Scale; COMT, catechol-*o*-methyltransferase; CS, conditioned stimulus; FPS, fear-potentiated startle; fMRI, functional magnetic resonance imaging, 5-HTTLPR, 5-HTT linked polymorphic region; HWE, Hardy–Weinberg equilibrium; ITI, Inter-trial interval; MAO-A, monoamine oxidase A; NPS, neuropeptide S; SCR, skin conductance response; UCS, unconditioned stimulus; VNTR, variable number of tandem repeat region.
?, Not specified in the respective publication.
+, Mean carriers, for example, s+ = carriers of the s-allele.
Note: For some studies HWE was not applicable (N/A) as individuals were selected or partly selected based on their respective genotype group.
[a]Screening based on a questionnaire, telephone interview or interview, but not a clinical diagnostic interview.
[b]Triallelic classification.
[c]$N = 42$ for the follow-up analyses that yielded genotype-specific findings, but $N = 45$ in total, number of females and males is given for the post-treatment sample.
[d]Drug screening using urine toxicological test.
[e]Genotypes defined by the triallelic method (5-HTTLPR/rs25531). 'High expression' = L_A/L_A; 'low expression' = all other genotypes.
[f]*PTSD patients*: The presence of lifetime history of bipolar disorder, psychotic disorders and the presence of substance dependence or abuse disorders (excluding nicotine and caffeine) in the previous 6 months were exclusion criteria. *Community sample*: Past history of drug abuse, use of an illegal drug, lifetime history of a psychiatric disorder or suffering from a psychiatric condition at the time of the evaluation was excluded. The presence of previous traumatic experiences was not evaluated in this group.
[g]Community sample.
[h]HWE PTSD+: yes; HWE PTSD−: no.
[i]$N = 70$ for the fMRI sample and $N = 72$ for the SCR sample.
[j]Although the genotype distributions suggest an *a priori* selection, as they do not reflect population allele frequencies, no information about participant selection is given, leaving open the possibility of a selective drop out, particularly in the light of the high drop-out rates reported.
[k]Clinical diagnostic interview, for example, MINI.
[l]Unclear as to how screening was performed.

themselves in the absence of the UCS. Group differences were reported in analyses that tested SCRs to the CS+ and the CS− separately; however, no statistics on CS+/CS− discrimination was given.

In sum, three experimental studies reported facilitated fear learning in *5-HTT*LPR s-allele carriers in at least one psychophysiological modality (SCR or FPS), an effect that appears to carry over into subsequent extinction. Importantly, as far as reported, groups did not differ in the intensity levels chosen for UCS presentations,[27,28] in SCRs to received UCSs, or in ITI raw startle (ref. 28).

PTSD is the prototypical anxiety disorder where fear conditioning makes an unquestionable contribution to disease aetiology (for example, see ref. 31). If *5-HTT*LPR genotype affects fear conditioning propensity, it should also be associated with PTSD vulnerability. Three epidemiological studies support this claim and thus underscore the translational potential of conditioning genetics.

In a sample of hurricane victims ($N=589$), PTSD risk was enhanced in individuals carrying the s/s genotype if they also received low social support[32] or if they also lived in high-risk environments (characterized, for example, by crime or unemployment).[33] By contrast, s/s-carriers had a lower risk to develop PTSD in low-risk environments.[33] However, both analyses were limited by the very low number of individuals with a current PTSD diagnosis ($N=19$, whereof $n=4$ *5-HTT*LPR s/s-carriers). Finally in a study in 424 unrelated refugees of the Rwandan civil war, Kolassa and co-workers found an enhanced risk for lifetime PTSD in s/s-carriers irrespective of trauma load (as assessed 12–13 years later by counting the number of different traumatic event types experienced/witnessed), whereas l-carriers (s/l and l/l) exhibited the expected dose–response relationship between trauma load and lifetime risk.[34] At very high traumatic load however (>15 events), no differences in lifetime risk were found between the genotype groups, suggesting that the influence of genetics decreases with increasing trauma load.

Hence, the clinical data are in agreement with the idea that low 5-HTT expression is associated with facilitated and more persistent fear conditioning, whereas high 5-HTT expression is associated with abnormal resistance to fear conditioning. However, it remains elusive if the apparent persistence of fear simply reflects a carryover of stronger fear into later exposure or perhaps deficits in the corrective safety learning that characterizes extinction. Unfortunately, the preclinical studies did not assess rates of extinction as one means to quantify learning. However, provided one accepts the idea of extinction learning as *the* major active ingredient to CBT, two recent therapy studies permit interesting conclusions.

Bryant and co-workers[35] investigated 42 unmedicated PTSD patients who were provided with weekly 90-min individual CBT sessions for 8 weeks. CBT reduced symptoms equally in both groups, and there were no significant genotype group differences in symptom scores before and immediately after treatment, significantly more individuals with inferred low *5-HTT* expression (s- and L_G-carriers) met PTSD diagnosis 6 months after treatment and also reported more symptoms as compared to non s- and non-L_G-carriers (L_A/L_A). Lonsdorf and co-workers[36,37] reported a similar finding of persistently higher symptom scores in s- and L_G-carriers in 69 PD patients treated with weekly CBT sessions (regular group or internet-based CBT) for 10 weeks. In contrast to the study by Bryant and co-workers[35] group differences in symptom scores reached significance also at pre- and post-treatment. Because in both studies, acute symptom reduction thought CBT succeeded equally well in both genotype groups (excluding deficits in corrective safety learning in s- and L_G-carriers), the explanation of the group differences of the 6-month follow-up scores most likely be sought in the persistence and durability of the fear memories generated during trauma.

It should be noted that there are currently no twin studies showing heritability of CBT. Nevertheless, if taken together, existing data on the bi- and triallelic *5-HTT*LPR genotype yield an impressively consistent picture across preclinical–experimental, epidemiological and therapy studies, making *5-HTT*LPR a prime example for successful translation of biochemical and molecular–genetic findings into human pathophysiological research.

***MAO-A* VNTR.** The human *MAO-A* gene contains an untranslated variable number of tandem repeat region (*MAO-A* uVNTR)[38] that yields six different alleles that vary in transcriptional efficiency ($2R<3R<3.5R=4R$). Functional data are inconsistent for the 5R[38,39] and absent for the 6R-allele (for a review, see ref. 23).

Garpenstand and co-workers[27] found no differences in SCR conditioning and extinction between individuals with putatively high (3.5R/4R) or low (3R/5R) *MAO-A* expression levels in an additional analysis of the sample described above.

Dopamine

Like 5-HT, the dopamine (DA) system yields a multitude of promising candidate genes, and studies on fear conditioning, extinction, CBT and PTSD development after trauma have investigated associations with polymorphisms in the catechol-O-methyltransferase (*COMT*), DA transporter (*DAT1*), D2 (*DRD2*) and D4 (*DRD4*) receptor genes.

***COMT* val158met (rs4680).** COMT degrades extracellular DA (for a review, see ref. 40) and is of primary importance in the prefrontal cortex, but less so in striatal areas.[41] The *COMT* gene harbors a functional A/G SNP, leading to the substitution of the amino-acid valine by methionine at codon 158 (*COMT*val158met). Homozygosity for the met allele leads to four times reduced enzymatic activity compared to homozygosity for the val-allele,[42] and thereby affects effectiveness of DA degradation by COMT and the availability of synaptic DA (higher in met-carriers).[43]

Two experimental and three clinical studies have to date investigated an association of *COMT*val158met with fear conditioning and/or extinction processes.

In a sample of 48 volunteers, partly selected *a priori* for *COMT*val158met genotype (and *5-HTT*LPR, see above[28]) Lonsdorf and co-workers[37] reported no association of *COMT*val158met genotype with FPS and SCR conditioning. However, during 24-h delayed extinction, met/met-carriers showed significantly enhanced CS+ potentiation compared

to val-carriers, suggesting resistance to extinction. No group differences in CS+/CS− discrimination, CS− potentiation, raw ITI startle or SCRs were observed. As a limitation of this study, the low number of homozygous met-carriers has to be mentioned.

In a subsequent clinical study, the same group[37] also investigated the efficacy of exposure-based CBT in 69 PD patients (see also above). Supporting the notion of extinction resistance, met/met-carriers seemed to benefit less from exposure-based treatment modules (vs cognitive modules) than val-carriers. Hence, COMT met/met-carriers do not seem to differ from val-carriers in their conditionability, but in their ability to use corrective experience for fear reduction, which is in line with the met-allele being associated with emotional perseveration, reduced cognitive flexibility, but enhanced stability.[44,45]

Raczka and co-workers[46] investigated 69 healthy male participants selected *a priori* based on their *COMT*val158met genotype (and a *DAT1* VNTR, see below) in an experiment involving conditioning, immediate extinction and immediate reconditioning. Like in the first *COMT* study,[26] *COMT* genotype had no measurable effect on indices of conditioning (SCR as well as subjective fear ratings intermittently provided throughout the experiment). However, there was also no association with extinction learning in SCR and fear ratings, as well as in a computational analysis of fear rating time series by virtue of a formal reinforcement learning model. The latter provides a possibility to estimate extinction learning rates and thus to gain a more fine-grained picture of the associative processes occurring during an exposure phase than simple averaging of CR scores. An apparent methodological difference to previous work was the use of immediate extinction, excluding potential effects of long-term fear memory consolidation processes on CRs measured in extinction. It is therefore possible that the extinction resistance observed by Lonsdorf and co-workers[28] reflects better fear memory consolidation in met/met-carriers rather than a deficit in safety learning. In this context, it is worth noting that DA has been implicated in memory consolidation processes in animal studies (for example, ref. 47).

Like the enhanced and persistent fear conditioning in low *5-HTT*-expressing individuals, the putatively enhanced fear memory consolidation in *COMT* met/met-carriers should be associated with enhanced risk for PTSD. Two epidemiological studies support this prediction. Kolassa and co-workers[48] observed that met/met-carriers, after experiencing at least one traumatic event, had a high risk for lifetime PTSD. By contrast, val-allele carriers showed the typical dose-dependent increase of lifetime PTSD risk with increasing trauma load. In analogy to the pattern observed with respect to *5-HTT*LPR genotype, the 'risk' genotype (met/met) conferred a higher lifetime PTSD risk in particular at *lower* trauma loads, and differences between the genotype groups vanished at high traumatic load (>15 events), again suggesting that the influence of genetics decreases with increasing trauma load. Importantly, genotype groups did not differ in the number or types of traumatic events experienced, rendering a gene–environment correlation (for example, exposure to trauma may depend on the individual's genotype),[49] rather unlikely.

In a similar vein, Valente and co-workers[50] found a significantly higher frequency of the *COMT*val158met met-allele in Brazilians who had developed PTSD after a *single* urban trauma than in individuals resilient to PTSD and in a community sample. Further, trauma-exposed individuals carrying a met-allele reported significantly more PTSD symptom severity than non-carriers. Limitations of this study include the rather small sample sizes for trauma exposed individuals ($N=99$, whereof 34 resistant to PTSD) and different genotype and allele frequencies in the three groups. As trauma exposure was not assessed in the community sample and different allele frequencies were observed in the different groups, a gene–environment correlation cannot be finally excluded.

In sum, the current literature points toward an important role for *COMT*val158met in fear memory consolidation, which also affects extinction success once sufficient time for consolidation of the fear memory has elapsed. Because exposure therapy occurs with a considerable delay to trauma, *COMT*-val158met genotype might turn out as a predictor of treatment response.

***DAT1* VNTR (rs28363170).** The DAT mediates DA reuptake and thus regulates the duration and amplitude of DAergic signaling, particularly in striatal areas.[51] The *DAT1* gene harbors a 40 bp-VNTR polymorphism in its 3′-untranslated region that most frequently occurs as 9 or 10 tandem repeats (R).

Of those studies finding VNTR effects on DAT expression, cell-based assays majorily indicate that the 9R-allele reduces expression,[52–54] whereas evidence from human studies is split.[55–58] According to current models, reduced DAT expression should amplify phasic DA signals.[51]

In their above sample, Raczka and co-workers[46] used formal computational modeling (see above) to show higher learning rates during extinction (but not conditioning) in *DAT1* 9R-carriers as compared to non-carriers. Of note, standard analyses comparing phase-averaged SCR and rating scores showed no group differences. Higher learning rates were accompanied by higher activation of the ventral striatum to the unexpected UCS omission in extinction. In associative learning theory, such 'prediction errors' are supposed to drive association formation (here, between the CS and the absence of the UCS) and phasic ventral–striatal DA release is currently the prime candidate for prediction error encoding in appetitive conditioning.[59] Drawing an analogy between learning to expect safety (in extinction) and learning to expect reward (in appetitive conditioning), the authors suggested a contribution of the meso-striatal DA system to extinction learning. No group differences in striatal prediction error encoding were observed in the conditioning phase.

***DRD2* C957T (rs6277).** The synonymous SNP in the *DRD2* gene, *DRD2* C957T (rs6277), was initially assumed to be functionally silent. Later, the T-allele was associated with decreased mRNA stability and protein synthesis *in vitro*[60] and higher DRD2 receptor affinity (C/C<C/T<T/T).[61]

In a sample of 60 individuals, Huertas and co-workers[62] found T-carriers to display significantly lower SCRs to CS+s in one late compared with one early conditioning trial (see

Table 2 for details). Non-carriers (C/C) in turn tended to show an increase. No differences between the genotype groups were found in CS− and UCS SCRs. A formal test of SCR discrimination (CS+ > CS−) was not reported. In extinction, no differences between the genotype groups were found. Limitations of the study include very unequal sample sizes and the use of single trials ($N = 1$–3) for statistical analyses (see Table 3).

***DRD4R* VNTR.** The *DRD4* gene contains a VNTR polymorphism of a 48 bp sequence that affects D4 receptor function *in vivo*.[63] The 7R variant leads to decreased inhibitory post-synaptic DA effects compared with the 4R and the 2R forms.[64] Caucasians are mostly grouped as 7R carriers vs non-carriers, but a new suggestion for functional classification has been proposed recently.[65,66]

Garpenstand and co-workers[27] (see above) found no *DRD4R* VNTR genotype variant (long: 6–8R vs short: 2–5R) over-represented in good or poor conditioning performers. Although no difference in SCRs were found during conditioning, long-allele carriers showed significantly more CS+/CS− discrimination during extinction. However, this association did not survive correction for multiple comparisons. In addition, extinction results in this sample must be interpreted in the awareness that participants were selected based on extreme performance during conditioning (see above).

Brain-derived neurotrophic factor

***BDNF val66met*.** Brain-derived neurotrophic factor (BDNF) is the most abundant neutrophin in the central nervous system and is implicated in synaptic plasticity.[67] The human *BDNF* gene harbors a functional G/A SNP in its pro-domain, leading to a valine to methionine substitution in codon 66 (*BDNF*val66met). The met-allele is associated with impairments in intracellular trafficking and activity-dependent BDNF secretion.[68,69]

Animal work has implicated BDNF in hippocampus-[70] and amydala-dependent[71] learning and memory, and to date, three human studies exist.

Hajcak and co-workers[72] used a fear generalization paradigm in 57 participants. A rectangle served as CS+, and three different rectangles, differing gradually in size from the CS+, served as CS−s (see Table 2 for details). A significant stimulus × genotype interaction on FPS was observed in the absence of differences in ITI startle reactivity, chosen UCS (shock) intensity or UCS likelihood ratings. Homozygous val-carriers showed significantly higher FPS to the CS+ than met-carriers, relative to the CS− that was maximally dissimilar from the CS+. No differences in FPS to the various CS−s were observed.

Similarly, Lonsdorf and co-workers[73] reported in a sample of 48 individuals more pronounced FPS CS+ potentiation and CS+/CS− discrimination in val-carriers as compared to non-carriers during late (but not early) conditioning. This carried over to the early (but not late) extinction phase 24 h later, manifesting as significantly more pronounced CS+ potentiation in homozygous val-carriers. Because genotype groups had reached similar fear reduction at the end of extinction, this most likely reflects enhanced fear memory retrieval, rather than a safety learning deficit. No difference was found in SCR discrimination. Both studies were limited by unequal numbers in the two genotype groups (see Table 3).

Soliman and co-workers recently[74] published a paradigm consisting of a conditioning, a reversal learning and an extinction phase following immediately upon each other in a sample that consisted of an equal number of met-carriers and non-carriers (total $N = 72$). During reversal learning, the stimulus that had served as CS+ during conditioning now served as the CS− and *vice versa*, and in extinction, both stimuli were unpaired (see Table 2 for details).

During fear conditioning, met-carriers showed an overall heightened SCR to both CS+ and CS− in the absence of group differences in SCR discrimination (CS+ > CS−). Stronger CS− responses during late conditioning in met-carriers than in val-homozygotes were interpreted as a deficit in safety learning. No SCR data from the subsequent reversal phase were reported. During extinction, there were again generally heightened SCRs in met-carriers. Specifically, during late extinction, responses to the CS+ (= CS− in reversal) were higher in met-carriers. CS+/CS− discrimination and CS− (= CS+ in reversal) responses were not reported. This and the unorthodox reversal manipulation preceding the extinction phase (resulting in the CS+ already being consistently presented unpaired with the UCS before extinction) calls for further qualification of the authors' interpretation of the data as reflecting an extinction deficit in met-carriers. A concurrent finding of decreased brain activation during extinction in met-carriers in the ventromedial prefrontal cortex and enhanced activation in the amygdala to CS+s (= CS− in reversal) relative to a fixation baseline would also require further information about preceding activations in conditioning and reversal, as well as responses to CS− (= CS+ in reversal) and CS+ vs CS− contrasts to draw firm conclusions. So far, it cannot be excluded that the results merely reflect the generally heightened CS responsivity in met-carriers.

The picture that emanates from these three studies is relatively inconsistent, the strongest overlap lying in the enhanced FPS conditioning in val-homozygotes. In an attempt to shed further light on potential *BDNF* genotype effects, we reanalyzed SCR and fear rating data from a previously published data set using a continuous conditioning–extinction–reconditioning paradigm in 46 val-homozygotes vs 23 met-carriers[75] (see Supplementary Information). Homoyzgous val-carriers showed generally heightened SCRs to both CS+s and CS−s during reconditioning only, in the absence of any group differences in discrimination. In fear ratings, val-homozygotes showed less CS+/CS− discrimination, caused by lower fear ratings to CS+s, relative to met-carriers, in both conditioning and reconditioning. Learning rates showed no genotype effects. Hence, these data rather enhance the disagreements currently existing in the literature.

To sum up, no clear picture emerges currently from data on the *BDNF*val66met genotype (for differences in design and methods see Tables 1 and 2) and results must be treated preliminary until replicated by independent laboratories. As animal studies have implicated BDNF in hippocampus-dependent learning and human studies have shown

associations of this SNP with hippocampus-dependent processes,[69] context conditioning, relying heavily on the hippocampus, may be a more promising candidate for future studies.

Other systems

***ANKK1 Taq*1A (rs1800497).** The novel *ankyrin repeat and kinase domain containing (ANKK1)* gene is involved in signal-transduction pathways[76] and harbors the *Taq*1A restriction fragment length polymorphism (Glu713Lys). The polymorphism was initially thought to be located within the nearby *DRD2* gene, but from the current state of knowledge, its initial association with altered D2 receptor density[77,78] is problematic.

Huertas and co-workers[79] (see above) found no association of the *ANKK1 Taq*1A restriction fragment length polymorphism with fear learning and (immediate) extinction. As for the authors' analysis of *DRD2* C957T in the same data set, unequal group sizes and the use of single trials for statistics (see above and Table 3) have to be mentioned as a limitation.

***NPSR1* Asn^{107}Ile (rs324981).** Neuropeptide S (NPS) is a recently discovered neuropeptide that animal studies have implicated in arousal, anxiety and fear learning (for a review, see ref. 80). The human NPS receptor gene *NPSR1* harbors a functional A/T SNP, leading to an amino-acid exchange from aspargine to isoleucine (Asn^{107}Ile). The T-allele is associated with increased NPSR cell surface expression and 10-fold enhanced efficacy of NPS at NPSR *in vitro.*[81,82]

Raczka and co-workers[75] (see above) performed conditioning, immediate extinction and immediate reconditioning in 66 healthy male volunteers. SCR results during the three phases revealed no genotype group differences in CS+/CS− discrimination or general CS responsivity. By contrast, T-allele carriers gave higher CR ratings to both CS+s and CS−s during conditioning (reappearing at trend level in reconditioning), suggesting that they may consciously over-perceive or over-interpret their conditioned responses. This was accompanied by CS+ hyper-responsivity of an area in the dorsal–medial prefrontal cortex previously associated with conscious threat appraisal.[16]

Paralleling these results, Domschke and co-workers[83] showed in 205 PD patients with agoraphobia that T-allele carriers report significantly stronger increases in perceived symptom intensity elicited by a panic-relevant stimulus (sitting in a small locked dark chamber) again in the absence of a corresponding genotype effect on physiological responding (heart rate).

Hence, there is converging evidence from two studies that the T-allele of the *NPSR1* Asn^{107}Ile SNP may be associated with amplified subjective experience and interpretation of fear reactions or stimuli, in the sense of catastrophizing over-interpretations, which is thought to be crucial for the development and maintenance of PD.[84,85] However, whether this SNP is also associated with disease-relevant fear learning and/or extinction processes remains an open question.

ADCYAP1R1 C/C (rs2267735). The pituitary adenylate cyclase-activating protein (PACAP) stimulates cAMP production in the anterior pituitary[86] and exerts pleiotropic functions in development, metabolism and cell signaling (cf. ref. 87).

Ressler and co-workers[87] identified the C/C genotype of an SNP in the *ADCYAP1R1* gene to be associated with PTSD in female, but not male, highly traumatized urban civilian subjects using a tag-SNP approach. In a sample of PTSD patients (see Table 3), they also observed an association between the C/C genotype and impaired CS+/CS− startle discrimination during late conditioning, again restricted to females. Separate analyses for CS+, CS− and ITI startle responses were not reported, and thus it remains unclear as to whether the effect was due to impaired excitatory (less CS+ responding) or inhibitory (too much CS− responding) learning. In support of amplified excitatory responding, females with the C/C genotype also showed significantly increased dark-enhanced startle than non-carrier females, whereas again no differences were found in males.

In sum, there is new promising evidence for a possible association of an *ADCYAP1R1* SNP with fear learning.

Summary

In our summary of genetic association studies on human fear learning- and extinction-related processes, as well as their clinical translations, two sets of findings clearly stand out.

First, there is now strong evidence (six positive reports (PR)) that genetic variation in the *5-HTT* gene affects conditionability, in the sense of facilitated and possibly more persistent fear conditioning in individuals with putative low *5-HTT* expression (*5-HTT*LPR s-allele or L_G-carriers), and that these individuals are also characterized by vulnerability to PTSD after trauma and possibly more severe clinical symptom profiles.

Second, there is good evidence (4PR, 1 negative report) that genetic variation in the *COMT* gene affects fear memory consolidation, in the sense of stronger and extinction-resistant fear memories in met-allele carriers, as well as associated increases in the risk for PTSD after trauma as well as resistance to exposure-based treatment in PD patients.

The work on *5-HTT*LPR and *COMT*val158met draws an impressive line between pharmacological work *in vitro*, animal models, human molecular genetics, behavioral genetics and clinical studies and support the validity of the molecular–genetic association study approach.

The available literature on the *BDNF*val66met genotype and conditioning- and extinction-related processes is paved by contradictory and unclear findings, and requires, given high clinical interest and promising animal work, further systematic studies in humans.

Other observations of high potential interest, which however require further confirmation and mechanistic clarification, concern associations of genetic variants in the *DAT1* gene (1 PR) in extinction and of the *ADCYAP1R1* gene (1PR) in conditioning in females. In addition, there is weak evidence for associations with the *DRD2* C957T polymorphism (1PR) and the *DRD4* VNTR (1PR), whereas single negative results were reported for the *MAO-A* VNTR, *ANKK1 Taq*1A

restriction fragment length polymorphism and the *NSPR1* Asn^{107}Ile SNP.

Translation of experimental findings into the clinical context is important and genetic association studies on the outcome of CBT were found for the (triallelic) *5-HTT*LPR (1PR in PTSD, 1 negative report in PD) and the *COMT*val158met polymorphism (1PR in PD), and both are also associated with the PTSD development after single or multiple traumata (2PR), whereas experimental exposure has been associated with the *NPSR1* Asn^{107}Ile polymorphism (1PR).

Studying conditioning: methodological aspects. Where necessary for an informed interpretation of the results, we have addressed choices of outcome measures, data reporting and study design, which, like many other methodological aspects (data preprocessing, data reduction, scoring, statistical analysis), differed considerably between studies (see also Table 3). Methodological variation is inevitable because every study is optimized for the specific question it is supposed to answer. Nevertheless, observance of some critical rules might help increase comparability between studies.

Perhaps most importantly, a formal statistical comparison of outcome scores between groups is an absolute requirement for inferring genotype effects, whereas relying solely on separate analyses for each different group is not informative. Of similar importance is the decision which scores to report. Specifically, in differential conditioning experiments, CS+/CS− contrasts as well as separate reporting of CS+ and CS− responses can provide valuable information about excitatory (CS+) and inhibitory (CS−) mechanisms, as well as general reactivity and sensitization effects. In this context, it is helpful to be aware that different indicators of fear learning tap slightly different processes and involve different neurobiological pathways, which is important for their interpretation. For instance, FPS, in contrast to SCR, is not only sensitive to the arousing properties of a stimulus but also to its valence, in that it is specifically potentiated by unpleasant or aversive stimuli[88] and inhibited by positive stimuli.[89] Furthermore, FPS facilitates translation of results from animal to human work given the well-delineated neural pathway involved in startle potentiation and the similar measurements employable in both species.[88] In this context, positive results in FPS in combination with negative results in SCR in several of the reviewed studies stick out. In addition to physiological indices, self-report measures (fear or shock expectancy ratings) can be informative, in particular as a manipulation check or in case subjective experience is of specific interest. However, their subjective nature renders them inherently vulnerable to experimenter demand and it may thus be important to provide accompanying information about a possible genotype influence on tendencies for reporting in a socially desirable manner (for example, quantified using appropriate questionnaires; ref. 90). In addition, the sharpening of contingency awareness that is induced by such ratings needs to be traded against the gain of information. We would also contend that data reporting should ideally include all experimental phases. For example, when solely interested in extinction, results from the conditioning phase (or any preceding phase) need to be reported in the same measurement modality to rule out preexisting group differences. Finally, we would like to draw the reader's attention to useful guidelines for psychophysiological data recording and analysis (http://www.sprweb.org/journal/index.cfm#guidelines).

A more specific issue is whether extinction should be conducted immediately following the conditioning phase or after a delay (for example, 24 h). Animal work has suggested that a distinction between *immediate* and *delayed* extinction is critical, as only the latter may involve inhibition processes. Immediate extinction may in turn lead to an erasure of the learned responses,[91] although mixed evidence has emerged lately from human research.[92,93] Critically, human studies mostly apply immediate extinction, whereas extinction commonly does not occur immediately after conditioning in animal studies or natural contexts, posing problems for translation of findings.

This brief and non-exhaustive discussion of what might appear to be small methodological details, which yet can have strong bearing on results, highlights the need for a detailed and comprehensive reporting of experimental procedures. Tables 2 and 3 have been included in an effort to enable the reader to draw his/her own conclusions, to facilitate comparisons and to provide an initial basis for the planning of future studies.

The association approach: limitations and suggestions. Notwithstanding the apparent successes of the genetic approach to human fear conditioning, some important limitations should be kept in mind when interpreting the results. The strongest limitation lies in the inherently correlative nature of association studies, precluding conclusions about causality. This is a particular concern when chance co-variation of a polymorphism with other potentially causal factors (other genetic variants, personality characteristics) can never be fully excluded or when no heritability measurements are available yet. Enlargement of sample sizes and reproduction in independent cohorts can to some extent protect against such confounds. In this context, it is worth noting that only four studies[27,37,75] reported negative results (for a particular polymorphism or measure), but all also included positive results for other polymorphisms[27,28,62] or measures.[75] Thus, to date, there is no single publication reporting negative findings, raising concerns about publication bias.

The need for replication studies is also highlighted by the fact that genotyping mostly was performed *a posteriori* (see Table 2). This often resulted in unequal genotype distributions (reflecting population allele frequencies) and multiple testing of identical samples. Therefore, replication studies should ideally be carried out in independent study populations. Generally, a *prospective* genotyping approach where participants are selected based on genotype and *a priori* hypotheses, and where genotype groups are matched for potentially relevant characteristics (for example, gender, ethnicity, socioeconomic status, personality measures), can be considered advantageous and provide more statistical power. We would also like to draw the reader's attention to the recommendations of the 'STrengthening the REporting of Genetic Association studies (STREGA) initiative'.[94]

Future directions. So far, most genetic association studies in the field of fear conditioning and extinction have tapped only very basic processes. Future studies should include more fine-grained analyses of learning and extinction processes, for example, by discriminating between extinction learning and extinction recall,[95] and by disentangling sensitization, consolidation and retention effects from true within-session learning effects. In particular, one major characteristic of learning has so far has been neglected with few exceptions:[46] change over time within an experimental phase (that is, for instance, changes across the trials of a conditioning phase). Instead, data were presented mostly as the mean of all reactions per experimental phase separately for the CS+ and CS−, and the difference between both means. Although this approach is by no means incorrect or uninformative, it limits interpretation of the data by a loss of resolution in time.

In general, the *specificity of the findings* to fear- and anxiety-relevant processes remains to be addressed. First, neurotransmitters have widespread pleiotrophic effects on biological processes as well as behavior and disease. Thus, the subtle changes in one bottleneck of the system induced by functional polymorphisms in a single gene cannot be expected to be more specific than the systems' general function. Thus, we are not searching for a 'gene for fear learning' or a 'gene for extinction', but rather for *modulators* on the DNA level.

However, also these modulators (for example, polymorphisms) rarely induce highly specific functional effects and it cannot be neglected that genetic polymorphisms are carried by an individual from the very early stages of embryonic existence, allowing the organism—in contrast to acute pharmacological interventions—to adapt to, and compensate for, small shifts in the functionality of a molecular system, both *within* and *between* systems. Hence, group differences associated with a polymorphism in transmitter system A might theoretically also be related to compensatory adaptations in transmitter system B. A related concern is that functional effects that are observed *in vitro* do not necessarily map one-to-one on *in vivo* functioning, due to possible compensatory mechanisms.

Although studies have so far been relying on the study of single polymorphism candidates or the study of multiple 'unrelated' polymorphisms in the same sample, '*systemic haplotypes*' are likely to provide interesting new information and partly overcome this limitation. Combining functional polymorphisms in critical bottlenecks of a single (transmitter) system and a subsequent grouping of individuals based on inferred functional status of the system may be a promising approach for future studies. Studies on single gene or single polymorphism associations may also generate hypotheses for subsequent pharmacological challenge studies, and together, both may provide convergent evidence for the involvement of a molecular pathway. In animals, an interesting alternative approach to association studies are gene expression studies, which give a better picture of the underlying biological pathways and mechanisms than genetics.[96] Still, it remains an unresolved challenge to identify gene expression patterns associated with learning processes in specific regions of the living human brain. Although human research so far mostly relies on tools like genetic association studies, functional brain imaging and pharmacological challenge tests to unravel the neurobiology of fear learning and extinction, animal work, where gene expression studies are easily feasible, can provide priority candidate genes and blood biomarkers that call to be tested in humans.[96] In this vein, a recent article by Le-Niculescu and co-workers[96] provides a list of candidate genes for anxiety disorders identified using a convergent functional genomics approach, whereof very few (for example, DRD2) have been investigated with respect to human fear conditioning and extinction or related clinical phenomena.

In sum, translational work employing a synergy between molecular genetics, neuroimaging, psychophysiology, psychopharmacology and, possibly also, neuroendocrinology will be powerful in unraveling the neurobiology of fear learning and extinction processes. Because a significant proportion of patients do not respond to or tolerate standard treatments, such advances may ultimately open up perspectives for new pharmacological interventions targeted at specific neurobiological pathways or genes as they activate during specific therapeutic learning and memory processes. Hence, combining pharmacological target-specificity with temporal process-specificity in the administration regimen should allow us to increase the efficacy of existing learning-based treatments, as in pharmacological enhancement of CBT (as already seen for D-cycloserine[97] and cortisol.[98] Although the study of CBT is still in its infancy, and suffers from the absence of evidence that CBT responsiveness is heritable, it holds big hopes for better anxiety treatments in the future.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements. We thank KA Raczka for providing the supplementary data. This work was funded by the Deutsche Forschungsgemeinschaft (Grant DFG KA1623/4-1 (TL, RK); Emmy Noether group DFG KA1623/3-1 (RK)).

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