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The Return of Fear: Variation of the Serotonin Transporter Gene Predicts Outcome of a Highly Standardized Exposure-Based One-Session Fear Treatment

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Keywords

Therapygenetics · Serotonin transporter gene-linked polymorphic region · Exposure therapy · Genetics · One-session treatments · Return of fear · Serotonin

Abstract

Background: Methodological problems of existing research, such as the application of unstandardized treatments in heterogeneous samples, has hampered clear conclusions about the extent and direction to which allelic variation of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) is associated with a differential response to psychological treatment. The present study aimed to investigate the effects of the 5-HTTLPR genotype on treatment outcome under highly standardized environmental conditions. ***Methods:*** We treated 222 medication-free adults highly fearful of spiders, dental surgeries or blood, injuries and injections with a highly standardized exposure-based 1-session treatment and genotyped them for the 5-HTTLPR. Participants' subjective fear was assessed before, immediately after treatment and at 7 months of follow-up. ***Results:*** There were no differences between 5-HTTLPR genotypes in treatment outcome effects at the immediate posttreatment assessment. However, we observed a highly significant genotype × treatment effect ($p = 0.004$) at the 7-month follow-up. Fear levels of homozygous S allele carriers differed from those heterozygous ($p = 0.026$) and homozygous ($p = 0.012$) for the L allele. Compared to posttreatment assessment, LL allele carriers exhibited a further fear decrease at the follow-up assessment. In contrast, SS allele carriers displayed a strong return of fear. ***Conclusions:*** Results suggest that genetic variation of the serotonin transporter is associated with differential stability of inhibitory learning processes, potentially reflecting heightened susceptibility for context-related processes that facilitate a return of fear in S allele carriers. If replicated, results suggest the 5-HTTLPR might represent a biomarker for the long-term outcome of brief exposure-based fear treatments and might inform genotype-based selection of psychotherapeutic interventions.

Introduction

There is substantial heterogeneity in the way individuals respond to environmental influences, and part of this heterogeneity is explained by differences in genetic make-

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up. Most research on gene-environment interaction has focused on the role of genetic factors in moderating the long-term effects of stressful or traumatic experience on mental health outcomes, with the serotonin transporter gene *(5HTT, SLC6A4)* as the most extensively studied candidate [1]. The first publication by Caspi et al. [2] in 2003 showed that carriers of the short (S) allele of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) who experienced childhood adversity were more liable than carriers of 2 long (L) alleles to suffer from depression in young adulthood. Many studies have replicated this finding while others have failed to do so. Two meta-analyses [3, 4] have confirmed the finding, whereas the most recent meta-analytic study [5] did not support the interaction hypothesis and rather suggested that the effect is not broadly generalizable and only observable in limited situations. Nonetheless, several endophenotypes have been identified so far which are influenced by genetic variation at the 5-HTTLPR locus, including hyperreactivity of the amygdala when viewing emotional stimuli [6], increased hormonal responses to stress [7], and a relative uncoupling in a functional feedback circuitry between perigenual cingulate and amygdala, a circuit critically involved in emotion processing and extinction of negative affect [8, 9] in S allele carriers. These alterations have been discussed to bias S allele carriers towards increased trait anxiety, as well as higher neuroticism and harm avoidance scores [10, 11], i.e., those personality traits that are associated with a poor response to psychological treatment and a tendency to relapse [12, 13].

It has been suggested, however, that a focus on the effects of unfavourable environments or adversity might be too narrow a view on gene-environmental interplay. The differential susceptibility hypothesis suggests that individuals are not just more vulnerable than others to the negative effects of adversity, but also disproportionately susceptible to the beneficial effects of supportive and enriching experiences [14]. Indeed, the S allele has also been identified as a protective factor with regard to depressive symptomatology if stressful life events were absent, or if individuals were raised under supportive environmental conditions or reported recent positive experiences [2, 15].

If S allele carriers are more sensitive to environmental context, both to adversity and the positive effects of enriching environmental experiences, they might respond better to the supportive influence provided by psychological interventions, which can be regarded as standardized manipulation of environmental context.

The research field analysing the interactions between the outcome of therapeutic intervention and genotype recently termed as "therapygenetics" [16] is still young. It aims to identify potential biomarkers, which predict a differential treatment response to psychological interventions such as cognitive behavioural treatments. Those markers could then be used to match particular groups of patients with treatments to which they are more likely to show a positive response in a framework of "stratified medicine" [17].

However, the limited research that addresses this issue presents a mixed picture. To the best of our knowledge, 12 studies have thus far investigated whether genetic variation at the 5-HTT promoter locus moderates the effects of psychological interventions on mood and anxiety symptom improvements [18–29]. In terms of therapy outcome, 3 studies [21, 24, 25] reported favourable effects of the S variant, and 1 [20] demonstrated a negative effect of the S allele concerning the long-term outcome. In all others, no significant genotype × treatment effects were reported.

The discrepancy might at least partially be explained by the heterogeneity of applied treatments, i.e. differences in content, dose, and form of delivery, as well as sample heterogeneity [16, 30]. Therapygenetic studies often pool both medicated and non-medicated participants suffering from different disorders, which makes it difficult to identify disorder-specific gene × treatment interactions or to disentangle pharmaco- and therapygenetic effects. The use of highly standardized treatments for specific disorders might increase the likelihood of uncovering more robust gene by treatment effects [31].

The present study investigated the effects of the 5-HTTLPR genotype on the outcome of exposure-based fear treatments under highly standardized environmental conditions. Treatment standardization as well as the mitigation of some of the above-mentioned methodological problems concerning sample heterogeneity might help to clarify the direction of the association between 5-HTTLPR genotype and treatment response. In a differential susceptibility framework, the prediction would be a more favourable treatment outcome in S allele carriers. Alternatively, based on findings reporting increased anxiety-related personality traits as well as anxiety-related endophenotypes in S allele carriers, one would predict the opposite. Given the mixed picture of previous results, we hypothesized a genotype-dependent differential effect on treatment response without specifying the direction of effect.

To test our hypothesis, we developed 1-session treatment formats with exposure as the main procedure suitable for application in large-group and individual settings

and already reported feasibility and effectiveness of the procedures [32, 33]. We applied them to 3 cohorts of spider fearful, dental treatment fearful, and blood/injury/injection (BII) fearful individuals (total $n = 222$) and assessed the genotype-related treatment outcome with regard to subjective fear levels immediately after treatment and at the 7-month follow-up.

Materials and Methods

The local Ethics Committee of the psychology faculty of the Ruhr University Bochum, where the study was conducted, approved the study. An informed consent procedure was carried out with participants.

Participants and Treatment

Participants aged between 18 and 70 years requested fear treatment at the Mental Health Research and Treatment Centre in Bochum, Germany. We advertised the 1-session fear treatment option on local radio, newspapers and social networks (spider, BII fear) and a local dental clinic, specialized in the treatment of highly dental fearful participants (dental fear). Participants received detailed information on the treatment programme for their respective fears on websites established for the project and registered for participation. The only inclusion criteria were subjective high and impairing fear of spiders, dental surgeries or BII. In case of dental fear and BII fear, participants could self-screen their subjective fear by use of a short questionnaire assessment and were recommended only to participate in the study if their scores indicated high fear or phobia. However, we did not apply fixed cut-off scores which in case of falling short would have led to exclusion. Nevertheless, mean scores of specific fear questionnaires applied to all cohorts were comparable to those reported in high fear cohorts or cohorts of individuals diagnosed with a specific phobia [for a more detailed description, see 32, 33].

Treatment was based on the recommendations for 1-session treatments by Öst [34] and modified for the analogue use in large-group settings. It was delivered as a highly standardized exposure-based training and targeted the respective situational fear. In all conditions, exposure was preceded by a psychoeducation phase, imparting information about the function of fear and aims of treatment. Furthermore, a video clip was presented, showing an expert on the respective field who deals with common misconceptions and myths about the feared stimuli. Exposure was delivered via video clips and followed by live exposure elements in all conditions. Dental fear and BII fear interventions additionally contained the practice of bodily coping techniques to be applied during the exposure exercises. Treatment lasted for 120 min for spider fear and 140 min for dental and BII fears. In 159 (71.6 % of total sample) participants treatment was provided in a large-group setting, where participants were gathered in an auditorium and treated simultaneously. Furthermore, 63 individuals (28.4% of total sample) were treated in individual 1-session treatments. During the individual 1-session treatments the very same contents (video clips, etc.) as in the large-group settings were administered by the same clinical psychologists for exactly the same length [for further information concerning the contents of treatments, see 32, 33]. Because 8 participants (3.6% of total; 3LL/3LS/2SS) reported to take selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, they were excluded from our genotype comparisons.

Measures

Subjective Fear. We assessed individuals' subjective fear before and after treatment and at follow-up on an 11-point scale (0 = not at all, 10 = extremely) in response to the following question, adapted for the respective fear: "Please imagine… to see a spider… to get a dental surgery… your personal worst situation regarding blood, injuries or injection. How fearful are you?" As expected, prescores were highly significantly correlated with all specific fear questionnaires applied as main outcome measures regarding subjective fear within each cohort, i.e. in the spider fear cohort a correlation of $r_{108} = 0.78$ with the German Spider Fear Screening [35] and a correlation of $r_{43} = 0.78$ with the Dental Anxiety Scale [36] in the dental cohort (Table 1). In injection fearful participants of the BII cohort the score was highly correlated ($r_{44} = 0.61$) with the injection fear subscale of the German "Blood Injury Injection Questionnaire" [37] and in those fearful of blood or injuries the correlation with the "blood/injury self" subscale was $r_{33} = 0.70$. Furthermore, pre to post ($r_{218} = 0.68$) as well as post to follow-up fear reduction ($r_{101} = 0.65$) assessed with the 11-point scale was highly significantly correlated with the standardized fear reduction assessed with those questionnaires. This suggests that our 11-point measure validly and cohort-comprehensively assesses subjective fear evoked by the feared stimulus and sensitively reflects short-term and long-term changes following the respective intervention.

Trait Anxiety, Depressiveness and Personality Traits Related to 5-HTTLPR. Prior to conducting the treatment, individuals' trait anxiety was assessed using the trait subscale of the State-Trait Anxiety Inventory [38]. Scores range from 20 (no anxiety) to 80 (high anxiety). The trait scale has a very good reliability ($r_{tt} = 0.96$) and proven validity. We found an internal consistency (Cronbach's α) of $r = 0.92$ within our sample. To assess genotype-related personality traits prior to treatment, we used the NEO Five-Factor Inventory [39], consisting of 60 items. The instrument is well evaluated and showed sufficient reliability and validity. In our sample the internal consistency scores (Cronbach's α) ranged between 0.73 (agreeableness) and 0.87 (consciousness). Additionally we assessed subjective levels of depressiveness using the Beck Depression Inventory [40] in the BII cohort and the depression subscale of the Depression-Anxiety-Stress Scale (DASS) [41] in the spider and dental cohorts. Both are well established instruments with proven reliability and validity. In our samples we calculated Cronbach's α = 0.81 for the Beck Depression Inventory and Cronbach's α = 0.87 for the DASS depression subscale.

DNA Extraction and Genotyping

DNA was extracted from buccal swabs using the Masterpure DNA purification kit (Epicentre) following the protocol provided with the kit. The 43-base pair insertion/deletion 5-HTTLPR polymorphism was genotyped using primers and PCR conditions as previously described [42].

Statistical Analysis

We conducted 3 (genotype) × 2 (time) repeated-measures ANOVA to analyse genotype-related effects on treatment response. In a second step, we included the follow-up data and con-

Table 1. Sociodemographic and treatment variables, personality traits, and fear levels of treatment cohorts

	Total (n = 222)	Spider (n = 104)	Dental (n = 43)	BII (n = 75)	Group comparisons	Post hoc test (Bonferroni corrected)
Age, years	33.98±13.83	32.68±12.52	50.56±11.30	26.12±7.34	$F(2, 215) = 71.38$, $p < 0.001$	BII < spider < dental
Sex[a]						
Male	29 (13.1%)	11 (10.6%)	9 (20.9%)	9 (10.8%)		
Female	191 (86.0%)	91 (87.5%)	34 (79.1%)	66 (89.2%)	$\chi^2(2) = 3.13$, $p = 0.21$	
Education, years	14.46±2.94	–	14.61±2.78	14.16±3.25	$F(1, 113) = 0.60$, $p = 0.44$	–
5-HTTLPR						
LL	69 (31.4%)	34 (32.7%)	14 (32.6%)	21 (28.0%)		
LS	113 (50.5%)	54 (51.9%)	22 (51.2%)	37 (49.3%)		
SS	40 (18.2%)	16 (15.4%)	7 (16.3%)	17 (22.7%)	$\chi^2(4) = 1.77$, $p = 0.77$	–
Treated in large group	159 (71.6%)	77 (74.0%)	43 (100%)	39 (52.0%)	$\chi^2(2) = 31.54$, $p < 0.001$	Dental < BII < spider
Treated individually	63 (28.4%)	27 (26.0%)	0 (0%)	36 (48.0%)		
Post-FU interval, months	6.93±2.64	8.83±1.87	4.04±0.20	7.26±2.51	$F(2, 98) = 38.86$, $p < 0.001$	Dental < BII < spider
Related personality traits						
STAI-Trait Anxiety	40.97±10.12	40.91±10.54	–	41.05±9.58	$F(2, 174) = 0.08$, $p = 0.93$	–
NEO-Neuroticism	1.92±0.69	1.87±0.65	1.98±0.81	1.97±0.66	$F(2, 181) = 0.53$, $p = 0.59$	–
NEO-Extraversion	2.44±0.58	2.46±0.52	2.37±0.61	2.48±0.69	$F(2, 181) = 0.43$, $p = 0.65$	–
NEO-Openness	2.48±0.59	2.52±0.57	2.47±0.68	2.36±0.56	$F(2, 181) = 0.94$, $p = 0.39$	–
NEO-Agreeableness	2.74±0.48	2.77±0.48	2.70±0.47	2.71±0.51	$F(2, 181) = 0.33$, $p = 0.72$	–
NEO-Conscientiousness	2.74±0.64	2.71±0.66	2.69±0.55	2.89±0.68	$F(2, 181) = 1.34$, $p = 0.26$	–
Depression						
DASS-Depression	3.82±4.00	3.44±3.94	4.85±4.03	–	$F(2, 141) = 3.57$, $p = 0.06$	–
BDI	8.11±5.81	–	–	8.11±5.81	–	–
Fear						
Fear rating pre (0–10)	8.14±2.09	7.12±2.33	8.42±1.55	9.39±0.99	$F(2, 219) = 33.23$, $p < 0.001$	Spider < dental < BII
Reduction (pre to post)	1.88±2.16	2.07±2.22	1.62±2.14	1.77±2.08	$F(2, 211) = 0.77$, $p = 0.46$	–
Reduction (post to FU)	0.35±2.67	0.55±2.75	0.79±2.40	0.00±2.76	$F(2, 98) = 0.82$, $p = 0.44$	–

BII, blood-injury-injection; FU, follow-up; STAI, State-Trait Anxiety Inventory; DASS, Depression Anxiety Stress Scales; BDI, Beck Depression Inventory; pre, pretreatment assessment; post, posttreatment assessment. [a] Missing information on sex for two participants.

ducted 3 (genotype) × 3 (time) repeated-measures ANOVA to analyse the differential long-term course of subjective fear ratings. Huynh-Feldt correction was applied if the assumption of sphericity was violated. Post hoc group comparisons were all Bonferroni corrected. All analyses were conducted using the IBM Statistics SPSS 24 software package.

Results

Genotype frequencies of the 5-HTTLPR were comparable to other Caucasian samples [43], and no deviation from Hardy-Weinberg equilibrium was observed (p = 0.59). Genotypes were equally distributed across the 3 treatment cohorts. Forty-five percent of the participants (n = 101) returned for follow-up assessment. Dropout was equally distributed and not related to genotype ($\chi^2(2) = 0.71$). Further, there were no age-, sex-, or education-related differences or any difference concerning the delivery of treatment or dropout between genotypes (see Table 2 for results and online suppl. material for more detailed information regarding sample characteristics and completer vs. dropout comparisons; see www.karger.com/doi/10.1159/000486100 for all online suppl. material). Baseline comparisons yielded differences between SS and LL allele carriers in trait anxiety (p = 0.04) and differences on a trend level in neuroticism (p = 0.08), with higher scores in SS allele carriers on both scales. Furthermore, LL allele carriers reported higher scores in terms of agreeableness compared to both other genotypes (p = 0.01; Table 2).

The analysis of subjective fear reduction at the posttreatment time point yielded a highly significant main effect of treatment ($F(1, 204) = 123.42$, $p < 0.0001$, $\eta^2 = 0.38$). No main effect of genotype ($F(2, 204) = 0.67$, $p = 0.51$) or genotype by treatment interaction effect ($F(2, 204) = 0.66$, $p = 0.52$) was observed (see online suppl. Fig. 1).

When including the follow-up data, the main effect of treatment remained significant ($F(2, 196) = 33.26$, $p < 0.0001$, $\eta^2 = 0.25$), and a genotype by treatment interac-

Table 2. Sociodemographic and treatment variables, personality traits, and fear levels of 5-HTTLPR genotypes

	Total (n = 214)	LL (n = 66)	LS (n = 110)	SS (n = 38)	Group comparisons	Post hoc test (Bonferroni corrected)
Age, years	33.58±13.73	35.48±15.79	32.95±12.09	32.13±14.65	$F(2, 207) = 0.94$, $p = 0.39$	–
Sex[a]						
Male	27 (12.6%)	8 (12.1%)	14 (12.7%)	5 (13.2%)		
Female	185 (86.4%)	56 (84.9%)	96 (87.3%)	33 (86.8%)	$\chi^2(2) = 0.01$, $p = 0.96$	–
Education, years	14.49±2.96	14.54±3.01	14.30±2.92	14.87±3.06	$F(2, 110) = 0.31$, $p = 0.73$	–
Treated in large group	153 (71.5%)	47 (71.2%)	79 (71.8%)	27 (71.1%)	$\chi^2(2) = 0.01$, $p = 0.99$	–
Treated individually	61 (28.5%)	19 (28.8%)	31 (28.2%)	11 (28.9%)		
Returned for FU	101 (47.2%)	29 (43.9%)	54 (49.1%)	18 (47.7%)	$\chi^2(2) = 0.44$, $p = 0.80$	–
Not returned for FU	113 (52.7%)	37 (56.1%)	56 (51.9%)	20 (52.3%)		
Post-FU interval, months	6.93±2.64	6.83±2.73	7.02±2.49	7.89±2.76	$F(2, 98) = 1.01$, $p = 0.37$	–
5-HTTLPR-related personality traits						
STAI-Trait Anxiety	40.59±9.91	38.63±9.46	40.39±9.98	44.34±9.68	$F(2, 171) = 3.42$, $p = 0.04$	SS > LL
NEO-Neuroticism	1.90±0.69	1.76±0.65	1.91±0.71	2.10±0.69	$F(2, 173) = 2.51$, $p = 0.08$	SS > LL[b]
NEO-Extraversion	2.47±0.57	2.59±0.51	2.42±0.60	2.35±0.56	$F(2, 173) = 2.38$, $p = 0.10$	–
NEO-Openness	2.48±0.59	2.46±0.56	2.49±0.63	2.49±0.62	$F(2, 173) = 0.52$, $p = 0.95$	–
NEO-Agreeableness	2.75±0.48	2.90±0.37	2.69±0.47	2.61±0.63	$F(2, 173) = 4.91$, $p = 0.01$	LL > LS, SS
NEO-Conscientiousness	2.76±0.64	2.76±0.59	2.77±0.63	2.74±0.67	$F(2, 173) = 0.26$, $p = 0.98$	–
Depressiveness						
z-score	0.00±1.00	–0.11±0.83	–0.05±1.00	0.34±1.19	$F(2, 207) = 2.74$, $p = 0.07$	SS > LL[b]
Fear						
Fear rating pre (0–10)	8.12±2.11	8.23±2.07	8.18±1.91	7.74±2.68	$F(2, 211) = 0.76$, $p = 0.47$	–
Reduction (pre to post)	1.86±2.14	1.65±2.18	2.02±2.24	1.76±1.74	$F(2, 204) = 0.66$, $p = 0.52$	–
Reduction (post to FU)	0.35±2.67	1.24±2.63	0.28±2.73	–1.11±1.97	$F(2, 98) = 4.61$, $p = 0.01$	LL > SS

SS, short/short; LS, long/short; LL, long/long; FU, follow-up; STAI, State-Trait Anxiety Inventory; z-score contains the z-standardized scores of the DASS-depression subscale of the spider and dental fear cohorts and the z-standardized BDI scores of the BII cohort; pre, pretreatment assessment; post, posttreatment assessment. [a] Missing information on sex for two participants; [b] marginally significant result.

tion effect emerged ($F(4, 196) = 4.13$, $p = 0.004$, $\eta^2 = 0.08$). Post hoc trend analyses revealed that in LL allele carriers fear decreased significantly within the posttreatment-to-follow-up interval ($F(1, 28) = 6.47$, $p = 0.017$, $\eta^2 = 0.19$) whereas in heterozygous LS allele carriers it remained unchanged ($F(1, 53) = 0.56$, $p = 0.458$). In contrast, we observed a return of fear in homozygous S allele carriers indicated by a linear increasing trend ($F(1, 17) = 5.74$, $p = 0.028$, $\eta^2 = 0.25$) (Fig. 1).

As shown in Figure 1, subjective fear levels at follow-up differed significantly between genotypes ($F(2, 98) = 4.76$, $p = 0.011$), with SS allele carriers reporting higher fear compared to LS ($p = 0.026$) and LL allele carriers ($p = 0.012$). Comparisons of pre-assessment with follow-up fear levels yielded no significant change in the SS group ($F(1, 17) = 1.06$, $p = 0.32$). However, there were highly significant changes in the LS ($F(1, 53) = 36.89$, $p < 0.001$, $\eta^2 = 0.41$) and LL groups ($F(1, 28) = 37.12$, $p < 0.001$, $\eta^2 = 0.57$), indicating a total pre-assessment-to-follow-up reduction of 25.0% (LS group) and 34.5% (LL group), respectively.

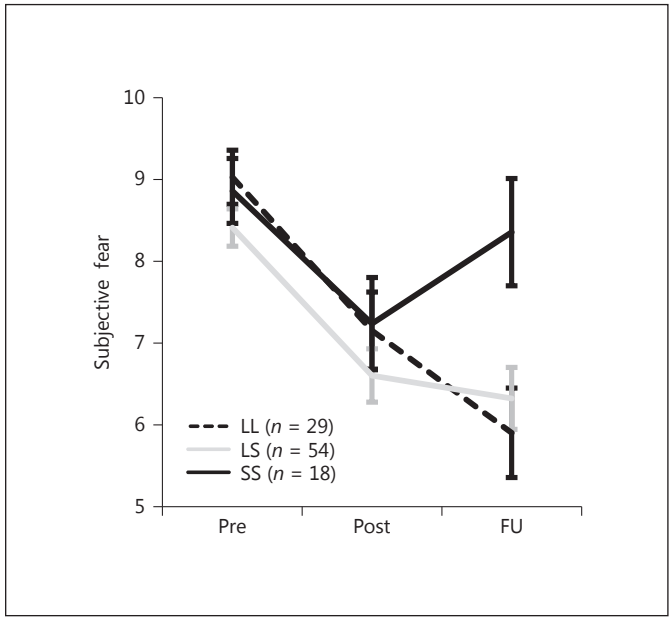

Fig. 1. Fear levels (means ± SEM) at pretreatment, posttreatment, and follow-up (FU) assessments of 5-HTTLPR genotypes.

Within the posttreatment-to-follow-up interval, 55.2% of LL allele carriers ($n = 16$), 50.0% of LS allele carriers (n = 27) but only 16.7% of SS allele carriers ($n = 3$) showed further fear reduction (follow-up < posttreatment) indicating a significant between-group difference ($\chi^2(2) = 7.57$, $p = 0.023$) (see online suppl. Fig. 2).

Discussion

We assessed differential effects of psychological treatment in homozygous LL, SS, and heterozygous 5-HTTLPR allele carriers across 3 cohorts of highly fearful individuals who all requested fear treatment. Aimed to eliminate some of the methodological problems identified in the field of therapygenetic studies [16], we applied highly standardized 1-session exposure as a treatment strategy delivered in medication-free individuals, suffering from situational fears.

Immediately after treatment, we observed a similarly strong treatment effect on fear reduction across genotype groups. At 7 months of follow-up, however, there was a strong gene × treatment interaction effect. The homozygous 5-HTTLPR SS genotype was strongly associated with a return of fear at that point. In contrast, carriers of the LL genotype displayed further improvement, and those heterozygous for 5-HTTLPR did not change from posttreatment to follow-up. This finding is consistent with a prior study conducted in posttraumatic stress disorder patients [20] reporting that individuals carrying at least 1 S allele displayed severer posttraumatic stress disorder symptoms 6 months following treatment compared to individuals homozygous for the L allele. In a study focussing on bulimia [44], the SS genotype was associated with poorer treatment outcome as well. However, opposite results have also been reported, demonstrating better therapy outcomes at the immediate posttreatment assessment [24, 25] or in the long term [21, 25] in individuals carrying the S allele compared to homozygous L allele carriers. A key difference to the present study is that the treatments applied in Eley et al. [21] and Kohen et al. [25] were not primarily based on exposure and contained a wide range of cognitive behavioural therapy and psychosocial interventions. Furthermore, they were applied to depressed individuals or children with different diagnoses across the anxiety spectrum. The parental training as part of the treatment applied in Eley et al. [21] can be seen as a direct manipulation of long-term environmental conditions, which might prove especially efficacious in those children highly susceptible for environmental conditions. However, the intervention described by Knuts et al. [24] was based on exposure in a homogeneous sample of agoraphobic individuals and therefore fairly well comparable to ours. As mentioned, they reported better outcomes in individuals with 1 or 2 copies of the S allele compared to homozygous L allele carriers at the immediate postassessment. Considering possible mechanisms underlying short- and long-term exposure treatments in light of enhanced contextual plasticity as postulated for the S allele [14] might contribute to integrate these seemingly contradictory findings.

Extinction is assumed to be the central process behind exposure therapy [45] and has been intensively investigated in laboratory fear-conditioning experiments. It is characterized as the gradual reduction of a conditioned fear response following the repeated presentation of a conditioned fear stimulus (CS) in the absence of an aversive unconditioned stimulus (UCS) [46, 47]. Several mechanisms underlying extinction have been postulated over the last few years; however, current research suggests inhibitory learning as the crucial mechanism, since it explains best why and under which conditions extinguished fear responses can reoccur [47–49]. The concept of inhibitory learning suggests that during extinction the original conditioned CS-UCS association is not erased but rather the new acquisition of a fear inhibitory CS-non-UCS association from then on competes with the original CS-UCS association, rendering it less accessible [for a detailed description, see 50]. Whether, after a delay, the new learned non-fear trace or the original fear association is retrieved refers to the amount of extinction retention. Evidence suggests that the amount of fear decrease following exposure does not predict fear levels observed at follow-up [51, see 52 for a review]. So far, research has identified mainly 3 processes that can disturb extinction recall and lead to partial or full return of fear at follow-up: spontaneous recovery, reinstatement, and renewal. Spontaneous recovery proportionally increases to the amount of time between extinction and retest [53]. Reinstatement occurs if the UCS is repeatedly presented in the extinction-to-follow-up interval [54], and renewal is likely to occur if the surrounding context between extinction and extinction recall has changed [48].

Our results as well as the existing gene-environment interaction literature on 5-HTTLPR suggest that homozygous S allele carriers might be especially vulnerable for all 3 processes due to their biologically enhanced sensitivity to contextual conditions associated with the S allele [2, 14, 15]. First, this might have increased their risk to show a return of fear due to fear renewal evoked by possible

contextual changes between extinction and retention test. Second, given that external and internal contexts dynamically develop over time, time can also be considered as a contextual factor [see 47 for more details]. Hence, the probability that extinction test and retention test contexts differ increases with the length of the test-retest interval and may vary with context sensitivity. Consequently, homozygous S allele carriers might also be more likely to experience spontaneous fear recovery. Third, in an animal experiment the reinstatement effect was shown to be highly context-dependent since it could be shown [55] that UCS presentations in a context other than extinction did not lead to fear reinstatement when rats were exposed to the CS in the extinction context.

On a neurobiological level, enhanced amygdala responsivity known to facilitate fear conditioning and fear expression has been discussed as a major neurobiological correlate of enhanced sensitivity to contextual cues in 5-HTTLPR S allele carriers [56, 57]. A clinical study in posttraumatic stress disorder patients [58] could directly demonstrate a negative correlation between hypersensitivity of the amygdala and long-term cognitive behavioural therapy outcome. Amygdala function is known to be implicated in both extinction learning and extinction recall whereas prefrontal cortex (PFC) regions appear to be key structures wielding an inhibitory influence on amygdala activity during extinction recall [59, 60]. In rats, lesions of infralimbic regions of the ventromedial (vm) PFC did not impair immediate fear extinction but led to extensive fear recovery at follow-up. Furthermore, neuronal responding of vmPFC regions to a CS was restricted to a delayed extinction test [60]. In humans, less bilateral vmPFC activation was associated with extinction retention failure [61].

Evidence resulting from animal as well as human studies reveals a strong link between serotonergic availability and altered extinction recall. For instance, a selective deficit in extinction retention as well as deviant morphology [62] and function [63] of brain structures relevant for extinction memory were both found in 5-HTT knockout mice. Consistently, altered serotonin signalling in humans carrying the risk allele of the serotonin transporter polyadenylation polymorphism (STPP/rs3813034) was associated with spontaneous fear recovery after extinction training [64]. Interestingly, all these studies reported unimpaired initial fear extinction regardless of whether conducted in mice or humans. Hartley et al. [64] therefore suggested extinction retention to be an endophenotype, mediating the effects of genetic variability in 5-HTT function on anxiety disorders and depression. Consistently, there are reports [8, 9] demonstrating a relative uncoupling between amygdala and cingulate cortex functioning in 5-HTTLPR S allele carriers that explained 30% of the observed variance in trait anxiety [8]. However, there is also a report of enhanced functional connectivity between amygdala and the vmPFC in humans carrying at least 1 S allele of the 5-HTTLPR compared to homozygous L allele carriers [65]. Considering the top-down control of the PFC repeatedly demonstrated by a parallel activity of the inhibitory vmPFC and excitatory amygdala during extinction retention [66], this has been suggested as a compensatory effort to regulate exaggerated amygdala responsivity in 5-HTTLPR S allele carriers.

We did not directly assess the amount of amygdala reactivity of our participants during exposure or retention. However, consistent to prior reports [67], we observed enhanced trait anxiety and a tendency in SS allele carriers towards enhanced neuroticism levels compared to LL allele carriers at baseline trait measures (State-Trait Anxiety Inventory and NEO Five-Factor Inventory), discussed as direct correlates of enhanced amygdala activity [57]. Interestingly, we also found relatively enhanced "agreeableness" scores in LL allele carriers. "Agreeableness" has been reported to be associated with enhanced affect regulation capacities [68] and increased prefrontal cortex activation in response to fearful faces [69]. Future research should shed light onto the extent to which this personality trait represents a beneficial factor in terms of fear extinction and affect regulation associated with the L allele of 5-HTTLPR.

Some limitations to our study need to be mentioned. Although the sample size is quite large, and the application of a highly standardized treatment across a relatively homogeneous sample will have increased the chances of finding gene by treatment effects, it has recently been suggested that genetic studies should use even larger samples [16]. We only report subjective fear ratings in individuals who, albeit expressing phobia-typical subjective fear levels, were not explicitly diagnosed for a specific phobia. Only about half of the participants returned for follow-up assessment, most likely related to the fact that participants were required to actively waive anonymity to be contacted and scheduled for a follow-up appointment. Furthermore, albeit our observations can well be integrated into the existing gene-environment interaction literature on 5-HTTLPR and current concepts regarding the return of fear, our interpretations and suggestions concerning possible underlying mechanisms remain highly speculative. This clearly restricts generalization of our re-

sults and interpretations on other fear levels and necessitates the replication of findings.

To summarize, the present study shows for the first time that 1-session exposure-based fear treatments might not be well suited for homozygous 5-HTTLPR S allele carriers, given their large return of fear at follow-up. This result might be due to enhanced context sensitivity in these individuals, increasing their vulnerability for all processes that can cause a return of extinguished fear responses. It is largely consistent with findings of enhanced context sensitivity and impaired extinction recall mediated by enhanced amygdala responsivity and altered prefrontal fear inhibition associated with the 5-HTTLPR. If replicable, the 5-HTTLPR genotype might represent a biomarker for the success of exposure-based 1-session fear treatments. Considering 1-session treatments have been recommended as the treatment of choice in phobia treatments [70], the clinical relevance of our finding is rather high. However, a meta-analytic study [71] has called the recommendation of 1-session treatments into question by showing less long-term improvement following 1-session compared to multisession treatments. This suggests that the phenotype-related drawback in long-term responding to exposure strategies we observed in S allele carriers might especially have an impact on 1-session treatments and decreases when multisession formats are used. Future research systematically varying the lengths and context of extinction and extinction recall of exposure-based therapies might answer the question whether our results were really due to enhanced context-related fear renewal in homozygous 5-HTTLPR S allele carriers. Furthermore, it would be interesting to know whether the implementation of tools known to optimize the success of exposure treatments [50, 52], e.g. a greater variability in exposure or retrieval cues may compensate for this. Our results also suggest that individuals homozygous for the L allele are likely to profit from very short and simple exposure strategies potentially due to their stronger robustness against context-related processes that might lead to a return of fear.

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Disclosure Statement

The authors report no biomedical financial interests or potential conflicts of interest.

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