

# Human fear reconsolidation and allelic differences in serotonergic and dopaminergic genes

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**Fear memory persistence, central for the development and maintenance of anxiety disorders, is partially genetically controlled. Recently, consolidation and reconsolidation processes have been reported to affect fear memory stability and integrity. This study explored the impact of reconsolidation processes and genetic make-up on fear reacquisition by manipulating reconsolidation, using extinction performed outside or inside a reconsolidation interval. Reacquisition measured by skin conductance responses was stronger in individuals that extinguished outside (6 h) than inside (10 min) the reconsolidation interval. However, the effect was predominantly present in val/val homozygotes of the functional val158met polymorphism of the catechol O-methyltransferase (COMT) enzyme and in short-allele carriers of the serotonin-transporter length 5-HTTLPR polymorphism. These results demonstrate that reconsolidation of human fear memory is influenced by dopamine and serotonin-related genes.**

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## Introduction

The acquisition and extinction of fear memories are crucial for the aetiology and symptomatology of anxiety disorders like post-traumatic stress disorder.<sup>1,2</sup> Recently, it has been demonstrated that consolidation and reconsolidation processes affect stability and durability of fear memories. A memory is initially labile and consolidate over time to a more stable form.<sup>3</sup> It is hypothesized that when a fear memory is reactivated, it is again transformed to a labile state, and the following stabilization is termed reconsolidation. Moreover, it is argued that during reconsolidation, memories can be updated to incorporate new information. Previous studies confirm that pharmacologically disrupted reconsolidation processes affect behaviour both in animals<sup>4</sup> and humans.<sup>5–7</sup> Most reconsolidation studies have used fear conditioning, the process where a fear memory is formed by repeated pairing of a neutral stimulus with an aversive unconditioned stimulus (UCS), subsequently leading to an aversive reaction to the neutral stimulus. Thus, the neutral stimulus becomes a conditioned stimulus (CS+). The conditioned reactions to CS+ can be weakened or abolished with extinction training, that is, by exposure to CS+ without UCS, but generally return with the passage of time (spontaneous recovery). Using extinction training during the reconsolidation phase in rodents, it has been demonstrated that reconsolidation of an activated fear memory can be influenced also non-pharmacologically in a way that permanently attenuate the fear memory.<sup>8</sup> In this vein, Schiller *et al.*<sup>9</sup> concluded that the return of fear reactions in humans was weakened when a previously reinforced stimulus was presented 10 min, but not 6 h before extinction training, that is inside, but not outside, of the reconsolidation interval.

In Schiller study,<sup>9</sup> subjects completed a fear-conditioning procedure to experimentally induce a fear memory. Twenty-four

hours after the initial conditioning session, subject returned and the fear memory was activated by a 2-min presentation of the CS+ in the absence of UCS. One group received extinction training 10 min after the fear memory activation and hence, early during the reconsolidation process. The other group received extinction training 6 h after the fear memory activation, hence after completion of reconsolidation. Another 24 h later, spontaneous recovery of fear was tested in a second extinction session. The results showed that the group given extinction training during the reconsolidation interval (i.e., 10 min after memory activation) exhibited less fear, as reflected by skin conductance response (SCR), when exposed to CS+, than the group that received extinction training 6 h after the memory activation. The effect of the manipulation lingered even after 1 year when the return of fear was tested with reinstatement, a process where extinguished responses reappear to CS+ after unpaired UCS presentations.

Anxiety disorders wax and wane: In post-traumatic stress disorder, for example, cues associated with trauma may repeatedly reactivate symptoms instigated by a single traumatic event. In addition, the remission rate after treatment is incomplete, because symptom reactivation occurs.<sup>10</sup> Hence, it is clinically motivated to study if reconsolidation processes influence not only the subsequent expression, but also the reacquisition of fear. In fear conditioning, reacquisition is a second session of fear conditioning performed to investigate how earlier manipulations of the memory affects a relapse into renewed fear expression for the conditioned stimulus.

Fear conditionability is a heritable characteristic<sup>11</sup> influenced by individual differences in serotonin- and dopamine-related polymorphisms. In particular, short-allele (s) carriers

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of the serotonin-transporter gene-linked polymorphic region (5-HTTLPR) display stronger acquisition and slower extinction compared with long-allele (l) homozygotes.<sup>12–14</sup> Moreover, 5-HTTLPR has been associated with anxiety-related personality traits,<sup>15</sup> development of psychopathology<sup>16</sup> and enhanced reactivity of the amygdala,<sup>17</sup> a key structure for fear conditioning,<sup>18</sup> suggesting a possible link between fear memory processes, psychopathology and serotonergic neurotransmission.

Animal experiments provide evidence that dopamine also impacts fear acquisition,<sup>19</sup> extinction<sup>20</sup> and consolidation.<sup>21</sup> Catechol-O-methyltransferase (COMT) is an enzyme vital to the elimination of dopamine in prefrontal areas and the functional polymorphism val158met (rs4680), where the val allele is associated with higher COMT activity,<sup>22</sup> enables an indirect way to study dopaminergic effects throughout the brain. Two studies have related fear conditioning to the COMT val158met genotype in humans, but with mixed findings. Lonsdorf *et al.*<sup>14</sup> noted slower extinction in met homozygotes, whereas Razcka *et al.*<sup>23</sup> noted stronger reacquisition in a val/met-group, but only in the presence of a certain dopamine transporter (DAT1) polymorphism.

As monoaminergic genetic polymorphisms modulate fear conditioning and as reconsolidation influence fear expression, the present study investigated if serotonin- and dopamine-related polymorphisms also affect reconsolidation. To these aims, the present study utilized the non-pharmacological human reconsolidation disruption effect reported by Schiller *et al.*<sup>9</sup> to study reacquisition of human fear indexed by SCRs. The *a priori* hypotheses were that extinction inside as compared to outside the reconsolidation interval should compromise reacquisition and that monoaminergic genes would modulate the effect. In addition, a previously reported<sup>5,9</sup> reconsolidation effect for reinstatement was predicted.

## Materials and methods

**Participants.** A total of 66 participants (38 females, age: mean  $\pm$  s.d. = 24.6  $\pm$  4.0) recruited by public advertisements were randomly assigned to one of two groups. In one group, extinction was given inside (10 min), and in the other group, outside (6 h) the reconsolidation interval after a 2-min fear memory reminder. Two subjects were excluded due to technical difficulties. Subjects received SEK 400 for participation.

## Materials

**Stimuli.** Stimuli were projected on a 17"-computer screen using E-prime 2.0. (Psychology Software Tools, Pittsburgh, PA, USA) and consisted of a photo of a neutral environment containing a lamp that was lit either in red or blue. One colour was paired with UCS and became the CS+, whereas the other colour was unpaired (CS-). The CS colour was counterbalanced across subjects. Each stimulus was shown for 6 s with 14-s intervals between trials when the environment was displayed with the lamp unlit. A 500-ms mild electric shock was delivered 250 ms before the CS+ ended.

**Psychophysiology equipment.** The electric shocks were administered by PsychLabs SHK 1 pain stimulator (Psychlab, Cambridge, MA, USA) and had a maximum strength of 5 mA. Electrodes (EL124), prepared with electrolyte medium to facilitate shock conduction were attached with surgical tape to the dorsal right-lower arm of the participants. The SCRs were measured in microsiemens with the Psychlab 24-bit Skin Conductance System, using two 8-mm Ag/AgCl electrodes filled with isotonic electrolyte gel attached to the hypothenar eminence of the left hand.<sup>24</sup>

**Genotyping.** The 5-HTTLPR polymorphism in the promoter of the serotonin transporter gene was amplified using the PCR primers 5'-ATGCCAGCACCTAACCCTAATGT-3' and 5'-GGACCGCAAGGTGGGCGGGA-3' yielding a product of 419 bp for the 16-repeat allele (l) and 375 bp for the 14-repeat allele (s). After an initial denaturation step of 15 min at 95 °C, 35 cycles were performed, including 30 s at 95 °C, 30 s at 66 °C, and an elongation step at 72 °C for 1 min. Genotyping was performed on 2% agarose gels. DNA was visualized by ethidium bromide. Short-allele carriers ( $n=46$ ) were grouped together and later compared with homozygotes of the long allele ( $n=16$ ).<sup>15,17</sup> For two subjects, the gene analysis failed to extract the 5-HTTLPR genotype.

The val/met polymorphism in the gene encoding COMT was analysed using the ABI 7900HT instrument with a TaqMan assay in accordance with the protocol from the manufacturer (Applied Biosystems, Foster City, CA, USA). Given the functionality of the polymorphism,<sup>25</sup> homozygotes of the val allele ( $n=15$ ) were grouped together and later compared with carriers of the met allele ( $n=46$ ). Gene analysis failed for three of the subjects.

## Procedure

**Day 1.** Participants signed informed consent and determined the strength of the unconditioned electric shock by following the instruction that it should be unpleasant, but endurable. They then underwent an acquisition session in which 16 CS+ and 16 CS- were presented in a random order, with the limitation that no stimulus type was repeated more than two times in a row. CS+ was always paired with UCS. After the session, subjects were asked if they identified a stimulus contingency and if so, asked to describe it. They rated the experienced distress of the experimental procedure on a scale from 1 to 10, with one indicating 'not distressful' and 10 denoting 'very distressful'.

**Day 2.** Twenty-four hours after acquisition, the participants returned, electrodes were attached in the same way and the CS+ reminder was shown for 2 min to facilitate memory activation. One group then received extinction 10 min after the memory activation (the 10-min group), whereas the other group received extinction after 6 h (the 6-h group). Extinction consisted of eight presentations of CS+ and CS- each. Shock electrodes were applied, but no shock was administered.

**Day 3.** Twenty-four hours after completing extinction, participants returned for reinstatement and reacquisition. Reinstatement consisted of four presentations of CS+ and CS- each, with four pseudorandom shocks administered within inter-trial intervals of about 30 s. Reacquisition consisted of four presentations of CS+ and CS- each. CS+ was always, and CS- never paired with a shock. Regrettably, due to a programming error, reinstatement data were compromised and could not be retrieved for all participants. Participants left a saliva sample for DNA analysis, using an Oragene DNA Genotek saliva sample container (DNA Genotek, Ottawa, Ontario, Canada).

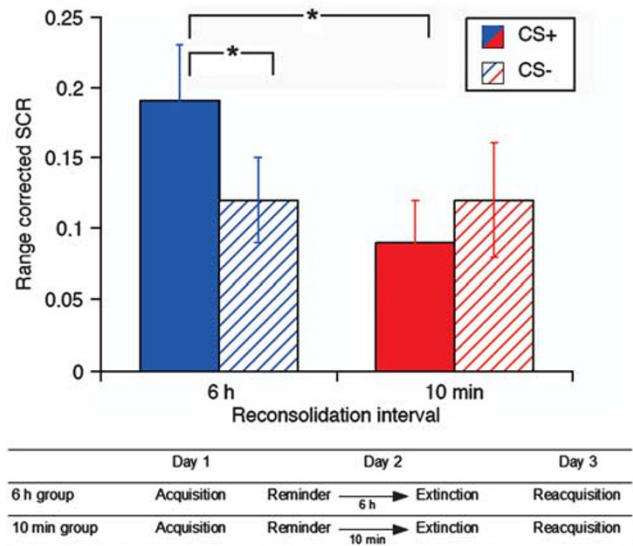
**Analyses.** Stimulus-induced SCRs were calculated by taking the maximum of the skin conductance deflection in the 1.5–5.75-s interval after stimulus onset subtracted by the immediate preceding baseline.<sup>26</sup> Thus, for CS+, the endpoint of the scoring interval coincided with UCS onset. All SCRs were range-corrected by dividing each reaction for every individual with that individual's maximum deflection (irrespective of stimuli and experimental phase).<sup>27</sup>

CS+ ( $0.23 \pm 0.02$ ) elicited greater responses than CS- ( $0.13 \pm 0.01$ );  $t(63) = 6.25$ ,  $P < 1 \times 10^{-5}$ . However, because data from participants that do not acquire a fear memory cannot be used to study reconsolidation processes, these subjects were excluded from further analyses. To distinguish those who did not acquire a conditioned reaction from those who did, every individual's 16 reactions to CS+ and CS- during acquisition were ordered in pairs, and 16 delta scores were calculated as follows: CS+<sub>1</sub>-CS-<sub>1</sub>, CS+<sub>2</sub>-CS-<sub>2</sub>...CS+<sub>16</sub>-CS-<sub>16</sub>. The average delta scores were tested against zero, using a one-tailed *t*-test with a statistical cutoff of  $P < 0.10$  as the within-subject conditioning criterion.

To evaluate fear conditioning, extinction, reinstatement and reacquisition, mean values of all CS+ and CS- trials, as well as a delta score (CS+ minus CS-) were calculated for each experimental phase (acquisition, extinction, reinstatement and reacquisition) and individual, respectively. These values were used in further analyses.

## Results

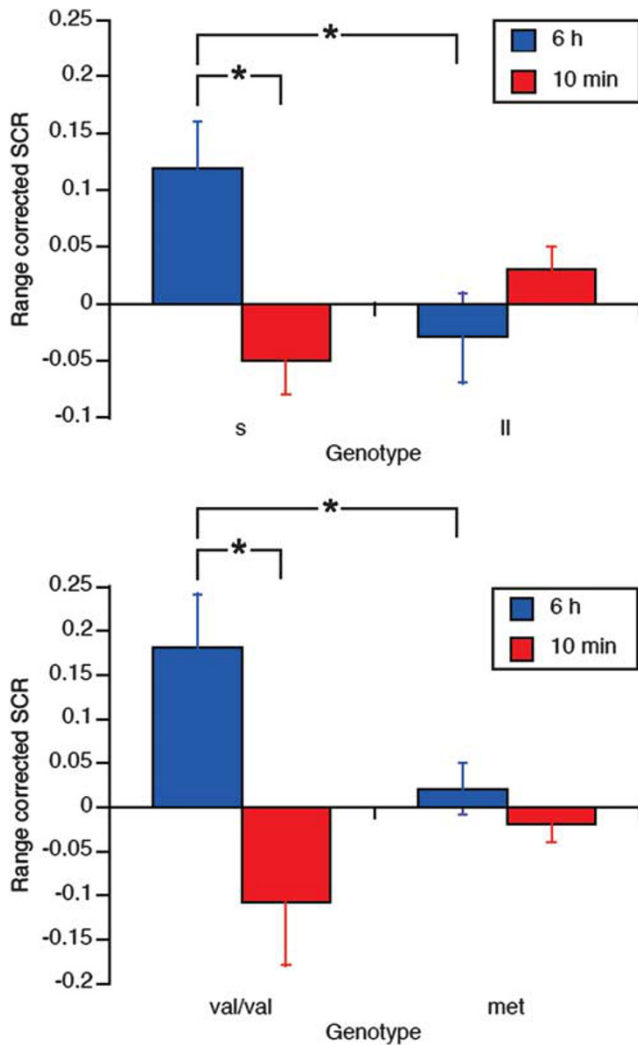
**Reacquisition.** During reacquisition, the 6-h group ( $n = 15$ ) discriminated CS+ from CS-,  $t(14) = 2.18$ ,  $P = 0.05$ , demonstrating relearning, whereas the 10-min group ( $n = 18$ ) did not,  $t(17) = -1.42$ ,  $P = 0.17$ , reflecting the absence of relearning, together resulting in a significant group (6 h vs 10 min)  $\times$  stimulus (CS+ vs CS-) interaction ( $F(1,31) = 7.15$ ,  $P = 0.01$ ; see Figure 1). Moreover, the reactions to CS+ were stronger in the 6-h group than the 10-min group,  $t(31) = 1.94$ ,  $P = 0.03$ , whereas the reactions to CS- were not,  $t(31) = 0.01$ ,  $P = 0.99$ . The two groups did not differ in acquisition (CS+ minus CS-)  $t(31) = 0.23$ ,  $P = 0.82$ , extinction (CS+ minus CS-)  $t(31) = 0.30$ ,  $P = 0.76$ , or max SCR  $t(31) = -0.36$ ,  $P = 0.72$  (6-h group mean  $\pm$  s.e.m. =  $0.63 \pm 0.14$   $\mu$ s; 10-min group mean  $\pm$  s.e.m. =  $0.69 \pm 0.11$   $\mu$ s). See Supplementary Table 1 for acquisition, extinction and reacquisition data and Supplementary Table 2 for an analysis of variance (ANOVA) summary.



**Figure 1** Extinction during reconsolidation attenuates reacquisition of fear. Mean range-corrected skin conductance responses (SCR) to the reinforced (CS+) and non-reinforced (CS-) cue during reacquisition day 3. Significant discrimination was evident in the 6-h group that extinguished outside of the reconsolidation interval, but not in the 10-min group that extinguished inside the reconsolidation interval, resulting in a significant group (6 h vs 10 min)  $\times$  stimuli (CS+ vs CS-) interaction (top panel). Error bars are s.e.m. Asterisks indicate significant differences. Experimental design and timeline (bottom panel).

To evaluate the gene  $\times$  group interaction, separate ANOVAs were performed for 5-HTTLPR and COMT, respectively, revealing gene (s vs ll, or val/val vs met)  $\times$  group (6 h vs 10 min) interactions both for 5-HTTLPR  $F(1,28) = 10.77$ ,  $P = 0.003$ , and COMT  $F(1,28) = 10.08$ ,  $P = 0.004$ . Follow-up *t*-tests for 5-HTTLPR revealed that short-allele carriers extinguishing outside compared with inside the reconsolidation interval demonstrated stronger reacquisition,  $t(21) = 4.07$ ,  $P < 0.001$ , whereas long-allele homozygotes did not,  $t(7) = -1.58$ ,  $P = 0.16$ . Moreover, within the 6-h group, short-allele carriers displayed reacquisition than long-allele homozygotes,  $t(12) = 2.54$ ,  $P = 0.03$  (see Figure 2 top panel, Supplementary Tables 3 and 4 for data summaries and Supplementary Table 5 for an ANOVA summary). Similarly, follow-up *t*-tests regarding the val158-met COMT polymorphism revealed that val/val homozygotes, which extinguished outside compared with inside the reconsolidation interval demonstrated stronger reacquisition,  $t(6) = 3.03$ ,  $P = 0.02$ , whereas met carriers did not,  $t(22) = 1.00$ ,  $P = 0.33$ . Within the 6-h group, val/val homozygotes displayed stronger acquisition than the met carriers,  $t(13) = 3.00$ ,  $P = 0.01$  (see Figure 2 bottom panel, Supplementary Tables 6 and 7 for data summaries and Supplementary Table 8 for an ANOVA summary).

Regarding the 5-HTTLPR groups, short-allele carriers ( $n = 23$ ) and long-allele homozygotes ( $n = 9$ ) did not differ in acquisition,  $t(30) = 1.10$ ,  $P = 0.28$  (Supplementary Tables 3 and 4), but short-allele carriers displayed increased resistance to extinction as compared with the ll homozygotes,  $t(30) = 3.87$ ,  $P < 0.001$ . To explore if extinction differences mediated the reconsolidation effect, a group (6 h vs



**Figure 2** The reconsolidation effect on reacquisition is modulated by genes. Mean differential skin conductance delta scores (CS+ minus CS-) during reacquisition of fear after extinction inside (10 min) and outside of (6 h) the reconsolidation interval in short allele carriers (s) and long-allele (ll) homozygotes of the serotonin-transporter length 5-HTTLPR polymorphism (top panel), and the val/val homozygotes and met carriers of the functional val158met polymorphism of the catechol O-methyltransferase (COMT) enzyme (bottom panel). Error bars are s.e.m. Asterisks indicate significant differences.

10 min)  $\times$  5-HTTLPR (s vs ll) analysis of covariance with extinction strength (CS+ minus CS-) as the covariate was performed. The group  $\times$  5-HTTLPR interaction effect was still significant,  $F(1,27) = 10.31$ ,  $P = 0.003$ , suggesting that extinction is unrelated to the reconsolidation effect (Supplementary Table 9).

Regarding the val158met COMT polymorphism groups, there was a trend towards better acquisition in the val/val homozygotes ( $n = 8$ ) as compared with the met carriers ( $n = 24$ ),  $t(30) = -1.88$ ,  $P = 0.07$ , but no difference in extinction,  $t(30) = -0.57$ ,  $P = 0.57$  (Supplementary Tables 7 and 8). To explore if the trend towards better acquisition among the val/val homozygotes affected the reconsolidation effect, a group (6 h vs 10 min)  $\times$  COMT (val/val vs met) analysis of covariance with acquisition (CS+ minus CS-) as the

covariate was performed. The Group  $\times$  COMT interaction was still significant,  $F(1,27) = 9.50$ ,  $P = 0.005$ , suggesting that acquisition strength is unrelated to the reconsolidation effect (Supplementary Table 10). There were not enough subjects to perform a 5-HTTLPR  $\times$  COMT-polymorphism ANOVA due to the genotype partition over subjects (Supplementary Table 11).

**Reinstatement.** Because of a programming error, the reinstatement data were compromised for most subjects. However, data retrieved from a minority of subjects revealed a trend towards a Group effect for delta scores (CS+ minus CS-),  $t(9) = 1.42$ , ( $P = 0.09$  one-tailed), suggesting that the 6-h group displayed more persistent fear memory than the 10-min group. This effect was mediated by CS+ responsivity, because the groups differed in response to CS+  $t(9) = 1.77$ , ( $P = 0.05$  one-tailed), but not CS-  $t(9) = 0.17$ ,  $P = 0.87$  (Supplementary Table 12). There were too few subjects for gene effects to be evaluated.

All principal results reported for range-corrected SCRs remained significant, also using untransformed data. A total of 62 out of the 64 subjects who completed acquisition reported contingency awareness, and as so few failed to report this, no comparisons between contingency aware and unaware subjects were performed. Accompanying differences in shock strength or distress ratings ( $P_s > 0.60$ ; see Supplementary Table 13) were not demonstrated for any of the comparisons reported above (6 h vs 10 min, s vs ll, and val/val vs met). Participants that did acquire conditioning were not different with aspect to genetic make-up from those that did not (Supplementary Table 14).

## Discussion

The present study demonstrates that reconsolidation disruption not only affect spontaneous recovery and reinstatement of fear as previously reported,<sup>9</sup> but also reacquisition, and that genetic make-up modulate the reconsolidation effect. Carriers of the short allele (but not the ll-homozygotes) of the serotonin-transporter length polymorphism (5-HTTLPR) and homozygotes of the val allele (but not met carriers) in the dopamine-related COMT val158met polymorphism demonstrated enhanced reacquisition after extinction outside, but not inside of, the reconsolidation window. This indicates that allelic differences modulate fear memory reconsolidation. Carriers of the met allele and long-allele homozygotes did not display reacquisition regardless of reconsolidation conditions, suggesting that different allele carriers may have different reconsolidation windows. Theoretically, it is also possible that long-allele and met alleles are associated with enhanced extinction retention. However, analyses evaluating the effect of extinction as related to reacquisition does not support that extinction differences are mediating the effect of reconsolidation disruption. This pattern indicates that allelic differences modulate fear memory reconsolidation in a complex way. Interestingly, the polymorphisms involved are also linked to fear conditioning,<sup>13,14</sup> as well as psychiatric disorders of the affective spectrum,<sup>28</sup> suggesting a possible genetic link between reconsolidation processes, fear conditioning and psychopathology.

In addition to the reconsolidation effect on reacquisition, 5-HTTLPR short-allele carriers demonstrated slower extinction than the long-allele homozygotes. This is consistent with earlier studies reporting that short-allele carriers have delayed extinction.<sup>12–14</sup> The effect of the reconsolidation manipulation was evident in the short-allele carriers, but not in the long-allele homozygotes. A previous cognitive behavioural treatment study of the post-traumatic stress disorder demonstrated better treatment effect in long-allele homozygotes as compared with the short-allele carriers.<sup>29</sup> The present findings suggests that a joint combination of retarded extinction and enhanced renewal of fear in subjects carrying the short-allele may be responsible for the blunted treatment response.

Possible molecular mechanisms underlying the 5-HTTLPR effect include structural nervous-system changes during neonatal neural development,<sup>30</sup> reflecting differences in grey matter volume, as well as altered functional connectivity of important structures in the emotional circuitry<sup>31,32</sup> and differences in the amount of extracellular serotonin between short-allele and long-allele carriers, possibly affecting 5HT1A- or 5HT6-receptors that have both been tied to memory consolidation processes.<sup>33–35</sup> However, studies of whether 5-HTTLPR short-allele carriers actually have more or less extracellular serotonin *in vivo* have yielded mixed results.<sup>36–38</sup>

Dopamine seems vital for the acquisition of fear conditioning. For instance, dopamine is required in the nucleus accumbens and the basolateral amygdala for the formation of long-term fear memories,<sup>19</sup> presumably because consolidation processes require dopamine.<sup>21</sup> In the present study, the influence of the reconsolidation manipulation on reacquisition was evident for val/val homozygotes, but not for the met carriers. Thus, val/val homozygotes maintain and update fear memories more effectively than met carriers supporting dopaminergic modulation of reconsolidation. The val/val homozygotes have an increased D1-receptor availability, likely resulting from the D1-receptor upregulation caused by chronic low levels of dopamine.<sup>25,39</sup> Both D1 and D2 receptors have been associated with fear memory consolidation.<sup>40,41</sup> However, the COMT polymorphism does not seem to alter cortical or striatal dopamine D2 receptor availability *in vivo*,<sup>42</sup> suggesting that D1-receptor activity is a putative modulator of reconsolidation.

Moreover, because amygdala reactivity has been associated both with fear conditionability<sup>43</sup> and a post-traumatic stress disorder diagnosis,<sup>44</sup> and as both the 5-HTTLPR<sup>17</sup> and the COMT polymorphism<sup>45–48</sup> have been associated with amygdala activation, there may be a link between the amygdala reactivity and the observed reconsolidation effects.

There are some limitations to the present study. First, reinstatement data were compromised and could only be analysed for a minority of the participants. Second, as most of the homozygotes of the COMT val allele appeared among the 5-HTTLPR short-allele carriers, it is hard to disentangle the effect of one genotype from the other. However, as the 5-HTTLPR, but not the COMT, polymorphism affected extinction, and COMT, but not 5-HTTLPR, tended to affect acquisition, there is reason to believe that the genetic influence from the two polymorphisms stem from different molecular mechanisms. Finally, whether reacquisition is a process in which a new memory is formed, or a renewal of the original memory, cannot be determined here. Nevertheless,

our results indicate that both the lasting expression of the original memory and renewal of fear through relearning are affected by reconsolidation processes.

In conclusion, this study demonstrates that human memory reconsolidation processes are influenced by serotonin and dopamine related genes.

### Conflict of interest

The authors declare no conflict of interest.

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