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Secondary extinction reduces reinstatement of threat expectancy and conditioned skin conductance responses in human fear conditioning

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ABSTRACT

Background and objectives: Secondary extinction refers to the phenomenon that extinction of one conditioned stimulus (CS) results in the reduction of conditioned responses for other CSs conditioned with the same unconditioned stimulus (US). Previous research with rats has demonstrated that secondary extinction can interfere with the return of conditioned fear after a reinstatement manipulation. Here we investigated this phenomenon in two pre-registered studies in humans.

Method: In both experiments, distinct CSs were paired with an electrical stimulation. Next, conditioned reactions to both CSs were extinguished and thereafter reinstated through the administration of three unsignaled electrical stimulations. Crucially, before participants continued with the reinstatement test, half of the participants received secondary extinction trials whereas the other half did not receive these trials.

Results: Our results indicate that secondary extinction reduced reinstatement of threat expectancies and skin conductance responses, but the effect on skin conductance was only found in the second experiment.

Limitations: The studies were conducted in a laboratory setting with healthy students. Additional research will be required to determine the feasibility of applying secondary extinction in a (sub)clinical context.

Conclusions: To our knowledge, this is the first demonstration of secondary extinction and its effect on reinstatement of conditioned fear in humans. We relate our findings to the earlier research with rats and discuss their relevance for exposure therapy.

1. Introduction

Conditioning is a well-established procedure in which a conditioned stimulus (CS) is paired repeatedly with a biologically significant unconditioned stimulus (US). Due to these pairings, the CS comes to elicit conditioned responses (CRs). When the CS is repeatedly presented without the US, CRs typically reduce – which is referred to as extinction. These processes are ubiquitous behavioral phenomena that are found in nearly all animals. Studying these basic processes has contributed considerably to the understanding of (pathological) human and non-human behavior, such as preferences (De Houwer, Thomas, & Baeyens, 2001), fear (Rachman, 1991) and addictions (O'Brien, 1976).

A related process that has received relatively little empirical evaluation is secondary extinction. Secondary extinction refers to the situation in which two (or more) CSs are conditioned with one US, and extinction of one CS attenuates CRs to the other CS that has not undergone extinction (Vurbic & Bouton, 2011). Secondary extinction was previously observed by Pavlov and his associates in their experiments on appetitive conditioning with dogs (Pavlov, 1927). Pavlov conditioned dogs with three distinct CSs (a buzzer, a metronome pulse and a tactile stimulus) that were paired a US that elicited salivation. Following conditioning, CRs to the metronome were extinguished by presenting the metronome without the US. Interestingly, this also reduced CRs to the CSs that had not undergone extinction.[1] These early findings were confirmed in studies that investigated conditioned suppression with rats using fear conditioning (Vurbic & Bouton, 2011). In these studies, rats were conditioned with an auditory (a tone) and a visual (a flashing light) CS that were paired with a US (an electric foot shock). Through these conditioning trials, presentation of the CSs reduced the rats' instrumental behavior to obtain food pellets by pressing a lever (i.e., conditioned suppression), which is considered indicative of acquired fear. Importantly, and in line with Pavlov's earlier work, these studies demonstrated that extinction of fear with one of the CSs (partly) transferred to the unextinguished CS.

Another important finding relating to secondary extinction is that it can

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[1] The use of perceptually distinct CSs excludes an explanation in terms of simple perceptual generalization of extinction effects (Vervliet et al., 2005).

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interfere with reinstatement of conditioned fear (i.e., return of CRs after extinction through the unpaired presentation of the US). Specifically, Rescorla and Cunningham (1977; 1978) conditioned rats by pairing two distinct CSs (CS1: a flashing light, CS2: a 1800-Hz tone) with a footshock. Then, CRs to both CSs were extinguished, after which CRs were reinstated by the presentation of four unsignaled foot shocks. Crucially, following the unsignaled shocks, one group received two unreinforced CS1 presentations followed by two unreinforced CS2 presentations, while another group only received two unreinforced CS2 presentations (unreinforced CS1 presentations were replaced by a waiting period). Reinstatement of fear to the CS2 was attenuated in the group that was first exposed to CS1, suggesting that secondary (re-) extinction interfered with fear reinstatement to CS2.[2] Similar results were obtained by Vurbic and Bouton (2011) for renewal of conditioned fear (i.e., the return of CRs after extinction through a context change). These results are of particular interest from a behavioral therapeutic perspective because reinstatement and renewal are thought to be important underlying mechanisms for relapse after exposure therapy (Bouton, 2002). Hence, the finding that secondary extinction interferes with reinstatement and renewal of conditioned fear points to new potential behavioral interventions that may attenuate the return of fear (such as, for instance, brief occasional exposure sessions to reduce relapse after exposure therapy).

Despite these reports on secondary extinction and the potential theoretical and clinical relevance, only a few studies have investigated this phenomenon. To our knowledge, no studies have been conducted with humans as participants. Therefore, the aim of the current experiments was to replicate these secondary extinction effects in humans and, particularly, to investigate whether secondary extinction can reduce reinstatement of conditioned fear.

We also assessed the role of stimulus equivalence in our experiments. We define stimulus equivalence as interchangeability of two CSs as a predictor for the US (for a more technical and extensive definition of stimulus equivalence see Barnes-Holmes, Barnes-Holmes, Smeets, Cullinan, & Leader, 2004). Vurbic and Bouton (2011) demonstrated that different CSs should be presented in an intermixed fashion during conditioning to obtain the secondary extinction effect. They interpreted this finding as indicating that rats learned to associate the two CSs, which allowed for the generalization of extinction between the two CSs. Indeed, other studies have shown that trained stimulus equivalence can allow for the generalization of acquired fear and extinction between cues (e.g., Dougher, Augustson, Markham, Greenway, & Wulfert, 1994; Honey & Hall, 1989). However, mere intermixing of trials may not be sufficient to learn the equivalence between CSs. Indeed, even for humans, learning stimulus equivalence often requires extensive training (see Barnes-Holmes et al., 2004). Therefore, to measure perceived stimulus equivalence we explicitly asked participants at the end of our studies whether they thought that the non-reinforcement of one CS would indicate the non-reinforcement of the other CS. We expected that secondary extinction would be particularly pronounced for participants answered yes to this question.

2. Experiment 1

2.1. Pre-registration

The power calculation, sample size, design, procedure and data analyses steps were pre-registered on the Open Science Framework prior to data collection (https://osf.io/c3dtn/).

[2] In a strict sense, the procedure employed by Rescorla and Cunningham (1977) cannot be considered to be secondary extinction because both CSs have undergone extinction. In fact, Rescorla and Cunningham (1977) did not refer to the term secondary extinction in their paper, but argue that their findings indicate that the non-associative US representation is destructed through extinction. Their study was later referred to as an example of secondary extinction by Vurbic and Bouton (2011). Strictly speaking, the procedure of Rescorla and Cunningham (1977) could be referred to as secondary re-extinction.

2.2. Participants

Sixty students (43 women) from Utrecht University participated in exchange for €4 or course credit. Participants were recruited through flyers and posters on campus and were screened for self-reported physical and mental health. Trait anxiety level of the participants was determined with the Dutch translation of the State-Trait Anxiety Inventory – trait version (STAI-T, range: 20–80; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983; van der Ploeg, Defares, & Spielberger, 2000). All participants completed an informed consent form and were instructed that they could discontinue the experiment at any point without any negative consequences. The procedure of this study was approved by the ethics committee of the Faculty of Social and Behavioral Science at Utrecht University (FETC16-054). Detailed demographic information about the participants in each of the conditions of the experiment can be found in Table 1.

2.3. Material

2.3.1. Apparatus

The experiment was programmed in Inquisit and was run on a HP Z230 desktop computer running Windows 8.1 Pro. The electrical simulation was generated with a Coulbourn Transcutaneous Aversive Finger Stimulator. Skin conductance was measured using a Biosemi bioamplifier and two Biosemi GSR electrodes filled with Signa electrode gel. Skin conductance data were collected with Actiview and further analyzed with Brainvision Analyzer 2.0.

2.3.2. Stimuli

The unconditioned stimulus was a 1000-ms electrical stimulation administered through two electrodes attached to the index and middle finger of the right hand. The intensity of this stimulus could vary between 0.2 and 4 mA and was individually set for each participant with a work-up procedure (see the Procedure section). As in the experiments by Rescorla and Cunningham (1977; 1978) and Vurbic and Bouton (2011) we used a visual and an auditory CS. These were a blue square (300 by 300 pixels) presented on a 23-inch screen with a resolution of 1920 by 1080 pixels and a 500-Hz tone (65 dB) binaurally presented for 8 s through Sennheiser headphones.

2.4. Design

Using alternating allocation, participants were assigned to one of the two conditions. All participants went through the same procedure until the reinstatement manipulation. After this manipulation, participants in the control group were first subjected to a brief waiting period, after which they were exposed to four trials of the CS2 (counterbalanced over participants either the square or tone). Participants in the secondary extinction (SE) group were first presented with the CS1 in a secondary extinction trial (also counterbalanced as the square or tone, orthogonal to the counterbalancing of CS2), and were then exposed to four trials of the CS2. The number of trials in the different phases of our experiment correspond with the number of sessions in the acquisition, extinction and secondary extinction intervention phases of the first experiment of Rescorla and Cunningham (1977). See Table 2 for an overview of the design of the experiment.

2.5. Procedure

2.5.1. Startup and work-up procedure

Upon arrival in the lab, participants washed their hands and were then asked to read the information letter about the experiment, provide informed consent and complete the STAI-T. Next, skin conductance and shock electrodes were attached. Participants were then lead through a work-up procedure in which the US intensity was determined. They were asked to select an intensity level that they found unpleasant but tolerable. To operationalize the intensity, participants were asked to score the intensity of the US on a 0 to 10 scale (ranging from 0 = *no pain at all* to 10 = *maximum level*

Table 1
Demographic information of the participants in Experiment 1.

	Age	Sex distribution	STAI-T	Electric stimulus intensity (mA)	Electric stimulus pain rating
Control (n = 31)	21.45 (1.65)	9 males/22 females	34.90 (6.39)	2.40 (1.09)	7.80 (0.72)
SE (n = 29)	21.45 (1.86)	8 males/21 females	33.90 (5.26)	2.90 (1.19)	7.56 (1.25)
Difference	$F < 1$	$\chi^2(1) < 1$	$F < 1$	$F = 2.91$*	$F < 1$

Note: SE = secondary extinction; *p = .093.

Table 2
Overview of the design of the experiment.

	Acquisition	Extinction	Reinstatement	SE	Reinstatement test
Control	5 CS1+ 5 CS2+	6 CS1- 6 CS2-	3 US		4 CS2-
SE	5 CS1+ 5 CS2+	6 CS1- 6 CS2-	3 US	1 CS1-	4 CS2-

Note. The + and – signs indicate the presence and absence of the US (an electrical stimulation), respectively. CSs were a blue square and a 500-Hz tone (counterbalanced). SE = secondary extinction.

to voluntarily tolerate). The work-up procedure was stopped when participants rated the intensity 7 or higher. The corresponding final intensity level was used in the experiment, unless participants indicated before reaching 7 that they did not want to increase the intensity further or unless the maximal intensity of the finger stimulator was reached (4 mA). In these latter cases, the final reached intensity was used (Mertens & De Houwer, 2016).

2.5.2. Acquisition phase

Before participants started with a fear conditioning phase, they were told that they would see a square, hear a tone, and feel the electrical stimulation. They were further instructed to indicate to what extent they expected that the electrical stimulation would occur on a scale at the bottom of the screen. The fear acquisition phase consisted of five presentations of each CS that were both always followed at offset by the US. Each CS was shown for 8 s and was followed, after the US administration, by an inter-trial-interval (ITI) of 12, 14 or 16 s. The order of CS presentations was semi-random with the restriction that the maximal number of identical consecutive trials was two. During CS presentations, participants could indicate their US expectancy ratings using a 9-point Likert scale presented at the bottom of the computer screen (1 = *certainly no stimulus*; 5 = *unsure*; 9 = *certainly a stimulation*).

2.5.3. Extinction phase

The extinction phase followed the acquisition phase without interruption and was identical with the exception that the US was never administered during this phase and that each CS was shown six instead of five times.

2.5.4. Reinstatement and secondary extinction phase

The extinction phase was followed by a reinstatement manipulation by presenting three unpaired presentations of the US (ITI: 7 s). Depending on the condition, this reinstatement manipulation was either followed by a waiting period (20, 22 or 24 s, which was the same duration as a regular trial plus the ITI) or by the presentation of one of the CSs (see Table 2). This waiting period or the secondary extinction trial was then followed by four presentations of one of the CSs (i.e., the other CS in the secondary extinction condition).

2.5.5. Questions regarding reinstatement and stimulus equivalence

The experiment ended with one or two questions (depending on the condition). In both the control and secondary extinction condition, participants were asked whether they expected that the US would be presented after the CSs again after the three sudden electric stimulations ("Did you think that the electrical stimulations would be presented again following the square and the tone after experiencing the sudden electrical stimulations?"). Participants could answer by selecting either yes, no, or uncertain. Furthermore, in the secondary extinction condition (but not in the control condition), participants were also asked whether they thought that the US would not be presented anymore because the tone (or, counterbalanced, the square) was not followed by the US after the administration of the sudden electric stimulations ("Did you think that there would be no more electrical stimulations following the square [/tone] because the tone [/square] was not followed by an electric stimulation after experiencing the sudden electrical stimulations?"). This question addressed participants' perceived equivalence of the two CSs. Again, they could answer by selecting either yes, no, or uncertain.

2.6. Data preprocessing and analysis

SCRs were calculated by subtracting the mean value of a baseline period (2 s before CS onset) from the highest peak during the 1–8 s interval post CS onset (Pineles, Orr, & Orr, 2009). Thereafter, skin conductance values were range corrected using the largest response for each participant and square root transformed to normalize the data (Dawson, Schell, Filion, & Berntson, 2007). A minimum response criterion was set at 0.02 μS. SCR data from one participant were lost due to equipment error.

US expectancy ratings and SCRs were analyzed with repeated measures ANOVAs. The acquisition and extinction phase were analyzed with the within-subjects factors CS (CS1, CS2) and trial number (acquisition phase: five trials; extinction phase: six trials) and the between-subjects factors condition (secondary extinction, control) and CS counterbalancing (CS1 = tone and CS2 = square, or vice versa). The effect of our manipulation on reinstatement was analyzed with a repeated measures ANOVA with the within-subject factor phase (last trial of the extinction phase, first trial of the reinstatement phase[3]), and the between-subjects factors condition and CS counterbalancing.

Finally, in order to explore the impact of participants' ideas about reinstatement and the functional equivalence of the two CSs, the analysis of reinstatement was repeated after: (1) excluding participants who did not think that the US would follow the CS after the reinstatement manipulation, and (2) excluding participants who did not think that the two CSs were equivalent (these analyses were pre-registered: https://osf.io/c3dtn/).

An alpha level of 0.05 was applied for statistical significance. Greenhouse-Geisser corrected statistics and degrees of freedom are reported when the sphericity assumption was violated.

2.7. Results

2.7.1. US expectancy ratings

2.7.1.1. Acquisition phase. Analyses of the acquisition phase revealed a main effect of trial number, $F(3.05, 170.67) = 47.51$, $p < .001$, $\eta_p^2 = .46$, and an interaction effect between CS and condition, $F(1, 56) = 4.62$,

[3] Note that the first trial in the secondary extinction condition after the reinstatement manipulation was the secondary extinction trial (see Table 2). This trial was ignored in the analyses of reinstatement.

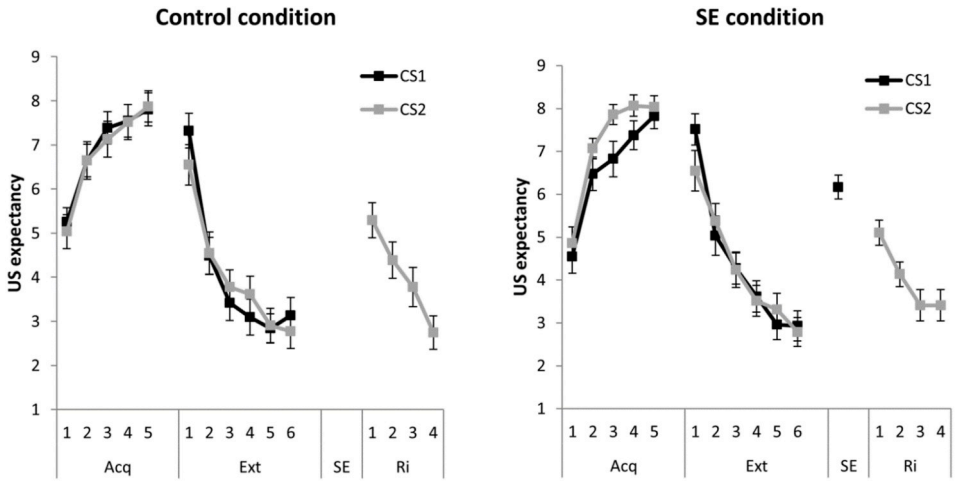

Fig. 1. US expectancy ratings in the two conditions of Experiment 1. Error bars indicate standard error. Acq = acquisition; Ext = extinction; SE = secondary extinction; Ri = reinstatement test. See the Supplementary Material for the results plotted separately according to CS (tone/square) counterbalancing.

$p = .036$, $\eta_p^2 = .08$. The main effect of trial number was due to an increase of US expectancy ratings for both CSs throughout the acquisition phase (see Fig. 1). The interaction effect between CS and condition was due to lower US expectancy ratings for CS1 than for CS2, particularly in the SE condition (see Fig. 1). Note however that this effect was not present anymore when considering only the last trial of the acquisition phase, $F < 1$. All other main and interaction effects were not significant, $Fs < 2.5$.

2.7.1.2. Extinction phase. Analyses of the extinction phase revealed a main effect of trial number, $F(3.23, 180.89) = 87.96$, $p < .001$, $\eta_p^2 = .61$, and a trend for an interaction effect between CS and CS counterbalancing, $F(1, 56) = 3.55$, $p = .065$, $\eta_p^2 = .06$. The main effect of trial number was due to a decrease of US expectancy ratings throughout the extinction phase. The observed trend for the interaction was due to slightly lower US expectancy ratings for CS1 when it was the square and slightly higher US expectancy ratings for CS1 when it was the tone (and the same applied for CS2; see Fig. 1 of the Supplementary Material). This effect was more pronounced at the end of the extinction phase, $F(1, 56) = 12.01$. $p = .001$, $\eta_p^2 = .18$, and indicates that US expectancy ratings were higher for the tone, particularly at the end of the extinction phase. All other main and interaction effects were not significant, $Fs < 2$.

2.7.1.3. Reinstatement test. Analyses of the results of the reinstatement phase, in which the last trial of the extinction phase was compared with first trial of the reinstatement phase, revealed a main effect of phase, $F(1, 56) = 115.18$, $p < .001$, $\eta_p^2 = .67$, an interaction between phase and CS counterbalancing, $F(1, 56) = 8.61$, $p = .005$, $\eta_p^2 = .13$, and a three-way interaction between phase, condition and CS counterbalancing, $F(1, 56) = 4.87$, $p = .031$, $\eta_p^2 = .08$. The interaction effect between phase and condition was not significant, $F < 1$. The main effect of phase indicates that the reinstatement procedure caused an increase in US expectancy ratings (see Fig. 1). The interaction between phase and CS counterbalancing could be explained by a less pronounced reinstatement effect for CS2 when this CS was the tone, primarily because US expectancy ratings were higher for the tone than for the square at the end of the extinction phase (see the Supplementary Material and Fig. 2). Finally, the three-way interaction between phase, condition and CS counterbalancing was due to a reduced reinstatement effect in the secondary extinction condition compared to the control condition when CS1 was the tone compared to when CS1 was the square (see Fig. 2). Indeed, when we explored this interaction further for each counterbalancing condition, we found a trend for and interaction effect between phase and condition when CS1 was the tone, $F(1, 29) = 3.61$, $p = .067$, $\eta_p^2 = .11$, but not when it was the square, $F(1, 27) = 1.54$, $p = .225$, $\eta_p^2 = .05$ (see Fig. 2).

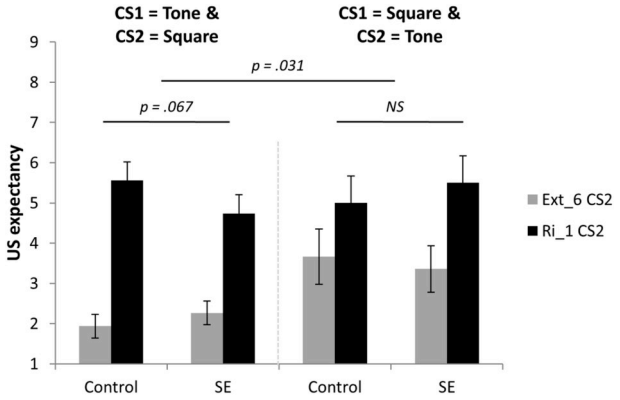

Fig. 2. Three-way interaction plot between time (end of extinction, first trial of reinstatement test), condition and counterbalancing of the CSs for US expectancy ratings in Experiment 1. Error bars indicate standard error. Note that the two-way interaction between time and condition in the CS1 = Tone & CS2 = Square counterbalancing condition was significant ($p = .030$) when excluding participants that indicated that the two CSs were not equivalent (see main text). Ext_6 = last trial extinction phase; SE = secondary extinction; Ri_1 = first trial reinstatement test phase.

2.7.2. Skin conductance responses

2.7.2.1. Acquisition phase. [4]Analyses of the acquisition phase revealed a main effect of trial number, $F(3.36, 147.83) = 8.98$, $p < .001$, $\eta_p^2 = .17$, and an interaction effect between CS and CS counterbalancing, $F(1, 44) = 16.79$, $p < .001$, $\eta_p^2 = .28$. The main effect of trial number was due to a decline in SCRs magnitude over trials (see Fig. 3).[5] The interaction effect between CS and CS counterbalancing was due larger SCRs to the CS1 when it was the tone compared to when it was the square (the same applied for CS2; see the Supplementary Material). Hence, the tone tended to elicit higher

[4] Note that for some participants the data of the first trial of the acquisition phase was missing (due to starting the psychophysiology recording software too late). Analyses without this first trial produced the same results. We only report the results including the first trial of the acquisition phase here.

[5] Note that SCRs are strongly affected by both the effects of conditioning (which would entail an increase of SCRs over trials) and the effects of non-associative factors such as habituation and sensitization (Dawson et al., 2007). Because we did not include a CS that was not paired with the US (i.e., a CS-), it is not possible to control for the effects of these non-associative factors and it is therefore difficult to interpret the effect of the factor trial number for SCRs.

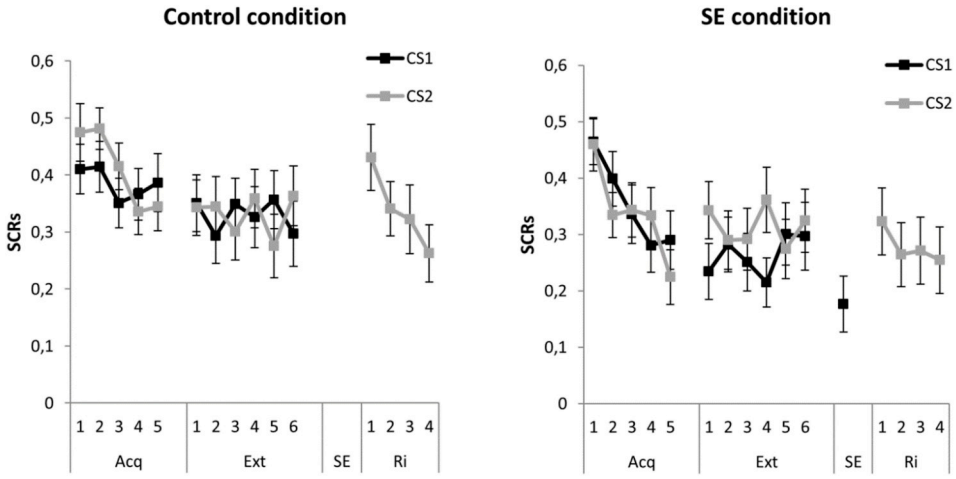

Fig. 3. Range corrected and square root transformed skin conductance responses (in μS) in the two conditions of Experiment 1. Error bars indicate standard error. Acq = acquisition; Ext = extinction; SE = secondary extinction; Ri = reinstatement test. See the Supplementary Material for the results plotted separately according to CS (tone/square) counterbalancing.

SCRs than the square during the acquisition phase. All other main and interaction effects were not significant, *Fs* < 1.8.

2.7.2.2. Extinction phase. Analyses of the extinction phase revealed a two-way interaction between CS and CS counterbalancing, $F(1, 55) = 17.87$, $p < .001$, $\eta_p^2 = .25$, and a three-way interaction between trial, condition and CS counterbalancing, $F(4.33, 238.22) = 3.61$, $p = .006$, $\eta_p^2 = .06$. As in the acquisition phase, the interaction between CS and CS counterbalancing was due to higher SCRs to the tone than to the square. The three-way interaction trial, condition and CS counterbalancing was due a more cubic pattern of the SCRs over trial in the extinction phase in the SE condition with CS1 as a square compared to the other conditions (see the Supplementary Material; however, this effect was small and unexpected and should be carefully interpreted). All other main and interaction effects were not significant, *Fs* < 2.9.

2.7.2.3. Reinstatement test. Analyses of the reinstatement phase again revealed an effect of CS counterbalancing, $F(1, 55) = 8.39$, $p = .005$, $\eta_p^2 = .13$. Again, this main effect of CS counterbalancing was due to higher SCRs for the tone than for the square (see the Supplementary Material). All other main or interaction effects were not significant, *Fs* < 1.9.

2.7.2.4. Analyses regarding beliefs about reinstatement and perceived CS equivalence. Forty-one participants (68%) believed that the CS would be followed by the US again after the reinstatement manipulation. Fifteen (25%) participants were unsure and four (7%) participants indicated that they did not expect the CS to be followed by the US again. These numbers were comparable in the two conditions (control condition: 19 yes, 9 unsure, 3 no; SE condition: 22 yes, 6 unsure, 1 no; $\chi^2(2) = 1.76$, $p = .416$). Exclusion of the four participants who indicated 'no' did not change the results of the analyses.

With regard to the question about the perceived equivalence of the two CSs, 11 (38%) participants in the secondary extinction condition indicated that they were unsure whether the two CSs were equivalent and 11 (38%) participants indicated that they did not think the two CSs were equivalent. Seven (24%) indicated that the two CSs were equivalent. These numbers were comparable for the two conditions (secondary extinction with the square: 4 yes, 5 unsure, 6 no; secondary extinction with the tone: 3 yes, 6 unsure, 5 no; $\chi^2(2) < 1$). Exclusion of the 11 participants who did not think the two CSs were equivalent changed the results of the US expectancy ratings for the reinstatement test. Specifically, the three-way interaction between phase, condition and CS counterbalancing remained significant, $F(1, 45) = 6.75$, $p = .013$, $\eta_p^2 = .13$, and the two-way interaction between phase and condition when CS1 was the tone was now fully significant (instead of a trend), $F(1, 23) = 5.35$, $p = .030$, $\eta_p^2 = .19$ (and it remained non-significant for the condition in which CS1 was the square, $F(1, 22) = 1.84$, $p = .189$, $\eta_p^2 = .08$). Conversely, when the seven participants who believed that the two CSs were equivalent were dropped from the analyses, the three-way interaction between phase, condition and CS counterbalancing was no longer significant, $F(1, 49) = 1.55$, $p = .220$, $\eta_p^2 = .03$. These analyses indicate that the observed secondary extinction effect for US expectancy ratings when CS1 was the tone was largely driven by the participants who believed that the two CSs were equivalent. Finally, inclusion or exclusion of participants on the basis of their beliefs about the equivalence of the CSs did not change the results of the SCR analyses (i.e., no secondary extinction effect was obtained regardless of including or excluding these participants).

2.8. Discussion

The results of this first experiment indicate that a single secondary extinction trial interferes with the reinstatement of US expectancy ratings. However, surprisingly, this effect depended on the stimulus that was used during secondary extinction: evidence for interference with reinstatement was found when the secondary extinction trial was a 500-Hz tone, but not when it was a blue square. This was an unexpected observation, so we can only provide post-hoc explanations for it (see the General Discussion).

Another observation was that the effect of secondary extinction on reinstatement was only observed for US expectancy ratings, and not for SCRs. One potential reason for this could be that reinstatement of SCRs was not sufficiently induced in the control condition. The lack of reinstatement of SCRs in the control condition is not exceptional. Approximately one-fourth to one-third of the human studies fail to find evidence for reinstatement with a range of dependent variables (Haaker, Golkar, Hermans, & Lonsdorf, 2014). A problem with the interpretation of the SCR results, however, is that we did not include a CS that was not paired with the US to control for non-associative factors that influence SCRs, such as habituation and sensitization (e.g., Lonsdorf et al., 2017). We did not include such a CS because we based the design of our experiment on the first experiment of Rescorla and Cunningham (1977), who did not include such a CS.

Finally, it should be noted that the effect of secondary extinction on reinstatement was modest. Two potential reasons for this are that the secondary extinction intervention was done with a CS that had already been extinguished (hence, more accurately, we used a secondary re-extinction intervention; see Footnote 2) and that only one secondary extinction intervention trial was used.

Table 3
Demographic information of the participants in Experiment 2.

	Age	Sex distribution	STAI-T	Electric stimulus intensity (mA)$^{+}$	Electric stimulus pain rating^{+}
Contro (n = 31)	21.87 (3.02)	6 males/25 females	33.74 (7.50)	1.90 (0.83)	7.52 (1.36)
SE (n = 29)	23.21 (4.17)	6 males/23 females	38.76 (8.13)	1.57 (0.76)	7.45 (1.41)
Difference	F = 2.04	$\chi^2(1) < 1$	F = 6.18*	F = 2.59	$F < 1$

Notes: SE = secondary extinction; *p = .016; + information about the electric stimulus intensity level and pain rating was missing for one participant.

3. Experiment 2

This second experiment was set-up to overcome some of the limitations of Experiment 1. Particularly, to be able to account for habituation of skin conductance responses, a CS that was not paired with the US was added (i.e., a CS-; see Lonsdorf et al., 2017). Furthermore, to avoid the stimulus-modality effects of Experiment 1, only visual stimuli were used. Finally, in order to strengthen the effects of the secondary extinction intervention, two secondary extinction trials were used instead of one.

3.1. Pre-registration

The sample size, design, procedure and data analyses steps were pre-registered on the Open Science Framework prior to data collection (https://osf.io/dxpb3/). No power calculation was performed for this second study. However, because we expected the secondary extinction to be stronger, we reasoned prior to conducting this study (see the pre-registration) that testing same number of participants as Experiment 1 would provide sufficient statistical power for this second experiment.

3.2. Participants

Participants for this second experiment were recruited in the same way as for Experiment 1. Detailed demographic information about them can be found in Table 3. There was a significant difference between the two conditions regarding trait anxiety levels. When STAI-T scores were added to the analyses as a covariate, the effects related to the factor condition remained similar or became even more pronounced. However, to maintain comparability with the results of the Experiment 1, the results of this experiment are reported without STAI-T as a covariate.

3.3. Material, design, and procedure

The material, design, and procedure of this second experiment were identical to Experiment 1, except for three adjustments: First, a third CS was added that was unpaired with the US to control for non-associative factors that influence SCRs. Second, instead of an auditory and a visual stimulus, three distinct visual stimuli were used. These were a geometric shape (a pentagon), a non-word ("VEG"), and a nonsense figure (a 'fribble'; taken from Barry, Griffith, De Rossi, & Hermans, 2014). We chose these three different visual stimuli because they are perceptually distinct, which makes an explanation of secondary extinction in terms of perceptual generalization unlikely. The stimuli (300 by 400 pixels) were presented on a 19-inch computer screen with a 1240 by 1024 resolution. Allocation of these three stimuli to the different CS types (CS1, CS2, CS-) was counterbalanced over participants.[6] Third, CS1 was presented twice after the reinstatement manipulation, instead of only once (see Table 2), to induce secondary extinction.

[6] One participant was accidently misallocated to another counterbalancing condition, resulting in a slightly imbalanced design. Because we used three comparably neutral stimuli, we do not think this mistake impacted our results. Indeed, including CS counterbalancing as a factor in the analyses of the acquisition and extinction phase did not reveal any significant main or interaction effects with this factor, F-values < 1.3.

3.4. Data preprocessing and analysis

Data preprocessing and analysis were identical to Experiment 1, except that the within-subjects factor CS consisted of three levels (CS1, CS2, CS-). Furthermore, the factor CS counterbalancing was omitted from the analyses because it did not influence the results in any meaningful way. SCR data from one participant was missing due to experimenter error (i.e., forgotten to save the SCR data) and SCR data from another participant was excluded because she did not show SCRs to any of the CSs.

3.5. Results

3.5.1. US expectancy ratings

3.5.1.1. Acquisition phase. Analysis of the acquisition phase revealed a main effect of CS, $F(1.32, 76.30) = 149.32$, $p < .001$, $\eta_p^2 = .72$, trial number, $F(3.32, 192.50) = 31.55$, $p < .001$, $\eta_p^2 = .35$, and an interaction effect between CS and trial number, $F(4.52, 262.11) = 69.47$, $p < .001$, $\eta_p^2 = .55$. These were due to an increase of US expectancy for the CS1 and CS2, while US expectancies for the CS- decreased (see Fig. 4). All other main and interaction effects were not significant, $Fs < 1.8$.

3.5.1.2. Extinction phase. Analysis of the extinction phase revealed a main effect of CS, $F(1.29, 75.08) = 68.54$, $p < .001$, $\eta_p^2 = .54$, trial number, $F(2.72, 157.61) = 111.52$, $p < .001$, $\eta_p^2 = .66$, and an interaction effect between CS and trial number, $F(5.59, 324.38) = 34.14$, $p < .001$, $\eta_p^2 = .37$. These main and interaction effects were due a decrease of US expectancy throughout the extinction phase, particularly for CS1 and CS2 (see Fig. 4). All other main and interaction effects were not significant, $Fs < 1.7$.

3.5.1.3. Reinstatement test. Comparison of the last extinction trial to the first reinstatement trial revealed a main effect of CS, $F(1, 58) = 22.89$, $p < .001$, $\eta_p^2 = .28$, phase, $F(1, 58) = 60.13$, $p < .001$, $\eta_p^2 = .51$, and an interaction effect between CS and condition, $F(1, 58) = 4.55$, $p = .037$, $\eta_p^2 = .07$. The main effect of phase was due to an increase of US expectancy ratings from the last trial of the extinction phase to the first trial of the reinstatement phase (see Fig. 4). The interaction between CS and condition was due to a smaller difference between CS2 and CS- in the secondary extinction condition ($M = 0.66$, $SD = 1.95$, $t(28) = 1.81$, $p = .081$) compared to the control condition ($M = 1.71$, $SD = 1.88$, $t(30) = 5.07$, $p < .001$). However, the crucial interaction between CS, phase, and condition was not significant, $F(1, 58) = 2.27$, $p = .138$, $\eta_p^2 = .04$. All other main and interaction effects were not significant, $Fs < 1.8$.

3.5.2. Skin conductance responses

3.5.2.1. Acquisition phase. Analysis of the acquisition phase revealed a main effect of CS, $F(2, 102) = 4.80$, $p = .010$, $\eta_p^2 = .09$, and trial number, $F(4, 204) = 20.47$, $p < .001$, $\eta_p^2 = .29$. The main effect of CS was due to larger SCRs to CS1 (M = 0.29, SD = 0.21) and CS2 (M = 0.30, SD = 0.21), than to CS- (M = 0.22, SD = 0.18). The main effect of trial was due a decline of SCRs over the trials of the acquisition phase (see Fig. 5). All other main and interaction effects were not significant, $Fs < 1.1$.

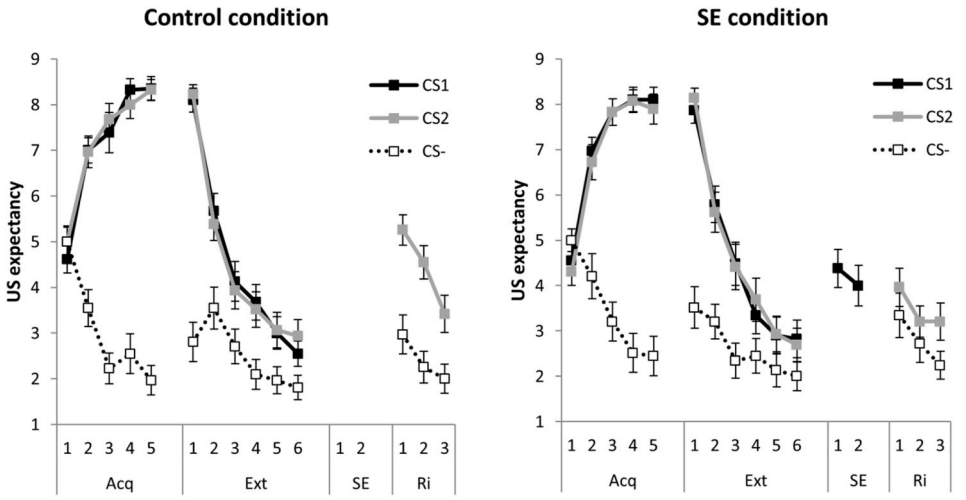

Fig. 4. US expectancy ratings in the two conditions of Experiment 2. Error bars indicate standard error. Acq = acquisition; Ext = extinction; SE = secondary extinction; Ri = reinstatement test.

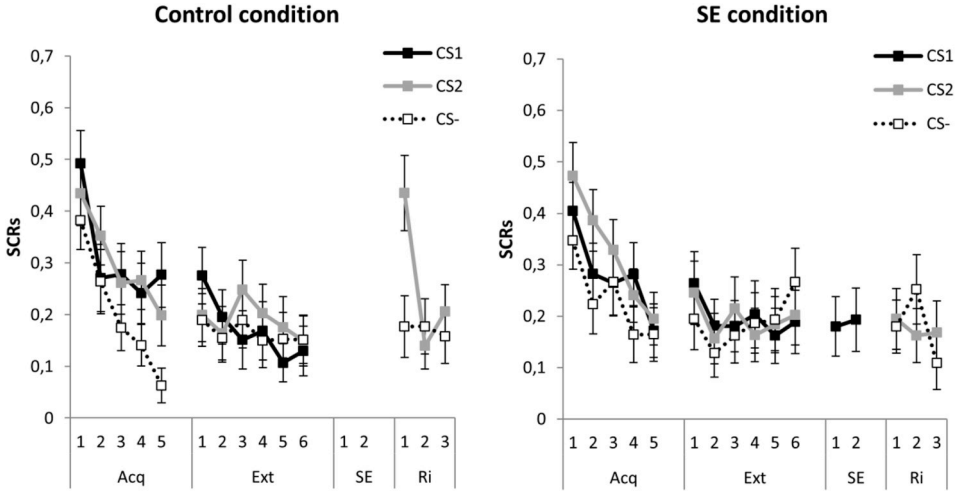

Fig. 5. Range corrected and square root transformed skin conductance responses (in μS) in the two conditions of Experiment 2. Error bars indicate standard error. Acq = acquisition; Ext = extinction; SE = secondary extinction; Ri = reinstatement test.

3.5.2.2. Extinction phase. Analysis of the extinction phase revealed no significant main or interaction effects, *Fs* < 1.6.

3.5.2.3. Reinstatement test. Comparison of the last extinction trial to the first reinstatement trial revealed a main effect of CS, $F(1, 58) = 4.27$, $p = .044$, $\eta_p^2 = .07$, and an interaction effect between CS and phase, $F(1, 58) = 5.72$, $p = .020$, $\eta_p^2 = .09$. This was due to higher SCRs to the CS2, particularly after the reinstatement intervention (see Fig. 5). Importantly, interactions between CS and condition, $F(1, 58) = 9.15$, $p = .004$, $\eta_p^2 = .14$, and between trial and condition, $F(1, 58) = 4.92$, $p = .031$, $\eta_p^2 = .08$, were found. The interaction between CS and condition was due to a smaller difference in SCRs between CS- and CS2 in the secondary extinction condition ($M = -0.02$, $SD = 0.20$, $t(27) = -0.64$, $p = .525$) than in the control condition ($M = 0.13$, $SD = 0.19$, $t(29) = 3.80$, $p = .001$). The interaction between phase and condition was due to the absence of an increase of SCRs from the end of the extinction phase to the first trial of the reinstatement phase in the secondary extinction condition ($M = -0.05$, $SD = 0.30$, $t(27) = -0.76$, $p = .457$), whereas such an increase of SCRs was observed in the control condition ($M = 0.16$, $SD = 0.36$, $t(29) = 2.34$, $p = .026$). The crucial interaction between CS, phase, and condition was not significant, $F(1, 56) = 1.64$, $p = .206$, $\eta_p^2 = .03$. All other main and interaction effects were not significant, *Fs* < 1.5.

3.5.2.4. Analyses regarding beliefs about reinstatement and perceived CS equivalence. Thirty participants (50%) believed that the CS would be followed by the US again after the reinstatement manipulation. Twenty-one (35%) were unsure and nine (15%) indicated that they did not expect the CS to be followed by the US again. These numbers did not differ significantly between the two conditions (control condition: 18 yes, 11 unsure, 2 no; SE condition: 12 yes, 10 unsure, 7 no; $\chi^2(2) = 3.96$, $p = .138$). When the nine participants who answered 'no' to this question were excluded from the analyses regarding the reinstatement effect, the interaction between CS and condition for US expectancy was no longer significant, $F(1, 49) = 2.38$, $p = .129$, $\eta_p^2 = .05$. Exclusion of these participants did not critically change the results regarding the reinstatement effect for the SCRs.

With regard to the question about perceived equivalence of the two CSs, 10 (34.5%) participants in the secondary extinction condition indicated that they were unsure whether the two CSs were equivalent and eight (27.5%) indicated that they did not think the two CSs were equivalent. Eleven (38%) participants did think that the two CSs were equivalent. Exclusion of the eight participants who did not think the two CSs were equivalent did not critically change the results regarding reinstatement of US expectancy ratings (i.e., the interaction between CS, phase, and condition remained non-significant, $F(1, 50) = 2.81$, $p = .100$, $\eta_p^2 = .05$). However, excluding these eight participants

changed the results regarding the reinstatement of SCRs. Particularly, the three-way interaction between CS, phase, and condition was now significant, $F(1, 48) = 5.72$, $p = .021$, $\eta_p^2 = .11$. This interaction was due to a significant reinstatement effect in the control condition (i.e., participants in this condition showed a specific increase of SCRs to CS2 from the last trial of the extinction phase to the first trial of the reinstatement phase; interaction between CS and phase: $F(1, 29) = 8.31$, $p = .007$, $\eta_p^2 = .22$), while no significant reinstatement effect was found in the secondary extinction condition (interaction between CS and phase: $F(1, 19) = 0.59$, $p = .452$, $\eta_p^2 = .03$). Conversely, when the 11 participants who believed that the two CSs were equivalent were dropped from the analyses, the interaction between CS and condition for US expectancy ratings, $F(1, 47) = 1.74$, $p = .193$, $\eta_p^2 = .04$, and the interaction between phase and condition for SCRs, $F(1, 45) = 3.23$, $p = .079$, $\eta_p^2 = .07$, were no longer significant (though the interaction between CS and condition for SCRs remained significant, $F(1, 48) = 4.81$, $p = .034$, $\eta_p^2 = .10$). These analyses indicate that the differences between the conditions in this second experiment were also largely driven by participants who believed that the two CSs were equivalent, which is in line with the findings of Experiment 1.

3.6. Discussion

In this second experiment, several limitations of the first experiment were addressed. The results replicate those of the first experiment. Particularly, the pattern of results for US expectancy ratings was similar to the first experiment, although the crucial interaction did not reach the significance threshold. Furthermore, the results of Experiment 2 extend the secondary extinction phenomenon to SCRs. That is, reinstatement of SCRs was eliminated by the secondary extinction intervention when considering the results of the participants who thought the CSs were equivalent or were unsure about whether the CSs were equivalent.

4. General Discussion

In two experiments, we set out to investigate whether secondary extinction interferes with the reinstatement of conditioned fear in humans. Our results indicate that secondary extinction reduces the reinstatement of US expectancy ratings and conditioned SCRs. These experiments provide, to our knowledge, the first demonstration of the secondary extinction phenomenon in humans.

These results replicate the first experiment of Rescorla and Cunningham (1977) with rats by demonstrating that secondary extinction can interfere with reinstatement of conditioned fear. Unexpectedly, we also found a significant moderation of the effect by the type of stimulus which was used as the secondary extinction trial in Experiment 1. That is, we found that a CS which elicits more fear (as indicated by US expectancy ratings and SCRs in the extinction phase of Experiment 1) is more effective to induce secondary extinction effects than a CS that elicits less fear. We presumed before conducting the experiment that the tone and the square would be comparably neutral, but the results from the US expectancy ratings and SCRs of Experiment 1, however, indicate that they are not. Because this finding was an unexpected, it should be interpreted with caution and requires further research. Nonetheless, it is interesting that this finding corresponds with the results from the second experiment by Rescorla and Cunningham (1977) in which they demonstrate that, in order to obtain the secondary extinction effect, the CS used for secondary extinction needs to elicit fear. One mechanistic explanation for these findings is that secondary extinction is a function of the amount of expectancy violation. That is, more secondary extinction will occur when there is a larger mismatch between what the participant expects (i.e., a shock, which is translated into higher US expectancy ratings and SCRs) and what actually happens (i.e., the absence of a shock) (the same mechanism is proposed to underlie regular extinction; e.g., Craske et al., 2008; Rescorla & Wagner, 1972). However, this interpretation is not supported by an analysis of the secondary extinction trial of Experiment 1: US expectancy ratings did not significantly differ between the tone ($M = 6.40$; $SD = 1.24$) and the square ($M = 5.93$; $SD = 1.73$), $F < 1$. Additionally, the results of Experiment 2 indicate that secondary extinction also occurs when the secondary extinction trial is a visual CS. Hence, secondary extinction seems a general phenomenon that may depend on the amount of fear or expectancy violation elicited by the secondary extinction intervention. More research is required to determine the conditions under which secondary extinction occurs.

The results of our experiments also correspond with the results of Vurbic and Bouton (2011) by providing preliminary evidence that the secondary extinction effect depends on the learned connection between the CSs. Vurbic and Bouton manipulated equivalence of the CSs by providing the conditioning trials of the two CSs either intermixed or in two separate blocks. We intermixed conditioning and extinction trials and assessed perceived equivalence by asking participants. Arguably, the results of both experiments point to the relevance of stimulus equivalence for secondary extinction. Nevertheless, a study with an experimental manipulation of equivalence will need to confirm this role of equivalence for secondary extinction with humans.

Our results may have relevance for exposure therapy. It is often assumed that some degree of perceptual overlap between the feared stimuli and the stimuli used in extinction and exposure therapy is required (Barry, Griffith, Vervliet, & Hermans, 2016; Vervliet, Vansteenwegen, Baeyens, Hermans, & Eelen, 2005; though see; Vervoort, Vervliet, Bennett, & Baeyens, 2014). However, our experiments demonstrate that extinction can generalize between two entirely perceptually distinct stimuli. We argue that this generalization is due to a conceptual overlap between these stimuli because they were paired with the same US (though secondary extinction can also be explained by an associative chain, without necessarily requiring conceptual overlap; see Vurbic & Bouton, 2011). Likewise, Preusser, Margraf, and Zlomuzica (2017) recently demonstrated that the effects of exposure therapy with spiders generalize to cockroaches. These authors similarly argued that this generalization of exposure therapy effects occurred because of the conceptual overlap between these two animals due to the fact that they are related to similar fear-evoking characteristics (such as the perceived speed and unpredictiveness of these animals and involuntary physical contact with the animals). Our experiments and the study by Preusser et al. (2017) thus suggest that secondary extinction allows for the generalization of the effects of extinction and exposure therapy to perceptually dissimilar (but conceptually related) stimuli (e.g., taking the elevator and traveling by bus, which may both be associated with panic attacks). Finally, the results of our studies also suggest that a simple intervention might suffice to reduce relapse after exposure therapy. That is, a single extinction or exposure session (e.g., taking a bus without a panic attack) might be helpful to reduce relapse rates after exposure treatment. However, additional sub-clinical and clinical studies are required to investigate whether the secondary extinction phenomenon can be used in clinical settings.

To conclude, our experiments provides the first evidence for secondary extinction and its effect on reinstatement of conditioned fear with human participants. Our results further correspond with studies with rats that demonstrate that the CS used for secondary extinction should elicit fear and that perceived stimulus equivalence is important for secondary extinction. These experiments provides a first step towards more extensive investigations of this phenomenon, both regarding its fundamental features and its clinical application.

Conflict of interest

We declare no conflict of interest with regard to the preparation of this manuscript and confirm that our manuscript is an original contribution which is not under review or published anywhere else.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbtep.2018.09.007.

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