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Can glucose facilitate fear exposure? Randomized, placebo-controlled trials on the effects of glucose administration on fear extinction processes

Alexander Hauck, Tanja Michael, Tobias C. Issler, Steven Klein, Johanna Lass-Hennemann, Diana S. Ferreira de Sá *

Division of Clinical Psychology and Psychotherapy, Department of Psychology, Saarland University, Saarbrücken, Germany

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ABSTRACT

Previous studies showed that glucose has beneficial effects on memory function and can enhance contextual fear learning. To derive potential therapeutic interventions, further research is needed regarding the effects of glucose on fear extinction. In two experimental studies with healthy participants (Study 1: $N = 68$, 39 females; Study 2: $N = 89$, 67 females), we investigated the effects of glucose on fear extinction learning and its consolidation. Participants completed a differential fear conditioning paradigm consisting of acquisition, extinction, and return of fear tests: reinstatement, and extinction recall. US-expectancy ratings, skin conductance response (SCR), and fear potentiated startle (FPS) were collected. Participants were pseudorandomized and double-blinded to one of two groups: They received either a drink containing glucose or saccharine 20 min before (Study 1) or immediately after extinction (Study 2). The glucose group showed a significantly stronger decrease in differential FPS during extinction (Study 1) and extinction recall (Study 2). Additionally, the glucose group showed a significantly lower contextual anxiety at test of reinstatement (Study 2). Our findings provide first evidence that glucose supports the process of fear extinction, and in particular the consolidation of fear extinction memory, and thus has potential as a beneficial adjuvant to extinction-based treatments.

Registered through the German Clinical Trials Registry (https://www.bfarm.de/EN/BfArM/Tasks/German-Clinical-Trials-Register/_node.html; Study 1: DRKS00010550; Study 2: DRKS00018933).

1. Introduction

Anxiety disorders (ADs) are among the most common psychological disorders and are responsible for a great burden of disease worldwide (Patel et al., 2018; Wittchen et al., 2011). In the wake of the COVID-19 pandemic, there has been a significant increase in prevalence rates for ADs (Salari et al., 2020; Santabárbara et al., 2021; Santomauro et al., 2021). Thus, following the central health challenge of the 21st century of providing better general treatment for mental illness, improving the treatment of ADs in particular has become extremely salient. First-line therapy for treating ADs is cognitive behavioral therapy (CBT) with special focus on exposure therapy (Hofmann et al., 2012; Kaczkurkin & Foa, 2015).

ADs may often be explained according to models of classical conditioning (Carpenter et al., 2019; De Houwer, 2020; Michael et al., 2007; Vervliet & Boddez, 2020). Although CBT and exposure therapy are safe and, most importantly, effective forms of treatment for ADs, not all patients benefit equally well from its effects (Arch & Craske, 2009; Carpenter et al., 2018; Hembree & Cahill, 2007; Markowitz & Fanselow, 2020). A key component to the success of exposure therapy is successful extinction learning (Forcadell et al., 2017), for which some studies demonstrate impairments for patients with AD (Arch & Craske, 2009; Blechert et al., 2007; Michael et al., 2007). Extinction learning is a process that has been well characterized and understood by a wealth of research on fear conditioning in humans and animals (Bouton et al., 2021; Carpenter et al., 2019; Salinas-Hernández et al., 2018). Recent studies confirmed the efficacy of exposure therapy when optimized according to the principles of fear extinction (Pittig et al., 2021, 2023). Thus, improving successful extinction learning is a key factor in further enhancing the effectiveness of exposure therapy. Numerous studies have identified adjuvant substances that appear to have positive effects on fear extinction, such as D-cycloserine (Davis, 2011; Ebrahimi et al.,

* Corresponding author. Division of Clinical Psychology and Psychotherapy, Department of Psychology, Saarland University Campus, Building A 1.3, Saarbrücken, Germany.
E-mail address: diana.ferreira@uni-saarland.de (D.S. Ferreira de Sá).

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2020; Inslicht et al., 2022), oxytocin (Eckstein et al., 2015, 2019), cortisol (Brueckner et al., 2019; Hagedorn et al., 2022; Lass-Hennemann & Michael, 2014; Merz et al., 2018) or insulin (Ferreira de Sá et al., 2020). While studies have shown mixed results regarding their use in exposure therapy (Giovanna et al., 2020; Kushner et al., 2007; Litz et al., 2012; Raeder et al., 2019; Rodrigues et al., 2014; Soravia et al., 2014), a major disadvantage of the mentioned substances is that they cannot be prescribed and used by non-medical psychotherapists in most countries. Additionally, they might have considerable physical secondary effects and might not be used unrestrictedly in all patients. Therefore, it is important to study alternative adjuvant substances that do not have significant secondary effects or greater limitations in their use, and that can easily be used by any practitioner in the therapeutic setting.

Glucose is a monosaccharide and acts as one of the most important cellular energy sources, with 20% of the total glucose intake relating to human brain functioning (Mergenthaler et al., 2013). Glucose plays an essential role in modulating cognitive processes (Mergenthaler et al., 2013; Messier, 2004; Smith et al., 2011) and can improve declarative memory and working memory in healthy participants (Korol & Gold, 1998; Martin & Benton, 1999; Messier, 2004; Scholey et al., 2013; Smith et al., 2011). In a study from Glenn et al. (2014), participants who received glucose after fear learning (versus placebo) showed an increase in fear response during a retention test, demonstrating that glucose has an influence on human fear conditioning processes. However, for a psychotherapeutic application of glucose it is essential to investigate whether it can support fear extinction, and to date this question remains open.

We conducted two separate double-blind, placebo-controlled studies to examine the effects of glucose on extinction learning, using a differential fear conditioning paradigm. A glucose drink (vs. placebo) was administered at two different times: before extinction learning, with blood glucose peak during memory encoding (Study 1); after extinction learning, to focus on direct effects on early consolidation (Study 2; see Brueckner et al. (2019)). Glucose effects in fear extinction learning and return of fear (ROF, here extinction recall and reinstatement) were analyzed. We hypothesized that glucose administration would result in better extinction learning and retention, as measured by psychophysiological and behavioral parameters, compared with placebo.

2. Methods and materials

2.1. Participants

In a preliminary interview, screening questions were used to check for the presence of exclusion criteria. To be eligible, participants required a normal body mass index (World Health Organization; WHO, 2023) no acute or chronic physical or mental illnesses (e.g., diabetes, thyroid disease, depression, or post-traumatic stress disorder), and no pregnancy. Female participants were required to use hormonal contraceptives to minimize hormonal differences. Regular use of medication, drugs, or excessive alcohol/nicotine were exclusion criteria.

Both studies were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Ethics Committee of the Faculty of Empirical Human Sciences at Saarland University). Registration for clinical trials was done through the German Clinical Trials Registry (Study 1: DRKS00010550; Study 2: DRKS00018933). Because Study 1 was conducted as a pilot study, no sample size calculation was performed. See supplement for more information on sample size determination of Study 1 and sample size calculations of Study 2. After completing the study, participants received either monetary compensation (Study 2) or academic credit if they were studying psychology at Saarland University (Studies 1 and 2).

For Study 1, 120 healthy students were recruited at Saarland University to participate with a final sample of 68 participants (39 female, sample description and CONSORT flow diagram in supplemental information, Schulz et al., 2010). For Study 2, 134 healthy students were recruited at Saarland University. The final sample consisted of 89 participants (67 female, sample description and CONSORT flow diagram in supplemental information, Schulz et al., 2010).

2.2. Group assignment and pharmacological manipulation

For both studies, a double-blind methodology was employed. Participants were blinded, sex matched, and pseudo-randomly assigned to either the glucose or placebo group (sex distribution per group in supplemental information). The glucose group received an opaque drinking bottle containing 25 g of glucose powder mixed with 300 ml of water, while the placebo group received 30 mg of saccharin powder mixed with the same amount of water. The amount of glucose administered proved optimal for improving cognitive abilities (Smith et al., 2011), while the amount of saccharin provided the same sweetness without affecting blood glucose levels (Scholey et al., 2013). The drink's administration was followed by a 20-min break during which participants read neutral magazines. This time interval was chosen based on data from a pilot study (supplemental information). Blood glucose levels were measured with a glucometer (Accu-Chek Aviva, Roche Diagnostics Deutschland, Mannheim, Germany) during the experiment: for Study 1 on arrival, 15 min after drink administration, and before departure, and for Study 2 upon arrival on day 2, and 15 min after the drink.

2.3. Stimuli and apparatus

The stimuli and apparatus used were based on the study by Ferreira de Sá et al. (2020). Stimuli included two male face pictures from the Radboud face database (Langner et al., 2010) that showed neutral expressions and were matched on valence and arousal ratings (Ferreira de Sá et al., 2020). These images served as conditioned stimuli (CSs). Each image was presented for 8s, followed by a black screen and a randomized intertrial interval (ITI) of 10–15s. At stimulus offset, one of the CSs was randomly associated with a moderate 200ms electrical shock to the left forearm and served as a reinforced conditioned stimulus (CS+), whereas the other CS was never paired with an electrical shock, serving as an unreinforced conditioned stimulus (CS–). The allocation of pictures to CS+ and CS– was counterbalanced and randomized between participants. The intensity of the electrical shock was individually adjusted (possible range: 1 mA–100 mA; DS3 Isolated Current Stimulator, Digitimer Ltd, Hertfordshire, United Kingdom) and applied via two electrodes (45 mm diameter; Kendall ECG electrodes H34SG, Cardinal Health, Dublin, USA) on the inside of the left forearm with an interelectrode distance of approximately 3 cm. The adjustment was made at the beginning of the experiment and was kept constant for all days of Study 2. A white noise (105 dB, 50ms, instantaneous rise time) was presented binaurally via 24-Bit sound card (Creative Sound Blaster Z, Creative Technology Ltd., Singapore) and audiometric headphones (Holmco PD-81, Holmberg GmbH & Co. KG, Berlin, Germany) on all CS trials 7s after picture onset, and 5s after picture offset during half of the ITI (noise alone, NA) and served as an auditory startle stimulus. The order of CS+ and CS– trials was pseudo-randomized: no more than two consecutive presentations of the same stimulus type, and a balanced number of trials of each type in each half of the conditioning phase.

2.4. Procedure

For Study 1, the differential fear-conditioning paradigm took place on a single day and included: 3min resting phase at the beginning and end of the session, startle habituation, picture habituation, acquisition, substance administration, extinction, reinstatement (including test of reinstatement [ToR]; Fig. 1). For Study 2, the differential fear-conditioning paradigm took place on three consecutive days and additionally included an extinction recall (retention test) before reinstatement on day 3 (Fig. 2).

To ensure a comparable glycemic state between participants, they

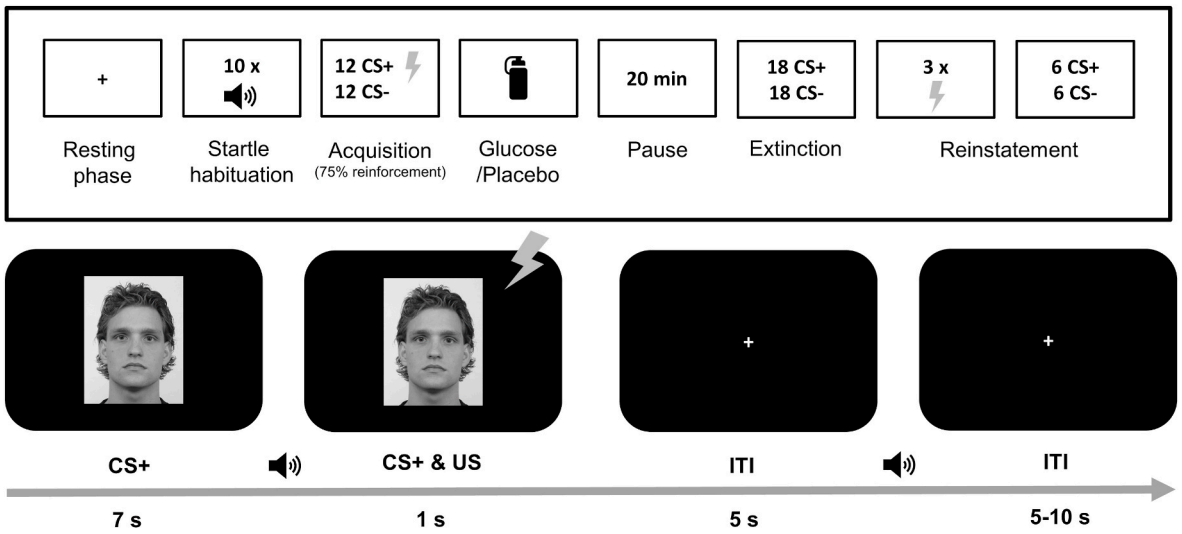

Fig. 1. Procedure of Study 1 and example of CS+ trial during acquisition.
Note: Study 1 consisted of a 1-day differential fear conditioning paradigm. Glucose was administered before fear extinction. Two male face pictures were used, one each as reinforced (CS+) and unreinforced conditioned stimulus (CS–). An electroshock was used as unconditioned stimulus (US).

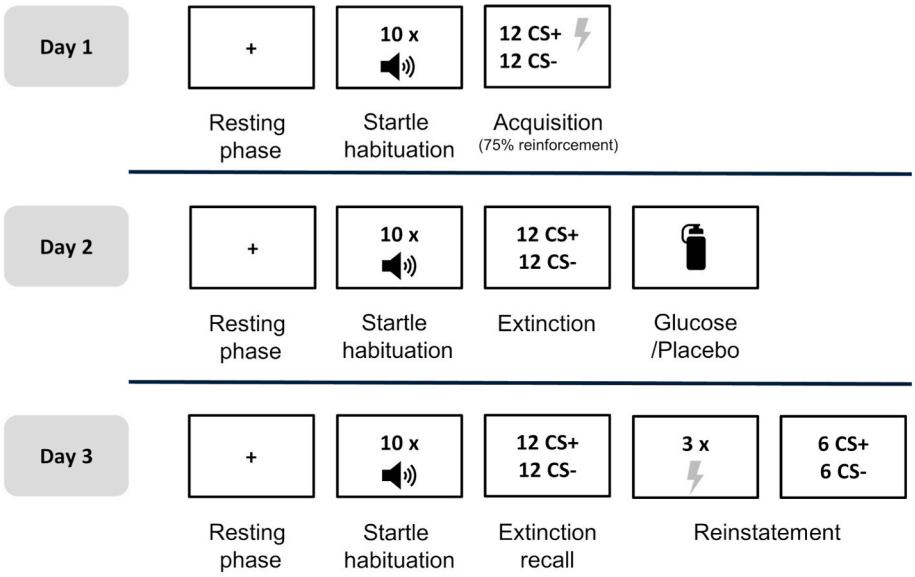

Fig. 2. Procedure of Study 2.
Note: The study took place on three consecutive days with a 24 h period between sessions. Glucose was administered at the end of day 2. Two male faces were used, one each as reinforced (CS+) and unreinforced conditioned stimulus (CS–). An electroshock was used as unconditioned stimulus (US).

were instructed to have their last meal before 10 p.m. the previous day. Additionally, they were asked not to consume caffeine, nicotine, or alcohol, and not to exercise on the day of the experiment. The study was conducted from 8 a.m. to 12 p.m. to ensure similar fasting states and to control for time of the day effects (Challet, 2015). As a cover story for increased compliance, participants were informed that a saliva sample would be collected to check their fasting status. Upon arrival, participants completed a routine recall from awakening to arrival ("What did you do from the time you got up until you got to the laboratory?"; Ferreira de Sá et al., 2014, 2020; Stone et al., 1991), and the saliva sample was collected. For a detailed description of the fear conditioning paradigm, see supplemental information.

2.5. Self-report and subjective measures

Prior to the experiment, participants completed several questionnaires via SoSci-Survey (Leiner, 2014): the depression and the anxiety module of the Patient Health Questionnaire (PHQ-9, Spitzer, 1999; GAD-7, Spitzer et al., 2006), as well as ratings of participants' US-expectancy ("How much do you expect that the electroshock will follow after this picture?") and CS-valence ("How unpleasant is this picture for you?") via a visual analog scale (VAS, 0–100, with higher ratings indicating higher US-expectancy and higher unpleasantness) at the beginning (pre), middle (mid), and end (post) of each conditioning phase. In addition, ratings of current anxiety level ("How anxious are you feeling right now?"), reported stress ("How stressed are you right now?"), and wakefulness ("How awake do you feel right now?") were collected at different times during the experiments via a VAS (0–100, with higher ratings indicating higher levels of wakefulness, reported stress, and anxiety):

- Study 1: a) before picture habituation, b) after acquisition, c) before extinction, d) before reinstatement, and e) after ToR.
- Study 2, day 1: a) before picture habituation, b) after acquisition; day 2: c) before extinction d) after extinction, e) after glucose administration; day 3: f) before re-extinction (extinction recall), g) before reinstatement, h) after reinstatement, and i) after ToR.

After fear acquisition, contingency awareness was assessed by asking participants to indicate which of the pictures was followed by the electroshock. For Study 2, additional contingency awareness was assessed at the end of day 3. At the end of both experiments, participants were asked to indicate which substance they believed was administered to them ("glucose", "placebo (sweetener)", "I don't know").

2.6. Physiological measures

Fear potentiated startle (FPS) and skin conductance responses (SCR) were collected to represent different dimensions of fear learning (see Lonsdorf et al., 2017). For FPS responses, EMG activity (μV) of the orbicularis oculi was measured using two active Ag–AgCl electrodes (11 × 17 × 4.5 mm; BioSemi FLAT Active electrode, BioSemi, Amsterdam, Netherlands). The amplitude of the startle response was calculated by computing the difference between baseline (mean EMG in a 50ms window before acoustic stimulus) and peak startle response (highest value within 20–150ms after acoustic stimulus), and trials with artifacts were scored as missing. Trials with no visible startle response were scored as zero, which were included in the calculation of FPS magnitudes. Startle responses during the presentation of CS+ and CS– were measured to assess fear learning, while startle responses during noise alone trials were measured to assess contextual fear (Ferreira de Sá et al., 2020; Haaker et al., 2014; Missig et al., 2010).

SCR (μS) was measured using two passive Nihon-Kohden electrodes (11 × 11 × 3 mm; BioSemi Galvanic Skin Response Sensor, BioSemi, Amsterdam, Netherlands), filled with isotonic gel and attached to thenar and hypothenar eminence of the participant's nondominant hand. The maximum responses (highest value within 0–7s after CS onset) were subtracted from the average baseline responses (mean SCR in a 2s window before CS onset) to obtain the SCR size (Bentz et al., 2013; Bos et al., 2012; Ferreira de Sá et al., 2020; Vriends et al., 2011; Wegerer et al., 2013).

Physiological data was recorded with ActiveTwo-Software (BioSemi, Amsterdam, Netherlands) at a sampling rate of 2048 Hz, and the data was further analyzed with Autonomic Nervous System Laboratory (ANSLAB) version 2.6 (Blechert et al., 2016) and by manual inspection. Missing data and outliers ($|Z|>3$) from startle (Study 1: 2.2%, Study 2: 1.8%) and SCR (Study 1: 1.6%, Study 2: 2.2%) were replaced by linear trend at point for each participant, and separately for each experimental phase and CS-type (Brueckner et al., 2019; Sevenster et al., 2014). In accordance with established guidelines, startle amplitudes (FPS) and SCR size were *T*-scored to minimize between-participants variability (Blumenthal et al., 2005; Boucsein et al., 2012; Dawson et al., 2007; Lonsdorf et al., 2017). For Study 2, standardization of physiological data was performed separately for each day of the study. To compare between-group differences in Study 1, analysis of NA startle reactions was conducted using raw scores and startle amplitudes were not standardized, since standardized NA startle reactions might be influenced by startle responses to CS+ and CS–. For analysis of NA startle reactions in Study 2, standardized NA startle reactions were used to better account for intra-individual differences between the three experimental days (e.g., due to slightly different placement of startle electrodes or different skin conductance; see supplemental information for analyses of NA startle reactions in Study 2 using raw scores).

2.7. Statistical analysis

Statistical analysis was performed using IBM SPSS (version 29; IBM, Armonk, USA) with a significance level of $\alpha = 0.05$. Similar to other studies with multiple outcome measures, data were analyzed separately by SCR, FPS, and US expectancy (Gerlicher et al., 2019; Mertens et al., 2021; Newsome et al., 2023).

For both studies, conditioning to the CS+ was assessed with a mixed-design ANOVA with Group as between-subjects factor, and CS-type (CS+ vs. CS–), as well as Time (physiological data: Block 1–6, each with two trials of each CS-type; US-expectancy: pre vs. mid vs. post) as within-subjects factor. To assess discrimination between CS types, difference scores (CS+ - CS–) of each outcome measure (SCR, FPS, and US-expectancy) were calculated for analyses of extinction, reinstatement, and ToR in Study 1 and for extinction, re-extinction, reinstatement, and ToR in Study 2 (Ferreira de Sá et al., 2020; LaBar et al., 1995; Norrholm et al., 2006).

In study 1, extinction and ToR of physiological data were divided into blocks to represent learning effects resulting from the preceding glucose administration (extinction: three blocks, ToR: two blocks; Brueckner et al., 2019; Eckstein et al., 2019; Ferreira de Sá et al., 2020; Lonsdorf et al., 2017). Mixed-design ANOVAs with Group as between-subjects factor and Time as within-subjects (extinction: early vs. mid vs. late, ToR: early vs. late, reinstatement: late extinction vs. early ToR) were performed. US-expectancy ratings were similarly analyzed with mixed-design ANOVAS with Group and Time (extinction and ToR: pre vs. mid vs. post, reinstatement: post-extinction vs. post-reinstatement). Follow-up analyses of two-way interactions were done with Bonferroni-adjusted pairwise comparisons for each time point, comparing placebo and glucose.

In Study 2, in order to study the effects of glucose administered after the fear extinction, mixed-design ANOVAs with Group as between-subjects factor and Time as within-subjects factor (extinction and re-extinction: early vs. late; reinstatement: late re-extinction vs. early ToR) were performed for the physiological data. US-expectancy ratings were analyzed with a mixed-design ANOVA with Group as between-subjects factor and Time (extinction, re-extinction and ToR: pre vs. mid vs. post; reinstatement: post-re-extinction and post-reinstatement). To additionally test the immediate effects of glucose administration on US-expectancy ratings, a mixed ANOVA was calculated with the between-subjects factor Group (glucose vs. placebo) and Time (post-extinction vs. post-glucose). Follow-up analyses of two-way interactions were done with Bonferroni-adjusted pairwise comparisons for each Time point, comparing placebo and glucose.

For both studies, NA startle trials were analyzed with a mixed-design ANOVA with Group as between-subjects factor and Phase as within-subjects factor (Study 1: acquisition, extinction, ToR; Study 2: acquisition, extinction, re-extinction, ToR).

In addition, and for both studies, subjective ratings of wakefulness, anxiety, stress, and unpleasantness of US were analyzed with mixed-design ANOVAs, with Group as between-subjects factor and Time (Study 1: pre-acquisition, post-acquisition, pre-extinction, post-extinction, post-test-of-reinstatement; Study 2: pre-acquisition, post-acquisition, pre-extinction, post-extinction, post-glucose, pre-re-extinction, post-re-extinction, post-test-of-reinstatement) as within-subjects factor.

When sphericity adjustment was required, the Greenhouse-Geisser correction was applied and adjusted *p*-values are reported in connection with epsilon. A follow-up analysis for contextual anxiety during ToR of Study 2 was performed, using a one-tailed *t*-test between both groups (since a beneficial effect of glucose is hypothesized for all measures).

3. Results

3.1. Study 1

There were no significant differences between groups regarding age, sex distribution, and questionnaire measures (all $ps > 0.05$). Additionally, there were no differences between groups in subjective ratings, nor in the glucose levels at the beginning of the experiment. A significant

increase in blood glucose level was found in participants of the glucose, but not the placebo group, after drink administration ($F_{2, 132} = 29.88$, $p < 0.001$, $\varepsilon = 0.83$, $\eta_p^2 = 0.31$; supplemental information).

3.1.1. Contextual anxiety: NA startle

A significant main effect of Phase ($F_{2, 124} = 29.93$, $p < 0.001$, $\eta_p^2 = 0.33$) indicated, that for all participants contextual anxiety decreased from acquisition ($M = 54.13$, $SE = 4.59$) to extinction ($M = 42.90$, $SE = 3.69$, $p < 0.001$, 95%-CI [6.01, 16.47]), and from extinction to ToR ($M = 39.32$, $SE = 3.74$, $p = 0.033$, 95%-CI [0.21, 6.95]). No main effect of Group ($F_{1, 62} = 2.06$, $p = 0.156$) and no interaction Phase*Group ($F_{2, 124} = 3.20$, $p = 0.058$) were found.

3.1.2. Acquisition

SCR: Acquisition was successful in SCR. Significant main effects of CS-type ($F_{1, 65} = 7.21$, $p = 0.009$, $\eta_p^2 = 0.10$) and Time ($F_{5, 325} = 28.76$, $p < 0.001$, $\varepsilon = 0.66$, $\eta_p^2 = 0.31$) were found. CS+ ($M = 51.88$, $SD = 8.87$) elicited a significantly higher SCR than the CS– ($M = 50.32$, $SD = 6.82$), while overall SCR continuously decreased from block 1 ($M = 55.93$, $SE = 1.01$) to block 2 ($M = 52.01$, $SE = 0.87$, $p < 0.001$, 95%-CI [2.42, 5.42]), and from block 2 to block 3 ($M = 49.51$, $SE = 0.85$; $p < 0.001$, 95%-CI [1.13, 3.88]). No interactions of CS-type*Time ($F_{5, 325} = 0.55$, $p = 0.681$, $\varepsilon = 0.71$), CS-type*Group ($F_{1, 325} = 0.18$, $p = 0.669$), Time*Group ($F_{5, 325} = 0.24$, $p = 0.889$, $\varepsilon = 0.66$), or CS-type*Time*Group ($F_{5, 65} = 0.90$, $p = 0.456$, $\varepsilon = 0.71$) were found (Fig. 3a).

FPS: Acquisition was successful in FPS. Significant main effects of CS-type ($F_{1, 62} = 31.16$, $p < 0.001$, $\eta_p^2 = 0.33$) and Time ($F_{5, 310} = 43.87$, $p < 0.001$, $\varepsilon = 0.85$, $\eta_p^2 = 0.41$) were found. CS+ ($M = 54.35$, $SD = 6.75$) elicited a significantly higher FPS than the CS– ($M = 51.46$, $SD = 6.43$), while overall FPS continuously decreased from block 1 ($M = 59.13$, $SE = 0.77$) to block 2 ($M = 55.12$, $SE = 0.72$, $p < 0.001$, 95%-CI [2.32, 5.70]), from block 2 to block 3 ($M = 52.27$, $SE = 0.62$, $p < 0.001$, 95%-CI [1.36, 4.34]), and from block 4 ($M = 51.84$, $SE = 0.54$) to block 5 ($M = 50.11$, $SE = 0.50$; $p = 0.007$, 95%-CI [0.50, 2.97]). No interactions of CS-type*Time ($F_{5, 310} = 0.89$, $p = 0.483$), CS-type*Group ($F_{1, 62} = 0.02$, $p = 0.891$), Time*Group ($F_{5, 310} = 1.44$, $p = 0.219$, $\varepsilon = 0.85$), or CS-type*Time*Group ($F_{5, 310} = 1.69$, $p = 0.143$, $\varepsilon = 0.85$) were found (Fig. 4a).

US-expectancy: Acquisition was successful in US-expectancy. A significant main effect of CS-type ($F_{1, 66} = 269.41$, $p < 0.001$, $\eta_p^2 = 0.80$) and a significant interaction CS-type*Time ($F_{2, 132} = 269.99$, $p < 0.001$, $\varepsilon = 0.73$, $\eta_p^2 = 0.80$) were found. While US-expectancy significantly increased from pre- ($M = 47.75$, $SE = 3.53$) to mid-acquisition ($M = 81.58$, $SE = 1.85$) for CS+ ($p < 0.001$, 95%-CI [–41.19, –26.47]), US-expectancy continuously decreased from pre- ($M = 52.23$, $SE = 3.41$) to mid- ($M = 19.43$, $SE = 2.63$, $p < 0.001$, 95%-CI [25.50, 40.11]) to post-acquisition ($M = 15.19$, $SE = 2.53$, $p = 0.007$, 95%-CI [1.20, 7.27]) for CS–. No main effect of Time ($F_{2, 132} = 0.16$, $p = 0.715$, $\varepsilon = 0.55$) and no interactions of CS-type*Group ($F_{1, 66} = 1.25$, $p = 0.268$), Time*Group ($F_{2, 132} = 0.01$, $p = 0.936$), or CS-type*Time*Group ($F_{2, 132} = 2.63$, $p = 0.093$, $\varepsilon = 0.73$) were found (Fig. 5a).

3.1.3. Extinction (20 minutes after glucose administration)

SCR: A significant main effect of Time ($F_{2, 130} = 4.53$, $p = 0.015$, $\eta_p^2 = 0.07$) was found. Differential SCR significantly decreased from early ($M = 2.40$, $SD = 6.51$) to late extinction ($M = -0.37$, $SD = 5.72$; $p = 0.009$, 95%-CI [0.75, 5.01]). No main effect of Group ($F_{1, 65} = 1.68$, $p = 0.200$) or interaction Time*Group ($F_{2, 130} = 1.67$, $p = 0.195$, $\varepsilon = 0.92$) were found (Figs. 3b and 6a).

FPS: A significant interaction Time*Group ($F_{2, 124} = 3.24$, $p = 0.041$, $\eta_p^2 = 0.05$) was found, with participants in the glucose group showing significantly smaller differential startle reactions than participants in the

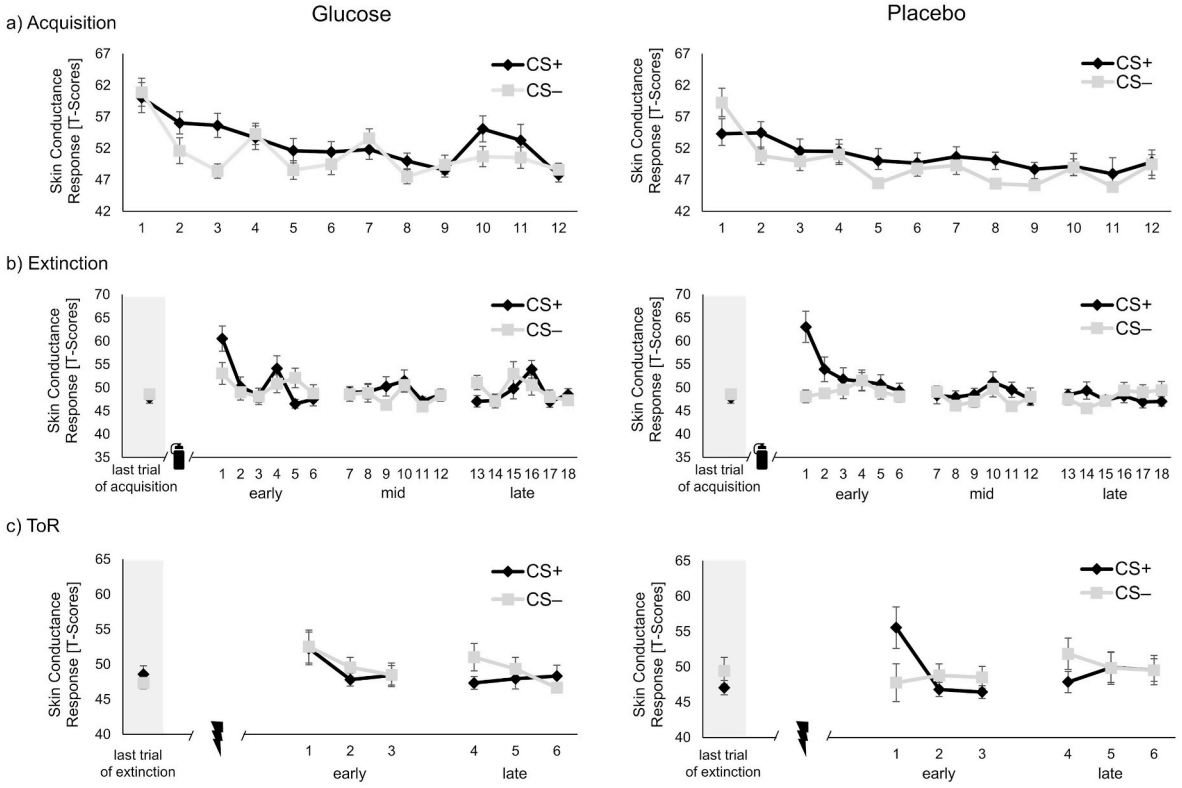

Fig. 3. SCR across phases of Study 1

Note: Standardized skin conductance responses and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, and c) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction and ToR, difference-scores were calculated. (b) Glucose was administered 20 min before extinction. Extinction was divided into three blocks (early, mid, late). Shaded area represents last trial of acquisition. (c) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction.

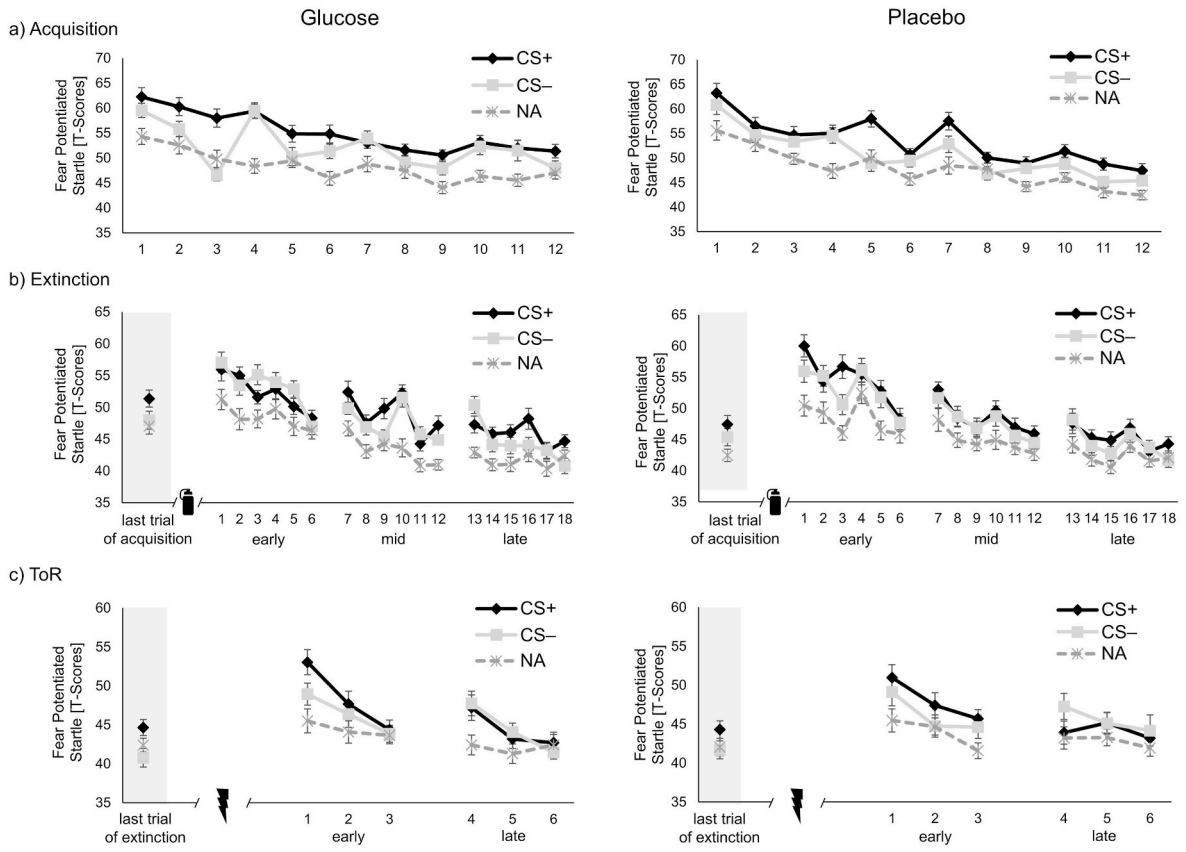

Fig. 4. FPS across phases of Study 1

Note: Standardized fear potentiated startle reactions and standard errors for CS+, CS–, and NA trials during each trial of a) acquisition, b) extinction, and c) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction and ToR, difference-scores were calculated. (b) Glucose was administered 20 min before extinction. Extinction was divided into three blocks (early, mid, late). Shaded area represents last trial of acquisition. (c) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction.

placebo group at early ($M_{glucose} = -0.93$, $SE_{glucose} = 4.32$, $M_{placebo} = 1.70$, $SE_{placebo} = 4.77$, $p = 0.024$, 95%-CI [0.35, 4.89]), but not mid ($M_{glucose} = 1.52$, $SE_{glucose} = 4.44$, $M_{placebo} = 0.81$, $SE_{placebo} = 4.39$, $p = 0.522$, 95%-CI [–2.92, 1.50]) or late extinction ($M_{glucose} = 1.44$, $SE_{glucose} = 3.60$, $M_{placebo} = 0.96$, $SE_{placebo} = 4.18$, $p = 0.625$, 95%-CI [–2.42, 1.47]). For participants in the glucose group, differential startle reactions significantly increased from early ($M_{glucose} = -0.93$, $SE_{glucose} = 4.32$) to mid ($M_{glucose} = 1.52$, $SE_{glucose} = 4.44$, $M_{placebo} = 0.81$, $p = 0.010$, 95%-CI [–4.30, –0.60]), but not from mid to late extinction ($M_{glucose} = 1.44$, $SE_{glucose} = 3.60$, $p = .935$, 95%-CI [–1.95, –2.11]). No main effects of Time ($F_{2, 124} = 0.81$, $p = 0.448$) and Group ($F_{1, 62} = 0.51$, $p = 0.508$) were found (Figs. 4b and 6b).

US-expectancy: A significant main effect of Time ($F_{2, 132} = 67.86$, $p < 0.001$, $\varepsilon = 0.62$, $\eta_p^2 = 0.51$) was found. Overall, US-expectancy decreased from pre- ($M = 58.07$, $SE = 4.48$) to mid- ($M = 22.74$, $SE = 2.44$, $p < 0.011$, 95%-CI [26.96, 43.71]) and from mid- to post-extinction ($M = 10.87$, $SE = 2.40$, $p < 0.001$, 95%-CI [7.11, 16.64]). No main effect of Group ($F_{1, 66} = 0.02$, $p = 0.886$) or interaction Time*Group ($F_{2, 132} = 0.27$, $p = 0.653$, $\varepsilon = 0.62$) were found (Fig. 5b).

3.1.4. Reinstatement

SCR: No main effects of Time ($F_{1, 65} = 0.32$, $p = 0.572$) or Group ($F_{1, 65} = 0.75$, $p = 0.390$) and no interaction Time*Group ($F_{1, 65} = 0.46$, $p = 0.501$) were found (Fig. 3c).

FPS: No main effects of Time ($F_{1, 61} = 0.51$, $p = 0.477$) or Group ($F_{1, 61} = 0.01$, $p = 0.992$) and no interaction Time*Group ($F_{1, 61} = 0.84$, $p = 0.772$) were found (Fig. 4c).

US-expectancy: A significant main effect of Time ($F_{1, 66} = 7.77$, $p = 0.007$, $\eta_p^2 = 0.11$) was found, with differential US-expectancy increasing from post-extinction ($M = 10.78$, $SD = 19.64$) to post-reinstatement ($M = 19.41$, $SD = 24.60$). No main effect of Group ($F_{1, 66} = 0.09$, $p = 0.763$) and no interaction Time*Group ($F_{1, 66} = 0.27$, $p = 0.608$) were found (Fig. 5c).

3.1.5. Test of reinstatement

SCR: No main effects of Time ($F_{1, 65} = 1.13$, $p = 0.292$) or Group ($F_{1, 65} = 0.45$, $p = 0.503$) and no interaction Time*Group ($F_{1, 65} = 0.57$, $p = 0.453$) were found (Fig. 3c).

FPS: A significant main effect of Time ($F_{1, 61} = 5.00$, $p = 0.029$, $\eta_p^2 = 0.08$) was found. Overall, differential FPS decreased from early ($M = 1.72$, $SD = 6.82$) to late ToR ($M = -0.87$, $SD = 5.75$). No main effect of Group ($F_{1, 61} = 0.14$, $p = 0.715$) and no interaction Time*Group ($F_{1, 61} = 0.33$, $p = 0.570$) were found (Fig. 4c).

US-expectancy: A significant main effect of Time ($F_{2, 132} = 4.19$, $p = 0.033$, $\varepsilon = 0.66$, $\eta_p^2 = 0.06$) was found. Differential US-expectancy significantly decreased from mid- ($M = 18.71$, $SE = 2.66$) to post-ToR ($M = 13.90$, $SE = 2.43$; $p < 0.001$, 95%-CI [2.31, 7.31]). No main effect of Group ($F_{1, 66} = 1.54$, $p = 0.219$) and no interaction Time*Group ($F_{2, 132} = 3.54$, $p = 0.051$, $\varepsilon = 0.66$) were found (Fig. 5c).

3.2. Study 2

There were no significant differences between groups regarding age, sex distribution, and questionnaire measures (all $ps > 0.05$). Additionally, there were no differences between groups in the subjective ratings. Glucose levels were comparable between groups at the beginning of the experiment, but, as expected, a significant increase in blood glucose was seen in the glucose group (vs. placebo) after drink administration

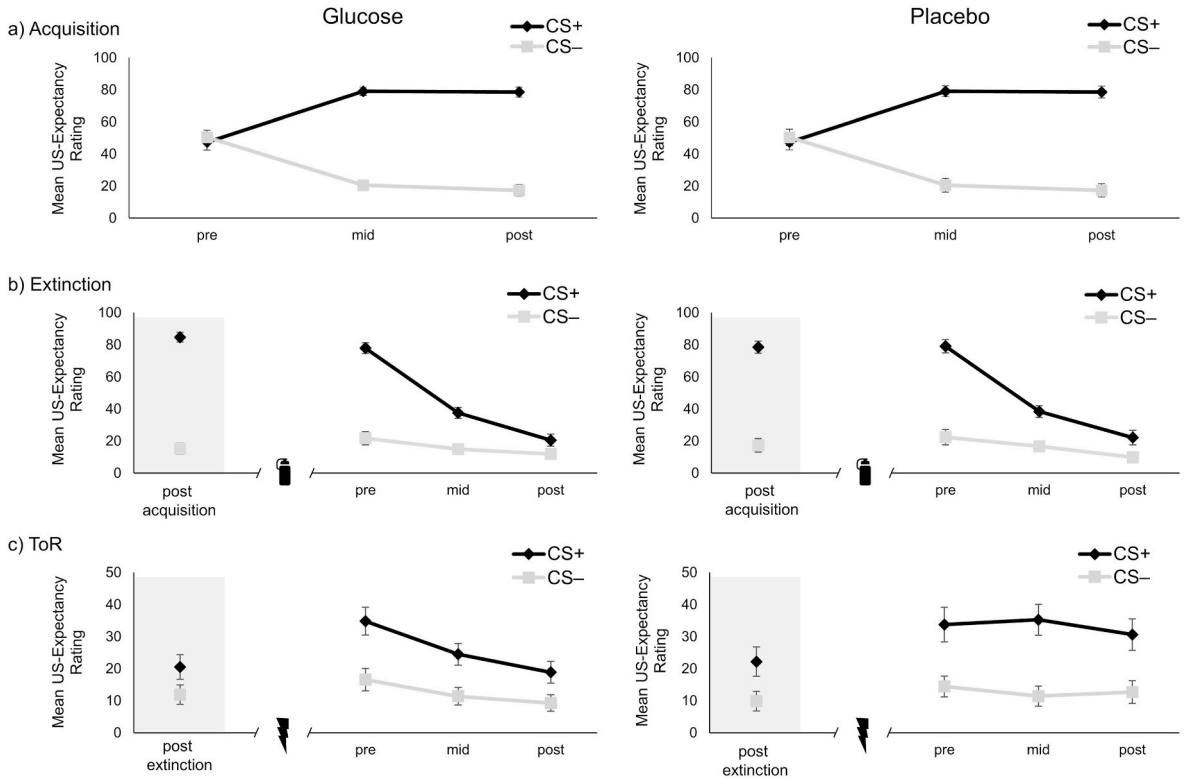

Fig. 5. US-expectancy across phases of Study 1
Note: Mean US-expectancy ratings and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, and c) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction and ToR, difference-scores were calculated. (b) Glucose was administered 20 min before extinction. Shaded area represents last rating after acquisition. (c) For ToR, shaded area represents rating after extinction.

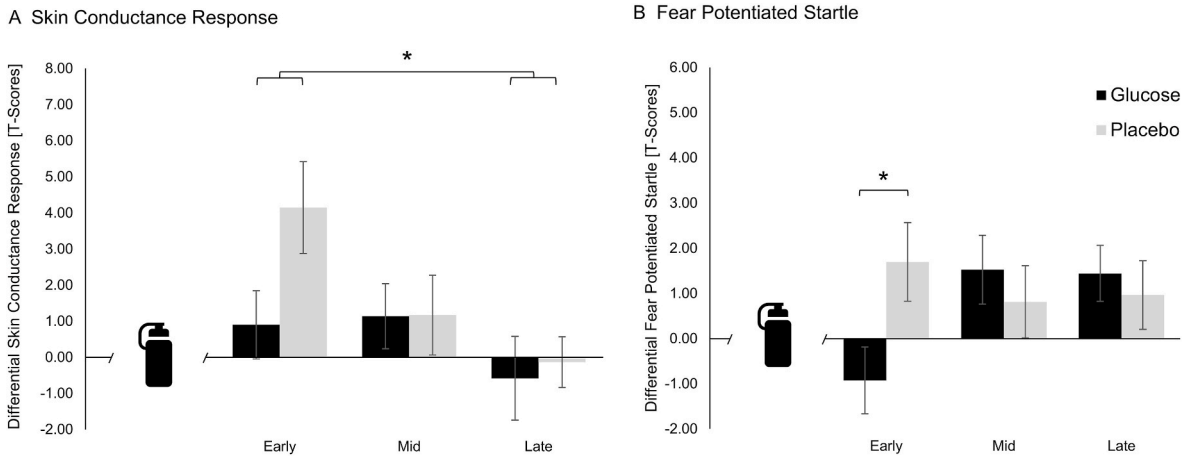

Fig. 6. Differential SCR and FPS during extinction of Study 1.
Note: Glucose was administered 20 min before extinction. *$p < 0.05$.

(Group*Time: $F_{1,\ 81} = 126.80$, $p < 0.001$, $\eta_p^2 = 0.61$; supplemental information).

3.2.1. Contextual anxiety: NA startle

A significant interaction Phase*Group ($F_{3,\ 219} = 3.84$, $p = 0.016$, $\varepsilon = 0.84$, $\eta_p^2 = 0.05$) was found. Descriptively, but not statistically significant, for participants in the glucose group the overall contextual anxiety decreased from acquisition ($M_{glucose} = 47.44$, $SE_{glucose} = 0.48$) to ToR ($M_{glucose} = 46.03$, $SE_{glucose} = 0.73$, $p = 0.316$, 95%-CI [–0.53, 3.35]), while it increased for participants in the placebo group (acquisition: $M_{placebo} = 46.59$, $SE_{placebo} = 0.49$, ToR: $M_{placebo} = 48.07$, $SE_{placebo} = 0.76$, $p = 0.30$, 95%-CI [–3.50, 0.53]; Fig. 7). Follow-up analysis for the ToR phase revealed a significant difference between the groups, with the glucose group showing less contextual anxiety than the placebo group ($t_{73} = 1.93$, $p = 0.029$, $d = 0.45$). No main effects of Phase ($F_{3,\ 219} = 0.30$, $p = 0.792$, $\varepsilon = 0.84$) and Group ($F_{1,\ 73} = 0.25$, $p = 0.622$) were found.

3.2.2. Acquisition (Day 1)

SCR: Acquisition was successful in SCR. A significant main effect of CS-type ($F_{1,\ 82} = 50.35$, $p < 0.001$, $\eta_p^2 = 0.38$), a significant main effect of Time ($F_{5,\ 410} = 38.90$, $p < 0.001$, $\varepsilon = 0.73$, $\eta_p^2 = 0.32$), and a significant interaction of CS-type*Time ($F_{5,\ 410} = 3.57$, $p = 0.008$, $\varepsilon = 0.78$, $\eta_p^2 =$

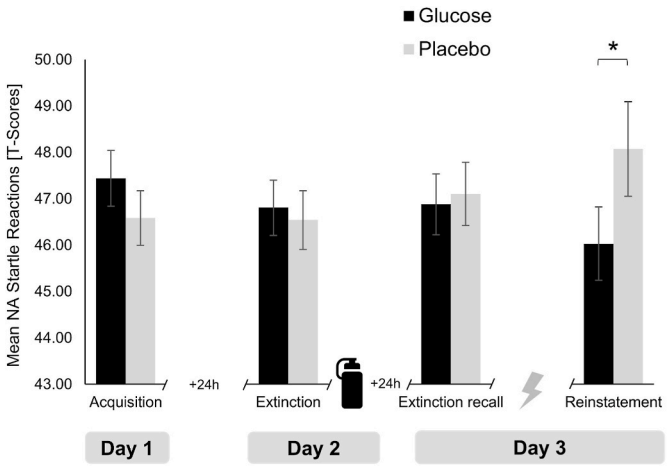

Fig. 7. NA startle reactions during Study 2.
Note: Mean *T*-scores and standard errors of NA startle reactions. Glucose was administered at the end of day 2. * $p < 0.05$.

0.04) were found. As expected, the CS+ elicited an overall higher SCR than the CS– ($M_{CS+} = 52.43$, $SD = 8.42$; $M_{CS-} = 48.78$, $SD = 6.64$). SCR continuously decreased from block 1 ($M = 56.57$, $SE = 0.95$) to block 2 ($M = 51.98$, $SE = 0.73$; $p < 0.001$, 95%-CI [2.06, 7.12]), from block 2 to block 3 ($M = 49.59$, $SE = 0.55$; $p = 0.017$, 95%-CI [0.25, 4.52]), and from block 4 ($M = 51.34$, $SE = 0.70$) to block 5 ($M = 47.18$, $SE = 0.49$; $p < 0.001$, 95%-CI [1.82, 6.51]), with higher SCR for CS+ than CS– at blocks 1–3 (block 1: $M_{CS+} = 59.25$, $SE_{CS+} = 1.21$, $M_{CS-} = 53.89$, $SE_{CS-} = 1.19$, $p < 0.001$, 95%-CI [2.44, 8.28]; block 2: $M_{CS+} = 55.21$, $SE_{CS+} = 1.13$, $M_{CS-} = 48.74$, $SE_{CS-} = 0.67$, $p < 0.001$, 95%-CI [4.19, 8.76]; block 3: $M_{CS+} = 51.36$, $SE_{CS+} = 0.85$, $M_{CS-} = 47.83$, $SE_{CS-} = 0.62$; $p < 0.001$, 95%-CI [1.55, 5.51]) and block 6 ($M_{CS+} = 48.64$, $SE_{CS+} = 0.68$, $M_{CS-} = 45.38$, $SE_{CS-} = 0.41$, $p < 0.001$, 95%-CI [1.87, 4.65]), but not at blocks 4 and 5 (block 4: $M_{CS+} = 52.45$, $SE_{CS+} = 0.98$, $M_{CS-} = 50.23$, $SE_{CS-} = 0.93$, $p = 0.094$, 95%-CI [–0.39, 4.82]; block 5: $M_{CS+} = 47.68$, $SE_{CS+} = 0.69$, $M_{CS-} = 46.67$, $SE_{CS-} = 0.54$; $p = 0.190$, 95%-CI [–0.51, 2.51]). No main effect of Group ($F_{1,\ 82} = 0.09$, $p = 0.771$) and no interactions CS-type*Group ($F_{1,\ 82} = 0.23$, $p = 0.634$), Time*Group ($F_{5,\ 410} = 0.61$, $p = 0.644$, $\varepsilon = 0.73$), and CS-type*Time*Group ($F_{5,\ 410} = 0.28$, $p = 0.886$, $\varepsilon = 0.78$) were found (Fig. 8a).

FPS: Acquisition was successful in FPS. A significant main effect of CS-type ($F_{1,\ 86} = 61.97$, $p < 0.001$, $\eta_p^2 = 0.42$) and a significant main

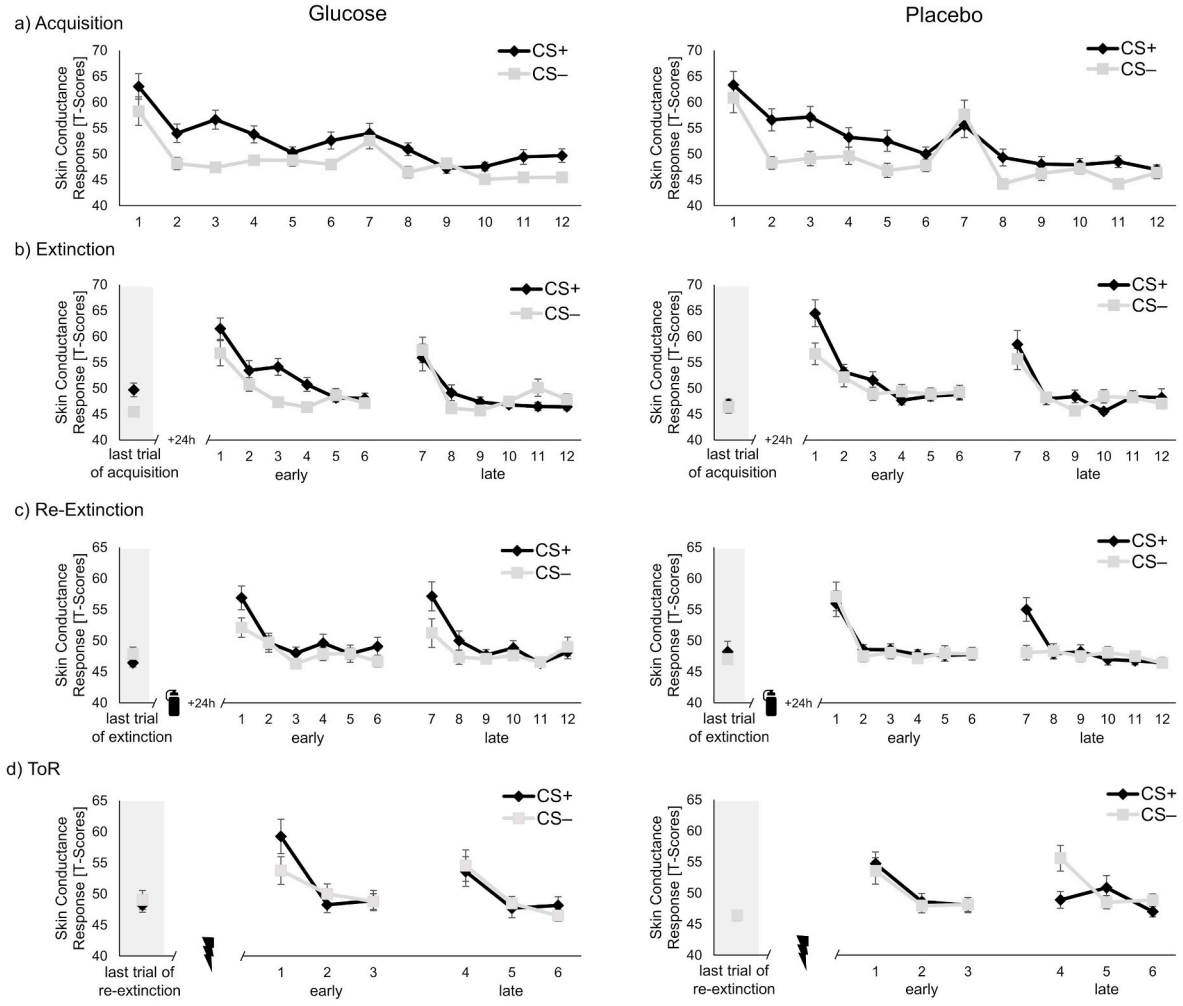

Fig. 8. SCR across phases of Study 2
Note: Standardized skin conductance responses and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, c) extinction recall, and d) test of reinstatement (ToR), separated by group (glucose vs. placebo). (b) Glucose was administered after extinction at day 2. Extinction was divided into two blocks (early, late). Shaded area represents last trial of acquisition at day 1. (c) Glucose was administered 24 h before extinction recall at day 3. Extinction recall was divided into two blocks (early, late). Shaded area represents last trial of extinction before glucose administration at day 2. (d) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction recall at day 3.

effect of Time ($F_{5,\ 430} = 36.11$, $p < 0.001$, $\varepsilon = 0.75$, $\eta_p^2 = 0.30$) were found. As expected, the CS+ elicited an overall higher FPS than the CS– ($M_{CS+} = 52.74$, $SD = 6.54$; $M_{CS-} = 49.18$, $SD = 6.04$). FPS significantly decreased from block 2 ($M = 53.17$, $SE = 0.50$) to block 3 ($M = 50.80$, $SE = 0.50$; $p = 0.005$, 95%-CI [0.46, 4.27]) and from block 4 ($M = 51.56$, $SE = 0.47$) to block 5 ($M = 47.92$, $SE = 0.44$, $p < 0.001$, 95%-CI [2.05, 5.24]). No main effect of Group ($F_{1,\ 86} = 0.25$, $p = 0.621$) and no interactions CS-type*Group ($F_{1,\ 86} = 0.21$, $p = 0.949$), Time*Group ($F_{5,\ 430} = 1.41$, $p = 0.226$, $\varepsilon = 0.87$), CS-type*Time ($F_{5,\ 430} = 2.10$, $p = 0.064$), and CS-type*Time*Group ($F_{5,\ 430} = 1.91$, $p = 0.096$, $\varepsilon = 0.87$) were found (Fig. 9a).

US-expectancy: A significant main effect of CS-type ($F_{1,\ 86} = 369.64$, $p < 0.001$, $\eta_p^2 = 0.81$), a significant interaction CS-type*Time ($F_{2,\ 172} = 188.80$, $p < 0.001$, $\varepsilon = 0.81$, $\eta_p^2 = 0.69$), and a significant interaction Time*Group ($F_{2,\ 172} = 6.53$, $p = 0.008$, $\varepsilon = 0.63$, $\eta_p^2 = 0.07$) were found. As expected, CS+ ($M = 70.27$, $SD = 20.92$) elicited overall significantly higher US-expectancy then the CS– ($M = 25.58$, $SD = 23.57$). While there was no difference in US-expectancy of CS+ and CS– at pre-acquisition ($M_{CS+} = 45.01$, $SE_{CS+} = 2.72$, $M_{CS-} = 44.92$, $SE_{CS-} = 2.76$, $p = 0.968$, 95%-CI [–4.28, 4.46]), significant differences are found at mid- ($M_{CS+} = 83.70$, $SE_{CS+} = 1.94$, $M_{CS-} = 16.96$, $SE_{CS-} = 2.48$, $p < 0.001$, 95%-CI [59.08, 74.41]) and post-acquisition ($M_{CS+} = 82.07$, $SE_{CS+} = 2.00$, $M_{CS-} = 15.25$, $SE_{CS-} = 2.32$, $p < 0.001$, 95%-CI [59.89, 73.74]), indicating successful discrimination at the end of acquisition. While groups did not differ at pre- ($M_{glucose} = 40.47$, $SE_{glucose} = 3.38$, $M_{placebo} = 49.45$, $SE_{placebo} = 3.71$, $p = 0.077$, 95%-CS [–1.00, 18.95]) and mid-acquisition ($M_{glucose} = 49.68$, $SE_{glucose} = 1.50$, $M_{placebo} = 50.98$, $SE_{placebo} = 1.64$, $p = 0.562$, 95%-CI [–3.12, 5.70]), participants in the placebo group showed a general tendency (both for CS+ and CS–) for lower US-expectancy ratings at post-acquisition ($M_{glucose} = 51.89$, $SE_{glucose} = 1.74$, $M_{placebo} = 45.44$, $SE_{placebo} = 1.90$, $p = 0.014$, 95%-CI [–11.57, –1.32]). No main effect of Time ($F_{2,\ 172} = 3.32$, $p = 0.062$, $\varepsilon = 0.63$), no interaction CS-type*Group ($F_{1,\ 86} = 0.42$, $p = 0.520$), and no interaction CS-type*Time*Group ($F_{2,\ 172} = 0.37$, $p = 0.643$, $\varepsilon = 0.81$) were found (Fig. 10a).

3.2.3. Extinction (Day 2)

SCR: A significant main effect of Time ($F_{1,\ 76} = 6.97$, $p = 0.010$, $\eta_p^2 = 0.08$) with a decrease in overall differential SCR from early ($M = 2.37$, $SD = 5.15$) to late extinction ($M = 0.06$, $SD = 5.41$) revealed successful extinction of fear. No main effect of Group ($F_{1,\ 76} = 0.15$, $p = 0.704$) and no interaction Time*Group ($F_{1,\ 76} = 2.42$, $p = 0.124$) were found

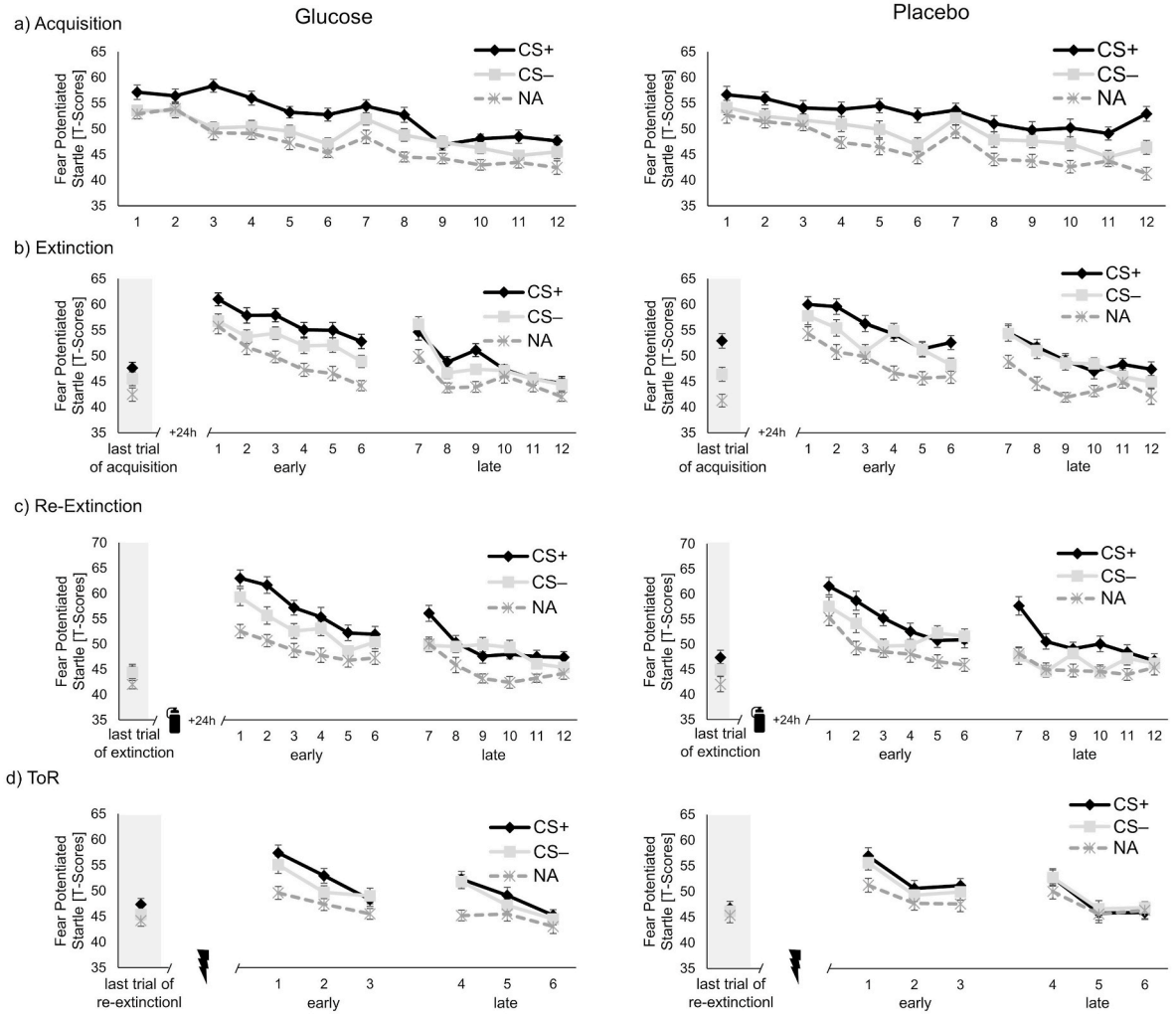

Fig. 9. FPS across phases of Study 2

Note: Standardized fear potentiated startle reactions and standard errors for CS+, CS–, and NA trials during each trial of a) acquisition, b) extinction, c) extinction recall, and d) test of reinstatement (ToR), separated by group (glucose vs. placebo). (b) Glucose was administered after extinction at day 2. Extinction was divided into two blocks (early, late). Shaded area represents last trial of acquisition at day 1. (c) Glucose was administered 24 h before extinction recall at day 3. Extinction recall was divided into two blocks (early, late). Shaded area represents last trial of extinction before glucose administration at day 2. (d) ToR was divided into two blocks (early, late). Shaded area represents last trial of extinction recall at day 3.

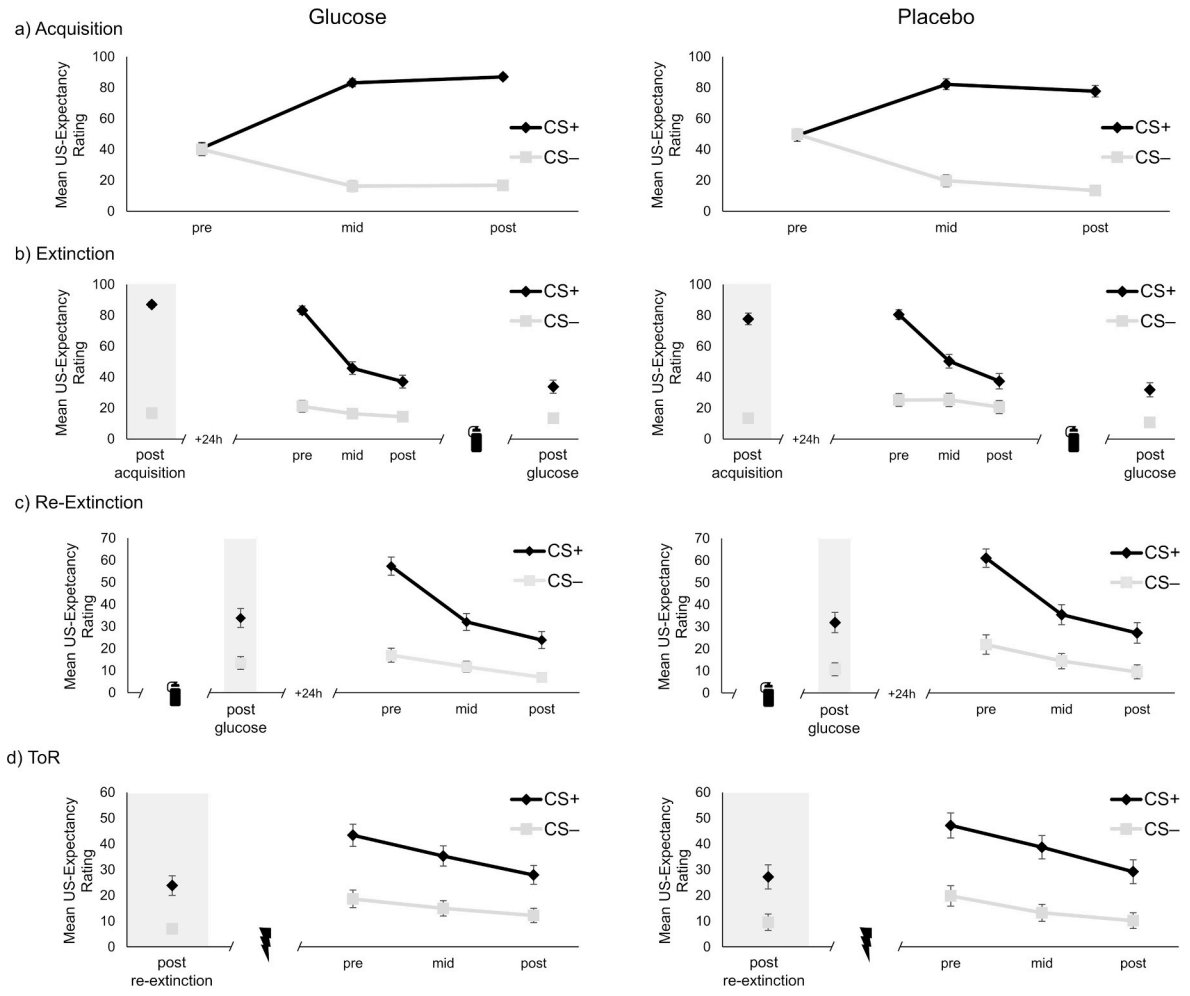

Fig. 10. US-expectancy across phases of Study 2

Note: Mean US-expectancy ratings and standard errors for CS+ and CS– during each trial of a) acquisition, b) extinction, c) extinction recall, and d) test of reinstatement (ToR), separated by group (glucose vs. placebo). For analysis of extinction, extinction recall, reinstatement and ToR, difference-scores were calculated. (b) Glucose was administered after extinction at day 2.20 min after administration, the US-expectancy was assessed again (post glucose). Shaded area represents last rating after acquisition at day 1. (c) Glucose was administered 24 h before extinction recall. Shaded area represents US-expectancy ratings after glucose administration at day 2. (d) For ToR, shaded area represents rating after extinction recall at day 3.

(Fig. 8b).

FPS: A significant main effect of Time ($F_{1, 74} = 7.98$, $p = 0.006$, $\eta_p^2 = 0.10$) with a decrease in overall differential FPS from early ($M = 3.17$, $SD = 5.97$) to late extinction ($M = 0.74$, $SD = 4.96$) revealed successful extinction of fear. No main effect of Group ($F_{1, 74} = 0.28$, $p = 0.598$ = and no interaction Time*Group ($F_{1, 74} = 0.42$, $p = 0.520$) were found (Fig. 9b).

US-expectancy: A significant main effect of Time ($F_{2, 164} = 62.42$, $p < 0.001$, $\varepsilon = 0.75$, $\eta_p^2 = 0.43$) indicated overall successful extinction of fear. Differential US-expectancy continuously decreased from pre- ($M = 58.12$, $SE = 4.21$) to mid- ($M = 26.23$, $SE = 3.09$, $p < 0.001$, 95%-CI [21.91, 41.87]), and from mid-to post-extinction ($M = 19.89$, $SE = 2.89$, $p = 0.030$, 95%-CI [0.46, 12.22]). No main effect of Group ($F_{1, 82} = 1.48$, $p = 0.228$) and no interaction Time*Group ($F_{2, 164} = 0.06$, $p = 0.895$, $\varepsilon = 0.75$) were found (Fig. 10b).

3.2.4. Immediate glucose effects: US-expectancy 20 min after administration (Day 2)

No significant main effects of Time ($F_{1, 81} = 0.19$, $p = 0.663$), Group ($F_{1, 81} = 0.19$, $p = 0.664$) and no interaction Time*Group ($F_{1, 81} = 3.16$, $p = 0.079$) were found (Fig. 10b).

3.2.5. Extinction recall (Day 3)

SCR: No main effects of Time ($F_{1, 72} = 0.32$, $p = 0.574$), Group ($F_{1, 72} = 2.01$, $p = 0.161$), and no interaction Time*Group ($F_{1, 72} = 0.93$, $p = 0.339$) were found (Fig. 8c).

FPS: A significant interaction Time*Group ($F_{1, 71} = 4.09$, $p = 0.047$, $\eta_p^2 = 0.05$) was found, with participants in the glucose group showing significantly smaller differential startle-reactions than participants in the placebo group at late ($M_{glucose} = 1.18$, $SE_{glucose} = 0.93$, $M_{placebo} = 3.91$, $SE_{placebo} = 0.97$, $p = 0.047$, 95%-CI [0.04, 5.40]) but not at early extinction recall ($M_{glucose} = 3.27$, $SE_{glucose} = 0.95$, $M_{placebo} = 2.54$, $SE_{placebo} = 0.97$, $p = 0.592$, 95%-CI [–3.45, 1.99]; Fig. 11b). No main effects of Time ($F_{1, 71} = 0.26$, $p = 0.614$) or Group ($F_{1, 71} = 0.89$, $p = 0.348$) were found (Fig. 9c).

US-expectancy: A significant main effect of Time ($F_{2, 158} = 47.52$, $p < 0.001$, $\varepsilon = 0.64$, $\eta_p^2 = 0.38$) was found, with US-expectancy difference scores decreasing from pre- ($M = 38.99$, $SE = 3.34$) to mid- ($M = 20.90$, $SE = 2.70$, $p < 0.001$, 95%-CI [11.99, 24.18]), and from mid- to post-extinction recall ($M = 17.44$, $SE = 2.60$, $p = 0.022$, 95%-CI [0.39, 6.54]). No main effect of Group ($F_{1, 79} = 0.01$, $p = 0.991$) and no interaction Time*Group ($F_{2, 158} = 0.50$, $p = 0.522$, $\varepsilon = 0.62$) were found (Fig. 10c).

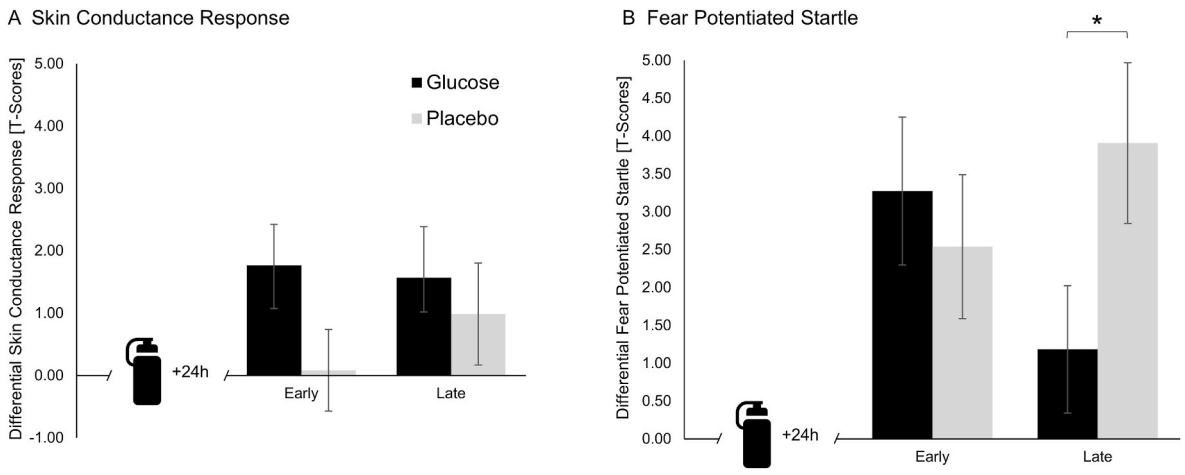

Fig. 11. Differential SCR and FPS during extinction recall of Study 2.
Note: Mean *T*-scores and standard errors of differential SCR and FPS. Glucose was administered 24 h before extinction recall. *$p < 0.05$.

3.2.6. Reinstatement

SCR: No significant main effects of Time ($F_{1, 72} = 0.07$, $p = 0.791$), Group ($F_{1, 72} = 0.40$, $p = 0.528$), and no interaction Time*Group ($F_{1, 72} = 0.01$, $p = 0.967$) were found (Fig. 8d).

FPS: No significant main effects of Time ($F_{1, 71} = 0.96$, $p = 0.332$), Group ($F_{1, 71} = 0.58$, $p = 0.447$), and no interaction Time*Group ($F_{1, 71} = 2.46$, $p = 0.121$) were found (Fig. 9d).

US-expectancy: A significant main effect of Time ($F_{1, 78} = 9.66$, $p = 0.003$, $\eta_p^2 = 0.11$) was found. Differential US-expectancy significantly increased from post-re-extinction ($M = 17.73$, $SD = 23.18$) to post-reinstatement ($M = 26.17$, $SD = 28.06$), indicating successful reinstatement of fear. No main effect of Group ($F_{1, 78} = 0.24$, $p = 0.627$) and no interaction Time*Group ($F_{1, 78} = 0.03$, $p = 0.865$) were found (Fig. 10d).

3.2.7. Test of reinstatement

SCR: No main effects of Time ($F_{1, 72} = 3.38$, $p = 0.070$), Group ($F_{1, 72} = 0.67$, $p = 0.417$), and no interaction Time*Group ($F_{1, 72} = 0.40$, $p = 0.528$) were found (Fig. 8d).

FPS: No main effects of Time ($F_{1, 71} = 1.90$, $p = 0.172$), Group ($F_{1, 71} = 0.50$, $p = 0.484$), and no interaction Time*Group ($F_{1, 71} = 0.15$, $p = 0.705$) were found (Fig. 9d).

US-expectancy: A significant main effect of Time ($F_{2, 156} = 6.11$, $p = 0.005$, $\varepsilon = 0.84$, $\eta_p^2 = 0.07$) was found. Differential US-expectancy ratings did not decrease from pre- ($M = 26.24$, $SE = 3.16$) to mid- ($M = 23.84$, $SE = 2.52$, $p = .999$, 95%-CI [–3.78, 8.58]), but from mid- to post-test-of-reinstatement ($M = 18.03$, $SE = 2.45$, $p = 0.007$, 95%-CI [1.31, 10.32]). No main effect of Group ($F_{1, 78} = 1.08$, $p = 0.302$) and no interaction Time*Group ($F_{2, 156} = 0.37$, $p = 0.654$, $\varepsilon = 0.84$) were found (Fig. 10d).

4. Discussion

The two studies reported here are, to our knowledge, the first to examine the effect of glucose administration on fear extinction processes in a classical fear conditioning paradigm. It can be concluded from both studies that additional to the effects on fear acquisition shown by Glenn et al. (2014), glucose can affect fear extinction and associated memory processes. In Study 1, glucose administration prior to extinction learning promoted faster extinction learning, although no effects on ROF could be found. To examine the effects on early consolidation, glucose was administered after extinction in Study 2. Results pointed to less ROF, namely extinction recall, and to less contextual anxiety during reinstatement on day 3 in the glucose group. However, for both studies, the beneficial effects of glucose were found only in the FPS but not in SCR or US-expectancy.

Acquisition of fear was successful in both studies. This is most evident for declarative learning, which is best illustrated by the US-expectancy results. Although the difference in fear response to CS+ and CS– in the physiological data did not change significantly over the course of the acquisition, the results reflect that participants learned to significantly discriminate between CS+ and CS–. Given that the stimuli were counterbalanced for CS+ and CS-, this effect can be considered essential for demonstrating successful acquisition.

The FPS results of Study 1 indicate differences between the glucose and placebo group in early extinction learning, indicating a faster extinction learning process for participants in the glucose group. This difference at early extinction appears to be due to a lack of potentiation of the CS+ compared to the CS– for participants in the glucose group. This is consistent with other studies in which the FPS response to CS+ was not potentiated at the onset of extinction (Hollandt et al., 2020). The lack of discrimination between CS+ and CS– may indicate an adaptive process of uncertainty that might occur after contextual changes or modified instructions (Hollandt et al., 2020; Mertens & De Houwer, 2016). Although there was no explicit change in the extinction instructions, there was a longer pause between acquisition and extinction, and the extinction instructions left open whether and on which stimulus the electrical stimulus followed. This could have led to an ambiguous evaluation of CS+ and CS–, resulting in higher defensive reflex measures, such as the FPS to the CS–. In a study of uncertainty-intolerant and anxious participants, it was shown that this effect was found only at low levels of intolerance and anxiety, suggesting that this process is adaptive and does not appear to occur in high-risk groups (Wroblewski et al., 2022). Since this effect was observed only in the glucose group, the results of Study 1 could further suggest that glucose specifically supports this functional adaptation process in terms of pronounced psychological flexibility during early extinction under increased uncertainty. This adaptation process is particularly effective at the beginning of a new situation. In Study 1, after the initial adaptation in extinction, the response of the glucose group quickly resembles that of the placebo group, which corresponds to an adequate response in an unchanged evaluative situation. The probability that the predictive content of CS+ and CS– has changed with respect to the US decreases again (i.e., the probability of the CS– predicting the US is low, the probability of the CS+ predicting the US is high), which is why the differentiation between CS+ and CS– consequently increases again.

In Study 2, the FPS results suggest that glucose administration after extinction learning may influence extinction memory consolidation and lead to a slightly lower ROF after 24 h. The fact that this effect is seen only in the late phase of extinction recall on day 3 may indicate that

glucose supports an entirely new learning process, re-extinction learning. However, since the glucose administration had already taken place 24 h before and can no longer have an active effect, this can only be explained by the fact that glucose must have initially influenced the consolidation of the extinction memory after learning on day 2. Re-extinction learning could be facilitated by a better consolidated extinction memory and thus lead to a lower ROF.

While SCR and US-expectancy are associated with declarative learning, FPS reflects automatic, reflexive processes that are relatively unaffected by conscious awareness (Grillon, 2002; Sevenster et al., 2014). Results of the two studies suggest that glucose facilitates the latter processes. These findings contrast numerous studies, which have found glucose to primarily affect declarative memory processes (Scholey et al., 2001; Sünram-Lea et al., 2002). However, given that the paradigm used is a very simple learning task, and that ceiling effects are present with respect to contingency awareness (all participants consciously reported the association between CS+ and US), it seems reasonable why glucose might not provide additional enhancement of declarative memory learning. Studies have shown that declarative fear learning is largely dependent on the hippocampus, whereas the amygdala appears to play an important role in unconscious conditioning processes (Bechara et al., 1995). It is important to note that glucose not only supports hippocampus-dependent processes, but also processes of the amygdala and dorsal striatum, both structures involved in processing emotional content (McGaugh et al., 1996; Owen et al., 2010). Thus, there seems to be a connection between glucose and unconscious fear learning processes, which may explain its beneficial effects seen in FPS.

Both studies presented here differed in timing of glucose administration and could show different effects on fear memory processes. The temporal sequence of acquisition and glucose administration is similar to the study by Glenn et al. (2014), where glucose was administered immediately after acquisition and enhanced acquisition learning. This effect was found 24 h after acquisition, allowing sufficient time for memory consolidation of fear acquisition. In Study 1, and in contrast to Glenn and colleagues, extinction took place 20 min after glucose administration, when blood glucose concentrations are expected to peak (see supplementary materials). For glucose to affect acquisition processes in Study 1, it would have to support both fear memory consolidation and extinction memory encoding simultaneously. Since the design of Study 1 does not allow conclusions to be drawn about consolidation processes, as there is not a sufficiently large time interval between processes, it can be assumed that the effects of glucose found are related solely to extinction processes. Thus, glucose administration prior to extinction learning seems to lead to a faster learning process, whereas subsequent administration leads to a more stable fear extinction memory. In general, glucose availability in the brain appears to have a greater impact on memory consolidation and long-term retrieval, than on short-term memory storage and recall. Studies found that consuming a glucose drink after performing a memory task improved participants' ability to recall the information 24 h, or even one week, after the initial learning session (Foster et al., 1998; Sünram-Lea et al., 2002). This corresponds with the findings from Study 2, where glucose led to a slightly better performance at the retention test 24 h after initial extinction learning. In contrast, the effects of glucose on short-term memory processes seem less consistent. Some studies found that glucose can improve working memory performance in healthy adults (Scholey et al., 2001). However, other studies failed to find an effect of glucose on short-term memory (Benton & Owens, 1993; Foster et al., 1998; Korol & Gold, 1998; Manning et al., 1990). Since a direct effect of glucose on discrimination performance during extinction was found in Study 1, it supports the assumption that glucose could also influence short-term memory processes. There are conflicting findings on the time interval between acquisition and extinction, with some studies arguing that immediate extinction is especially protective against ROF and delayed extinction enhances inhibitory learning in particular (Myers et al., 2006). This could explain why no effects were found during reinstatement in Study 1, whereas a significant effect was found in the ROF manipulation of Study 2. However, other studies found no differences between immediate and delayed extinction (Lonsdorf et al., 2017; Maren, 2014).

Consistent with the improved retention of contextual fear learning shown by Glenn et al. (2014), in Study 2, the glucose group showed reduced extension of fear to ambiguous contextual stimuli. These results on contextual fear further suggest that glucose not only affects fear extinction learning, but also fear expression itself, in which it seems to be protective against arousal effects of the reinstatement. This effect is consistent with the finding of both studies, that glucose supports affective learning processes as indicated by the FPS, as well as suggestions from other studies that glucose can support processes of the amygdala and dorsal striatum (McGaugh et al., 1996; Owen et al., 2010).

Various neurocognitive mechanisms are discussed that underlie the memory-enhancing effect of glucose (see Smith et al., 2011). On the one hand, it is suggested that glucose may mediate insulin as well as acetylcholine delivery to the hippocampus and thus improve memory (Ghasemi et al., 2013). Both acetylcholine and insulin delivery in the hippocampus are central to cognitive functions, since the release of the neurotransmitter acetylcholine is also associated with changes in memory performance (Alzheimer & Wess, 2005; Baxter & Crimins, 2018; Hasselmo, 2006; Kopf et al., 2001). In addition, according to other hypotheses, glucose can increase intraneural adenosine triphosphate (ATP) concentration, which initially leads to blockade of potassium ATP channels and in turn causes depolarization of neurons and increased release of neurotransmitters (Stefani & Gold, 2001). Moreover, there is suggestions that glucose administration leads to increased extracellular glucose concentrations in the hippocampal region, which may in turn increase the overall availability of glucose under conditions of higher demand and thus lead to an overall improvement in memory (McNay et al., 2000, 2001).

Compared to the reference values from the study by Schäfer and Schwarz (2019) for pre-registered between-subjects design studies in the field of psychology, the effects found can be described as rather small to moderate. Because the glucose intervention was aimed at improving specific anxiety responses, it may have shown more subtle effects in the healthy sample studied, which may be more difficult to quantify than in a study with a clinical sample. In addition, a major limitation of both studies is the small sample size, and in particular the unequal sex distribution, as well as the restriction to young, healthy participants. Although there were no group differences in sex distribution, overall, more women participated in both studies. In a study by Craft et al. (1994), older men benefited more from memory-enhancing effects of glucose than younger men, or older and younger women. Moreover, in a study investigating the effects of intranasal insulin on fear learning processes, women were found to benefit more from memory-enhancing effects of insulin (Ferreira de Sá et al., 2020). Since women are at higher risk for developing ADs (Jalnapurkar et al., 2018; McLean et al., 2011) and there are also sex differences in glucose-sensitive brain structures of anxiety patients, such as in hippocampus and amygdala (Irle et al., 2010), it would be relevant to examine the extent of which glucose affects fear memory processes differently between sexes. This should be investigated in future studies with bigger sample sizes and comparable sex distribution.

In addition, both studies show a pattern of sudden increases in fear responses in the middle of each conditioning phase. This pattern is best explained by the behavioral ratings that took place in the middle of each phase. As described above, these interruptions could trigger uncertainty processes similar to those in context change studies (e.g., Hollandt et al., 2020; Mertens & De Houwer, 2016), leading to a short-term re-evaluation, especially of CS–, and thus to changes in the discrimination performance of CS+ and CS–. This effect may have influenced the pattern of fear conditioning responses presented here, although it is important to note, that this was similar for both groups and therefore cannot explain the group differences found. Similar to the interruption caused by

ratings in the laboratory studies described here, interruptions also occur in the real world, and even between or within individual exposure therapy sessions. If such brief interruptions can have an effect on fear conditioning processes, as shown in both studies, the implications for everyday, real-world or applied psychotherapeutic work need to be considered. In summary, the two studies presented here provide first evidence that glucose can enhance extinction of fear in healthy participants. Extending the findings by Glenn et al. (2014) on fear acquisition, this study provides first results regarding beneficial effects of glucose on fear extinction processes as glucose appears to be particularly beneficial for the consolidation and long-term retrieval of extinction memory content. In particular, the results confirm the positive influence of glucose on fear memory processes when administered after extinction. Glucose could therefore be administered in a therapeutic context, particularly after successful exposure, which would not only eliminate the potential fear-enhancing effects (Glenn et al., 2014) of failed exposure sessions, but also further improve the success of exposure therapy itself. Further research should investigate additional fear conditioning processes important to the maintenance of psychopathology and resistance to therapy. Additionally, studies with subclinical or clinical samples should also follow. The present results show that glucose is a promising adjuvant to support exposure therapy and its maintenance with the great advantage of being simple to administer, inexpensive, and not unpleasant or invasive to the patient.

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CRediT authorship contribution statement

Alexander Hauck: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tanja Michael:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition. **Tobias C. Issler:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Steven Klein:** Writing – review & editing, Validation, Investigation. **Johanna Lass-Hennemann:** Writing – review & editing, Validation, Methodology. **Diana S. Ferreira de Sá:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data of Study 1. Data of Study 2 will be made available upon request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2024.104553.

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