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Subsequent memory effects on event-related potentials in associative fear learning

Julian Wiemer,[1] Franziska Leimeister,[1] and Paul Pauli[1,2]

[1]Institute of Psychology (Biological Psychology Clinical Psychology, and Psychotherapy), University of Würzburg, Würzburg, Germany, and [2]Center of Mental Health, Medical Faculty, University of Würzburg, Würzburg, Germany

Correspondence should be addressed to Julian Wiemer, Department of Psychology, University of Würzburg, Marcusstr. 9-11, 97070, Würzburg, Germany. E-mail: julian.wiemer@uni-wuerzburg.de.

Abstract

Studies of human fear learning suggest that a reliable discrimination between safe and threatening stimuli is important for survival and mental health. In the current study, we applied the subsequent memory paradigm in order to identify neurophysiological correlates of successful threat and safety learning. We recorded event-related potentials, while participants incidentally learned associations between multiple neutral faces and an aversive outcome [unconditioned stimulus (US)/conditioned stimulus (CS)+] or no outcome (noUS/CS−). We found that an enhanced late positive potential (LPP) to both CS+ and CS− during learning predicted subsequent memory. A quadratic relationship between LPP and confidence in memory indicates a possible role in both correct and false fear memory. Importantly, the P300 to the omission of the US (following CS−) was enhanced for remembered CS−, while there was a positive correlation between P300 amplitude to both US occurrence and omission and individual memory performance. A following re-exposure phase indicated that memory was indeed related to subjective fear of the CS+/CS−. These results highlight the importance of cognitive resource allocation to both threat and safety for the acquisition of fear and suggest a potential role of the P300 to US omission as an electrophysiological marker of successful safety learning.

Key words: subsequent memory effects; fear conditioning; event-related potentials; P300; LPP

Introduction

Learning about threats in the environment is an important ability of virtually any living organism and essential for our life. Aversive conditioning has become the most widely applied paradigm to study the acquisition of memory and behavior dealing with aversive experiences (Lissek *et al.*, 2005; Duits *et al.*, 2015; LeDoux and Pine, 2016; Lonsdorf *et al.*, 2017). In aversive conditioning, a neutral stimulus (conditioned stimulus, CS+) is paired with an innately aversive stimulus (unconditioned stimulus, US). After (usually multiple) pairings, the CS+acquires aversive qualities itself and triggers defensive responses and (potentially) feelings of fear. Usually, an additional control stimulus unpaired with the US predicts safety (CS−). Aversive conditioning studies have advanced our knowledge about the processes involved in fear learning and their associated brain structures, and evidence of aberrant aversive conditioning in anxiety disorders suggests its clinical importance (Lissek *et al.*, 2005; Duits *et al.*, 2015; Ahrens *et al.*, 2016; Marin *et al.*, 2017;

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Cooper *et al.*, 2018). Recently, the necessity has been highlighted to distinguish between conditioned defensive responses and conscious feelings of fear, the latter being at the core of suffering in anxiety disorders (LeDoux, 2014; LeDoux and Pine, 2016).

In its mostly applied version, aversive conditioning involves only a few different CSs, and relatively many pairings with the US, leading to a certain focus on well-learned, subcortically mediated responses. We would like to complement this line of research by shedding light on higher-order cognitive processes, such as the explicit memory of fear-relevant associations. Such explicit memory might be crucial for the generation of conscious feelings of fear and pathological anxiety. Indeed, neuroimaging studies reveal abnormalities in key structures of explicit memory formation. Hippocampus volume predicts successful treatment of panic disorder by cognitive behavior therapy, as well as symptom severity of post-traumatic stress disorder (PTSD) (Reinecke *et al.*, 2014). Further, PTSD patients have been found to suffer from poorer memory performance, which was related to altered activity in fronto-temporal areas (Geuze *et al.*, 2008; Guez *et al.*, 2011).

If explicit memory processes contribute to the formation of pathological fear memory, it would be important to unravel the underlying mechanisms. One particularly useful paradigm for this purpose is the subsequent memory paradigm (Friedman and Johnson, 2000; Paller and Wagner, 2002). In this approach, neural activity during a learning phase is recorded and classified depending on a person's later memory of learned items. This difference in neural responses to correctly and not remembered material, called Dm effect (difference due to memory) or subsequent memory effect (SME), can help to identify memory encoding processes. Studies using neuroimaging found close correlations between the activity of the medial temporal lobe and lateral prefrontal areas and successful recall or recognition of learned items, such as words or faces (Paller and Wagner, 2002). Likewise, electroencephalography (EEG) and event-related potentials (ERPs) reliably differentiated between remembered and forgotten materials. Typically, SMEs in ERPs show a positive deflection usually starting at around 400 ms after stimulus onset for remembered items, but the exact nature of the effects depends on stimulus characteristics and mental operations during encoding (Friedman and Johnson, 2000). For example, distinctive single item encoding with later recall seems to provoke positive amplitudes especially over parietal electrodes, overlapping with the P300 component (Otten and Donchin, 2000). As more associative and elaborative strategies are involved, SMEs are also observed at longer latencies more widely distributed to frontal areas of the scalp, possibly reflecting working memory processes (Fabiani *et al.*, 1986, 1990; Otten and Donchin, 2000; Kamp *et al.*, 2017). In general, while SMEs occur within the first second of stimulus processing, SMEs can continue as slow wave amplitudes beyond 1 s after stimulus onset (Friedman and Johnson, 2000).

ERPs are suited well to capture cognitive processes during associative fear learning due to its high temporal resolution and the possibility to differentiate well between activity related to CS and US and even to the omission of the US. The latter should be particularly interesting considering the meta-analytic findings that in anxiety disorders, increased responses to safety stimuli may be even more relevant than increased fear responses to threat stimuli (Lissek *et al.*, 2005; Duits *et al.*, 2015). Moreover, recent theoretical considerations about optimizing exposure therapy of anxiety disorders emphasize the importance of attention to the non-occurrence of the US (Craske *et al.*, 2014). We agree with this assessment and hypothesize that ERPs can help to capture these attentional processes.

Threatening stimuli in general were found to increase various ERPs like the P300 (Radilová, 1982) and the LPP (late positive potential; Cuthbert *et al.*, 2000; Hajcak *et al.*, 2009, 2010). The P300 is assumed to reflect an incidental working memory update that facilitates memory encoding (Polich, 2012), while the LPP probably reflects sustained attentional processing that varies with emotional arousal (Cuthbert *et al.*, 2000; Schupp *et al.*, 2000; Hajcak *et al.*, 2010). Several aversive conditioning experiments also observed an increased LPP to the CS+ relative to the CS− (Pizzagalli *et al.*, 2003; Kastner *et al.*, 2016; Ventura-Bort *et al.*, 2016).

Based on these findings, we designed a modified subsequent memory paradigm to identify processes that predict successful threat and safety learning. To this end, healthy adults were shown 60 different faces (CS) with half of them associated with an aversive electrical stimulus (US/CS+). After this incidental learning phase, they were asked to identify faces presented with or without an US, and ERPs of remembered *vs* forgotten CS+ and CS− were compared. ERP analyses focused on P300 and LPP, since they were found to be modulated by both threatening stimuli and subsequent memory. While evidence suggests that enhanced LPP responses to the CS+ should be associated with later memory, predictions about CS− are less clear. On one hand, an enhanced LPP should predict better memory of the CS− and the absence of the US. On the other hand, worse memory of its safety character and uncertainty may lead to higher arousal and an enhanced LPP.

Besides responses to CSs, responses to CS outcomes (i.e. the US following CS+ and the omission of the US following CS−) should contribute to associative fear memory as well. Especially, the encoding of the absence of threat might predict successful safety learning. Despite the widespread theory of prediction error signals contributing to associative reward and fear learning (Li and McNally, 2014), outcome responses in aversive conditioning are rarely analyzed. Regarding ERPs to US occurrence, somatosensory evoked potentials are evoked in case of commonly used mildly painful electrical stimuli. Previous investigations showed a positive potential 220–350 ms after US occurrence, temporarily coinciding with the P300 and varying with motivated attention (Kenntner-Mabiala and Pauli, 2005). Regarding ERPs to the omission of a stimulus, early ERP studies demonstrated that the omission of an expected stimulus evokes a P300 wave that seems to be topographically and functionally equivalent to the P300 evoked by admitted stimuli (Sutton *et al.*, 1967; Ruchkin *et al.*, 1981). However, to our best knowledge, ERPs triggered by US omission, respectively CS− offset, have not been investigated so far. Therefore, we examined whether CS− offset in associative fear learning evokes a P300-like potential predicting subsequent memory of the CS− (i.e. memory of safety).

In addition to ERPs, larger pupil diameters also predict later item recall (Goldinger and Papesh, 2012; Kucewicz *et al.*, 2018). Thus, pupil diameter was also recorded as a second measure of SMEs, since it might offer similar results while being a cheaper and faster method.

In order to examine if explicit memory also affects later fear of the CS, we implemented a re-exposure phase in which

participants saw all CSs again and rated the experienced fear, while skin conductance responses (SCRs) and pupil dilation were also measured as indicators of emotional arousal.

In sum, we applied the subsequent memory paradigm to associative fear learning with multiple cues, in order to examine if ERPs during fear acquisition predict successful memory of threat and safety. We expected higher P300 amplitudes to CS+ onset and to both CS+ and CS− offsets, i.e. US occurrence and US omission, respectively, as well as a larger LPP to CS+ onset for remembered *vs* forgotten associations. Moreover, we tested if the P300 and the LPP to CS− onset differed according to subsequent memory in any direction.

Method

Participants

In total, 48 participants took part in this within-subjects designed experiment. One participant did not complete the task, three participants did not generate a sufficient number of 20 remembered trials per condition and three participants were excluded due to EEG artifacts. Thus, the final sample involved $N = 41$ participants. Mean age was $M = 25.88$ years (s.d. $= 6.89$). The sample size was mainly chosen to detect medium effect sizes of SMEs in ERPs. An according power analysis suggested a required sample size of $N = 34$ for a statistical power of 0.80 to detect a medium sized effect (Faul *et al.*, 2007). Since we did not find any previous reports of SMEs to fear-relevant stimuli, we aimed at a sample size of $N = 40$. Participants were recruited via an online recruitment portal of the University of Würzburg. They were compensated with course credit or 30 Euros. Participants had normal or corrected-to-normal vision, and by self-report, had neither suffered from any psychiatric or neurological disease within the past 10 years, nor did they take any psychoactive drugs or medication.

Stimuli

Visual stimuli (CS). Visual stimuli were presented on a 19-inch monitor with a refresh rate of 60 Hz. We used 60 different black and white pictures of male and female neutral facial expressions as conditioned stimuli. The pictures were obtained from the Karolinska Directed Emotional Faces (Lundqvist *et al.*, 1998), the Radboud Faces Database (Langner *et al.*, 2010) and the NimStim Set of Facial Expressions (Tottenham *et al.*, 2009). The pictures were separated into two subsets of 30 pictures each, one serving as CS+ and one as CS−, within one session. The assignment to CS+ and CS− was counter-balanced between participants. In addition, the two subsets were matched for the sex of the models, arousal, attractiveness, and luminance ($P > 0.72$).

Electrical stimulus (US). The aversive US was a mildly painful electrical stimulus applied to the inner side of the left calf via a current stimulator (Digitimer DS7A; Digitimer Ltd, Welwyn GardenCity, UK) and two steel surface electrodes (9-mm diameter; GVB-geliMED, Bad Segeberg, Germany). The electrical stimulation was set to 400 V for 40 ms (10 pulses of 2 ms stimulation with 2 ms breaks). Current intensity was adjusted to individual pain threshold prior to the experimental procedure. Mean current intensity was ($M = 2.56 \pm 1.63$).

Procedure. This study was approved by the ethics committee of the psychological department of the University of Würzburg. First, participants signed formed consent and filled out questionnaires about demographic data. Then, they sat down on a chair in a sound-attenuated, dimly lit testing room, before EEG, SCR and electrical stimulation electrodes were applied.

After adjusting the electrical stimulation to the individual pain threshold, the experiment started with the learning phase. The participants were instructed to pay close attention to the stimuli but were not informed about the subsequent memory rating in the following retrieval phase. All 60 faces were presented once in each of four consecutive blocks with short breaks in between. Thus, every CS+ and every CS− was presented four times with 240 trials in total. The black and white pictures were displayed for 4 s on a grey background (RGB = 144), resembling the luminance of the faces. US were applied at the offset of the pictures. In the inter-trial interval (ITI), a black fixation cross was displayed in the middle of the screen at a random duration of 8–10 s.

Between the learning phase and the retrieval task, participants engaged in a 15 min visuo-spatial cognition task, in which they had to solve three-dimensional puzzles in order to prevent further engaging in the incidental memory task. After this, they saw every CS again and were asked to indicate whether a given picture had been associated with a US, while also indicating the certainty in their judgment. The eight-point scale ranged from −4 (very certain that there was no US) to +4 (very certain that there was a US), leaving out zero. In addition, valence and arousal ratings were obtained for every picture, ranging from 0 (very unpleasant very calm) to 100 (very pleasant very arousing).

Finally, participants were re-exposed to every CS and asked to rate the intensity of fear during the presentation of each CS on a visual analogue scale, ranging from 0 (no fear at all) to 100 (very intense fear). To this end, this re-exposure phase was set up similar to the learning phase, with a picture duration of 4 s and an ITI of 8–10 s. In this phase, 50% of the CS+were followed by a US.

Psychophysiological data acquisition and preprocessing

Electrophysiological data. EEG was recorded using a 32-channel system (ActiCap; Brain Products, Munich, Germany) based on active Ag/AgCl electrodes, placed according to the 10–20 system. Electrophysiological data were registered, amplified (Brainamp; Brain Products, Munich, Germany), referenced to mastoid electrodes and online filtered between 0.01 and 250 Hz at a sampling rate of 1000 Hz. Electrode impedances were kept below 5 kΩ. An electrooculogram was obtained from two horizontal and two vertical eye electrodes. Data collection was controlled with Brain Vision Recorder Version 1.05 and ActiCap Control Software (Brain Products, Munich, Germany).

EEG was offline analyzed using EEGlab v2019.1 (Delorme and Makeig, 2004). The data were first down-sampled to 250 Hz. Bad channels were excluded and interpolated (spherical spline method) based on visual inspection of individual channel power spectra. Across all participants, 16 channels (1.3%) were replaced by this procedure, while the analyzed midline electrodes (Fz, Cz and Pz) were not affected. The data were then decomposed using independent component analysis (Lee *et al.*, 1999) in order to correct for various artifacts. In order to get a replicable classification of artifacts, the EEGlab plugin IClabel (Pion-Tonachini *et al.*, 2019) was used to reject components with a probability of $\geq$0.70 of being classified as either an eye artifact, muscle artifact, heart artifact, line noise or channel noise. In addition,

Table 1. Number of trials in conditions

		CS− remembered	CS− forgotten	CS+ remembered	CS+ forgotten
	Total	42.05 ± 17.40	77.95 ± 17.40	46.15 ± 17.77	73.85 ± 17.77
CS onset	EEG	39.46 ± 16.27	71.88 ± 16.43	43.71 ± 15.77	67.39 ± 16.64
CS offset	EEG	39.71 ± 16.56	72.54 ± 16.17	41.27 ± 16.35	62.39 ± 16.42

Note: Mean number of trials (±s.d.) per condition in total and left after artifact rejection for EEG analysis.

in three participants, a strong electrical shock artifact was visible over Fz and removed by manually identifying the according component. The data were then high-pass filtered (0.1 Hz) and segmented into epochs between −200 ms pre-stimulus and 1000 ms post-stimulus. Artifact rejection was based on an amplitude threshold (−100 to +100 μV) and a joint probability threshold (s.d. = 5). Four participants were discarded from the following analysis, because more than 25% of trials were rejected. The application of such an a priori criterion follows recommendations by Luck (2014). The remaining participants displayed an average rejection rate of 8.5%. Mean rejection rates per condition can be obtained from Table 1. Epochs were averaged for each of the following conditions: CS+ remembered, CS+ forgotten, CS− remembered and CS− forgotten. Since both the P300 and the LPP are typically observed at centro-parietal electrodes (Picton, 1992; Schupp *et al.*, 2000), we focused on the three midline electrodes Fz, Cz and Pz. The amplitude of the P300 was calculated as the mean amplitude between 200 and 400 ms following the CS onset or offset, as the peak of the P300 occurs around 300 ms in rather simple tasks (Picton, 1992) and did so in the present experiment—regardless of conditions. The amplitude of the LPP was calculated as the mean amplitude between 400 and 1000 ms following the CS onset, since the LPP is conceptualized as occurring after the P300 and can be observed until one second after stimulus presentation and beyond (Hajcak *et al.*, 2010). For ERP plots, data were low pass filtered (20 Hz).

Pupil dilation and skin conductance. A detailed description of pupil dilation and skin conductance analysis can be found in Supplementary details.

Data analysis

The data were analyzed using SPSS Statistics (Version 25, IBM) Ratings, ERPs, pupil dilation and SCRs were analyzed with repeated-measures ANOVAs. Remembered and forgotten associations were based on individual memory ratings and defined as follows: in general, high confidence hits (+4 and +3 for CS+; −4 and −3 for CS−) were averaged to the remembered condition, while all other items were averaged to the forgotten condition. Since the distribution of confidence ratings differed between individuals and P300 amplitude seems to stabilize at around 20 trials per condition (Cohen and Polich, 1997), the remembered condition was extended to +2 (−2), if +4 and +3 ratings (−4 and −3, respectively) summed up to less than 20 trials ($n = 11$). However, the exclusion of these participants did not change the significance of the reported SMEs.

We further conducted an exploratory trend analysis along memory confidence ratings. Therefore, for each of the analyzed ERP components (P300 to CS+, LPP to CS+, P300 to CS−, LPP to CS−, P300 to US and P300 to US omission), we extracted the mean amplitudes at the electrode where the peak of the component was observed (Pz and Cz), for each of the eight possible memory confidence ratings (−4 to +4). Missing values were substituted by the mean of the whole sample for a given rating category. Substituted values per category ranged from 0 to 16 of 41 participants. Error bars calculated by the original sample size per category can be obtained from Figure 3. Then, one-factorial repeated measure analyses of variance (ANOVAs) were conducted to test for linear and quadratic trends along the confidence ratings.

As supplementary analyses, we also investigated the P100, the N170 and a slow wave between 1 and 4 s post-stimulus. Moreover, a multilevel linear model was run to test for effects of different face identities (see Supplementary details).

If sphericity was violated in ANOVAs, we used Greenhouse–Geisser corrected *P*-values. *T*-tests (two-tailed if not otherwise specified) were run as follow-up tests in order to further resolve significant effects. Means are reported ± standard deviations with Cohen's *d* for repeated measures. In addition, the 95% confidence intervals (CI) are reported for difference values. Finally, we tested Pearson correlations between ERPs and inter-individual differences in memory performance for CS+ and CS− separately. For all analyses, *P*-values below an α-level of 0.05 were considered as statistically significant.

Results

Memory and emotion ratings

Memory. In order to test, if participants were on average able to remember the associations between faces (CS) and electrical stimuli (US), we compared the memory ratings between CS+ and CS−. CS+ ($M = 0.95 \pm 0.98$) received significantly more positive ratings than CS− ($M = -0.61 \pm 0.95$), $t(40) = 7.51$, $P < 0.001$, $d = 1.19$, 95% CI [1.14, 1.98]. Both CS+, $P < 0.001$ and CS− significantly diverged from zero, $P < 0.001$. On average, 39% of CS+ and 35% of CS− were classified as remembered (see Table 1).

Valence. A repeated measures ANOVA with the factors CS (CS+ and CS−) and memory (remembered and forgotten) revealed a significant main effect of CS, $F(1,40) = 31.67$, $P < 0.001$, $\eta_p^2 = 0.44$, and a significant interaction between CS and memory, $F(1,40) = 50.44$, $P < 0.001$, $\eta_p^2 = 0.56$. Further post hoc testing of this interaction revealed that remembered CS− ($M = 58.58 \pm 12.33$) were rated with significantly more positive valence than forgotten CS− ($M = 45.60 \pm 7.33$), $t(40) = 6.72$, $P < 0.001$, $d = 1.28$, 95% CI [9.08, 16.88], while remembered CS+ ($M = 35.42 \pm 13.34$) were rated with significantly less valence than forgotten CS+ ($M = 48.15 \pm 7.68$), $t(40) = 5.80$, $P < 0.001$, $d = 1.17$, 95% CI [8.29, 17.16].

Arousal. A repeated measures ANOVA with the factors CS (CS+, CS−) and memory (remembered and forgotten) resulted in a significant main effect of CS, $F(1, 40) = 63.40$, $P < 0.001$, $\eta_p^2 = 0.61$ and a significant interaction between CS and memory, $F(1, 40) = 79.26$, $P < 0.001$, $\eta_p^2 = 0.67$. Remembered CS+ ($M = 55.77 \pm 22.64$) were reported with significantly higher

arousal than forgotten CS+ ($M = 38.98 \pm 14.92$), $t(40) = 8.12$, $P < 0.001$, $d = 0.88$, 95% CI [12.61, 20.97], while remembered CS− ($M = 25.62 \pm 13.87$) were reported with significantly less arousal than forgotten CS− ($M = 43.28 \pm 15.97$), $t(40) = 7.97$, $P < 001$, $d = 1.18$, 95% CI [−22.14, −13.18].

Learning phase:ERPs

P300 to CS (200–400 ms). The repeated measures ANOVA with the factors CS (CS+, CS−), memory (remembered and forgotten) and electrode (Fz, Cz and Pz), resulted in a significant main effect of electrode, $F(2, 80) = 81.11$, $P < 0.001$, $\eta_p^2 = 0.67$, $\varepsilon_{GG} = 0.65$, as well as significant interactions of CS X Memory, $F(1, 40) = 5.16$, $P = 0.029$, $\eta_p^2 = 0.11$ and Memory X Electrode, $F(2, 80) = 4.16$, $P = 0.035$, $\eta_p^2 = 0.09$, $\varepsilon_{GG} = 0.68$. In order to reveal the direction of these effects, we compared remembered and forgotten associations for each CS and each electrode separately.

Memory effects were significant for CS+, $t(40) = 2.12$, $P = 0.040$, $d = 0.33$, 95% CI [0.03, 1.11], with a larger P300 for remembered ($M = 4.36 \pm 3.90$) *vs* forgotten associations ($M = 3.80 \pm 3.77$), but not for CS−, $P = 0.20$. Regarding the overall location of the SME, we found a difference between remembered and forgotten associations over Pz, $t(40) = 2.35$, $P = 0.024$, $d = 0.34$, 95% CI [0.05, 0.67], but not over Fz or Cz, $P \geq 0.68$ (Figure 1).

LPP to CS (400–1000 ms). A repeated measures ANOVA containing the factors CS (CS+, CS−), memory (remembered, forgotten) and electrode (Fz, Cz, Pz) returned significant main effects of memory, $F(1, 40) = 20.29$, $P < 0.001$, $\eta_p^2 = 0.34$ and electrode, $F(2, 80) = 77.69$, $P < 0.001$, $\eta_p^2 = 0.66$, as well as a significant interaction of Memory X Electrode, $F(2, 80) = 4.69$, $P = 0.022$, $\eta_p^2 = 0.11$, $\varepsilon_{GG} = 0.72$.

The difference between remembered and forgotten associations—irrespective of CS type—was significant for Fz ($M_\Delta = 0.44 \pm 1.14$), $P = 0.018$, Cz ($M_\Delta = 0.77 \pm 1.25$), $P < 0.001$ and

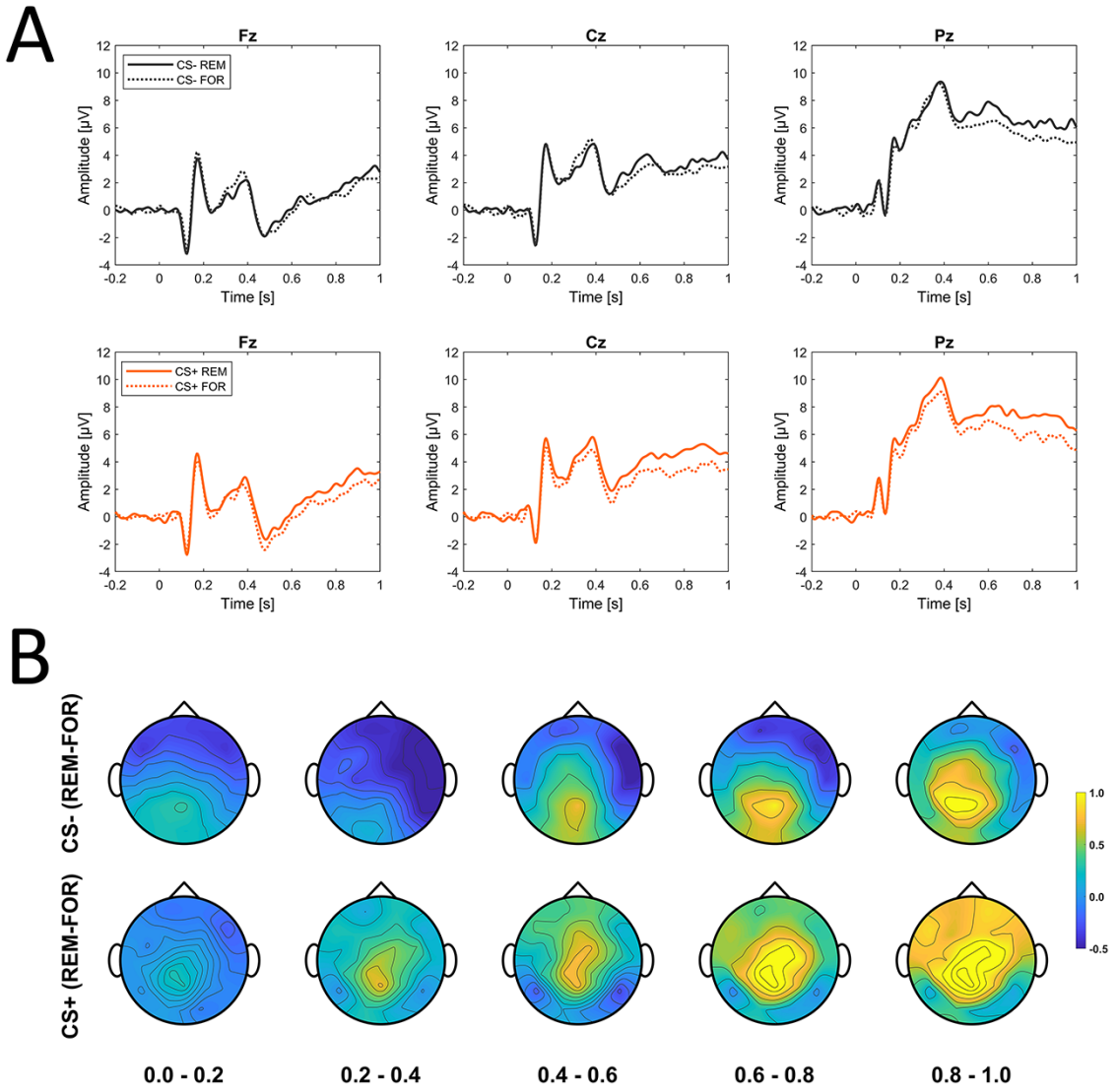

Fig. 1. (A) ERPs in response to CS− (black) and CS+ (orange) onsets. Solid lines depict subsequently remembered associations and dotted lines depict subsequently forgotten associations. An SME was significant for the P300 (200–400 ms) to CS+, but not CS−. For both CS+ and CS−, there was a significant SME for the LPP (400–1000 ms), which was strongest at Pz. (B) ERP topography for SMEs as indicated by the difference between remembered and forgotten CS−/CS+ .

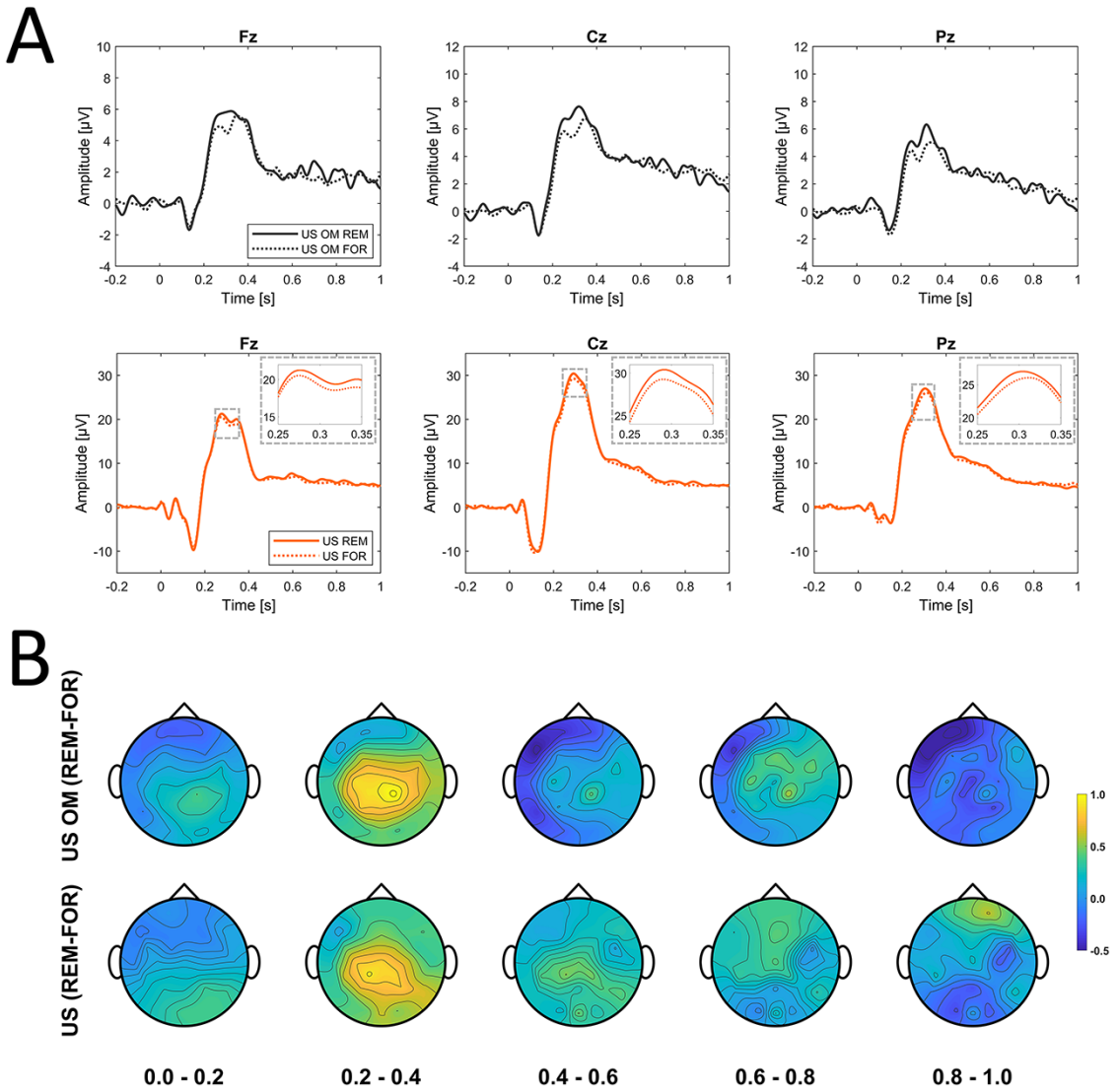

Fig. 2. (A) ERPs in response to US omission (US OM = CS− offset; black) and US (US = CS+ offset; orange). Solid lines depict subsequently remembered associations and dotted lines depict subsequently forgotten associations. A SME was significant for the P300 (200–400 ms) to US omission and for the US. (B) ERP topography for SMEs as indicated by the difference between remembered and forgotten CS− and CS+ offsets.

Pz ($M_{\Delta} = 1.07 \pm 1.54$), $P < 0.001$. However, as indicated by the significant interaction of Memory X Electrode, this SME linearly increased from Fz to Pz, $F(1, 40) = 5.77$, $P = 0.021$ and $\eta_p^2 = 0.13$ (Figure 1). An exploratory analysis of a late slow wave potential from 1 to 4 s suggests that the positive SME continued until the end of CS presentation (see Supplementary details).

P300 to US(200–400 ms). The repeated measures ANOVA containing the factors memory (remembered and forgotten) and electrode (Fz, Cz, Pz) resulted in a significant main effect of memory, $F(1, 40) = 5.34$, $P = 0.026$, $\eta_p^2 = 0.12$, and electrode, $F(2, 80) = 34.72$, $P < 0.001$, $\eta_p^2 = 0.47$, $\varepsilon_{GG} = 0.82$. P300 amplitudes were larger for remembered ($M = 21.18 \pm 6.67$) than forgotten associations ($M = 20.54 \pm 6.48$), $t(40) = 2.31$, $P = 0.026$, $d = 0.36$, 95% CI [0.08, 1.20]. In general, P300 was larger at Cz compared to both Fz and Pz, both $P \leq 0.001$ (Figure 2).

P300 to US omission (200–400 ms). The repeated measures ANOVA containing the factors memory (remembered, forgotten) and electrode (Fz, Cz and Pz) resulted in significant main effects of memory, $F(1, 40) = 12.14$, $P = 0.001$, $\eta_p^2 = 0.23$, and electrode, $F(2, 80) = 11.44$, $P < 0.001$, $\eta_p^2 = 0.22$, $\varepsilon_{GG} = 0.83$; P300 amplitudes were larger for remembered ($M = 5.50 \pm 3.48$) than forgotten associations ($M = 4.69 \pm 3.23$), $t(40) = 3.48$, $P = 0.001$, $d = 0.55$, 95% CI [0.34, 1.27], and more pronounced over Cz than both Fz and Pz, $P < 0.001$ (Figure 2).

Trend analysis for memory confidence and ERPs. For the P300 to CS+, we found a significant quadratic trend, $F(1, 40) = 16.27$, $P < 0.001$, $\eta_p^2 = 0.29$, $\varepsilon_{GG} = 0.76$, but no linear trend, $P = 0.64$. For the LPP to CS+, too, we found a significant quadratic trend, $F(1, 40) = 11.86$, $P = 0.001$, $\eta_p^2 = 0.23$, but no linear trend, $P = 0.14$. For the P300 to CS−, we did not observe linear or quadratic trends, $P \geq 0.44$. For the LPP to CS−, we found a significant quadratic trend, $F(1, 40) = 16.89$, $P < 0.001$, $\eta_p^2 = 0.30$, but no linear trend, $P = 0.46$ (Figure 3).

For the P300 to the US, we found a significant linear trend, $F(1, 40) = 6.14$, $P = 0.018$, $\eta_p^2 = 0.13$, but no quadratic trend,

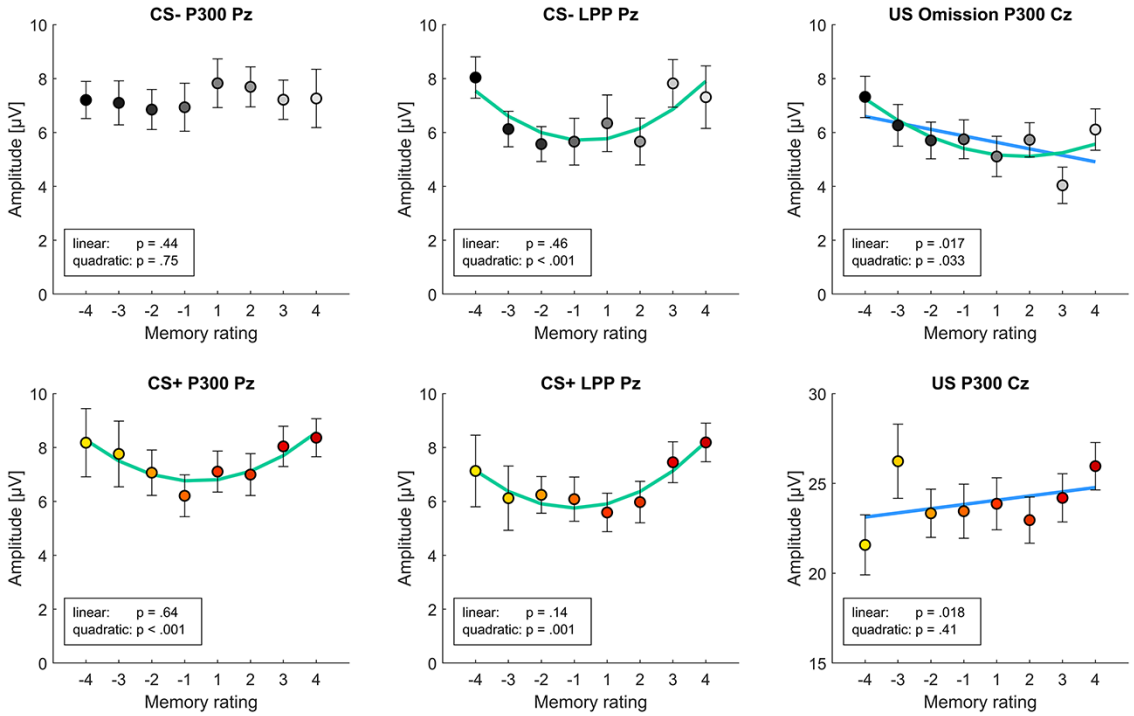

Fig. 3. Exploratory analysis of relationships between ERPs and memory confidence ratings. Blue lines indicate significant linear trends and green lines indicate significant quadratic trends. Quadratic trends may either suggest disproportionately large contributions of high confidence hits to SMEs and/or an additional role of SMEs in high confidence *false* memory. Error bars indicate standard errors of the mean.

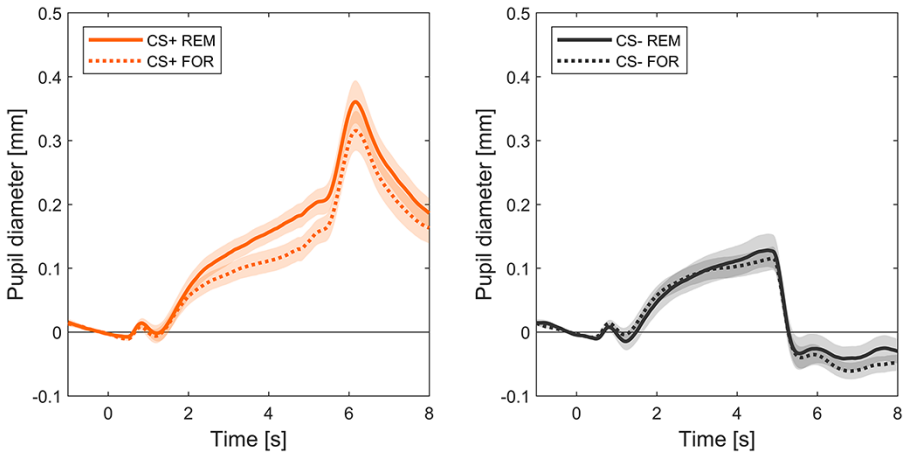

Fig. 4. Pupil dilation in response to CS+ (left) and CS− (right). Solid lines indicate remembered associations, dotted lines indicate subsequently forgotten associations. There was an SME for CS+ between 2 and 4 s. Shaded areas indicate standard errors of the mean.

$P = 0.41$. Finally, for the P300 to US omission, we found both a significant linear trend, $F(1, 40) = 6.21$, $P = 0.017$, $\eta_p^2 = 0.13$, $\varepsilon_{GG} = 0.72$, and a significant quadratic trend, $F(1, 40) = 4.89$, $P = 0.033$, $\eta_p^2 = 0.11$ (Figure 3).

Learning phase: pupil dilation

Pupil dilation was larger for later remembered CS+, but no SME for CS− was found (see Figure 4 and Supplementary details).

Re-exposure phase: fear ratings

In a repeated measures ANOVA with the factors CS (CS+, CS−) and memory (remembered, forgotten), we found a significant main effect of CS, $F(1, 40) = 44.61$, $P < 0.001$, $\eta_p^2 = 0.53$, and a significant interaction between CS and memory, $F(1, 40) = 56.81$, $P < 0.001$, $\eta_p^2 = 0.59$. Remembered CS+ ($M = 50.38 \pm 25.70$) evoked more fear than forgotten CS+ ($M = 36.95 \pm 17.22$), $t(40) = 6.82$, $P < 0.001$, $d = 1.17$, 95% CI [9.95, 17.42], while remembered CS− ($M = 22.29 \pm 13.18$) led to less reported fear than forgotten

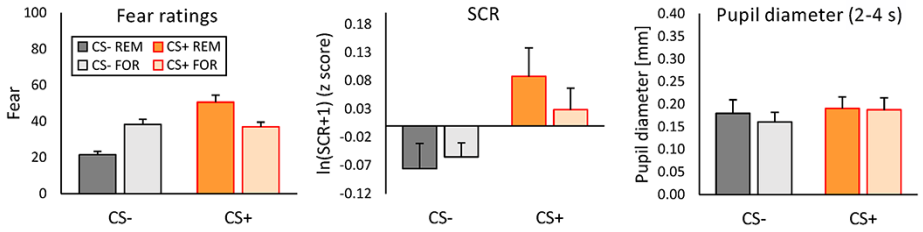

Fig. 5. Responses to CS+ and CS− in the re-exposure phase. Dark colors indicate remembered and light colors indicate forgotten associations. Self-reported fear ratings revealed more fear of remembered CS+ than forgotten CS+ and more fear of forgotten CS− than remembered CS−. SCRs were larger for CS+ than for CS−, but not significantly associated with memory. Pupil diameter did not differ between conditions. Error bars indicate standard errors of the mean.

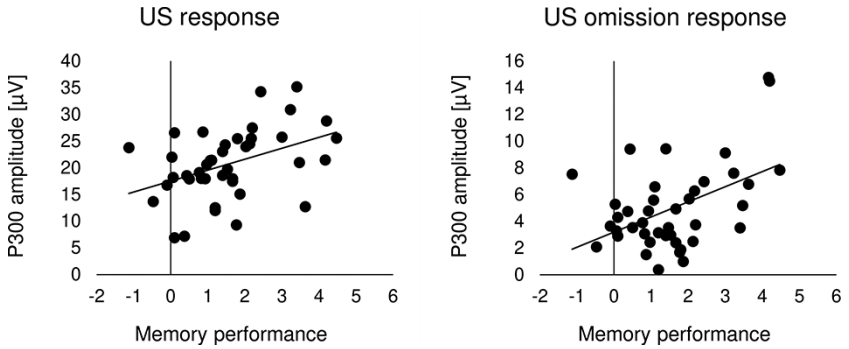

Fig. 6. Across subjects correlations between P300 amplitude to CS+ and CS− outcomes and individual memory performance. Memory performance was calculated as the difference between CS+ and CS− confidence ratings. That is, memory performance was determined by positive ratings for CS+ and negative ratings for CS− with 8 as perfect memory and 0 as random choice.

CS− ($M = 38.07 \pm 18.71$), $t(40) = 6.82$, $P < 0.001$, $d = 1.36$, 95% CI [11.09, 20.47] (Figure 5).

Re-exposure phase: pupil dilation and skin conductance

Pupil dilation did not differ between CS+ and CS−, or remembered and forgotten trials in the re-exposure phase. SCRs were larger for CS+ than CS−, but like pupil dilation, there was no memory effect (see Figure 5 and Supplementary details).

Correlations between ERPs and memory performance

Memory performance significantly correlated with P300 amplitudes to US occurrence, $r = 0.42$, $P = 0.003$ (one-sided), 95% CI [0.13, 0.64], and US omission (Figure 6), $r = 0.47$, $P < 0.001$ (one-sided), 95% CI [0.19, 0.68]. The correlations between memory performance and onset-related ERPs were not significant, $P \geq 0.18$ (one-sided; see Supplementary details).

Discussion

The present study investigating SMEs in an associative fear learning experiment is, to our knowledge, the first that demonstrates relationships between ERPs during fear learning and later explicit memory of threat and safety stimuli. We found that the LPP was enhanced during learning for both remembered CS+ and CS−, relative to forgotten CS+ and CS−, respectively, while the earlier P300 only predicted subsequent memory for CS+, but not for CS−. CS− memory could be predicted by the P300 to US omission (at CS− offset), while CS+ memory was related to P300 to US occurrence (at CS+ offset). Overall, these findings suggest that cognitive resource allocation to the absence of threat is an important prerequisite for successful safety learning and can be measured with ERPs.

Learning an association requires the processing of two stimuli, in the case of conditioning the CSs and the US. Therefore, we also analyzed the participants' electrophysiological responses to CS+ and CS− outcomes, i.e. US occurrence and US omission. Considering that the P300 has also been linked to sensory prediction error signals (Palidis *et al.*, 2019) and the magnitude of prediction error signals is related to subsequent memory in humans (e.g. Jang *et al.*, 2019), the US and its omission might trigger a prediction error and a P300 which ultimately leads to better memory. Here, the effect size of the SME was slightly larger for US omission than the US, suggesting that the P300 response to the outcome may be more important for safety than threat learning. However, this hypothesis is based only on a modest difference in effect sizes.

In addition, the intra-individual differences between remembered and forgotten US omission responses were further confirmed by significant correlations between memory performance and P300 amplitude to US omission. This demonstrates that the SME is independent of our classification of remembered and forgotten trials, i.e. for this correlation it is irrelevant if a confidence rating of 2, 3 or 4 is defined as remembered. Moreover, it should also be independent of stimulus-related features. In contrast, ERPs to CS onsets were not correlated with memory performance, suggesting that these SMEs to CS onsets can be less attributed to inter-individual differences in attention allocation and memory storage processes, but more likely to stimulus-related features, implying that certain stimuli might have been easier to remember than others. In fact, multilevel linear modeling revealed that memory depended on the identity of the faces (see Supplementary details). On the other hand, inter-individual differences in attention and memory seem to be relevant for US

delivery and omission. In this circumstance, differences in neurotransmitter release should be considered as important mediators, especially of these inter-individual effects. Dopamine has been shown to influence P300 (Sohn *et al.*, 1998) and episodic memory formation (Bethus *et al.*, 2010). Similar assumptions could be made for the locus coeruleus-norepinephrine system (Nieuwenhuis *et al.*, 2005; Tully and Bolshakov, 2010).

The finding that the LPP was associated with better memory of the CS+ is in accordance with our expectations and previous experiments showing that subsequently remembered items evoke more positive potentials over midline electrodes during learning (Friedman and Johnson, 2000; Friedman and Trott, 2000). Indeed, an SME in the LPP time window (400–800 ms) had already been demonstrated for emotional pictures (Dolcos and Cabeza, 2002), and the current findings extend this observation to threat conditioned stimuli. Our predictions regarding SMEs in response to the CS− onset were less clear than for the CS+ onset (see introduction). However, the present results show that a positive SME either dominates any potential positivity due to uncertainty, or uncertainty itself promotes subsequent memory, similar to the memory-supporting effect of incongruency or expectancy violations (Stangor and McMillan, 1992).

The LPP is enhanced for both positive and negative emotionally arousing stimuli (Cuthbert *et al.*, 2000; Hajcak *et al.*, 2010). Previous studies showed that this effect is driven by both automatic bottom-up processes and voluntary top-down influences (Codispoti *et al.*, 2006; Hajcak and Nieuwenhuis, 2006; Ferrari *et al.*, 2008). On the neurobiological level, this co-dependency on bottom-up and top-down processes is reflected in functional connectivity between the right prefrontal cortex and bilateral occipito-parietal areas (Moratti *et al.*, 2011). The present results suggest that stronger activity in this network supports the integration of visual information and goal-directed higher order cognitive processing, which increases the chance of explicit memory formation.

For the P300, we found SME effects for the CS+, but not the CS−. These results imply an early onset of memory-related processes for stimuli associated with threat. There is a remarkable amount of evidence showing that emotional stimuli are processed fast and with high priority, as indexed by early neural responses (Pizzagalli *et al.*, 2003), responses to subliminally presented (Liddell *et al.*, 2004) or unidentified fear-relevant stimuli (Wiemer *et al.*, 2013). Also, in the present study, the P100 over Cz was enhanced for CS+ *vs* CS− (see Supplementary details). The results of an early SME for CS+ suggests that this prioritization also primes earlier explicit memory encoding or decoding of fear-relevant associations. Indeed, it has been proposed that the P300 consists of two subcomponents, the P3a and the P3b, while the frontally generated P3a reflects attentional orienting towards a novel or otherwise significant stimulus, and the P3b reflects following temporal-parietal memory storage operations (Polich, 2007, 2012). This initiation of attention and memory processes appears to occur earlier and possibly more bottom-up driven for CS+ than for CS−.

Notably, an exploratory analysis of the relationship between ERPs and memory confidence revealed that the present SMEs are partly qualified by a quadratic relationship with confidence ratings, especially the LPP to CS+ and CS−, and the P300 to CS+. This may be in part explained by a disproportionately strong contribution of high confidence hits to parietal SMEs (Woodruff *et al.*, 2006; Wynn *et al.*, 2019). It suggests that the present results are more related to recollection than familiarity. However, the quadratic trend seemed to be driven not only by high confidence hits, but also by high confidence false alarms. Especially for CS−, the positive parietal component may not only reflect recollection processes, but also increased motivated attention due to false expectations of threat. Future studies may attempt to confirm these findings in order to unravel the underlying mechanisms of false fear memory, which might be especially relevant for pathological fear.

Since the present task was an associative memory task (Mayes *et al.*, 2007), it is likely that the hippocampus was involved in the encoding and the retrieval process. Along with the notion that recollection depends largely on the hippocampus (Skinner and Fernandes, 2007), this indicates that the present SMEs might have been closely accompanied by hippocampal activity. This, however, cannot be examined on the basis of the present EEG data, but may be in the focus of future fMRI studies.

The question which psychological and neural processes underlie successful safety learning has important clinical implications. The present results suggest that enhanced allocation of attentional resources to the CS− and to the offset of the CS− promotes the explicit memory of its safety quality. Very importantly, we also show here that increased explicit memory of the CS− is also associated with decreased feelings of fear when participants were re-exposed to all stimuli after memory retrieval. Overall, this implies that focused attention to the moment in which 'nothing happens' during learning may be one of the most important prerequisites of successful safety learning. It further supports recent suggestions of optimizing exposure therapy of anxiety disorders (Craske *et al.*, 2014). For instance, the first strategy to optimize exposure therapy, suggested by Craske *et al.* (2014), involves expectancy violation and 'attention to both the CS and the non-occurrence of the US'. The present findings strengthen this statement, highlight the importance of explicit memory and shed more light on the underlying neural processes with high temporal resolution. Moreover, the significant correlation across individuals may be a good precondition for the P300 to US omission as a biomarker for successful safety learning. Clinical psychologists might capture P300 responses to measure covered risk factors to guide diagnostics and adjust therapy.

Along with ERPs, we also found enhanced pupil dilation for remembered CS+ in comparison to forgotten CS+, but no SME for CS−. Pupil responses are tightly connected to phasic noradrenergic activity in the brain, and both the pupil and the P300 have been linked to the noradrenergic arousal system in the brain (Murphy *et al.*, 2011; Reimer *et al.*, 2016). The present results suggest that this system might partially mediate memory effects in threat learning. However, unlike ERPs, the pupil was insensitive to CS− memory, possibly due to mutual cancelation of arousal and attention.

As one limitation, it should be noted that the present results regarding SMEs do not allow for a discrimination between initial encoding and following retrieval processes. Unlike most previous subsequent memory experiments, we presented CS–US associations repeatedly in order to generate a sufficient number of remembered associations. The rather low average confidence ratings seem to confirm this approach. As an advantage, the learning phase in this study resembles more the acquisition phase in traditional aversive conditioning paradigms, while at the same time preventing an excessive degree of learning as in aversive conditioning involving only a few different cues.

Further, while fear ratings in the re-exposure phase clearly indicated that the SMEs here were associated with sustained feelings of fear, we did not find any differences due to memory in SCRs. This may be because explicit memory is less important

for the maintenance of fear on the physiological level or habituation of SCRs may have dampened the effects (Leuchs *et al.*, 2019).

In conclusion, this study presents evidence for electrophysiological SMEs in fear learning, with more positive potentials over parietal sites predicting the memory of CS–US associations. While this was true for both CS+ and CS−, the effect showed an earlier onset for CS+. The US omission response highlights the importance of attention to safe outcomes in safety learning and complements recent insights into the optimization of exposure therapy with the P300 as a potential biomarker.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary data

Supplementary data are available at *SCAN* online.

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