scientific reports

OPEN

The impact of emotion on temporal prediction ability in different timing contexts

Sara Terranova[1], Alessandro Botta[2], Martina Putzolu[1,2], Gaia Bonassi[2,3], Carola Cosentino[3], Susanna Mezzarobba[2,3], Elisa Ravizzotti[3], Giovanna Lagravinese[2], Elisa Pelosin[2,3]✉ & Laura Avanzino[1,2]

Our ability to predict temporal events (TP) is dynamically modulated by contextual factors (i.e., different predictive contexts) and closely intertwined with emotional states, shaping our adaptive responses within the environment. While studies have extensively probed how emotions distort time perception, their impact on predictive ability remains unexplored. Here, we investigated emotions' impact on temporal prediction. Participants ($N = 23$) completed a standard implicit TP task and its emotional version (TP-E), using positive (i.e., joy), negative (i.e., fear), and neutral faces as visual stimuli. Reaction times (RTs) to the target were recorded in two predictive contexts: rhythmic (i.e., interstimulus intervals (ISIs) were constant, 900 ms) and single-interval condition (i.e., target's timing estimation was based on the prior exposure of the train of stimuli) and random (no-time context). We found a specific decrease in RTs, in the single-interval context, when fearful stimuli were used, compared to neutral stimuli. This suggests that negative emotion influences temporal prediction, aligning with emotional adjustments in processing threatening situations, including modulation of physiological arousal, cognitive appraisal, and time estimation. Indeed, such modulation of RTs, specifically in the single-interval condition, may be attributed to improved memory and attention, essential cognitive abilities for single-based predictions, enhanced by the exposure to fearful stimuli.

Keywords Time, Temporal prediction, Emotion, Single-interval, Rhythmic

The inner sense of time in humans is a highly flexible system that allows adaptive responses to the environment. Our perception of elapsed time is not always the same, bottom-up (e.g., physiological arousal) and top-down (e.g., attention or cognitive evaluation of stimuli) mechanisms distort its representation (see[1]). This dynamic modulation of temporal perception makes this ability crucial for social interaction[2]. A strand of studies using various standardized emotional stimuli (e.g., facial expression, scenic picture, sound, and video) has indicated a substantial alteration in the perception of elapsed time induced by emotions[3–6]. The emotion-induced distortions have been studied using different temporal paradigms such as time estimation, time reproduction, and duration discrimination[7], leaving the role of emotion in temporal prediction unexplored.

Humans use temporal information to shape behaviour extracting the temporal regularities of an event to predict its future timing properties[8]. This ability is dynamically modulated by contextual features (i.e., different predictive contexts): rhythmic (e.g., speech or music) or memory-based (e.g., the interval between a green and red traffic signal)[9]. Studies using functional magnetic resonance imaging (fMRI)[10,11] and non-invasive brain stimulation techniques[12–14] have elucidated that a large network dealing with temporal prediction includes action- and attention-related cortical areas and subcortical structures, such as basal ganglia and cerebellum. Going deeper into the role of subcortical structures in temporal prediction, a recent work has revealed a double dissociation in neural processes underpinning this ability in a context-dependent manner; basal ganglia has been involved in the formation of temporal predictions in a rhythmic context and cerebellum in building temporal prediction based on single-interval association[9,14]. Specifically, the cerebellum has been observed to be crucial during the building of prediction for longer stimuli (e.g., 900 or 1000 ms of interstimulus intervals (ISIs)) in a single-interval context, integrating the representation of time interval stored in memory with the elapsed time[14].

[1]Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Largo Paolo Daneo 3, 16132 Genoa, Italy. [2]IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [3]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genoa, 16132 Genoa, Italy. ✉email: elisa.pelosin@unige.it

In keeping with this contextual dichotomy in the temporal function, it could be assumed that basal ganglia and cerebellum could participate differently in the modulation of relevant temporal patterns during an emotional event. Indeed, both basal ganglia and cerebellum have been proven to be involved in all components of human emotions, making temporal prediction potentially largely susceptible to emotional-related information[15]. The basal ganglia have been described to have a role in synchronising cortical and subcortical structures processing relevant information to automate response selection[15]. Basal ganglia's role in extracting recurrent emotional sequences could be relevant in rhythmic temporal prediction to automate the motor response during temporal processing. The cerebellum, instead, would more likely modulate emotional processing by encoding subtle differences in irregular temporal patterns embedded in context. Hence, its ability to create internal temporally structure events would allow an effective processing of salient parameters for proper emotional processing[15]. It could be assumed that the cerebellum could fine-tune the emotional and temporal salience to optimize the selection of motor response. Such integration could be pivotal in a memory-based context such as the single interval adopted here.

From these observations, theoretically, emotions may influence temporal prediction ability, potentially observable in both rhythmic and memory-based predictive contexts. However, there exist other differences in the neural processes underlying temporal prediction in rhythmic or memory-based contexts, which may influence the effects of emotion over temporal prediction ability. Whereas rhythmic contexts minimize memory demands because temporal information is embedded in the sensory stream, timing isolated intervals depends on a memory representation of the target interval. This is supported by the finding that isolated interval, but not rhythmic temporal prediction is hampered by a concurrent working memory load[16,17].

Relative to emotionally induced responses, negative stimuli, such as fear, when compared to neutral or positive ones, have been shown to enhance episodic memory for temporal information and to elicit a greater engagement of attentional resources[18]. Consequently, negative stimuli hold a privileged position in memory, leading to a richer encoding and more effective recall[18,19]. Theoretically, the influence of emotions over memory and attention could make temporal prediction in a memory-based context more susceptible to changes in performance in emotional (particularly negative) situations.

Here, we investigated the effect of emotional stimuli on temporal prediction. Twenty-three subjects were exposed to two versions of an implicit temporal prediction task: the standard temporal prediction task (TP) (adapted by[9]) and the emotional version of the TP task (TP-E). In TP-E task we tested whether the exposure to fear, joy, and neutral faces (Facial Action Coding System, FACS) influenced temporal prediction. In both tasks, reaction times (RTs) to the target were recorded in three predictive contexts: rhythmic (i.e., interstimulus intervals (ISIs) were constant, 900 ms) and single-interval condition (i.e., the estimation of the timing of the target was based on the prior exposure of the train of stimuli) and random (no-time context).

According to the evolutionary significance of emotionally induced responses, which heighten sensory, motor, and cognitive responses[20], we hypothesize that emotional stimuli processing may improve the formation of temporal prediction, in predictive temporal contexts, likely fastening RTs, compared to neutral ones. However, we expect that fear-inducing stimuli would exert a greater impact on the formation of temporal predictions, compared to joy stimuli. Notably, negative emotions (such as fear and/or anger), increase the output from an amygdala-centered "pre-attentive threat evaluation mechanisms" and skew attention toward threat-related stimuli[21].

Finally, it can be reasonably argued that random (in which no prediction is required) and rhythmic contexts would not be affected by such improvement in temporal prediction ability. Specifically, fear-induced responses, are also marked by increased engagement of attentional resources and improved episodic memory for temporal information. Indeed, in the rhythmic context, the influence of the emotional content of the stimuli may be less relevant, considering that this context is less dependent on attention and memory, as it comprises an automatic processing of temporal information that may remain unaffected by emotional processing.

Materials and methods

Participants

Twenty-three subjects took part in the study (Female: 13; mean age ± SD: 23.1 ± 2.2 years). Participants were right-handed according to the standard handedness inventory[22], had normal or corrected-to-normal vision, intact colour vision. Subjects with professional musical training or engagement in amateur-level musical activities (within the 3 years preceding the experiment)[9] were not included in the study.

All participants were naïve to the purposes of the experiment and, prior to participation, provided written informed consent. The experimental protocol received approval from the ethics committee at the University of Genoa and was conducted in accordance with legal requirements and international standards outlined in the updated Declaration of Helsinki (2001)[23]. The sample size for our within-subjects experiment was determined a-priori considering the mean sample size of previous studies reported in a recent meta-analysis on the effect of emotion on time perception[7].

Procedure

The experiment took place in a quiet room, participants sat comfortably at 60 cm from the screen. Stimuli presentation and response acquisition were controlled using E-Prime software (E-Prime 3.0, http://www.pstnet.com/eprime). They were required to complete two computerized tasks related to temporal prediction: a standard temporal prediction (TP) task and an emotional temporal prediction (TP-E) task, in two separate sessions (one week apart (7 ± 2 days)).

Temporal prediction (TP) task

The temporal prediction task used in this study was adapted from that proposed by Breska and Ivry (2018). Each trial started with two or three red squares, followed by a fixation cross (served as a Warning Signal (WS)), and then a green square (served as a target). The red squares, the WS and the target were displayed on a 17-inch computer screen, for 100 ms (~3.5° visual angle per side). Participants were asked to press with the right hand the spacebar on the keyboard as quickly as possible once the target appeared. The trials were divided into blocks that differed in their temporal structure: random, rhythmic, and single-interval. The interstimulus intervals (ISIs) between the stimuli changed according to the temporal features of the block, but the ISI between the WS and the target was fixed, across all blocks, at 900 ms. In the rhythmic block, each trial was composed of three red squares, followed by the WS and the target, and ISIs between all stimuli were always the same (i.e., 900 ms); in this condition, all stimuli appeared rhythmically, thus, the target timing was fully predictable. In the single-interval block, each trial consisted of only two red squares, instead of three, followed by the fixation cross and the target. The ISIs between the first two red squares and the WS, as well as the one between the WS and the target, were fixed at 900 ms. However, the ISI between the last red square and the WS was varied randomly, with a mean duration of 2.5 times the WS-target interval (900 ms), resulting in an average of 2.250 ms (jittered variations: −13.3%, −6.6%, 0%, +6.6%, +13.3% of 2.250 ms). In each trial, due to this jittered window, the rhythmicity of the stimuli train was interrupted, and the timing prediction of the target was influenced by the 'beat' established by the repetition of the fixed interval between the two red squares[24].

In the random block, each trial was composed of three red squares, followed by the WS and the target. The ISIs between all stimuli, except for the WS-target interval, were randomly jittered around 900 ms (−33.3%, −16.6%, 0%, +16.6%, +33.3%, uniform distribution). In this block, the timing of the target was unpredictable due to the variability of the intervals.

Before the experimental session, participants performed a practice session of the TP task. The practice session encompassed three blocks (random, rhythmic, and single-interval blocks, 8 trials). After the practice session, the experimental session started including the three blocks (random, rhythmic, and single-interval). Each block consisted of 16 trials (i.e., 16 for random, 16 for rhythmic, 16 for single interval conditions). The order of the block was randomized across participants. Four trials (25%) were catch trials to minimize the anticipatory responses. Each time participants responded too late (3 s from target onset), too early (before the onset of the target) or they responded on a catch trial, a feedback message was sent to the screen.

Emotional temporal prediction (TP-E) task

In the TP-E task, we replaced the visual stimuli used in the TP task with fearful, joyful, and neutral facial stimuli from the Facial Action Coding System database[25]. The stimuli have been displayed on a 17-inches computer screen (4.0° [width] × 6.13° [height]) for 100 ms. The stimuli selected from the FACS database were ovalized to exclude any bias in emotional recognition due to facial external features (e.g., hairstyle, ears)[26].

Additionally, to control for potential confounding factors related to the low-level visual features of the stimuli, first we ensured consistent visual presentation by controlling the refresh rate of the screen via a photosensor and matching it for all the images (data processed via E-Prime 3.0). Furthermore, we kept constant the size of the images (4.0° [width] × 6.13° [height]) for all conditions[27] and for the FACS stimuli, they were presented in 8-bit grayscale, removing potential confounds due to the color tone.

To further rule out bias due to other visual features, we calculated contrast and luminance for each FACS image using MATLAB. To quantify luminance, we calculated the mean pixel intensity for each image, while the contrast was calculated as the standard deviation of the pixel intensities; a higher contrast value indicates an image with more variation. Test-t between the two emotions (fear vs. joy), revealed no significant difference in the luminance (197.3 ± 8.6, 202.2 ± 4.06 $p=0.19$) and contrast values (68.7 ± 8.8, 63.9 ± 10.11 $p=0.24$).

Noteworthy, twenty-eight participants (mean age ± SD: 24.0 ± 3.2 years), not included in the main study, evaluated these stimuli, completing a questionnaire for all the images used in the TP-E task, for ensuring that that stimuli were accurately judged in terms of arousal and valence. Ratings for valence and arousal were assigned on a Likert scale ranging from 1 to 9. A score of 1 signified 'completely unpleasant,' progressing to 9 indicating 'utterly pleasant' for valence. Likewise, a rating of 1 represented 'lack of arousal,' while a score of 9 reflected 'high levels of arousal' on the arousal assessment scale.

During the TP-E task, two or three faces appeared on the computer screen followed by a scramble (served as a Warning Signal (WS)) and a face with glasses (served as a Target) (Ref[28]). The target pictures were made by modifying FACS stimuli chosen as visual stimuli in the experiment. The WS images were created by the same FACS stimuli, pixelated, and scrambled with GIMP software (GIMP 2.10; http://www.gimp.org).

The instructions given to the participant, the temporal structure of the blocks (i.e., random, rhythmic and single-interval), the ISIs chosen for each trial, and the structure of the trials were identical to those for the TP (for the details see the task description in the "Temporal prediction (TP) task" paragraph). As in TP, participants were instructed to press the spacebar as soon as they saw the target (i.e., face with glasses). Differently, trials were also organized into blocks that varied in their emotional content (e.g., random fear, random joy, and random neutral). Within each block (e.g., random fear), all stimuli shared the same emotional expression, including the target (e.g., fear). The practice session consisted of three blocks (random, rhythmic, and single-interval). In each block (e.g., random), there were 4 trials per emotional category (i.e., fear, joy and neutral, 1 catch trials for emotion, 25%), for a total of 12 trials for emotion (e.g., random fear, rhythmic fear, single-interval fear). After the practice session, the experimental session started. It included the three blocks (random, rhythmic, and single-interval) divided for the emotional stimuli used in the trials; Each block consisted of 24 trials, divided into 8 trials per emotion (including 2 catch trials per emotion, 25%). The total number of trials were 72 (24 random, 24 rhythmic, 24 single-interval) (Fig. 1). The order of the block was randomized across participants.

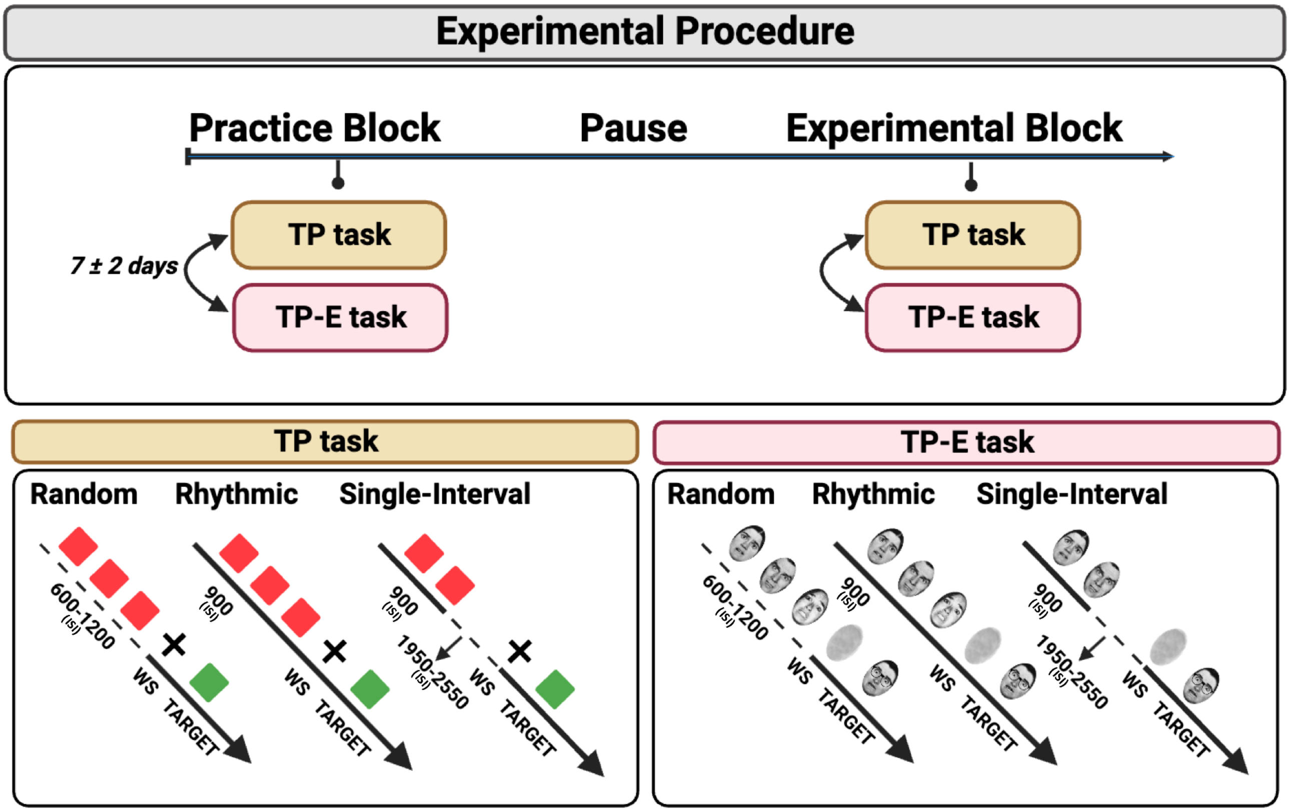

Fig. 1. Overview of the experimental procedure and task design. Participants completed a practice block followed by an experimental block, including the two tasks (i.e., Temporal Prediction (TP) (left panel) task and Emotional Temporal Prediction (TP-E) task (right panel)) in two separate sessions (7 ± 2 days). Both tasks include three temporal conditions: (i) "random", the stream was aperiodic, and no prediction on target appearance can be done; (ii) "rhythmic", the stream was periodic, and the appearance of the target was fully predictable and (iii) "single-interval", the target appearance was predictable based on aperiodic repeated presentation of pairs of stimuli that defined the target interval. In each condition, participants were instructed to press the spacebar when the target appeared (a green square for the TP task, and a face with glasses for the TP-E task). The interval shown in the figure indicates the intervals between successive stimuli within each condition. These intervals are variable according to the temporal feature of the block (i.e., random, rhythmic, and single-interval). In all conditions, however, the interval between the warning signal (WS) and the target was fixed at 900 ms, and the duration of each stimulus was 100 ms. WS, warning signal; ISI, interstimulus interval. Faces depicted in the right panel (TP-E task) were taken from the Facial Action Coding System (FACS) database[25], copyright information available in[25].

Data analysis

We collected the reaction time (RTs) in response to the target. RTs shorter than 100 ms or longer than 3000 ms were discarded (2% of the trials no significant difference between conditions) (see[24]). The RTs from the remaining trials were log-transformed to reduce the skewness inherent in RT distribution[9]. Trials were then discarded if the transformed RT was more than three SDs above or below the mean transformed RT, separately for each condition and target interval (0.5% of trials no significant difference between conditions).

Statistical analysis

Firstly, we used the Shapiro–Wilk test to evaluate if all variables were normally distributed and the Mauchly's test to verify if the sphericity was respected.

Valence and arousal

The mean valence and arousal ratings of the emotional stimuli, obtained from a preliminary experiment (conducted with twenty-eight participants, not included in the main study) were analyzed using nonparametric Friedman ANOVAs, with Emotion (3 levels: Fear, Neutral, and Joy) as a within-subject factor. Post-hoc comparisons were conducted using the Wilcoxon signed-rank test, and effect sizes were estimated using the Kendall's W coefficient for the ANOVA and the r coefficient for the post-hoc tests.

Reaction times

For RT, mean log RTs data of the TP-E task were analyzed via 3 × 3 × 2 RM ANOVA with Emotion (3 levels: Fear, Joy, and Neutral), and Predictive context (3 levels: Random, Rhythmic, and Single-Interval) as within factors.

	Fear	Joy	Neutral	*P*-value
Valence	3.41 ± 1.13	7.29 ± 1.21	4.12 ± 1.23	< 0.001
Arousal	4.60 ± 2.01	6.51 ± 1.56	2.92 ± 1.51	< 0.001

Table 1. Mean ratings (mean ± SD) of valence and arousal for the three emotions (fear, joy, and neutral).

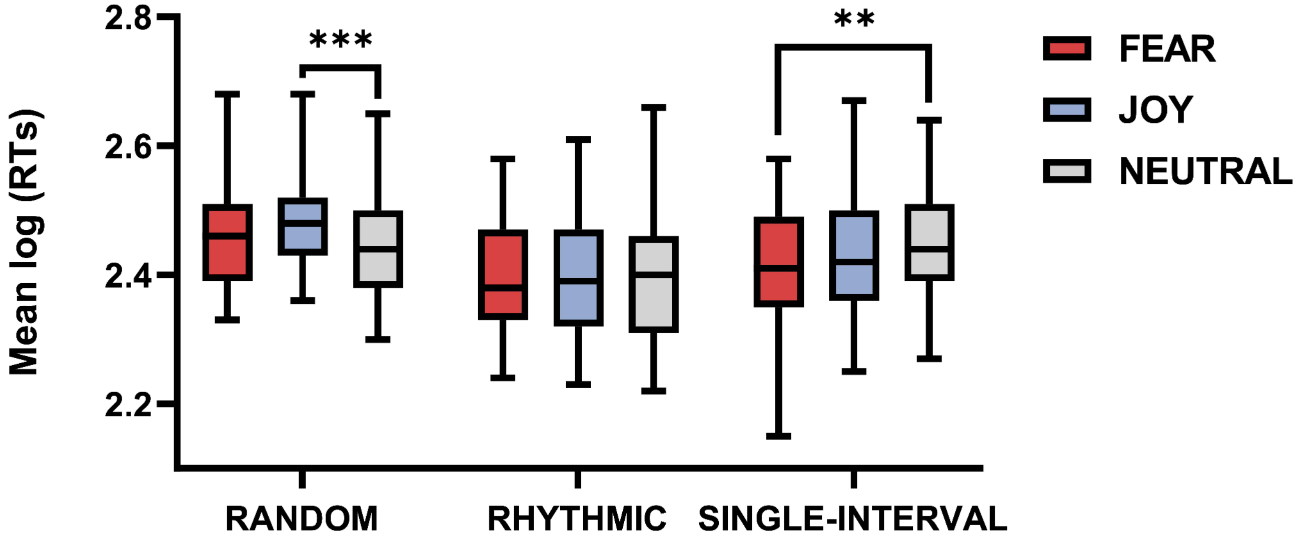

Fig. 2. Mean log reaction times (RTs) data. Results of the significant interaction Condition × Predictive context, RTs were shorter in the neutral condition compared to the joy in the random context. For the single-interval context, RTs were shorter in the fear condition compared to the neutral one. Error bars represent SEM. $^{**}p \leq 0.01$, $^{***}p \leq 0.001$. The values plotted are the minimum and the maximum (whiskers), the median, the 25th percentile and the 75th percentile (hinges).

Then, to exclude baseline differences due to the complexity of biological stimuli (i.e., faces) compared to simple geometric shapes (i.e., squares), we compared the mean log RTs data of the TP task with the neutral condition of the TP-E task. Hence, we conducted a 2 × 3 × 2 RM ANOVA with Task (2 levels: TP, TP-E Neutral) and Predictive context (3 levels: Random, Rhythmic, and Single-Interval) as within factors.

Statistical analyses were performed using Jamovi [The jamovi project (2021). jamovi (Version 1.6) [Computer Software. Retrieved from https://www.jamovi.org]. The significance level was set at $p < 0.05$ and significant interactions were analysed using post-hoc comparisons with Bonferroni correction for multiple comparison.

Results

Ratings of valence and arousal are reported in Table 1. Friedman ANOVAs conducted on mean ratings of arousal and valence were found to be statistically significant (arousal: $\chi^2 = 40.0$, W = 0.49, valence: $\chi^2 = 45.50$, W = 0.56 all $p < 0.001$). Post-hoc analysis revealed that valence scores for fear were significantly lower compared to those for joy and neutral stimuli, while joy scores were significantly higher compared to neutral and fear stimuli (all $p < 0.001$, all $r > 0.55$). Additionally, for arousal, neutral images (all $p < 0.009$) exhibited significantly lower arousal scores compared to joy and fear stimuli and arousal scores for joy were significantly higher than those for fear and neutral (all $p < 0.001$, all $r > 0.73$).

The effect of emotions on temporal prediction ability

The RM ANOVA on mean log RTs obtained from the TP-E task revealed a significant effect of Predictive context [F (2,44) = 16.30; $p = 0.00$, $\eta p^2 = 0.42$]. Post hoc analysis of the main effect revealed shorter RTs in the rhythmic condition (2.40 ± 0.01) compared to single-interval (2.42 ± 0.02, $p = 0.03$) and random ones (2.46 ± 0.01, $p = 0.00$). Furthermore, we found a significant Emotion × Predictive context interaction [F (4,88) = 3.95; $p = 0.005$, $\eta p^2 = 0.15$]. Post hoc analysis of the Emotion × Predictive context interaction showed that in the single-interval predictive context, RTs were shorter in the fear situation (2.41 ± 0.02) compared to neutral ones (2.44 ± 0.01, $p = 0.01$).

No significant differences between the emotional situations were found in the rhythmic context ($p > 0.05$). In the random context, log mean RTs were increased in the joy situation compared to the neutral one (2.47 ± 0.01, 2.44 ± 0.01, $p = 0.00$). No significant differences were found between joy and fear situations ($p > 0.05$) (Fig. 2).

Furthermore, the post hoc analysis of the Emotion × Predictive context interaction showed also that log mean RTs for joy and fear in rhythmic (2.40 ± 0.021, 2.40 ± 0.019). and single-interval (2.42 ± 0.020, 2.41 ± 0.02) contexts were similarly reduced with respect RTs for joy and fear in the random context (2.47 ± 0.15, 2.46 ± 0.018).

No other main effects or Interactions were significant In the ANOVA (all $p > 0.05$).

The effect of biological stimuli (FACS) vs. non biological stimuli on temporal prediction ability

Mean log RTs obtained from TP task were compared to that obtained from TP-E with the neutral situation. The RM ANOVA on mean log RTs revealed a significant effect of Task [F (1,22) = 8.11; $p = 0.00$; $\eta p^2 = 0.26$]. Post *hoc* analysis of the main effect disclosed that RTs during the TP were decreased compared to the TP-E neutral (2.39 ± 0.01, 2.42 ± 0.01, $p < 0.001$) (Fig. 3).

Furthermore, the analysis showed again, as in the TP-E task, a significant effect of Predictive context [F (2,44) = 21.43; $p = 0.00$; $\eta p^2 = 0.49$]. Post hoc analysis revealed that log RTs were shorter in the rhythmic context (2.38 ± 0.012) compared to the random (2.43 ± 0.014, $p = 0.00$) and the single-interval one (2.42 ±, $p = 0.00$) (Fig. 4). No interaction Predictive context × Task was significant in the ANOVA ($p > 0.05$). These findings suggest that in general, a simple shape target fastens RTs, but this doesn't influence temporal prediction per *se*.

Discussion

In this study, we investigated whether emotional stimuli, specifically fear and joy, influence temporal prediction. We utilized an emotional version of a temporal prediction (TP) task, as previously described by Breska and Ivry (2018). Our objective was to determine if the presentation of facial stimuli depicting positive and negative emotions (joy and fear)[25] modulates temporal prediction compared to neutral facial stimuli. We hypothesized that emotional stimuli would impact motor responses in a time-dependent manner.

The main finding of our study is the one related to the influence of emotional stimuli on temporal prediction ability. Accordingly, to our a priori hypothesis, our results show a specific decrease of RTs, in the single-interval task, when fearful stimuli were used, with respect to neutral stimuli. Differently, from our a priori hypothesis we also found a specific increase in RTs for joy stimuli in the random context (i.e., no-time condition) compared to neutral stimuli.

It's important to note that the emotional valence of the stimuli used in the TP-E task was validated independently. Specifically, twenty-eight participants not included in the main study, evaluated the valence and arousal of the stimuli used. For valence, fear FACS were judged significantly unpleasant compared to neutral and joy ones. Furthermore, joy FACS displayed significantly higher valence ratings compared to fear and neutral stimuli.

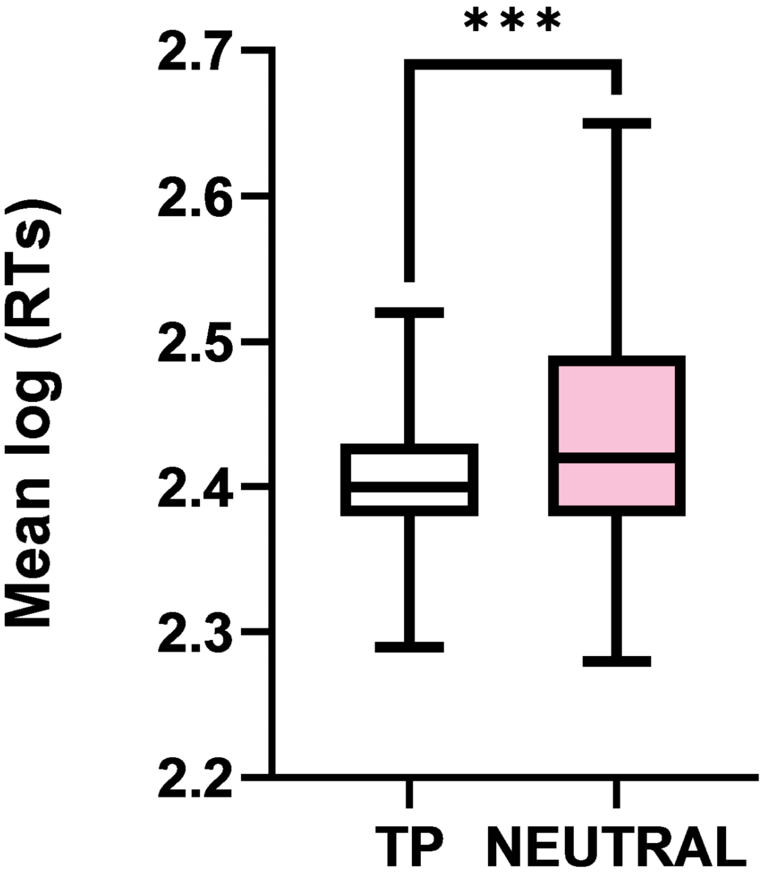

Fig. 3. Mean log Reaction Times (RTs) data. Results of the main effect of Task, RTs were shorter in the TP task compared to the TP-E neutral one. Error bars represent SEM. ***$p \leq 0.001$. The values plotted are the minimum and the maximum (whiskers), the median, the 25th percentile, and the 75th percentile (hinges).

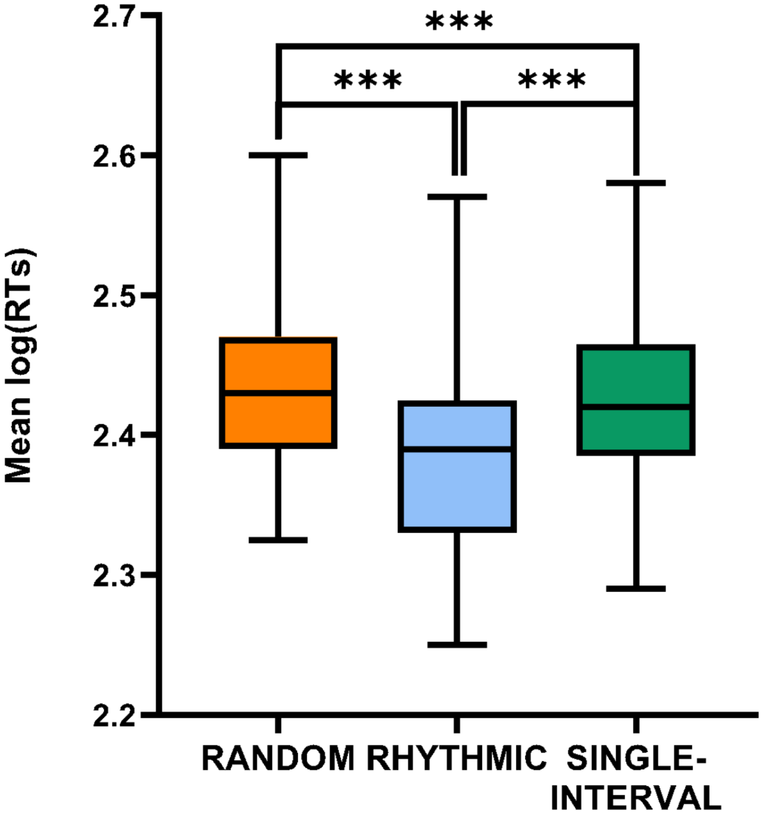

Fig. 4. Mean log Reaction Times (RTs) data. Results of the main effect of Predictive context, RTs were shorter in the rhythmic condition compared to the random and the single-interval one. Error bars represent SEM. ***$p \leq 0.001$. The values plotted are the minimum and the maximum (whiskers), the median, the 25th percentile, and the 75th percentile (hinges).

The effect of emotion on temporal prediction ability

Predictive contexts: single-interval and rhythmic

Our finding concerning the motor response facilitation for fear stimuli, compared to neutral and joy, in the single interval context aligns with previous research suggesting that decreased RTs may reflect enhanced motor system readiness in the context of the processing of negative emotion[29]. As an example, we recently investigated the capacity to process emotional body postures in a three-choice categorization task[29]. Our findings showed significantly decreased RTs for pictures depicting fearful (i.e., negative) body postures when compared with happy (i.e., positive) or neutral postures. Furthermore, RTs to negative body postures were not significantly different from RT to negative scenes taken from the International Affective Picture System (IAPS), suggesting a general augmented processing speed and resource allocation for fearful stimuli belonging to different categories.

Negative emotional stimuli have been demonstrated to modify early components of event-related potentials already after 100 ms of stimulus initiation, indicating a quick allocation of attentional resources[30,31]. The "negativity bias" for negative emotional stimuli has been reported for brain regions involved in emotion processing (e.g., the amygdala, the orbitofrontal cortex, or the insula) but also for motor areas involved in motor representation and planning (e.g., premotor cortex, supplementary motor area, and parietal cortex), and the primary motor cortex[32,33]. Early activation of sensorimotor regions is assumed to be the neurophysiological correlate of the rapid motor response observed in response to negative emotional stimuli[29,33]. Notably, enhanced readiness of the motor system is supposed to represent just one of the corollaries of emotional adjustments in the processing of threatening situations, including physiological arousal and cognitive appraisal[34,35]. Moreover, the modulation of temporal perception is one of these emotional adjustments attributed to readiness for threatening situations in emotional contexts (for a review see[4]). Specifically, studies, using aversive or negative emotional stimuli (faces with an emotional expression of fear or anger), have pointed out that the exposure to these stimuli induces an overestimation of elapsed time in time judgment tasks[5,36]. This behavioral response has been explained considering the internal-clock model of interval timing[37–39]. This model claims the existence of different stages underlying the perception and the estimation of time, positing the existence of an internal "clock" in the brain, regulating the sense of time. Time representation originates in a pacemaker-accumulator system; the pacemaker emits pulses at a constant rate that are counted in the accumulator. The greater the number of accumulated pulses is, the longer the duration is judged to be[4]. In addition, the content of the accumulator is retained in working memory and compared with stored duration in long-term memory to build time judgment (memory and decisional stages)[4,37,39,40]. In the context of the relation between time and emotion, the idea is that the internal clock speeds up in emotional contexts representing threatening situations, thus causing more pulses to accumulate for the same physical unit of time[4]. When the clock runs faster and more pulses are accumulated, the duration is judged longer.

Here, even if we did not explicitly assess time judgment using ad hoc protocol, such as temporal discrimination task, the facilitation of RTs for fear in the single-interval context could be explained in the framework of the internal clock model. We can infer, from our result, that RT decrease in temporal prediction, in fear situations, could be linked to increased readiness that indeed occurs in threatening situations. Moreover, we can also hypothesize that modulation of temporal perception, in terms of an overestimation of elapsed time, may have facilitated a decrease of RT in a temporal prediction task. This latter hypothesis should be properly addressed in a study combining time judgment and temporal prediction. In favour of our hypothesis, the overestimation effect of anger and fear on the perception of time was supposed to result from an automatic process linked to dopamine activity which allows humans to anticipate an event by preparing them to act quickly[4]. The more rapidly time passes, the sooner humans are ready to act. This speculation is largely consistent with our findings of reduced RTs in temporal prediction when the fear stimuli were used.

It is noteworthy to underlie that RTs decrease with fear stimuli was observed only when temporal prediction was based on an interval representation (i.e., single-interval context) and not when the prediction was derived from a rhythmic stream. Hence, in rhythmic context, there was no significant difference between emotional (fear and joy) and non-emotional (neutral) stimuli, suggesting that when temporal regularity is strongly established the predictability of the task itself overrides any modulation by emotional valence or arousal. Indeed, this is the only temporal context where RTs for neutral stimuli were comparable to those for emotional stimuli.

One possible explanation could be related to the fact that single-interval-based predictions are strongly dependent on cognitive abilities, such as attention and memory[41]. Negative emotions have been demonstrated to influence to the greatest extent cognitive functions such as memory or attention with negative context benefitting from prioritized processes in memory, compared to neutral ones, richly encoded, and recollected[42,43]. Furthermore, studies, exploring the influence of emotion on memory for temporal information, have underlined that negative stimuli also enhance a greater episodic encoding and recall for the temporal information of those stimuli, compared to positive and neutral ones[18,19]. When confronted with angry or fearful faces, the acceleration in clock speed described above in temporal estimation is accompanied by increased attention to the duration dimension of those stimuli associated with the fear-provoking event (for a review see[4]). It could be inferred that our result about the improvement in predictive ability (i.e., decrease in RT) for fear in the single-interval context, compared to neutral and joy, could also reflect enhanced attention to the duration dimension of the stimuli and an improvement in mnemonic encoding and recall for temporal information for negative stimuli. It is important to emphasize that there was no statistically significant difference between joy and fear in the single-interval context, which aligns with previous studies suggesting that both positively and negatively valenced arousing stimuli typically lead to transient overestimations of temporal durations[7]. Notably, the magnitude of this effect is generally larger for negative stimuli[44] .In this case (e.g., memory-based context), our finding supports the idea that fear holds a privileged position, compared to joy, in memory and attention, potentially enhancing temporal prediction abilities in this context.

The second possible explanation could rely on the different cortical-subcortical networks implicated in temporal prediction in the two different contexts (interval-based vs. rhythmic)[9]. A pivotal role of the cerebellum in interval-based predictions has also been shown by Breska and Ivry (2018)[9] and supported by other works in patients with cerebellar degeneration[45,46] and in healthy subjects using neuromodulation[14]. In the last years, the hypothesis of cerebellar involvement in emotional processes has been reinforced[47]. Using emotional pictures, researchers have demonstrated cerebellar activations following the presentation of aversive pictures[48], with temporal hierarchical processing of arousal and valence. Specifically, in the cerebellum, arousal was firstly processed (occurring in both vermal (VI and VIIIa) and hemispheric (left Crus II) lobules) followed by valence and its interaction with arousal (occurring in left V and VI lobules and Crus I)[49]. Arousal, specifically, has been identified as the component underlying the increased readiness response to threatening situations, as reported in response to expressions or body postures expressing fear or anger. Thus, we can assume that a preferred fast activation of the cerebellum in orchestrating the response to emotional stimuli may have facilitated temporal prediction in single-based predictions, that is when the cerebellum is preferentially engaged. It is worth noting that these two explanations are not mutually exclusive, and both hypotheses may theoretically explain the selective decrease in RT in temporal prediction based on an interval representation (single interval) when fearful faces were utilized.

No-predictive context: random

An equally important result to consider is the specific increase in RTs observed for joy stimuli in the random context (i.e., no-time condition), compared to neutral.

Excluding the temporal properties of the context, since in the random context there was no temporal information to be implicitly acquired, a possible explanation could be related to the influence of emotional arousal on reaction times. Here, the preliminary evaluation of the stimuli used in the study showed that joy FACS were rated as significantly more arousing than both neutral and fear FACS. The relationship between arousal and motor performance has been described as a curvilinear relationship[50,51]. This model[50] described that motor or cognitive performance improves with physiological or perceived arousal, reaching the optimal performance at an intermediate level of arousal. When arousal levels become excessively high, performance tends to decline. Likewise, we observed that RTs were significantly faster for neutral stimuli perceived with low to intermediate arousal levels compared to joy and fear. Noteworthy, in this study, we performed a subjective self-rating evaluation and to strengthen our hypothesis related to arousal influence on motor responses in no predictive context, it would be interesting, in future studies, to record physiological responses related to arousal (e.g., skin conductance) since the subjective evaluation of arousal and his psychophysiological measure may be dissociated[52].

Thus, in a random (non-predictive context), the absence of temporal structure appears to favour emotional neutrality, providing an advantage in terms of faster reaction times compared to positive emotional states. This might be because positive emotions, like joy, induce high-arousal processing of stimuli, increasing cognitive load. Conversely, in predictive contexts, arousal-driven mechanisms do not impair motor performance; on the contrary, emotions enhance temporal prediction. Indeed, RTs for joy and fear in predictive contexts (rhythmic and single-interval) were similarly reduced with respect to RTs for joy and fear in the non-predictive context. This suggests that emotions could support predictive anticipation of the temporal features of the stimuli, enhancing the ability to predict future events and to respond more efficiently to anticipated stimuli overshadowing the effect of arousal highlighted only in no predictive contexts. In the rhythmic context, where the predictive advantage is maximized due to the regular structure, all emotional stimuli are equally effective. Conversely, in single-interval contexts, where attentional and mnemonic demands are higher, the benefit is particularly evident for fear, which benefits from its strong role in mnemonic encoding within memory-based contexts, further amplifying its predictive utility.

The effect of biological stimuli on temporal prediction ability

To address differences in temporal prediction due to the complexity of biological stimuli (i.e., faces), we compared RT obtained in the classic TP task employing simple geometric shapes (i.e., squares), with RT obtained in our modified TP emotional task, only with neutral faces.

We found that in the classic TP task RTs were significantly reduced compared to the TP-E task. Such enhancement in RT could be explained by the perceptual complexity of FACS stimuli used in TP-E compared to the colored squares used in the TP task. Previous studies on perception have underlined the hierarchical structure of the visual system. Specifically, lower levels of visual processing are specialized in detecting simple features, while higher visual areas are engaged in processing complex stimuli[53]. The involvement of later stages of visual processing in the processing of complex stimuli, compared to simple ones, has a distinct impact on behavioral performance[54]. This idea has been explained by the "stimulus-complexity effect"[55] on reaction times, whereby reaction times increase as the complexity of the stimulus increases.

Additionally, a further distinction could be attributed to the difference in the targets used in TP and TP-E tasks. In the TP task the target was a green square compared to a stream of red squares; in this scenario, changing the color could make it easier to distinguish the target from the other stimuli, and fasten motor readiness and response. In the TP-E the targets used were the same stimuli with the addition of a detail, the glasses. This could make it harder to identify the target, by elaborating on subtle characteristics of the target.

It can be assumed that the perceptual complexity of the stimuli and the targets used can have a significant impact on RT due to its influence on the demand for cognitive resources and the perceptual system's ability to process complex features of the face.

This result seems to be at odds with a strand of literature showing that faces yield privileged processing in cortical and subcortical neural structures compared to other types of visual stimuli (for a review see[56]). Specifically, electroencephalographic studies have pointed out that faces with an emotional expression elicited an earlier neural response in a pre-attentional and automatic manner[57,58]. In visual processing, studies have underlined that emotion enhances perceptual processing per se[59,60]. Neurophysiological evidence reported that emotional stimuli induced an early freezing-like response in the motor system and later motor facilitation[29,61,62].

However, it is noteworthy to underline that in the above-mentioned studies, FACS were compared to not embodied stimuli, as in our study. Moreover, at difference with our study, these stimuli were characterized by similar perceptual complexity (FACS vs. emotional scenes taken from IAPS). Here we used stimuli with simple shape (i.e., square), very easy to be process.

Limitation of the study

In this paragraph, we will discuss some limitations of the present study. First, we focused our experiment on two types of emotional FACS (i.e., joy and fear). It would be of interest in future studies to expand this research to other emotional states as anger or shame, or to another set of stimuli, embodied (bodily expression) or not embodied (emotional scenes, IAPS), and to systematically address valence and arousal effect on temporal prediction. Indeed, when the effect of emotion on time judgment was evaluated, it has been emphasized the importance of investigating in detail the dimensions of emotion, both arousal and valence, because the effects of emotion might change in a systematic fashion with dimension changes.

Second, we speculate that the cerebellum may be involved in mediating the decrease of RTs in interval-based predictions, when faces expressing fear were used as stimuli, given the quick involvement of the cerebellum in emotional processing, already at the arousal level and the specific role of the cerebellum in interval-based predictions. However, at this point, this remains a pure speculation, and to address the neuroanatomical network involved in temporal prediction in an emotional context is a topic to be addressed in future studies.

Third, to study temporal prediction in different temporal (single-based and rhythmic) and emotional (fear, happiness, etc.) contexts in patients with basal ganglia or cerebellar disorders would elucidate the role of these subcortical structures in modulating temporal prediction ability, also in relation to emotional stimuli.

Conclusions

In this study we demonstrated, for the first time, that negative emotion influences temporal prediction, with RTs decrease in the fear situation when temporal prediction was based on an interval representation (single-interval) and not when the prediction was derived from a rhythmic stream.

Increased motor readiness, represented by a decrease of RTs, aligns with emotional adjustments in processing threatening situations, including modulation of physiological arousal, cognitive appraisal, and time estimation. Indeed, such modulation of RTs, specifically in the single-interval condition, may be attributed to improved memory and attention, essential cognitive abilities for single-based predictions, enhanced by exposure to fearful stimuli.

Data availability

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Received: 17 July 2024; Accepted: 22 January 2025

References

1. Droit-Volet, S. & Gil, S. The time-emotion paradox. *Philos. Trans. R Soc. B Biol. Sci.* **364**, 1943–1953. https://doi.org/10.1098/rstb.2009.0013 (2009).
2. Droit-Volet, S., Fayolle, S., Lamotte, M. & Gil, S. Time, emotion and the embodiment of timing. *Timing Time Percept.* **1**, 99–126 (2013).
3. Angrilli, A., Cherubini, P., Pavese, A. & Manfredini, S. The influence of affective factors on time perception. *Percept. Psychophys.* **59**, 972–982 (1997).
4. Gil, S. & Droit-Volet, S. Time perception, depression and sadness. *Behav. Process.* **80**, 169–176 (2009).
5. Mioni, G., Wittmann, M., Prunetti, E. & Stablum, F. Time perspective and the subjective passage of time in patients with borderline personality disorders. *Timing Time Percept.* **8** (2020).
6. Yin, H. et al. The effects of angry expressions and fearful expressions on duration perception: an ERP study. *Front. Psychol.* **12** (2021).
7. Cui, X. et al. The role of valence, arousal, stimulus type, and temporal paradigm in the effect of emotion on time perception: a meta-analysis. *Psychon. Bull. Rev.* **30**, 1–21 (2023).
8. Nobre, A. C. & Van Ede, F. Anticipated moments: temporal structure in attention. *Nat. Rev. Neurosci.* **19**, 34–48. https://doi.org/10.1038/nrn.2017.141 (2018).
9. Breska, A. & Ivry, R. B. Double dissociation of single-interval and rhythmic temporal prediction in cerebellar degeneration and Parkinson's disease. *Proc. Natl. Acad. Sci. USA* **115**, 12283–12288 (2018).
10. Lewis, P. A. & Miall, R. C. Brain activation patterns during measurement of sub- and supra-second intervals. *Neuropsychologia* **41**, 1583–1592 (2003).
11. Davranche, K., Nazarian, B., Vidal, F. & Coull, J. Orienting attention in time activates left intraparietal sulcus for both perceptual and motor task goals. *J. Cogn. Neurosci.* **23**, 3318–3330 (2011).
12. Koch, G. et al. Repetitive TMS of cerebellum interferes with millisecond time processing. *Exp. Brain Res.* **179**, 291–299 (2007).
13. Vicario, C. M., Martino, D. & Koch, G. Temporal accuracy and variability in the left and right posterior parietal cortex. *Neuroscience* **245**, 121–128 (2013).
14. Terranova, S. et al. Cerebellar direct current stimulation reveals the causal role of the cerebellum in temporal prediction. *Cerebellum.* https://doi.org/10.1007/s12311-023-01649-8 (2023).
15. Thomasson, M. & Péron, J. Principles of brain and emotion: beyond the cortico-centric bias 13–24. (2022). https://doi.org/10.1007/978-3-030-99550-8_2
16. de la Rosa, M. D., Sanabria, D., Capizzi, M. & Correa, A. Temporal preparation driven by rhythms is resistant to working memory interference. *Front. Psychol.* **3** (2012).
17. Capizzi, M., Sanabria, D. & Correa, Á. Dissociating controlled from automatic processing in temporal preparation. *Cognition* **123**, 293–302 (2012).
18. D'Argembeau, A. & Van der Linden, M. Influence of emotion on memory for temporal information. *Emotion* **5**, 503–507 (2005).
19. Ochsner, K. N. Are affective events richly recollected or simply familiar? The experience and process of recognizing feelings past. *J. Exp. Psychol. Gen.* **129**, 242–261 (2000).
20. Brosch, T., Scherer, K., Grandjean, D. & Sander, D. The impact of emotion on perception, attention, memory, and decision-making. *Swiss Med. Wkly.* https://doi.org/10.4414/smw.2013.13786 (2013).
21. Bishop, S. J. Neurocognitive mechanisms of anxiety: an integrative account. *Trends Cogn. Sci.* **11**, 307–316 (2007).
22. Oldfield, R. C. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* **9**, 97–113 (1971).
23. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bull. World Health Organ.* **79**, 373–374 (2001).
24. Breska, A. & Ivry, R. B. Double dissociation of single-interval and rhythmic temporal prediction in cerebellar degeneration and Parkinson's disease. *Proc. Natl. Acad. Sci.* **115**, 12283–12288 (2018).
25. Ekman, P. & F. W. V. Facial Action Coding System (FACS) [Database record]. *APA PsycTests* (1978).
26. Goshen-Gottstein, Y. & Ganel, T. Repetition priming for familiar and unfamiliar faces in a sex-judgment task: evidence for a common route for the processing of sex and identity. *J. Exp. Psychol. Learn. Mem. Cogn.* **26**, 1198–1214 (2000).
27. De Cesarei, A. & Codispoti, M. When does size not matter? Effects of stimulus size on affective modulation. *Psychophysiology* **43**, 207–215 (2006).
28. Kimura, M., Kondo, H., Ohira, H. & Schroger, E. Unintentional temporal context-based prediction of emotional faces: an electrophysiological study. *Cereb. Cortex.* **22**, 1774–1785 (2012).
29. Botta, A., Lagravinese, G., Bove, M., Avenanti, A. & Avanzino, L. Modulation of response times during processing of emotional body language. *Front. Psychol.* **12** (2021).
30. van Heijnsbergen, C. C. R. J., Meeren, H. K. M., Grèzes, J. & de Gelder, B. Rapid detection of fear in body expressions, an ERP study. *Brain Res.* **1186**, 233–241 (2007).
31. Botta, A. et al. Early modulations of neural oscillations during the processing of emotional body language. *Psychophysiology* **61** (2024).
32. Borgomaneri, S., Gazzola, V. & Avenanti, A. Motor mapping of implied actions during perception of emotional body language. *Brain Stimul.* **5**, 70–76 (2012).
33. Botta, A. et al. Sensorimotor inhibition during emotional processing. *Sci. Rep.* **12**, 6998 (2022).
34. LeDoux, J. E. Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23**, 155–184 (2000).
35. Damasio, A. R. et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat. Neurosci.* **3**, 1049–1056 (2000).
36. Grondin, S., Laflamme, V. & Gontier, É. Effect on perceived duration and sensitivity to time when observing disgusted faces and disgusting mutilation pictures. *Atten. Percept. Psychophys* **76** (2014).
37. Gibbon, J., Church, R. M. & Meck, W. H. *Scalar Timing Memory* **423** (1984).

38. Treisman, M. Temporal discrimination and the indifference interval. Implications for a model of the 'internal clock'. *Psychol. Monogr.* **77** (1963).
39. Zakay, D. & Block, R. A. Temporal cognition. *Curr. Dir. Psychol. Sci.* **6**, 12–16 (1997).
40. Bar-Haim, Y., Kerem, A., Lamy, D. & Zakay, D. When time slows down: the influence of threat on time perception in anxiety. *Cogn. Emot.* **24**, 255–263 (2010).
41. Cravo, A. M., Rohenkohl, G., Santos, K. M. & Nobre, A. C. Temporal anticipation based on memory. *J. Cogn. Neurosci.* **29**, 2081–2089 (2017).
42. D'Argembeau, A. & Van der Linden, M. Influence of affective meaning on memory for contextual information. *Emotion* **4**, 173–188 (2004).
43. Kensinger, E. A. & Corkin, S. Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words? *Mem. Cognit.* **31**, 1169–1180 (2003).
44. Lake, J. I., LaBar, K. S. & Meck, W. H. Emotional modulation of interval timing and time perception. *Neurosci. Biobehav Rev.* **64**, 403–420. https://doi.org/10.1016/j.neubiorev.2016.03.003 (2016).
45. Breska, A. & Ivry, R. B. The human cerebellum is essential for modulating perceptual sensitivity based on temporal expectations. *Elife* **10** (2021).
46. Breska, A. & Ivry, R. B. Context-specific control over the neural dynamics of temporal attention by the human cerebellum. *Sci. Adv.* **6** (2020).
47. Adamaszek, M. et al. Impairment of emotional facial expression and prosody discrimination due to ischemic cerebellar lesions. *Cerebellum* **13**, 338–345 (2014).
48. Bermpohl, F. et al. Dissociable networks for the expectancy and perception of emotional stimuli in the human brain. *Neuroimage* **30**, 588–600 (2006).
49. Styliadis, C., Ioannides, A. A., Bamidis, P. D. & Papadelis, C. Distinct cerebellar lobules process arousal, valence and their interaction in parallel following a temporal hierarchy. *Neuroimage* **110**, 149–161 (2015).
50. Yerkes, R. M. & Dodson, J. D. The relation of strength of stimulus to rapidity of habit-formation. *J. Comp. Neurol. Psychol.* **18**, 459–482 (1908).
51. Diamond, D. M., Campbell, A. M., Park, C. R., Halonen, J. & Zoladz, P. R. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson Law. *Neural Plast.* 1–33 (2007).
52. Alpers, G. W., Adolph, D. & Pauli, P. Emotional scenes and facial expressions elicit different psychophysiological responses. *Int. J. Psychophysiol.* **80**, 173–181 (2011).
53. Maunsell, J. H. R. & Newsome, W. T. Visual processing in monkey extrastriate cortex. *Annu. Rev. Neurosci.* **10**, 363–401 (1987).
54. Song, Y. et al. Neural substrates of visual perceptual learning of simple and complex stimuli. *Clin. Neurophysiol.* **116**, 632–639 (2005).
55. Pellegrino, J. W., Fischer, S. C., Doane, S. M. & Alderton, D. Stimulus complexity effects in visual comparisons: the effects of practice and learning context. *J. Exp. Psychol. Hum. Percept. Perform.* **17** (1991).
56. Behrmann, M., Scherf, K. S. & Avidan, G. Neural mechanisms of face perception, their emergence over development, and their breakdown. *WIREs Cogn. Sci.* **7**, 247–263 (2016).
57. Pizzagalli, D., Regard, M. & Lehmann, D. Rapid emotional face processing in the human right and left brain hemispheres. *Neuroreport* **10**, 2691–2698 (1999).
58. Balconi, M. & Lucchiari, C. EEG correlates (event-related desynchronization) of emotional face elaboration: a temporal analysis. *Neurosci. Lett.* **392**, 118–123 (2006).
59. Phelps, E. A., Ling, S. & Carrasco, M. Emotion facilitates perception and potentiates the perceptual benefits of attention. *Psychol. Sci.* **17**, 292–299 (2006).
60. Lee, T. H., Lim, S. L., Lee, K. Y. & Choi, J. S. Facilitation of visual processing by masked presentation of a conditioned facial stimulus. *Neuroreport* **20**, 750–754 (2009).
61. Schutter, D. J. L. G., Hofman, D. & Van Honk, J. Fearful faces selectively increase corticospinal motor tract excitability: a transcranial magnetic stimulation study. *Psychophysiology* **45**, 345–348 (2008).
62. Borgomaneri, S., Gazzola, V. & Avenanti, A. Temporal dynamics of motor cortex excitability during perception of natural emotional scenes. *Soc. Cogn. Affect. Neurosci.* **9**, 1451–1457 (2014).

Author contributions

Conceptualization: [Sara Terranova, Elisa Pelosin, Laura Avanzino]; Methodology: [Sara Terranova, Elisa Pelosin, Laura Avanzino, Carola Cosentino, Susanna Mezzarobba, Elisa Ravizzotti]; Formal analysis and investigation: [Sara Terranova, Alessandro Botta, Martina Putzolu, Gaia Bonassi, Giovanna Lagravinese]; Writing - original draft preparation: [Sara Terranova, Elisa Pelosin, Laura Avanzino]; Writing - review and editing: [Sara Terranova, Alessandro Botta, Martina Putzolu, Gaia Bonassi, Carola Cosentino Susanna Mezzarobba, Elisa Ravizzotti, Giovanna Lagravinese, Elisa Pelosin, Laura Avanzino]; Funding acquisition: [Laura Avanzino]; Supervision: [Elisa Pelosin, Laura Avanzino]

Funding

Work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022).

Declarations

Competing interests

The authors declare no competing interests.

Financial disclosures

S. Terranova, A. Botta, G. Bonassi, M. Putzolu M, C. Cosentino, S. Mezzarobba, E. Ravizzotti, G.Lagravinese has nothing to declare. L. Avanzino, has received speaker honoraria from Zambon and Bial and received research supports (Grants) from the EU Joint Programme—Neurodegenerative Disease Research (JPND) (2022 call) and Michael J. Fox Foundation (Fall 2022 biomarkers to support therapeutic trials program). She received research support from FRESCO foundation and the Italian Ministry of Health (Ricerca Finalizzata 2022 and 5 × 1000). E. Pelosin, is part of an Advisory Board for M.J. Fox Foundation. She has received grants

from Italian Ministry of University and Research (PRIN 2022) and Michael J. Fox Foundation (Fall 2022 biomarkers to support therapeutic trials program), and research supports from Italian Ministry of Health (Ricerca Finalizzata 2022) and IRCCS Policlinico San Martino, Genova (5 × 1000, 2022).

Additional information

Correspondence and requests for materials should be addressed to E.P.

Reprints and permissions information is available at www.nature.com/reprints.