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RAPID REPORT

Higher Neural Functions and Behavior

Associative learning in peripersonal space: fear responses are acquired in hand-centered coordinates

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Abstract

Space coding affects perception of stimuli associated to negative valence: threatening stimuli presented within the peripersonal space (PPS) speed up behavioral responses compared with nonthreatening events. However, it remains unclear whether the association between stimuli and their negative valence is acquired in a body part-centered reference system, a main feature of the PPS coding. Here we test the hypothesis that associative learning takes place in hand-centered coordinates and can therefore remap according to hand displacement. In two experiments, we used a Pavlovian fear-learning paradigm to associate a visual stimulus [light circle, the conditioned stimulus (CS)] with an aversive stimulus (electrocutaneous shock) applied on the right hand only when the CS was displayed close (CS+) but when not far from it (CS−). Measuring the skin conductance response (SCR), we observed successful fear conditioning, with increased anticipatory fear responses associated with CS+. Crucially, *experiment I* showed a remapping of these responses following hand displacement, with a generalization to both types of CS. *Experiment II* corroborated and further extended our findings by ruling out the novelty of the experimental context as a driving factor of such modulations. Indeed, fear responses were present only for stimuli within the PPS but not for new stimuli displayed outside the PPS. By revealing a hand-centered (re)mapping of the conditioning effect, these findings indicate that associative learning can arise in hand-centered coordinates. They further suggest that the threatening valence of an object also depends on its basic spatial relationship with our body.

NEW & NOTEWORTHY Associative fear learning takes place in hand-centered coordinates. Using a Pavlovian fear-learning paradigm, we show that the anticipatory skin conductance response indicating the association between the negative value and an initially neutral stimulus is acquired and then remapped in space when the stimulated body part moves to a different position. These results demonstrate the relationship between the representation of peripersonal space and the encoding of threatening stimuli. Hypotheses concerning the underlying neural network are discussed.

associative learning; fear learning; hand-centered space; peripersonal space; skin conductance

INTRODUCTION

The portion of space close to our body, termed peripersonal space [PPS (1)], represents a safety zone against close or threatening approaching stimuli (2–4). Early studies in nonhuman primates revealed that fronto-parietal neurons code for objects in this region thanks to multisensory receptive fields (RFs), displaying tactile RFs centered on a specific body part (e.g., the hand) and visual ones

overlapping and anchored to them (1, 5–8). Neuroimaging evidence in humans highlighted a similar circuit involving the ventral and anterior intraparietal sulcus, the ventral and dorsal premotor cortices, and the putamen (9–15), dedicated to the integration of visual, tactile, and proprioceptive signals in body part-centered reference frames. PPS interfaces perception to action, allowing us to protect our body and interact with the surrounding environment. This view is supported by behavioral evidence: responses



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to touches delivered to parts of the body are boosted when a visual stimulus is presented near compared to far from them (16, 17). This feature allows PPS to support both goal-directed reach-to-grasp actions and rapid detection of near threats. Threatening stimuli within PPS can be more dangerous, their proximity to the body coming with reduced time available to react. Accordingly, anticipating the position of a threat with respect to our body would spare time to respond (18). Several studies have documented the relationship between aversive stimuli and PPS representation: be it acoustic (19, 20) or visual (16, 21), perception of a negatively connoted stimulus within PPS is boosted, in keeping with other behavioral (22, 23) and neural (24–28) findings. Thus, there is evidence that threatening stimuli are encoded according to their distance from the body (21, 24). However, a critical question remains open: does the association of a negative valence to a stimulus occur within a body part-centered reference frame? If this were true, one would predict that a learned association would remap as a function of the displacement of the body part involved. This would indicate a role of PPS representation in associative learning, implementing an efficient mechanism to encode threats close to the body.

To test this hypothesis, we ran two experiments adopting a Pavlovian associative learning protocol assessing whether humans learn the negative value of a stimulus within a reference frame centered on a specific part of the body (e.g., the hand). In particular, we used associative fear learning, where an initially neutral stimulus [conditioned stimulus (CS)] is associated with an aversive stimulus [unconditioned stimulus (US)]. After repeated associations, the presentation of the CS alone begins to produce in the subject the autonomic responses generally produced by the US.

MATERIALS AND METHODS

Participants

Twenty-one (12 females; mean age \pm SD: 26.6 \pm 3.44 yr) and forty-one (28 females; 24.8 \pm 4.87 yr) participants took part in *experiment I* (within-subject design) and *experiment II* (between-subject design), respectively. Two subjects were excluded because they were nonresponders [no skin conductance response (SCR) fluctuation]. All participants reported normal/corrected-to-normal vision, normal tactile sensitivity, and no history of psychiatric disorders. Except for two left-handed and one ambidextrous participant in *experiment II*, all participants were right-handed by the Edinburgh handedness test. They gave their written informed consent before the study, which was approved by the national French ethics committee (CPP SUD EST IV France) and was in line with the Declaration of Helsinki.

Stimuli and Apparatus

Participants sat at a table, in a dark room, with the head on a chinrest (30 cm high). A projector (Panasonic PT-LM1E_C) controlled by Presentation displayed visual stimuli on the table. A fixation cross (2.5 cm) was projected aligned to the participant's sagittal axis. Two-dimensional (2-D) circles (diameter 2.5 cm, duration 6 s) were presented in either a yellow (CS_{yellow}; RGB = 0,255,127) or purple (CS_{purple};

RGB = 255,0,127) hue, in one of two visual positions, 20 cm to the right (CS_{yellow_right}, CS_{purple_right}) and to the left (CS_{yellow_left}, CS_{purple_left}) of the body's sagittal axis, respectively, equidistant from the fixation cross and 20 cm from the participant's body (Fig. 1). Depending on the condition, either color was associated with a US, an electrocutaneous stimulation (2,000 μ s, 400 mV) delivered to the right index finger via a constant-current stimulator (DS7A; Digitimer, UK) through a pair of disposable pregelled electrodes (1.5 \times 1.9 cm, Neuroline; Ambu, Denmark). Intertrial interval jittered between 12 and 15 s (21, 22, 29).

We recorded the SCR signal through Ag/AgCl electrodes (EL507; BIOPAC, Goleta, CA) filled with isotonic gel (0.5% chloride salt) and applied on the second phalanx of the second and third fingers of the left hand, placed under the table on an armrest. A MP-150 BIOPAC Systems SCR module amplified this signal, recorded at a rate of 1,000 Hz.

Procedure

Participants had to stare at the fixation cross during *experiment I*, involving three phases: familiarization (8 trials), learning (48 trials) and test (24 trials).

As illustrated in Fig. 1, the right hand was placed ipsilaterally on the table, 24 cm rightward of the sagittal body's axis, during the familiarization and learning phases. In the test phase, the hand was moved 16 cm to the left of the sagittal body's axis, granting an identical distance between hand and CS across postures (4 cm).

Before familiarization, the intensity of tactile stimuli was set through an ascending staircase procedure: participants had to judge tactile shocks with a number between 1 (not unpleasant) and 7 (very unpleasant but not painful). At each stimulation, intensity was increased by steps of 1 μ A. The procedure terminated when the participant judged the unpleasantness at 7 for two consecutive pulses, and the corresponding intensity was applied during the learning phase. If participants judged the stimulation as "painful," intensity was decreased in 0.5- μ A steps, until a double evaluation of "7" was reached. The mean intensity was 8.9 \pm 5.6 μ A (mean \pm SD) for *experiment I* and 7.5 \pm 4.1 μ A for *experiment II*.

The familiarization phase had a twofold purpose: familiarizing participants with the procedures and obtaining color and position SCR baselines. Two stimuli per color and position were presented, without any tactile stimulation.

In the learning phase, the conditioned color (CS+) was counterbalanced across participants. Twelve repetitions of each color were randomly displayed in the right (close to the hand) and left (far from the hand) visual positions. In \sim 80% of the CS+ hand-close trials, this visual stimulus was associated with the US (10 of 12 trials). Since the duration of the US was 2 ms, in these trials the onset of the US occurred 5.998 s after the onset of the visual stimulus. Four CS types are therefore defined: CS_{+right}, CS_{+left}, CS_{-right}, and CS_{-left}. Both the CS- and CS_{+left} were never associated with the US.

In the test phase, visual stimulation was identical, but the hand was positioned close to the circles presented on the left side. It should be noted that no electrocutaneous stimulation was delivered during this phase, making any variation of the

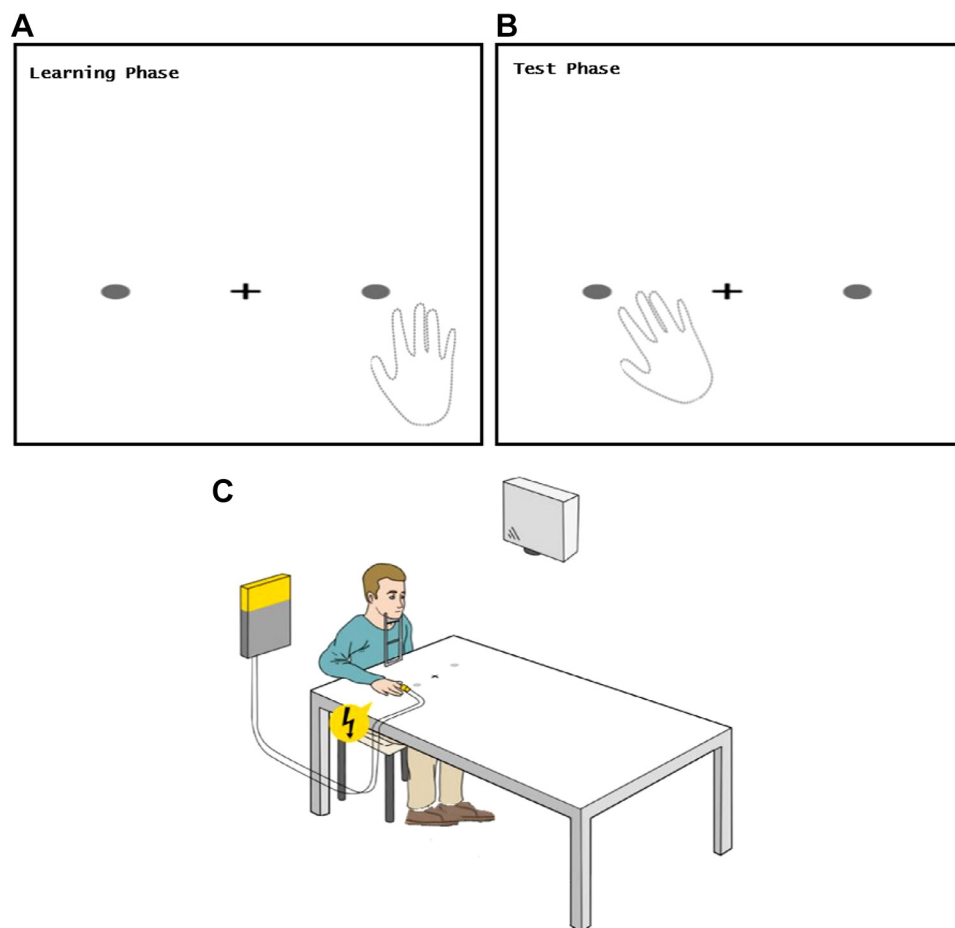


Figure 1. Experimental setup. *A*: positions of right hand, fixation cross, and visual stimuli during learning phases of *experiment I* and *II* and in the 2nd test phase of *experiment II*. *B*: positions of right hand, fixation cross, and visual stimuli during the test phase in *experiment I* and the 1st test phase in *experiment II*. *C*: representation of the experimental setup during learning phases. Tactile stimulation in this phase was applied to the right index finger and was associated to conditioned stimuli (CS+) such that tactile offset corresponded to visual offset.

SCR due only to the previously learned association. Six repetitions per CS type were randomly presented.

Before the learning phase, participants were warned of the possible presence of tactile stimuli but had no information about the CS/US contingency. At the end of the test phase, participants were debriefed.

In *experiment II*, visual and tactile stimuli were identical to *experiment I*, but participants underwent five phases: familiarization (4 trials), 1st learning (24 trials), 1st test (6 trials), 2nd learning (24 trials), and 2nd test (6 trials). Their right hand was placed ipsilaterally during the familiarization, the learning phases, and the 2nd test phase (Fig. 1). In the 1st test phase, their hand was placed on the same left position as *experiment I*.

Similarly, in the two learning phases, 12 repetitions of the visual stimulus of the selected color were presented in each position of visual stimulation (12 CS_{right}, 12 CS_{left}). Only CS_{right}, presented close to the hand, coterminated in 80% of cases (10 of 12 trials) with the US (CS+), whereas CS_{left} was never associated with it (CS-).

In the 1st test phase, as in *experiment I*, participants had their right hand close to the left visual positions. Depending on the group, six repetitions of the same CS were presented close to the hand (in the same left position as the learning phases) or 40 cm farther away (to ensure the same distance previously existing between the right and left stimulations). This between-subjects design allowed subjects to experience

stimulation either within or outside the perihand space. In the 2nd test phase, six repetitions of the CS were presented near or 40 cm far away from the right hand (depending on the group of the 1st test phase), positioned ipsilaterally. Thus, we replicated the experimental conditions of the 1st test phase in terms of distance of visual stimuli from the hand. However, in this test phase visual stimuli were of the opposite color to the conditioned one: if the participant had been shown only yellow stimuli now the visual stimuli were purple, and vice versa.

Analyses

Experiment I.

Trials were averaged to obtain four scores per participant (CS_{yellow_right}, CS_{purple_right}, CS_{yellow_left}, CS_{purple_left}). Separate analyses were performed for each phase on SCR waveforms with AcqKnowledge software. We measured the SCR for each trial as the base-to-peak amplitude difference in skin conductance (in microsiemens) in the 0- to 6-s time window following CS onset. The recorded SCR waveform was smoothed at 100 points and then resampled at 15 samples/s; then, raw SCR scores were square-root transformed to normalize the distribution (29), and then, to reduce variance due to individual differences, we divided these scores by the participant's maximal response (30, 31).

To estimate baseline SCR, we performed a Color (yellow/purple) × Side (left/right) repeated-measures ANOVA on

square-root SCR scores in the familiarization phase. In both the learning and testing phases, we carried out a first ANOVA with Color (yellow/purple) as factor to verify possible SCR differences related only to the chromatic aspect. Subsequently, we performed a Side (left/right) \times Association (CS+/CS-) \times Trial (from 2 to 12) repeated-measure ANOVA on SCR scores of the learning phase, excluding the first trial of each condition in order to analyze only the responses following the subject's first experience with electrocutaneous stimulation. In the test phase, considering the rapid extinction of this kind of conditioning effect (32–34), we performed a Trial (from 1 to 6) \times Side (left/right) \times Association (CS+/CS-) ANOVA on the SCR scores.

Experiment II.

Preprocessing of SCR data was identical to *experiment I*. Because the between-subject design may require us to compare potentially different absolute values, we performed a preliminary ANOVA on the individual maximum values in response to stimuli falling near and far from the hand in the two test phases, with Position (close/far) and Phase (1st test/2nd test) as between and within factors, respectively. This revealed a significant main effect of Position ($F_{1,38} = 6.31$, $P = 0.02$, $\eta_p^2 = 0.143$), confirming that the maximum SCR obtained with Far stimulations (mean \pm SE = 0.12 ± 0.03) was lower than that of Close stimulations (0.24 ± 0.03). Because of this, and at odds with *experiment I*, here the square-rooted SCR (not divided by the maximum value) was entered into the analysis and averaged to obtain, depending on the experimental phase, two average scores per participant: CS_{right}/CS_{left} or CS_{close}/CS_{far}.

As in *experiment I*, we ran a repeated-measure ANOVA on SCR values of the familiarization phase, considering Position (left/right) as within factor and Color (yellow/purple) as between factor. This analysis allows assessment for possible differences before the conditioning process, related to basic spatial or chromatic aspects.

For the same reason, we performed a *t* test to compare the effect of Color between groups in each learning phase. We then performed an ANOVA with Position (left/right) and Trial (from 2 to 12) as within factors on SCR scores, excluding the first trial of each condition in order to analyze only the responses following the subject's first experience with US.

In the 1st and 2nd test phases we performed an ANOVA on square-rooted SCR scores with Position (close/far) and Trial (from 1 to 6) as between and within factors, respectively.

Data and materials are available online (https://osf.io/ryhms/?view_only=9bbd1a5d84ff4b2c9a7568ba1bd0da9f).

RESULTS

Experiment I

In the familiarization phase, no significant main effect (Color: $F_{1,19} = 0.41$, $P = 0.53$; Side: $F_{1,19} = 1.82$, $P = 0.19$) or interaction (Color \times Side: $F_{1,19} = 0.94$, $P = 0.34$) emerged, indicating comparable amounts of SCR for stimuli differing in color or position before conditioning.

In both learning and test phases, the ANOVA on Color reported nonsignificant effects (learning: $F_{1,19} = 2.12$, $P = 0.16$, test: $F_{1,19} = 0.04$, $P = 0.85$). We thus collapsed the two levels of this factor in the subsequent analyses, investigating the

differential impact of CS+ and CS- independently of color. In the learning phase, the ANOVA highlighted significant main effects of Side ($F_{1,19} = 15.35$, $P < 0.001$, $\eta_p^2 = 0.45$), Association ($F_{1,19} = 7.83$, $P = 0.01$, $\eta_p^2 = 0.29$), and Trial ($F_{3,83,72,82} = 5.64$, $P < 0.001$, $\eta_p^2 = 0.23$). Considering the trial, post hoc comparisons corrected for false discovery rate (FDR) showed higher responses for the second trial compared with all the others (all $P < 0.05$ except 2nd trial vs. 3rd trial, $P = 0.07$). The response trend is similar between the four stimulation combinations (Side \times Association; Fig. 2C). Furthermore, Side and Association interacted ($F_{1,19} = 5.94$, $P = 0.02$, $\eta_p^2 = 0.24$): FDR-corrected post hoc comparisons showed higher SCR for CS+ on the right (mean \pm SE = 2.97 ± 0.46) compared with those on the left (2.36 ± 0.38 , $P < 0.001$) but no difference for CS- ($P = 0.13$; Fig. 2A). This confirms the emergence of a conditioning effect, specific to the CS+ displayed close to the hand.

We then analyzed the test phase to ascertain the hand-centered mapping of this effect. In the Trial \times Side \times Association ANOVA, the only significant term, observed for the first trial ($P = 0.002$; Fig. 2D), was the Trial \times Side interaction ($F_{3,93,74,69} = 3.45$, $P = 0.01$, $\eta_p^2 = 0.15$), revealing that early stimuli presented on the left now evoked a greater SCR (mean \pm SE = 5.83 ± 0.86) than those presented on the right (4.72 ± 0.71).

Experiment II

In the familiarization phase, neither the main effect of Color ($F_{1,38} = 0.21$, $P = 0.65$) nor that of Position ($F_{1,38} = 1.44$, $P = 0.24$) was significant, as their interaction was nonsignificant ($F_{1,38} = 0.36$, $P = 0.55$). Again, before conditioning, stimuli differing by color or position evoked comparable SCR. Similarly, the Welch two-sample *t* tests in both the 1st and 2nd learning phases did not show significant differences between colors (1st: $t_{37,09} = 1.05$, $P = 0.30$; 2nd: $t_{37,96} = 0.052$, $P = 0.96$), which we thus collapsed in the subsequent analyses.

The Position (right/left) \times Trial (from 2 to 12) ANOVA of the 1st learning phase highlighted a significant main effect of both factors (Position: $F_{1,39} = 37.62$, $P < 0.001$, $\eta_p^2 = 0.49$; Trial: $F_{5,48,213,65} = 6.72$, $P < 0.001$, $\eta_p^2 = 0.15$). In particular, it was possible to observe that the conditioning was successful, as the SCR for CS+ (mean \pm SE = 0.336 ± 0.03) was greater than that for CS- (0.249 ± 0.03). This confirms that participants learned the association between visual stimuli close to the hand and the US (Fig. 3A). FDR-corrected post hoc comparisons showed greater responses for the 2nd trial compared with all the others (all $P < 0.01$) and for the 3rd trial compared with all the trials between the 6th and the 11th (all $P < 0.05$). The response trend is similar for the two stimulus positions (Fig. 3C).

In the 1st test phase (hand displaced leftward), the Position (close_left/far_left) \times Trial (from 1 to 6) ANOVA showed a significant effect of both the within (Trial: $F_{3,37,128,1} = 5.53$, $P < 0.001$, $\eta_p^2 = 0.13$) and the between (Position: $F_{1,38} = 10.40$, $P = 0.003$, $\eta_p^2 = 0.22$) factors. Similar to *experiment I*, FDR-corrected post hoc comparison revealed a significantly higher SCR in the 1st trial compared with all the others (all $P < 0.05$) except the 2nd trials, which in turn was statistically greater than the 3rd, 4th, and 5th trials (all $P < 0.05$; Fig. 3D). Moreover, the significant effect of Position showed higher SCR for the stimuli presented close to the hand (mean \pm

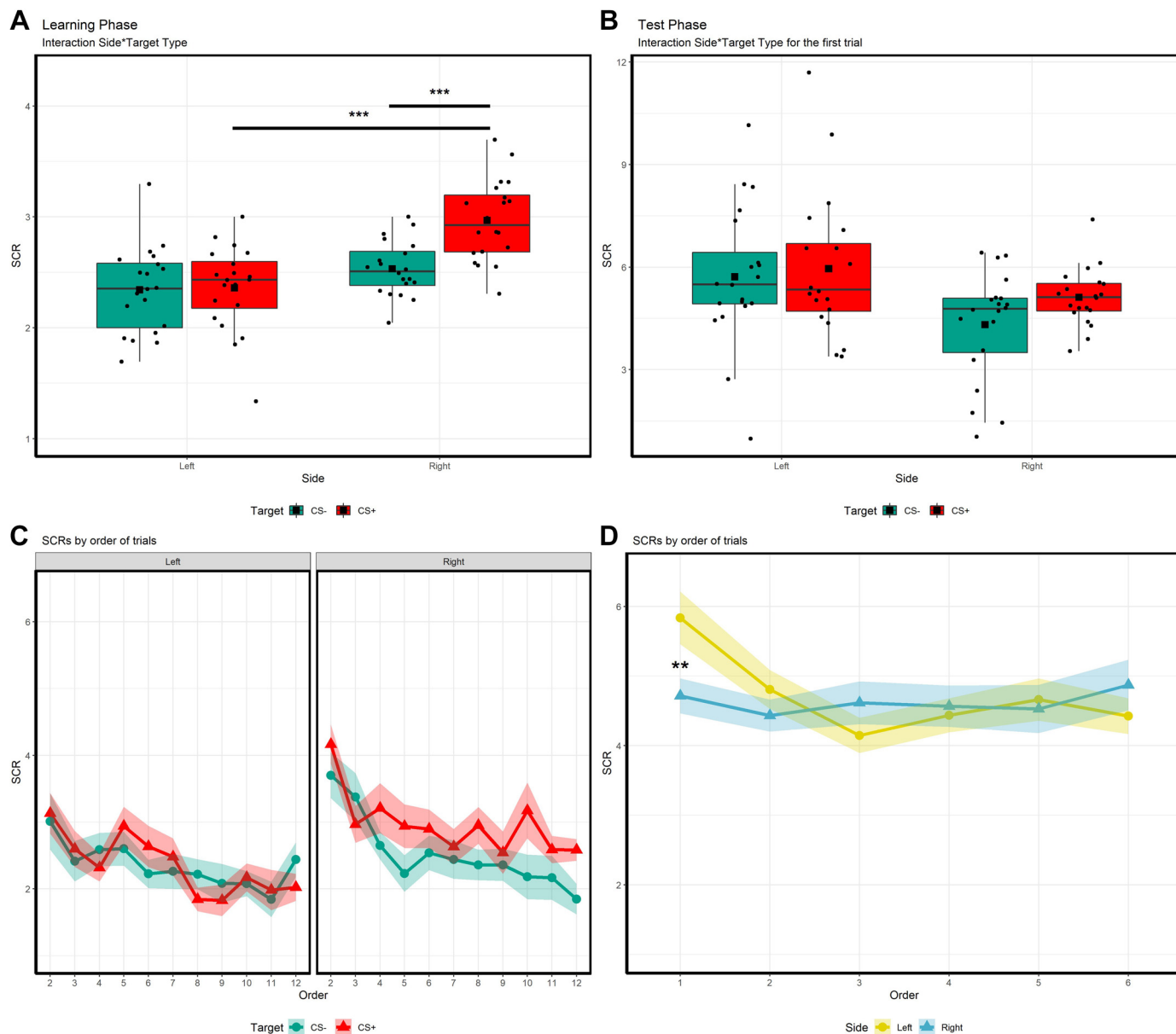


Figure 2. A and B: mean skin conductance response (SCR) to conditioned (CS+) and control (CS-) stimuli presented on the right or on the left side during the learning phase (A) and the 1st trial of the test phase (B) of *experiment 1*. Error bars show SE. Significant differences: *** $P < 0.001$. ●, Individual means; ■, sample mean per condition. C: representation of the SCR pattern for the 4 experimental conditions (Side \times Association Type) of the learning phase of *experiment 1* as a function of the presentation order of the trials. D: SCR pattern for stimuli presented on the left and on the right in the test phase of *experiment 1*. Significant differences: ** $P < 0.01$.

SE = 0.392 ± 0.04) compared with those far from it (0.215 ± 0.04 ; Fig. 3B). This result confirms those of *experiment 1*'s test phase, highlighting a remapping of the associative fear learning in a hand-centered fashion. The Position \times Trial interaction did not reach significance ($F_{3,37,128,1} = 1.76$, $P = 0.15$).

The Position (right/left) \times Trial (from 2 to 12) ANOVA on the SCR scores of the 2nd learning phase showed a significant main effect of Position ($F_{1,39} = 40.36$, $P < 0.001$, $\eta_p^2 = 0.51$), indicating greater responses for stimuli presented close to the hand (mean \pm SE = 0.322 ± 0.02) compared with those presented on the left of the table (0.242 ± 0.02 ; Fig. 4A). Neither the main effect of Trial ($F_{6,58,256,59} = 1.04$, $P = 0.40$) nor the Position \times Trial interaction ($F_{6,72,262,23} = 1.56$, $P =$

0.15) was significant. These results on one side confirmed the reestablishment of the conditioning effect, and on the other showed the absence of an order effect (Fig. 4C).

Finally, the Position (close_right/far_right) \times Trial (from 1 to 6) ANOVA on SCRs scores of the 2nd test phase displayed a significant main effect of both Position ($F_{1,38} = 6.73$, $P = 0.01$, $\eta_p^2 = 0.15$) and Trial ($F_{3,16,119,97} = 10.44$, $P < 0.001$, $\eta_p^2 = 0.22$) and their interaction ($F_{3,16,119,97} = 3.1$, $P = 0.027$, $\eta_p^2 = 0.08$). FDR-corrected post hoc comparison showed higher SCRs for stimuli presented close to the hand compared with those presented far from it. This difference was significant in the 1st ($P = 0.007$) and 2nd ($P = 0.004$; Fig. 4, B and D) trials. All the other differences were nonsignificant.

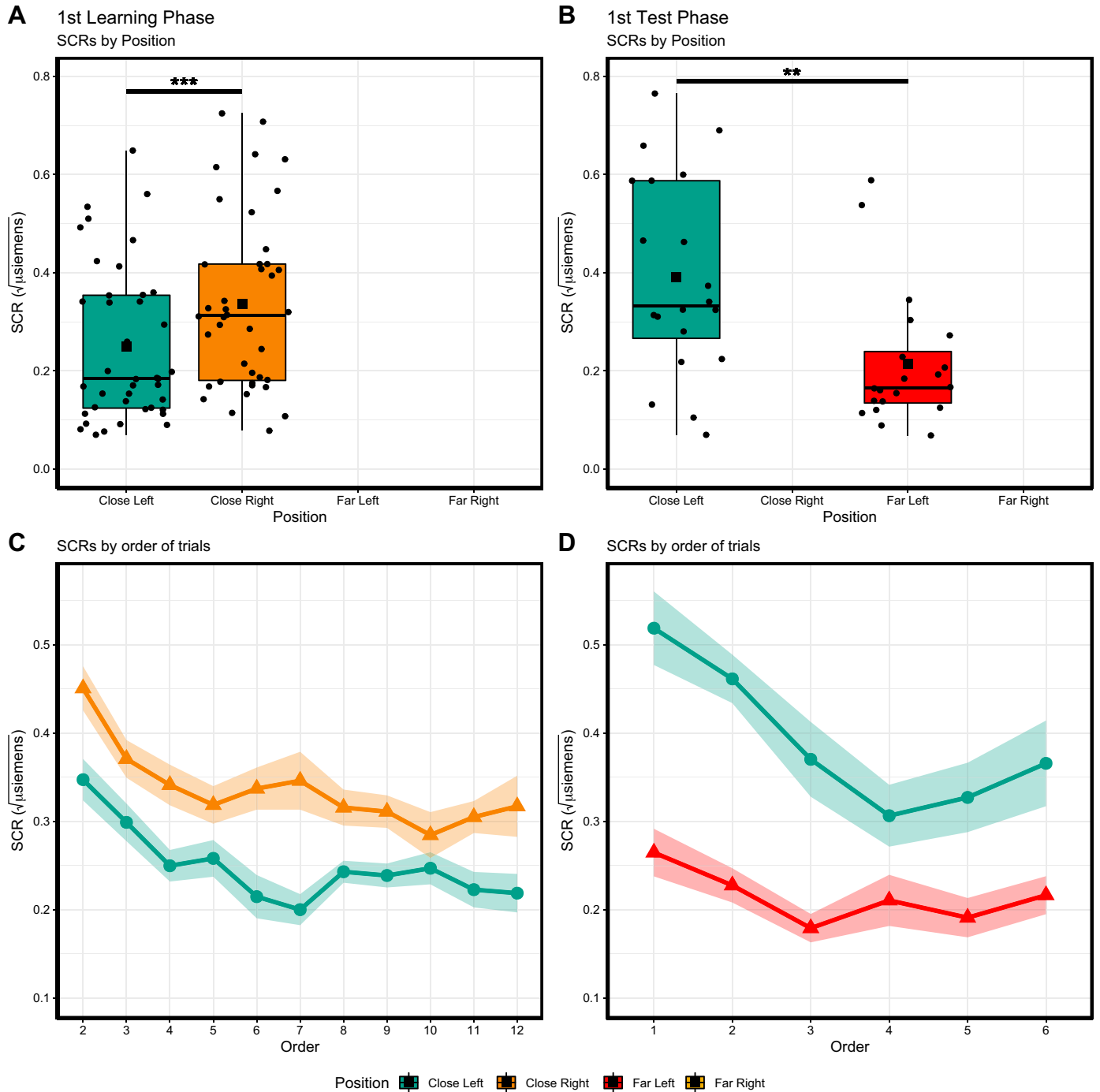


Figure 3. A: mean skin conductance response (SCR) to conditioned (CS+) and control (CS-) stimuli presented on the right or on the left side, respectively, during the 1st learning phase of *experiment II*. B: the same responses, but to stimuli presented close to or far from the hand during the 1st test phase of *experiment II*. Error bars show SE. Significant differences: ** $P < 0.01$, *** $P < 0.001$. ●, Individual means; ■, sample mean per condition. C: representation of the SCR pattern for the 2 positions of visual stimulation of the 1st learning phase of *experiment II* as a function of the presentation order of the trials. D: SCR pattern for stimuli presented close to or far from the hand in the 1st test phase of *experiment II*.

DISCUSSION

This study provides empirical support to the hypothesis that humans can learn to react to nearby fearful stimuli by establishing stimulus-response associations within a hand-centered reference system. Consistent with the body part-centered nature of PPS mapping (10, 11, 17, 35–37), here we

report that acquired fear responses “follow” the hand to a new position. Because of this remapping, previously innocuous stimuli are then regarded as threatening ones, merely by virtue of their spatial “vicinity” status.

Learning is a skill that allows us to shape and adapt our behavior according to the events of the external world (38). A particular type of learning is the one that concerns fear,

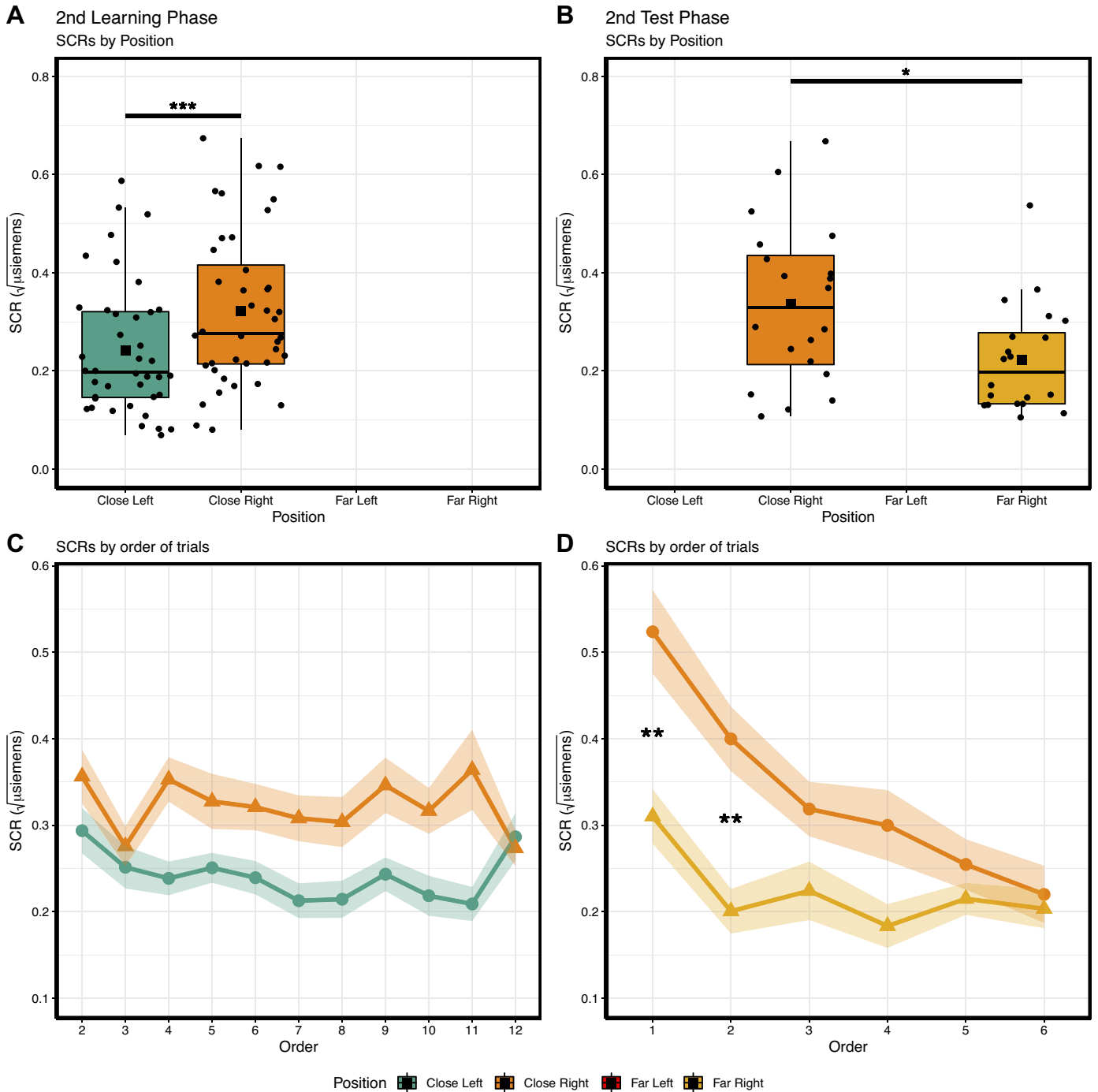


Figure 4. A: mean skin conductance response (SCR) to conditioned (CS+) and control (CS-) stimuli presented on the right or on the left side, respectively, during the 2nd learning phase of *experiment II*. B: the same responses, but to stimuli presented close to or far from the hand during the 2nd test phase of *experiment II*. Error bars show SE. Significant differences: * $P = 0.05$, *** $P < 0.001$. ●, Individual means; ■, sample mean per condition. C: representation of the SCR patterns for the 2 positions of visual stimulation of the 2nd learning phase of *experiment II* as a function of the presentation order of the trials. D: SCR patterns for stimuli presented close to or far from the hand in the 2nd test phase of *experiment II*. Significant differences: ** $P < 0.01$.

considered as the set of unconscious and measurable physiological responses to threat (see Ref. 39). Previous studies have shown the influence of aversive stimuli on the extent of the PPS: coherently with its defensive function, its extension increases when facing threatening stimuli directed toward the body, allowing us to anticipate danger and plan an

appropriate response (16, 19–21). However, these studies used stimuli aversive by nature, in some cases finding an effect only in the presence of a corresponding and preexisting phobia (19, 20) or individual idiosyncratic reaction. Indeed, here we found that nearby stimuli are not threatening per se. Although these stimuli are known to boost multisensory

processing when presented close compared with far from the hand (16), here the SCR did not vary for this sheer metric feature. This finding suggests that although PPS representation may code space for a defensive function, this may be not the default one. In stark contrast, when nearby stimuli start being associated to aversive ones, their metric dimension becomes relevant.

In *experiment I* we observed that the anticipatory fear response occurs in the learning phase only for the CS+ and only for the conditioned position, demonstrating that participants learned the CS+/US contingency. In the test phase, the hand being displaced in a novel, unconditioned position, a greater anticipatory fear response was associated to visual stimuli displayed in that near-hand position. This was true despite the fact that participants never experienced unpleasant stimulations associated with a CS in this novel hand position. This clearly indicates that the CS+/US association took place in a reference frame centered on the hand and not in a more general egocentric spatial reference system. So far, studies of fear learning in PPS have tested, broadly speaking, egocentric stimuli: toward the head (19, 20) or the hand (16, 40), which were kept in the same position. These studies showed a modulation of PPS representation and supported its defensive role. Our results considerably widen this perspective, indicating not only that an external threat is encoded as a function of its position relative to a specific body part but that the spatial relationship between them is maintained when that body part moves in space. Compatible with the dynamic properties observed in the domain of voluntary actions (41–43), here we additionally report that PPS allows us to learn new associations of stimuli in body part-centered coordinates.

Interestingly, this remapping showed some degree of generalization. Participants generalized the learned association to another, unconditioned stimulus, provided it was close to the new position occupied by the hand. This effect could not be due to insufficient differentiation of the stimuli used, because participants clearly differentiate between CS+ and CS– during the learning phase. It cannot be due to the simple spatial proximity between visual stimulus and hand either, as in the familiarization phase, before any conditioning takes place, this effect did not emerge. In addition, in the learning phase, the observed effect was clearly specific for the CS+ and not for any nearby visual stimulus. It might instead reflect an adaptive learning mechanism: moving the hand in space, the position of the threat is remapped, but in the absence of further information, all stimulations in the “dangerous” position are considered as a potential threat. Alternatively, the fear response observed only in the 1st trial of the test phase could be driven by novelty, the new experimental context. This possibility would be consistent with the order effect observed also in the learning phase of *experiment I*: regardless of the type of stimulus, the response rapidly decays after some trials. However, the results of *experiment II* speak against this alternative and instead support our hypothesis of hand-centered remapping and generalization of the CS/US association. If the effect observed in *experiment I* was mainly related to novelty, then the 1st test phase of *experiment II* should reveal similar responses between the near-hand and far-hand groups, contextual novelty being comparable. Yet the fear response was greater when visual stimuli

appeared near the hand, rather than far from it. Furthermore, in the 2nd test phase of *experiment II* two previous effects are replicated: the effect of greater response for stimulations within PPS and that of the generalization of this response. In this phase, both stimulations are novel by the feature of color, and they have never been associated with US. Yet, again, fear responses were higher when stimuli were presented in the position previously associated with them, close to the hand. Therefore, novelty effects can be observed but do not account for our findings.

It is noteworthy that no order effect was observed in the 2nd learning phase of *experiment II*. We might speculate that this relates to the level of uncertainty, varying with the growing confidence participants may acquire regarding the CS/US association: higher drifts may appear in the early stages of learning (and testing) when any stimulation could lead to the US. Through repetitions, uncertainty lowers, as well as the response magnitude. In the 2nd learning phase (*experiment II*), participants’ uncertainty may be lower since the beginning, which could result in less signal drift. This possibility deserves dedicated testing in future studies.

These findings provide previously unavailable evidence that humans encode new and arbitrarily learned associations of nearby stimuli within a body part-centered reference frame. This might reflect an adaptive mechanism: a threatening stimulus inside PPS is more dangerous for the part of the body more proximal to its position. Its detection in relation to this body part therefore becomes more relevant for the preparation of adequate avoidance responses. This is in agreement with the findings of Makin and colleagues, who argued the existence of a neuronal “fast track” capable of bypassing some stages of the processing of visual information relative to the hand (44) and to the position of objects in hand-centered coordinates (45). Learning to associate the threatening valence of a stimulus with respect to the threatened body part could contribute to make this fast update (~70 ms), by exploiting direct cortical and subcortical pathways (46). By coding information about the threats and the hand in a common reference frame, PPS would allow the online control of action and the ability to perform quick hand-object interactions. Although our study highlights this characteristic for threatening stimuli, the same mechanism can be hypothesized for stimuli having a positive value (rewards), which already seem to be coded differently according to their distance from the body (47, 48). Furthermore, here we investigated the influence of a visual stimulus on the perception of an electrocutaneous stimulation, but the reverse path is also conceivable: Filbrich and colleagues (49) have brilliantly demonstrated how a nociceptive stimulation applied to the hand affects the temporal judgment performance of visual stimuli presented close to or far from it. It is possible to say, in a more general way, that the defensive function of the PPS prioritizes the processing of multisensory information coming from the threatened part of the body.

The potential neural mechanism underlying hand-centered learning of the valence of nearby stimuli is worth discussing. Fear learning involves a network of regions including the anterior cingulate cortex, the anterior insula, the hippocampus, and the amygdala (see Ref. 50 for review), an important hub for the processing of fear and fear learning (51–54). Specifically, the lateral and basal nuclei of the amygdala are

the primary sensory input centers of these processes (52, 53, 55, 56), receiving multisensory information of auditory, somatosensory, nociceptive (57–59), and visual (60, 61) origin. These nuclei display enhanced responses to conditioned auditory stimuli in fear-learning protocols, and this modulation may occur for conditioned visual stimuli, through their direct connection with the visual nuclei of the pulvinar (61). According to a hypothesis, this pathway could represent a fast alerting system (52), capable of attributing an emotional value to incoming visual information, even before accessing conscious awareness. This idea is coherent with the defensive function of PPS: the closer the threat is to the body, the faster the response must be. A possible connection of the network underlying the representation of the PPS and that of the fear response, therefore, could represent an important adaptive mechanism.

At what point the PPS and fear learning circuits communicate with each other is not yet clear. The pulvinar, thanks to its important connection with the different portions of the intraparietal sulcus, the posterior medial intraparietal area (62; see 63 for review), and the putamen (64), could prove to be the hub of this communication. These areas are part of the fronto-parietal network underlying the PPS coding (9–13, 15), involved in planning reaching, grasping, and defensive movements (65). It therefore seems legitimate to suggest that its communication with a network of areas capable of evaluating and learning the threats present in the surroundings may help ensuring greater chances of survival. Activity of the left ventral premotor cortex (PMv) may also contribute to the phenomenon newly reported here. In addition to being an important region for the representation of PPS (10, 11), this area has shown strong activations in response to threatening stimuli presented near the body (24). In this perspective, further neuroimaging studies are necessary to better understand how the dialog between these systems may take place.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.Z., R.S., A.F., and C.B. conceived and designed research; A.Z. performed experiments; A.Z. analyzed data; A.Z., A.F., and C.B. interpreted results of experiments; A.Z. prepared figures; A.Z. drafted manuscript; A.Z., R.S., A.F., and C.B. edited and revised

manuscript; A.Z., R.S., A.F., and C.B. approved final version of manuscript.

ENDNOTE

At the request of the authors, readers are herein alerted to the fact that additional materials related to this manuscript may be found at https://osf.io/ryhms/?view_only=9bbd1a5d84ff4b2c9a7568ba1bd0da9f. These materials are not a part of this manuscript and have not undergone peer review by the American Physiological Society (APS). APS and the journal editors take no responsibility for these materials, for the website address, or for any links to or from it.

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