Psychoneuroendocrinology 142 (2022) 105790

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Acute stress affects peripersonal space representation in cortisol stress responders

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ARTICLE INFO

Keywords:
Stress
Cortisol
Peripersonal space
Multisensory integration

ABSTRACT

Peripersonal space is the representation of the space near the body. It is implemented by a dedicated multisensory-motor network, whose purpose is to predict and plan interactions with the environment, and which can vary depending on environmental circumstances. Here, we investigated the effect on the PPS representation of an experimentally induced stress response and compared it to a control, non-stressful, manipulation. We assessed PPS representation in healthy humans, before and after a stressful manipulation, by quantifying visuotactile interactions as a function of the distance from the body, while monitoring salivary cortisol concentration. While PPS representation was not significantly different between the control and experimental group, a relation between cortisol response and changes in PPS emerged within the experimental group. Participants who showed a cortisol stress response presented enhanced visuotactile integration for stimuli close to the body and reduced for far stimuli. Conversely, individuals with a less pronounced cortisol response showed a reduced difference in visuotactile integration between the near and the far space. In our interpretation, physiological stress resulted in a freezing-like response, where multisensory-motor resources are allocated only to the area immediately surrounding the body.

1. Introduction

The space immediately surrounding the body, where the individual can physically interact with external stimuli in the environment, is defined as the peripersonal space (PPS). PPS has a dedicated representation in the primate brain, which is thought to be involved in implementing behavioural responses to environmental changes, such as the avoidance of potential threats or the reaching of appetitive stimuli. PPS representation is based on the multisensory integration of tactile stimuli with visual or auditory stimuli specifically presented close to the body, in a body-centred reference frame (Rizzolatti et al., 1997; Cléry et al., 2015; Graziano and Cooke, 2006; Làdavas and Serino, 2008; Serino, 2019). Original knowledge about PPS representation came from single-cell recordings in monkeys (see for a review Graziano and Cooke, 2006); neuroimaging studies in humans further revealed responses to near-body stimulation localized in posterior parietal and premotor areas of the human brain, largely corresponding to the regions where PPS neurons have been described in the monkey brain (see Grivaz, Blanke and Serino, 2017, for a review).

Those areas are directly connected, or are even part of the motor system, and, indeed direct electrical stimulation of these premotor and parietal regions hosting PPS neurons in monkeys, results in defensive movements (Cooke and Graziano, 2003). In humans, close, auditory (Serino, Annella and Avenanti, 2009; Finisguerra et al., 2015) or visual (Makin et al., 2009; Cardellicchio, Sinigaglia and Costantini, 2011), stimuli seems to affect the excitability of the corticospinal tract, by either inhibiting or enhancing its responsiveness, as to prepare freezing-like or active responses to stimuli within the subject's action space. Thus, the multisensory representation of PPS is immediately transformed into automatic overt or potential reactions.

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https://doi.org/10.1016/j.psyneuen.2022.105790
Received 26 November 2021; Received in revised form 18 March 2022; Accepted 27 April 2022
Available online 7 May 2022

A wide body of evidence also shows that the extent of PPS representation is highly plastic, and modulated as a function of the potential interactions with stimuli in the environment. Recent data suggest that not only sensory-motor (see Maravita et al., 2002, for a review), but also social factors affect PPS representation. PPS contracts when facing a stranger (Teneggi et al., 2013) or a person who is perceived as immoral (Iachini et al., 2015; Pellencin et al., 2018), and it extends towards people that participants are willing to interact with (Pellencin et al., 2018; Teneggi et al., 2013). Personality traits, such as anxiety (Sambo and Iannetti, 2013), and phobias (Taffou and Viaud-Delmon, 2014; Cartaud et al., 2018; Lourenco, Longo and Pathman, 2011) also contribute to defining the extent of PPS.

Stress defines a cluster of psycho-physiological responses aimed at activating resources to face challenging situations and restoring and maintaining the organism's homeostasis (Karatsoreos and McEwen, 2011; McEwen, 2013). According to Schauer and Elbert's model (2010; see also Kozlowska et al., 2015), animals' defensive responses to imminent threats are organized into coherent sequences, which escalate with danger's proximity (i.e., freeze, flight/fight, fright, flag, faint). The response-cascade's unfolding modulates relatively to the context, such as the nature of the threat and the availability of resources. The sympathetic activation, predominant in the flight/fight response ("acute stress"; Canon, 1929), implies an enhanced ability to use the diverse metabolic substrates, with blood pressure, heart rate and glycolysis increases, and an enhanced blood supply to the central nervous and to the locomotor system, to mediate a withdrawal or aggressive behavior. This response is observed when the distance from the danger is reduced, and an overt reaction is needed. The flight/fight phase can be preceded by a transient state of "freezing" (Roelofs, 2017), or "orienting response", in which physiological features of both sympathetic and parasympathetic systems are present. This state of "attentive immobility" occurs at the very beginning of the stress response and it involves a tense body posture with an increased muscle tone, reduced heart rate (bradycardia), heightened attention and sensory perception, and an enhanced vigilance to threat cues. All these changes would support contextual information gathering to prepare action mobilization in further stages. Freezing is different from "tonic immobility", or fright, which instead follows a prolonged threat exposure, for which neither escape nor fighting is possible. Here, although the individual is intensely aroused, it appears unresponsive and rigid.

Considering the role of PPS representation in mediating environmental interactions and the impact of stress on such interactions, in the present study we asked whether and how the induction of a stress response would affect PPS representation in humans.

To this aim, we adapted a well-known experimental manipulation used to induce stress in human subjects, i.e., the Fear Factor stress test (Du Plooy et al., 2014) and we studied its effect on PPS representation. Before and after the stress manipulation, PPS representation was measured through a multisensory task (Canzoneri, Magosso and Serino, 2012). This task quantifies the amount of visuo-tactile interactions induced by external stimuli as a function of their distance from the body, as a proxy of PPS encoding. This allows measuring the spatial extent of PPS representation, and the amount of differentiation between the near and the far space.

Given the defensive role of PPS representation (Bisio et al., 2017; de Vignemont and Iannetti, 2015; Sambo et al., 2012; Taffou and Viaud-Delmon, 2014; Vagnoni et al., 2012), a response to acute stress might be reflected by an extension of PPS representation, as to anticipate potential contacts with external stimuli. Alternatively, if a stress response is characterized by a "freezing" behaviour (Hagenaars, Oitzl and Roelofs, 2014; Roelofs, 2017), we would expect an enhancement of information processing in the near space, and in a reduction of resources allocated to the far space (de Haan et al., 2016).

To verify the effectiveness of the stressor manipulation, and to measure the neuroendocrine stress response, we collected salivary samples to quantify the salivary cortisol concentration (Hellhammer, Wüst and Kudielka, 2009). Based on the cortisol response, we distinguished between glucocorticoid responders (*C-Responders*) and non-responders (*Non-C-Responders*) following the exposition to the stressor (Du Plooy et al., 2014; Quaedflieg et al., 2017; Kudielka et al., 2009). Therefore, we compared not only PPS representation between the experimental and control group but also within the experimental group, between responders and non-responders.

2. Materials and Methods

2.1. Participants and sample size

Due to the novelty of the proposed study, no previous data was available to estimate an expected effect size. Using the G*Power 3.1 software (G*Power, Faul et al., 2007), with an effect size of $f = 0.25$ (medium effect size), an alpha of 0.05 and a power ($1 - \beta$) of 0.9 for a repeated measures, within-factor analysis of variance (ANOVA) with no covariates, it was determined that an $N > 18$ would be needed to detect this effect. Thus, we recruited 38 participants (divided into two groups). Note that our sample size is in line with previous studies using a similar methodology to assess PPS representation, and studying its modulation by social and personality factors (Pellencin et al., 2018; Spaccasassi and Maravita, 2020; Teneggi et al., 2013; Noel et al., 2021). These studies used sample sizes of 18–34 participants for within-subjects comparisons, and 41 subjects for between-subjects (16 vs 25) comparisons.

Given the sex differences in anxiety and cortisol responsiveness (e.g., Bale and Epperson, 2015; Boettcher et al., 2017; Kudielka and Kirschbaum, 2005), only male participants were included in the present study. The mean age of participants in the control group was 22.8 ± 3 (SD), ranging from 19 to 30, and 23.1 ± 6.45 (SD) in the experimental group, ranging from 19 to 44. A t-test showed no significant difference in age between the two groups ($t = -0.182$, $p = 0.857$). None of the subjects reported a history of neurological or psychiatric disorders and all were naïve to the aim of the experiment. The experiment was conducted in accordance with the principles of the 1964 Declaration of Helsinki and was approved by the Ethical Committee of the Brain and Mind Institute, EPFL. Each participant gave written informed consent prior to participating.

2.2. Procedure

Participants were randomly assigned to one of the two groups: *Experimental* ($n = 19$) and *Control* group ($n = 19$). Once informed about the structure and aims of the experiment, they signed the consent form. In a first phase (the experiment timeline is illustrated in Fig. 1), that preceded the experimental manipulation (0–30 min after the start of the experiment), the stress level was measured. Two samples of saliva were collected as a physiological index of stress, and two Likert scales were administered, as a measure of subjective stress, in two timepoints (T1-T2). In this first phase, PPS representation was assessed via a visuo-tactile interaction task (see below for task description). The task was split into two blocks. The first was performed after the first Stress Measure (PPS-1a), and the second PPS block after the second stress measure (PPS-1b). Successively (30–80 min), the experimental group was exposed to a modified version of the Fear Factor stress test (Du Plooy et al., 2014; detailed in the next paragraph), which combines two validated tasks aimed at inducing psychophysical stress (STRESSOR1--STRESSOR2) for a sufficient amount of time. After the stress manipulation, PPS was once more assessed, again in two blocks. One block was presented after the first stressor manipulation (STRESSOR1; PPS-2a) and the other after the second (STRESSOR 2; PPS-2b). Also, cortisol and a subjective stress measure were collected in this phase (T3-T4). The Control group went through the same procedure with the exception that, instead of the experimental manipulation, two non-stressful tasks (CONTROL1-CONTROL2) were proposed (see below for control task description).

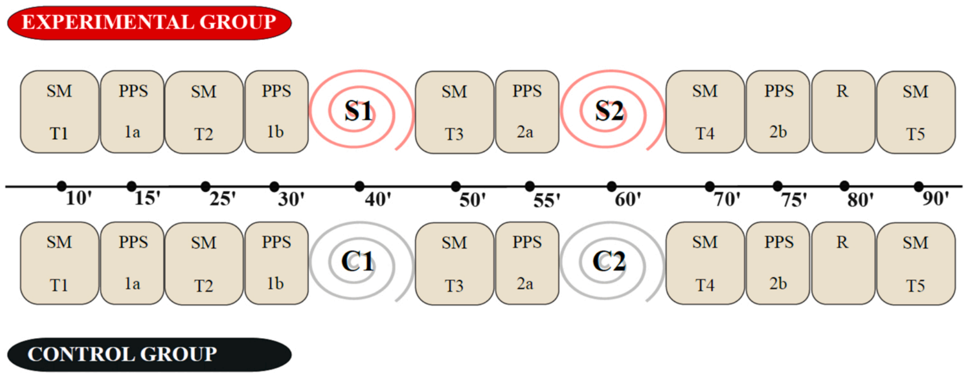

Fig. 1. Overview of the procedure. (SM): Stress Measure. (PPS): Peripersonal Space task. (S1-S2): Stress Manipulations. (R): Release phase. (C1-C2): Control Manipulation. A between-subjects design was used: measurements from the Experimental group were compared with the Control group. The Experimental group was exposed to the stress protocol (S1 +S2) while, the Control group, was exposed to a non-stressing condition (C1 +C2).

After the manipulation and the related stress measurements, participants underwent the final step (80–90 min), the *Release* phase (R), in which they were asked to complete a self-report to assess trait anxiety and perform a distance judgment paradigm (similar to the one used for the PPS task; see below) to validate the obtained PPS measure. Finally, another cortisol sample and subjective stress measures were taken (T5). Each participant was then debriefed and paid.

2.2.1. Stressor manipulation: the fear factor stress test and the control condition

The participants underwent a modified version of the Fear Factor Stress Test (Du Plooy et al., 2014). This stressor combines elements of the Trier Social Stress Test (Kirschbaum et al., 1993) and the Cold Pressor Task (CPT; Hines and Brown, 1936), the two protocols most widely used as stressors in this field of research.

Participants were asked to prepare for 2 min a motivational presentation to participate in a TV-reality show “Fear Factor” and then to deliver the presentation in front of a video camera.

After the motivational speech, the subjects were asked to perform a challenging arithmetic task (subtraction task) in front of the camera (STRESSOR1). The control group undertook instead a simple writing and reading task with neutral content, followed by a basic counting task instead of subtraction. No recording occurred for the control group (CONTROL1).

The Cold Pressor task (CPT) is widely used in the psychology literature (Lovallo, 1975), and consists of the dominant arm’s immersion in cold water (~4 °C) to just above the elbow, for 2 min. Participants from the experimental group were video-recorded during the entire water-immersion task to add a socio-evaluative component (STRESSOR2). The arm of the control participants was immersed in comfortably warm water (~35–40 °C) for the same amount of time, with no video recording (CONTROL2).

2.2.2. Stress measurements: Salivary cortisol levels and the subjective stress

To measure the level of stress, both physiological (cortisol concentration) and subjective measures were collected (STRESS MEASURE, see Fig. 1).

2.3. Cortisol concentration measure

To measure the cortisol level at regular time-ranges, saliva samples were taken at five time-points (Stress measure: T1-T2-T3-T4-T5; see Fig. 1). A sample of approximately 0.8–1.4 mL of saliva was obtained at each collection in 10 mL polypropylene tubes and frozen below − 20 °C until processed. Samples were then centrifuged at 3000 rpm for 15 min at room temperature, and salivary cortisol concentrations were measured by enzyme immunoassay according to the manufacturer’s instructions (Salimetrics, Newmarket, Suffolk, United Kingdom). The samples were used to analyse cortisol baseline levels and hormonal changes taking place during the experiment. To control for the circadian rhythm of cortisol, all experimental sessions were scheduled between 1 PM and 7 PM.

2.4. Analysis of cortisol concentration values

To compute a reliable index of cortisol-change due to the experimental manipulation, we considered the maximum value of the two samples collected right after the manipulation (T3 and T4) as *Post-manipulation* cortisol, and the minimum of the values referred to the samples outside the manipulation windows (before, T1 and T2, and at the end of the experiment, T5), as a measure of *Rest* cortisol. Cortisol response (CR) values were defined as the difference between Post-manipulation and Rest cortisol concentration values.

2.5. Assessment of subjective stress

To provide a measure of individual subjective evaluations in response to stress exposure, participants reported subjective ratings of stress. Subjects rated their perceived level of stress on a 1 (low) to 5 (high) Likert scale. The measurements of the Subjective Stress were collected on five occasions (Stress measure: T1-T2-T3-T4-T5; see Fig. 1).

2.6. State-trait anxiety inventory (STAI)

Participants rated their level of personal anxiety using the Trait form of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 2017). Trait anxiety reflects a predisposition to anxiety as determined by the personality pattern. A French version of the STAI was used.

2.7. Peripersonal space representation task

To assess PPS representation we adopted a visuo-tactile interaction task, implemented into the RealiSM software (Laboratory of Cognitive Neurosciences, EPFL) as described in Serino and colleagues (2018; see also Pellencin et al., 2018). In this task, subjects receive a tactile stimulus on their body, to which they are instructed to reply as fast as possible, while task-irrelevant auditory or visual stimuli (that must be ignored) approach (or recede from) the body. In different conditions, tactile stimuli are delivered when the external stimuli are perceived at a different distance from the body. Several studies show that participants respond progressively more rapidly with the external stimuli’s approach (Canzoneri et al., 2012).

The task consisted of a total of 150 trials of 5 s of duration, presented in different conditions, in a randomized order. In 108 trials (72% of the total amount) both visual and tactile stimuli were presented (visuo-tactile condition). Tactile stimuli could be delivered at a different delay from the beginning of the trial (1.82 s, 2.15 s, 2.475 s, 2.80 s, 3.12 s or 3.45 s), which implies that tactile information was processed when the visual stimulus was at one out of 6 distances from the participants (equally spaced from the farthest, D6 = 90 cm to the closest D1 = 30 cm). In 24 trials (16%) only tactile stimuli were presented and no visual stimuli were shown (unimodal tactile condition). Tactile stimuli were delivered at the same six delays as for visuo-tactile stimulation. Finally, in a set of 18 trials (12%), only visual stimuli were presented (unimodal visual condition). No response was expected, and these trials were used as catch trials to reduce overt expectations.

The whole PPS paradigm was split into two blocks (PPS 1a/1b; PPS 2a/2b), administered as described in the procedure.

2.7.1. *Stimuli*

Tactile stimuli were provided on the right jaw via a small vibrator (100 ms of duration, as in Noel et al., 2016). Visual stimuli were presented in a head-mounted display (HMD, model Oculus Rift, stereoscopic resolution 1280 ×800, diagonal field-of-view 110°), and consisted in looming volleyballs in an augmented reality scenario, where the scene background consisted of a projection of the real scene in front of the participant which was acquired by a camera (Duo3D MLX, 752 × 480 at 56 Hz) mounted on the HMD.

2.7.2. *Distance estimation task*

To verify the validity of the distance manipulation, at the end of the experimental session, participants performed a distance estimation task. They were asked to estimate the distance, in meters, of the perceived looming ball position, at the different times of tactile stimulation. Distance estimation judgments provided the indication that every subject could actually discriminate six different distances (averaged values: D6 was perceived at 82 cm (SD = 14.4) far from the subject, D5 at 80 cm (SD = 6.60), D4 at 71 cm (SD = 9), D3 at 60 cm (SD = 8.5), D2 at 51 cm (SD = 9.7) and D1 at 37 cm meters (SD=9.4).

2.7.3. *PPS data analysis*

In line with previous studies (Pellencin et al., 2018; Serino et al., 2015), to provide a measure of the multisensory facilitation induced by visuo-tactile stimuli on tactile processing, RT in the visuo-tactile condition were referred to the RT in unimodal tactile condition (vibration but no ball shown). For each subject, the fastest unimodal RT (after averaging per each temporal delay) was subtracted from the distance-averaged visuo-tactile RT (baseline correction RT). This correction allows estimating the multisensory gain, that is, the facilitation effect induced by multisensory stimuli as compared to unisensory ones.

The relation between tactile reaction times and the position of the external stimulus in space (from here, the PPS function) is used to measure the features of PPS representation at the individual level (Ferri et al., 2015; Serino et al., 2018). To mathematically synthesize these features, the relationship between tactile reaction times and distance was fitted with a linear or sigmoidal function, similarly to what was done in previous works. The central point of the fitted sigmoidal function provides a measure of the spatial position at which a looming stimulus starts to be integrated with tactile processing and affects motor reactions, thus indicating the spatial boundary of PPS (Canzoneri et al., 2012; Serino et al., 2015). The slope of the linear fit quantifies the difference between the effects of near and far visual stimuli on tactile processing, providing a proxy of the amount of differentiation between peri and extrapersonal space (Noel et al., 2018; Salomon et al., 2017). Steeper PPS slopes indicate a more selective processing and motor preparation for near-body stimuli, whereas flatter slopes suggest more homogeneous monitoring of near and far stimuli with respect to potential interactions with the body. Units are defined so that the linear slope is expressed in the millisecond of multisensory facilitation per meter.

2.7.4. *Statistical analyses*

To statistically compare Cortisol Concentration values between the control and the experimental groups, we used a mixed ANOVA with *Time* (T1/T2/T3/T4/T5) and *Group* (Experimental/Control) as factors. Similarly, the differences in the salivary parameters in the *Post-Manipulatio*n and *Rest* cortisol, in the two groups, were compared with a two-way mixed ANOVA.

We compared changes in PPS representation, both for the central point and the slope, at the group level (the Experimental and the Control group), with two mixed ANOVAs with Group (Experimental/Control) and Manipulation (Pre/Post Manipulation).

To address individual differences within the experimental group, two separate ANOVAs were performed on the central point and on the slope of the fitted function with Cortisol Response (C-Responders and Non-C-Responders) as between-subjects factor, and Manipulation (Pre/Post Manipulation) as within-subjects factor. To replicate the previous analysis through a measure that does not depend on the definition of C Responders, we assessed correlations between changes in PPS slope and central point, and CR values. Due to the strongly non-Gaussian distribution of Cortisol Response values (W = 0.797, p = 0.001), Spearman correlation values were used, but the main results reported do not change using Pearson correlations. All post-hoc analyses on ANOVAs were corrected with the Neuman Keuls method.

2.8. *Data and code availability*

Behavioural data and R code for reproducing the main results are available in the following OSF repository: https://osf.io/kpdw6/?view_only= 836db15416e94e51b256d524a77cde52.

3. Results

3.1. *Cortisol concentration*

To confirm that our experimental manipulation correctly modulated stress level, we compared mean concentrations of salivary cortisol across the five measurements for the two groups (for details on saliva sampling, see Fig. 1A). We found a main effect of *Time* ($F(4,144)= 6.35$; $p < 0.001$), of *Group*($F(1,36)= 10.46$; $p = 0.004$) and a *Group* X *Time* interaction ($F(4,144)= 4.61$; $p = 0.002$). Post-hoc comparisons revealed, in the *Experimental Group*, an increase in Cortisol level from T1-T2 (which were not different from each other; p = .17) to T3 (both p-values<.001) and T4 (both p-values<.001). At T5, cortisol level then decreased to pre-manipulation levels (not different from T1 and T2, both p-values>.34). Thus, cortisol level increased after the stress manipulation and then returned to the baseline level. There was no significant difference between the five measurements in the control group (all p-values>.52), thus showing no changes in cortisol level across the different testing sessions for participants not exposed to the stress manipulation.

When comparing Post-manipulation and Rest cortisol concentration values, we found a main effect of *Group* ($F(1,36)= 12.50$; $p = 0.001$), a main effect of the *Manipulation* (Rest cortisol/ Post manipulation cortisol) ($F(1,36)= 33.50$; $p < 0.001$), and a significant interaction ($F(1,36)= 12.19$; $p = 0.001$). Post-hoc comparisons revealed that in the experimental group, the mean values of the salivary cortisol concentration of the post manipulation (M=0.531; SD=0.306) strongly increased as compared with the *Rest cortisol* values (M=0.191; SD=0.086; $p < 0.001$). In the control group the *Post manipulation cortisol* (M=0.244; SD=0.155) did not differ from the baseline values (M=0.160; SD=0.056; p = 0.25). The mean values at *Rest cortisol* were not different between the two groups p = 0.62), whereas the experimental group showed higher cortisol levels than the control group in both post-manipulation measures (both p-values <0.001).

Finally, we analysed Cortisol Response (CR) values. As shown in Fig. 2 A, while CR was small and homogenous in the control group (except for a single individual with CR>0.3 μg/dL), there was great variability in CR in the experimental group (see Fig. 2B). Here, cortisol response exhibited a bimodal distribution, with seven individuals showing high changes in CR, more than 0.3 μg/dL (Fig. 2 C), and the remaining participants showing CR changes smaller than 0.3 μg/dL. On this basis, we considered a threshold at < 0.3 μg/dL as an index of cortisol response to the stress and we accordingly divided the experimental group into two sub-groups, the "*C-Responders*" and the "*C-Non-responders*" (CR<0.3 μg/dL) group. According to this criterion, 7 out of the 19 participants in the Experimental group resulted to be C-Responders, and 12 resulted to be C-Non-Responders. C-Responders had an average age of 20.8 ± 1.6 (SD) years, while Non-C-Responders were aged 24.1 ± 7.6 (SD) years, with no significant difference in age between the two groups (p = .16). To test the robustness of such splitting criterion, we replicated the analysis in a purely data-driven approach by using K-means clustering to split subjects in two groups according to cortisol response (Fig. S2). This method yielded the same results as our threshold, which was also the case when defining the cortisol response based on average values rather than min-max values (Figs. S1-S2).

3.2. Subjective stress

We then test whether the experimental manipulation and the associated induced change in cortisol concentrations were reflected at the subjective level, measured with a 5-points Likert scale. Mean values of the subjective stress ratings across time were compared for the Experimental and the Control groups via non-parametric Friedman tests with the factor *Time-points (*T1, T2, T3, T4, T5), as the scores were not normally distributed. Subjective stress reports did not significantly vary across time points neither for the experimental nor the control group ($X^2(4,19)= 7.85$; p = .1; $X^2(4,19)= 8.30$; p = .08), respectively).

To quantify the magnitude of the changes in the perceived subjective stress, induced by the experimental manipulation, we considered the mean value of the two measures collected right after the manipulation (T3 and T4) as Post-manipulation Subjective Stress, and the mean of the values referred to the measures outside the manipulation windows (before, T1 and T2, and at the end of the experiment, T5), as a measure of Rest Subjective Stress. Then, for each participant, the values of the *Rest* Subjective Stress were subtracted from those at the *Post-manipulation* Subjective Stress, to derive an index of the *Subjective Stress Response* (SSR).

We tested a possible relation between the subjective stress ratings and the cortisol concentration. There was no correlation between CR values and changes in SSR (p = 0.41). Thus, changes in stress level as induced by the experimental manipulation and found in the cortisol level were not reflected in subjective ratings.

3.3. Stress and PPS representation

To test whether the implicit neuroendocrine stress response was related to changes in the relation between near and far space, we analysed the two key parameters describing individuals' PPS, i.e. the central point of the sigmoidal function, as a marker of the extent of the PPS, and the slope of the linear function, as a marker of the amount of near-far segregation in PPS representation. Unlike in other previous (e.g. Canzoneri, 2012) reports (but not all, see e.g., Noel, 2015; Serino et al., 2021), we found that linear fits were providing the best description for the data. When using a paired t-test to compare R2 values between linear and sigmoidal fits, we found linear fits to provide a better fit both in the pre-manipulation (linear R2: 0.555 ± 0.051 S.E.M., sigmoidal R2: 0.406 ± 0.057 S.E.M., p = .048) and in the post-manipulation session (linear R2: 0.498 ± 0.046 S.E.M., sigmoidal R2: 0.337 ± 0.051 S.E.M., p = .004). Therefore, in further analyses we will focus mainly on linear fits and will briefly mention results of sigmoidal fitting for completeness.

RTs for individual distances and the fitted linear function for different experimental conditions are shown in Fig. 3.

At the whole groups level, for the central point, there was no effect of Group, no effect of Manipulation, nor Interaction (all p-values>0.48). Similarly, no effects were found on the Slope (all p-values > 0.63). (Fig. 4 A, right). The absence of interaction with the experimental group suggests that stressful manipulation does not change PPS representation at the group level.

However, as seen from the analyses of cortisol concentration, the stress manipulation did not affect equally participants from the experimental group. Thus, to study the effect of induced physiological changes, we compared PPS representation between cortisol responders and non-responders in the experimental group. We therefore performed further analyses within the experimental group, with Cortisol Response (C-Responders and Non-C-Responders) as a between-subjects factor. For the central point, the ANOVA showed no effects (all p-values>.13). Instead, for the Slope, we found a significant two-way interaction (F (1,17)= 4.93; p = .040). Visual inspection of the pattern of multisensory slopes across the two experimental sessions shows that slopes in the C-Responders group increased after the manipulation, while it decreased in the Non-C-Responders group (Fig. 4 A, left). In the pre-manipulation session no difference was found between the C-Responders and Non-C-Responders (C-Responders: M = 7.27, SD = 6.87, Non-C-Responders: Pre: M = 8.91, SD = 6.39, t(12) = 0.51, p = .62), while a trend toward significance was found in the post-manipulation session (C-Responders: M = 9.56, SD = 4.86, Non-C-Responders: M = 5.39, SD = 4.19, t(12) = −1.89, p = .084). Direct comparison between pre-post sessions in C-Responders and Non-Responders, showed a significant decrease in the slope for the Non-C-Responders (Pre: M = 0.891, SD = 0.639, Post: M = 0.539, SD = 0.419, t(11) = −2.41, p = .034), and an opposite direction, yet non-significant effect for C-Responders (Pre: M = 0.727, SD = 0.687, Post: M = 0.956, SD = 0.486, t(6) = 0.973, p = .36).

We then compared the effect of the Manipulation of the Non-C-Responders group with that of the Control group. We found a significant main effect of Manipulation (Pre: M = 8.25, SD = 5.57, Post: M = 5.70, SD = 5.22, F(1,29) = 8.27, p = .007), which did not interact with the Group (p = .41). The decrease of slopes in the Non-C-Responders group is comparable to the decrease observed in the control group (Pre: M = 7.83, SD = 5.13, Post: M = 5.89, SD = 5.88, t(18) = −1.627, p = .12), possibly reflecting a test-retest effect.

To further interpret the observed effect through a measure that is not sensitive to the threshold used to split the Experimental group based on cortisol response, we computed the difference in multisensory slope before and after the manipulation ($\Delta slope = Slope_{Post} - Slope_{Pre}$) and computed the correlation between Δslope and Cortisol Response.

The correlation was significant (Spearman's R = 0.535, p = .02) and the positive coefficient indicates that participants with a stronger cortisol response had a larger increase in the multisensory slope, i.e.: in the amount of segregation between close and far space (Fig. 4B). The same analysis on the control group yields no significant result (p = .28).

To rule out the possibility that the relation between changes in PPS and cortisol response may be driven by overt expectations, we repeated our main analyses after subtracting the unimodal RT (which reflects purely temporal effects) to the corresponding multisensory RT in the PPS task. As seen in Fig. S3, this method yielded largely overlapping results.

Furthermore, we tested whether an explicit measure of the stress response, detected by the *SSR* index, was related to changes in the PPS representation, measured on the slope and the central point values. Dividing both the control and the experimental group by the median values of the SSR, we obtained a "*low SSR*" group and a "*high SSR*" group. No changes in sigmoidal central point or linear fit slope between pre and post manipulation were highlighted in PPS representation by two-way ANOVAs, either for the control or the experimental group (all p-values > 0.12).

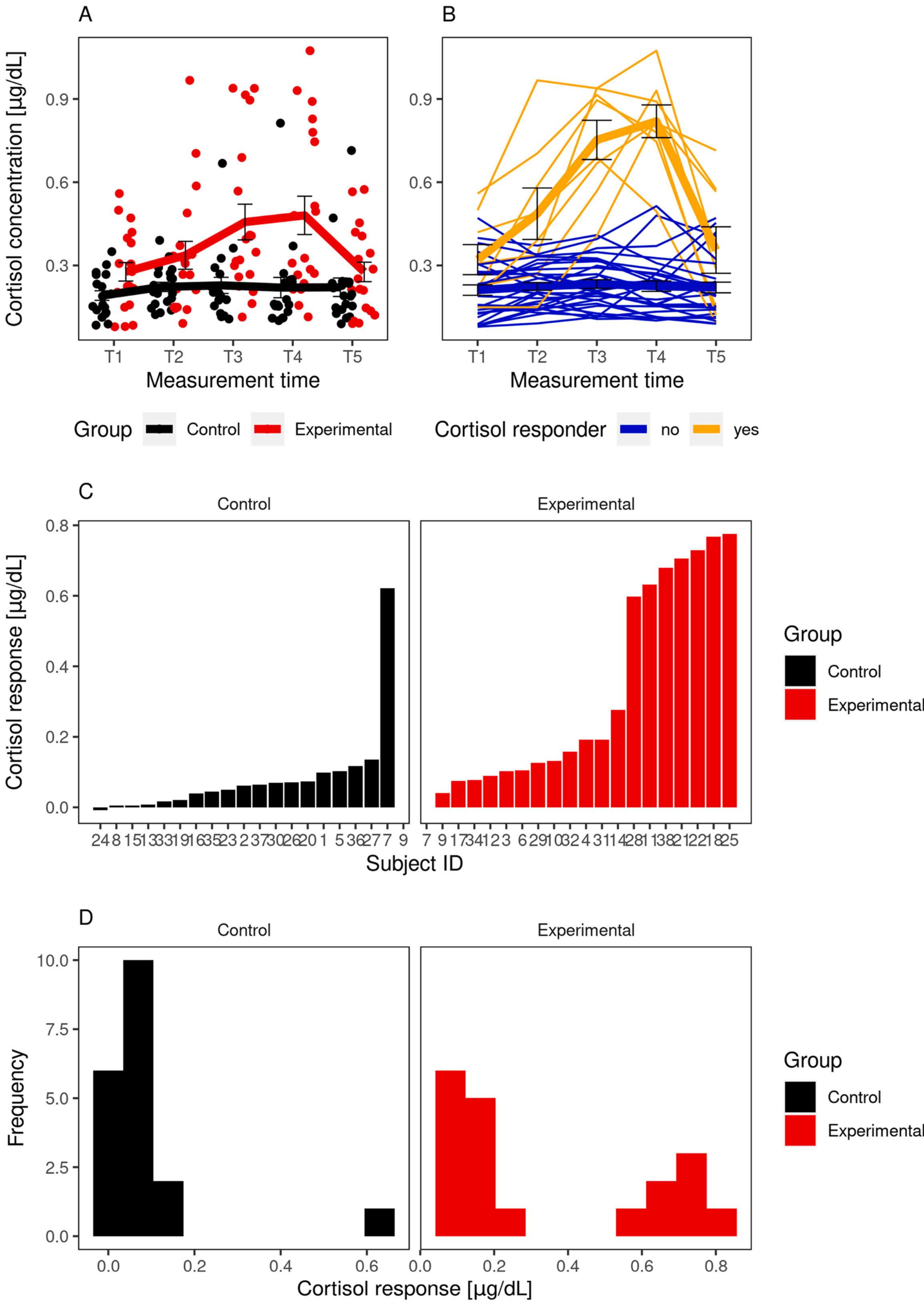

Fig. 2. Cortisol response. (A). Individual salivary cortisol concentration expressed in µg/dL across the five Time-points for the Experimental (red) and Control (black) participants; bold lines indicate the group average, error bars represent S.E.M. (B) Individual trend of cortisol concentration of the experimental group, orange lines are representing the C-Responders, blue lines, the Non-C-Responders; bold lines indicate the group average, error bars represent S.E.M. (C) Bar plots representing the individual CR values of the cortisol concentration in the Control and the Experimental group. Values are obtained, for each participant, from the difference between the values of the Post-manipulation cortisol concentration (T3-T5) and the Rest cortisol concentration (T1, T2, T5). (D). Histograms displaying the distribution of cortisol response values for Controls (left) and subjects from the Experimental group (right).

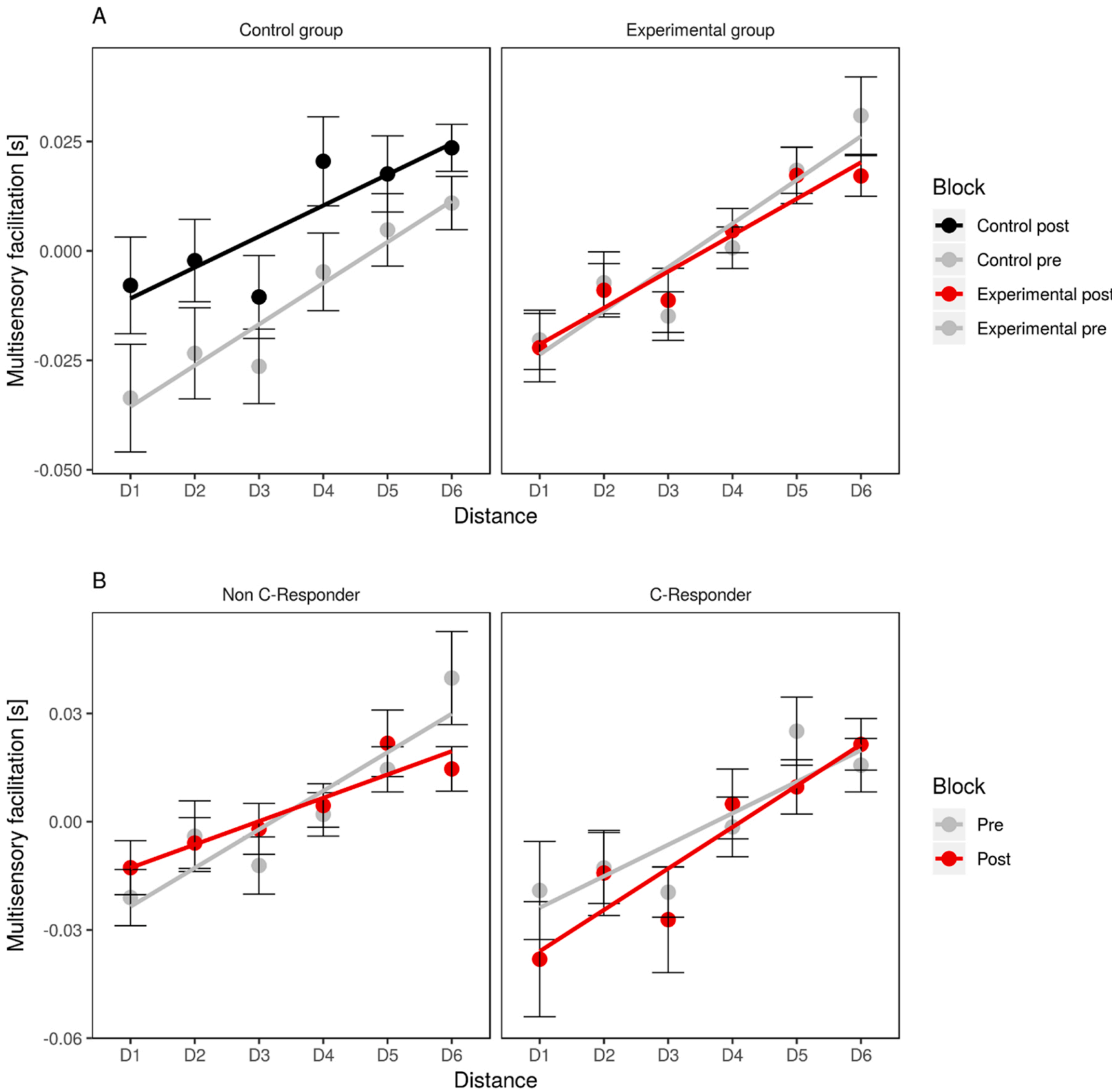

Fig. 3. Peripersonal Space Results (RTs). (A). Multisensory facilitation (seconds) across distances, in the Pre and Post manipulation measurements. The left panel represents the results from the experimental group, the right panel, the results from the control group. The solid line represents the linear trend line (slope) of the distribution. Error bars represent S.E.M. (B). Multisensory facilitation (seconds) across distances, in the Pre and Post manipulation sessions, in the Non-C-Responders (left) and the C-Responders (right) sub-groups from the experimental group.

3.4. *Trait anxiety*

As complementary analyses, we investigated the relationship between trait anxiety, measured by the Trait subscale of STAI, and neuroendocrine stress responses. Importantly, the two groups were not different from each other for the Trait-Anxiety Scores (Control: M=29.84, SD=8.62, N = 19; Experimental: M=31.11, SD=5.56, N = 19; p = 0.59). Furthermore, we found no difference in trait anxiety between the sub-groups of "*C-Responder*" (M=30.75, SD=4.41, N = 12) and "*Non-C-Responder*" (M=31.71, SD=7.499, N = 7) (p = 0.72).

However, we found a relationship between trait anxiety and stress, both at the subjective and physiological levels. Trait Anxiety Scores correlated with the Subjective Stress scores, both at the Baseline (*Control* group: R^2 =0.52, p = 0.0005; *Experimental* group: R^2 =0.43, p = 0.002) and the post-Manipulation level for both groups (*Control* group: R^2 =0.60, $p < 0.001$; *Experimental* group: R^2 =0.18, p = 0.034). Trait Anxiety also correlated with cortisol level at *Baseline* (R^2 =0.169; p = 0.011). However, trait anxiety scores did not predict changes in cortisol (*CR* values) induced by the experimental manipulations (*Control* group: R^2 =0.0001, p = 0.96; Experimental group: R^2 =0.01, p = 0.66).

Finally, we investigated whether our main dependent variable, the PPS slope, was also affected by the level of trait anxiety of the participant. We found no relation between trait anxiety scores and PPS slope in the pre-manipulation block (p = 0.24, control and experimental group together), and no relation with the change in PPS slope in the experimental group (p = 0.73). When using a multiple regression predicting the change in slope with trait anxiety scores and cortisol responses, only the latter was found to have a significant effect, as in our main analyses (cortisol response: p = 0.03; trait anxiety: p = 0.52).

4. Discussion

PPS representation can be mainly conceived as a multimodal sensory-motor interface that mediates the interaction between the body and external objects by integrating information about external stimuli (i.e., visual stimuli) with body-related cues (i.e., tactile stimuli) to prime appropriate reactions (Graziano and Cooke, 2006; Làdavas and Serino, 2008; Cléry et al., 2015). In the present study, we tested whether acute

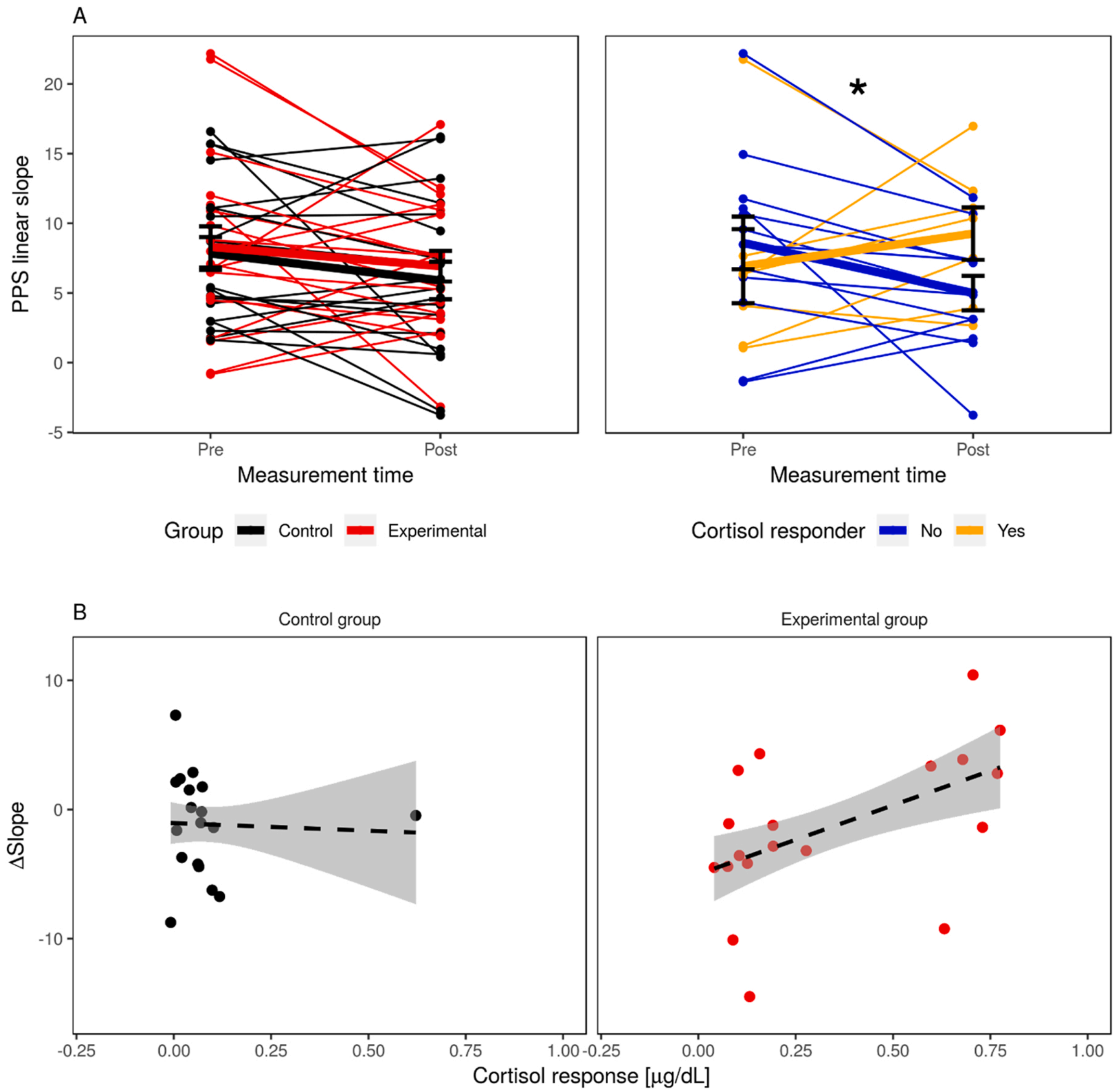

Fig. 4. Peripersonal Space Results at the individual level (linear slopes). (A) In the left panel, PPS linear slopes for individual participants in the control (black) and experimental (red) group, are shown before and after the manipulation. In the right panel, PPS linear slopes for the experimental group, are split between C-Responders (orange) and Non-C-Responders (blue). Solid lines represent group means and their error bars represent S.E.M. (B). Scatterplot showing the relationship between Cortisol Response (µg/dL) and a difference in the PPS slope before and after the stressor manipulation (Δslope) in the Control group (left panel) and in the Experimental group (right panel). The dashed line represents the linear regression line. The more the participants were showing an increase in the cortisol response, the steeper the slope was after the stressor manipulation.

stress, eliciting a significant neuroendocrine response, affects PPS representation, measured by changes in the processing of body-related multisensory stimuli in space. Importantly, given the significant individual differences in stress responsiveness described in the literature, we tested whether the magnitude of the cortisol level increase determined the changes in PPS representation. Thus, we distinguished two subgroups in the participants exposed to the stressor manipulation, accordingly to whether there was a sensible and meaningful change in their neuroendocrine response, *C-Responders* or *Non-C-Responders*.

At the group level, we did not find a general PPS change in the experimental group as compared to the control group consequent to the stressor manipulation. However, the changes in PPS representation, associated with the manipulation, were different among individuals who did, or did not, show a neuroendocrine stress response after stress exposure. In the experimental group, the PPS linear slope increased in participants who showed a cortisol response to the stressful manipulation, whereas it decreased in participants who did not have such a response. The decrease in slope in *Non-C-Responders* was comparable to what was observed in the control group, suggesting this effect can be due to habituation to the experimental task. The central point of the sigmoidal fit was not affected by the manipulation either, indicating that the stress response does not affect the extent of PPS. Moreover, subjects from the control group, who were not exposed to a stressful situation, did not show any difference in PPS representation measured before and after the manipulation, neither in terms of slope nor of the central point. Taken together, this evidence suggests that stressful events which result in a strong cortisol response affect PPS representation in terms of a change in the way external stimuli in space interact with the processing of tactile information on the body. Namely, individuals presenting a significant physiological stress response - i.e., *C-Responders* - showed an enhanced differentiation between the close and the far space after the stressful manipulation. This effect is in line with a recent study by Spacassassi and Maravita (2020), demonstrating, with a multisensory temporal order task, an enhanced multisensory interaction for stimuli presented in the near as compared to the far space, after an anxiety-inducing manipulation. Importantly, the change was significant only when considering individual differences in the sensitivity to the manipulation and anxiety levels.

The steeper slopes of the PPS in *C-Responders* reflect an increase of multisensory processing within a more limited area around their body, and thus a stronger differentiation between near and far space compared with the baseline. Previous studies showed an increased PPS linear slope in the presence of looming stimuli, specifically when considered relevant, as in the case of a threat (de Haan et al., 2016). We propose that such an increase in PPS segregation might be considered as a form of defensive-freezing reaction, whereby resources are more allocated to the body and space immediately surrounding it (Schmidt et al., 2008; Roelofs, 2017). This defensive response serves the evolutionary purpose of optimizing the selection of an appropriate coping response by enhancing perceptual and attentional processes (Lang, Davis and Öhman, 2000; Erickson, Drevets and Schulkin, 2003), that become more automatic and less controlled (Arnsten, 2009; Sänger et al., 2014; Elling et al., 2012) and in action preparation (Gladwin et al., 2016).

There is a complex interaction between motor responses, PPS representation and stress reaction. To interact with external objects, the individual has to be able to predict the spatio-temporal relationship between an external stimulus and one's own body (Noel et al., 2015; Serino et al., 2011). Multisensory integration within the PPS is a key mechanism underlying such prediction (Cléry et al., 2015), and its immediate translation in a potential action in a dynamic environment, via modulation of the motor system (Finisguerra et al., 2015; Makin et al., 2009; Serino et al., 2009). Results have shown that PPS dynamically shapes according to the experience of controlling the course of events through one's actions (D′Angelo et al., 2018), according to the characteristics of external stimuli (e.g., velocity; Noel et al., 2018), previous exposure to the specific movement (Brozzoli et al., 2010) and the dimension of the acting space (Bassolino et al., 2010, 2014; Canzoneri et al., 2013). Conversely, previous studies in mice models have highlighted that an active control over a stressor, or the possibility to act, modulate the dynamics of the stress response (Fox et al., 2006). Rodents that underwent uncontrollable stressful situations, for a prolonged time, showed less inhibited behaviour and less depressive traits when they could act over the stressor, as compared with the individuals constrained in a passive condition (Kunz, 2022). Interestingly, within the domain of the social-spatial representations, Iachini and colleagues (2014) demonstrated that, when participants have active control over social interaction, they are less sensitive to a confederate intruding on their comfort space. Similarly, the increased allocation of multisensor-motor resources to the far space in cortisol non-responders, as opposed to responders, may indicate a tendency to actively cope with the stressful situation.

In our study, the relationship between responsiveness to stress and changes in PPS representation was limited to the physiological measures of stress, as we did not find any difference in participants showing a higher increase of subjective stress as compared to those showing a lower increase. However, subjective stress ratings were generally low, their change between baseline and post-manipulation assessments did not even distinguish between the control and the experimental group, and finally, they were not related to cortisol response. Exposure to psycho-physiological stressors is expected to induce both the activation of the HPA axis, with cortisol release, and concurrent subjective responses with a certain degree of coherence (Campbell and Ehlert, 2012; Buzgoova et al., 2020). Nonetheless, several contributions have pointed out a weak or non-existent association between physiological and subjective stress responses (Campbell and Ehlert, 2012; Dalile et al., 2022; Dickerson and Kemeny, 2004; Mauss et al., 2005). In the case of our study, the null effect of the manipulation on subjective stress response and the absence of relation with the physiological measurements can be explained by considering different factors. First, the measure adopted to quantify subjective stress might be unable to fully capture subjective stress states (low sensitivity). A 10-points Likert scale or a VAS with continuous responses might have been more appropriate to detect any difference between the groups. Further, as in Admon and colleagues (2017), subjective stress responses may be more accurately measured by multidimensional scales (Admon et al., 2017) together with integration with other measures of positive and negative affect (PANAS; Watson et al., 1988) and state anxiety (STAI-S; Spielberger et al., 2017). Lastly, implicit measures of subjective stress would have been preferable to overcome the desirability bias (Mossink et al., 2015). Second, the possible relation between the two response components might have been best explained by considering potential mediators. Appraisals (Lazarus and Folkman, 1984), or the cognitive evaluation of stressfulness, may vary depending on interindividual differences in acceding to the cognitive content of the stress reaction (Pulopulos et al., 2020); personality traits (e.g., neuroticism; Christensen et al., 2019), experience with the stimulus and the perceived self-efficacy may play a role (Lazarus and Folkman, 1984; Thornton and Andersen, 2006). Moreover, subjective stress evaluation has also been related to interoceptive accuracy (Schulz and Vögele, 2015; Garfinkel et al., 2015; Fairclough and Goodwin, 2007), and alexithymia seems to mediate this relation (Palser et al., 2018). Thus, further studies may include personality questionnaires (i.e., Eysenck Personality Questionnaire; Eysenck and Eysenck, 1975; Toronto Alexithymia Scale-TAS; Taylor et al., 1985) to control for interindividual differences on relevant dimensions, such as neuroticism and alexithymia. Third, as mentioned above, to avoid biases due to sex differences in stress reactivity, our sample was composed of male subjects only. Nonetheless, it has been shown by Ali et al. (2020) that particularly females, rather than males, tend to report subjective stress following dysregulation of the stress system. Thus, counterbalancing the sample for the sex of the participants might have led to more generalizable subjective stress results.

Alternatively, the physiological cortisol response does truly relate to a different component of the stress phenomenon. Considering together physiological and PPS results, the effect produced by our manipulation is best interpreted with a freezing-like response. Subjective evaluation of stress might be more linked to later stages of the response cascade (i.e., flight/fight; Schauer and Elbert, 2015), when there is an effective and consolidated sympathetic activation and an active reaction to facing the stressor is organized. To corroborate this interpretation (freezing versus flight/fight), further studies may include other measures like heart rate and body sway. Finally, to identify predictors of responsiveness to stress, we also collected and analysed trait anxiety scores from the present sample. First, although anxiety scores were correlated with the level of stress at the baseline, both for subjective and cortisol measures, they were not related to the stress changes induced by the manipulation for either measure. Also, anxiety scores were not correlated with the indices of PPS representation, unlike in previous studies by Sambo and Iannetti (2013) and Iachini and colleagues (2015), who found that higher levels of anxiety were associated with a more extended PPS, as to increase monitoring of potential threats. This difference might depend on the nature of the PPS task implemented. Here, stimuli were more neutral, while, in the above-cited studies, stimuli were highly arousing (eye-blink reflex induced by median nerve electric shock, or intrusion by an estranger into one's own comfort space). Thus, a relationship between anxiety and PPS might emerge if more salient or arousing stimuli are involved.

To summarize, here we report a novel relation between the cortisol response induced by a stressor manipulation and changes in multisensory integration of stimuli in space. Namely, we showed an increased differentiation between the multisensory processing of near vs. far stimuli in participants classifying as strong responders to a physiological stress measure, which might reflect a freezing-like response at the PPS level. Given the role of PPS representation in processing multisensory stimuli to prepare appropriate motor responses, the present results suggest that if the chain of defensive neurophysiological responses, induced by a stressor, results in significant cortisol response, this is accompanied by a re-allocation of multisensory-motor resources in the space immediately surrounding the body. Therefore, these findings could provide useful insights on how an easily obtainable biometric measure, such as cortisol concentration, could predict individuals' capability to monitor the multisensory space and act in a stressful situation, allowing them to better define and counteract its negative impact.

Limitations

A possible limitation of the present study should be acknowledged. In our design, the effect of stress was to be investigated by comparing the experimental group with a control group. However, the effect of the experimental manipulation was best explained by considering interindividual differences in the stress response within the experimental group, reducing the effective sample size to the experimental group only. Albeit contrary to our initial hypothesis, this should not be entirely surprising. Indeed, large variability in sensitivity to stress and related cortisol response is observed routinely in stress studies (e.g., Hellhammer, 2009). Therefore, it is indeed possible that behavioural differences between individuals showing different levels of cortisol response maybe even stronger than differences between the control group and the group undergoing a stressful manipulation. Still, further investigations should address this limitation by applying the stressful manipulation on a larger sample (comparable to the whole sample of the present study, about 40 subjects), and directly using a within-subjects design, allowing to maximize statistical power.

CRediT authorship contribution statement

Giulia Ellena: Formal analysis, Writing – original draft, Visualization. **Tommaso Bertoni:** Formal analysis, Writing – original draft, Visualization. **Manon Durand-Ruel:** Conceptualization, Methodology, Investigation. **John Thoresen:** Conceptualization, Methodology, Investigation. **Carmen Sandi:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision. **Andrea Serino:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

Acknowledgements

This research was funded by a Swiss National Science Foundation Professorship Grant to Andrea Serino (PP00P3_163951). The authors thank Olivia Zanoletti for performing the cortisol analyses, Elisa Pellencin for pilot data collection, Jean-Paul Noel for protocol optimization, Javier Belo-Ruiz, Robin Mange, Bruno Herbelin and Olaf Blanke for using the RealiSM technology.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105790.

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