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Sex-dependent effects of stress on brain correlates to empathy for pain

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ABSTRACT

Empathy is a fundamental attribute required for appropriate social functioning. The extent to which we empathize with others in pain is influenced by numerous factors. Being highly social species, humans face social stress on a regular basis, which undoubtedly affects how we react to our environment. It is not yet known how social stress may modulate our neural mechanisms when we empathize with others in painful circumstances, and its effects on empathic behavior are still unclear. For this reason, we recorded the electroencephalography (EEG) of healthy men and women, half of which were previously exposed to psychosocial stress, while they observed photographs of hands in painful and neutral situations. At the behavioral level, stress induced higher unpleasantness ratings to painful stimuli, and lower ratings to neutral pictures, independent of sex. At the neurophysiological level, we found that early (N110 over fronto-central sites) event-related potentials (ERPs) were not affected by stress, while late (P3 over centro-parietal regions) components showed a sex-dependent differential effect of stress. Correlation analyses further indicated a strong association between N110 with trait markers of empathy in all participants, while P3 was associated with the change in cortisol in stressed males. Our findings suggest that sex-dependent effects of social stress on the neural responses to empathy for pain give rise to comparable behaviors in men and women in the paradigm we employed, implying that each sex may engage in distinct mechanisms to cope with stress. Moreover, stress seems to modulate late neural mechanisms of empathy but not our early perception.

1. Introduction

The ability to empathize with others is essential for appropriate social functioning. Empathy is the capacity to build a mental representation of another individual's affective state by mapping another's emotion onto one's own emotional system (Gallese, 2003; Preston and de Waal, 2002). In addition, it requires an understanding of the cause of the other's feelings (Gonzalez-Liencres et al., 2013). Despite the value of empathy in our daily lives, we do not empathize with everyone to the same extent (Bernhardt and Singer, 2012; Stewart-Williams, 2007). This may depend, on the one hand, on whom we are empathizing with, and on the other hand, on our current state and our promptness to perceive social cues.

An exploratory study on the neurophysiological underpinnings of pain empathy showed an early effect of stimulus valence (i.e. painful vs. neutral stimuli) starting at 140 ms after stimulus onset over fronto-central regions (which some authors later analyzed as the N110 component), which correlated with subjective ratings of unpleasantness and of the other's perceived pain, and this effect lasted until after 600 ms after stimulus onset; and an effect of task (i.e. attention towards vs. away from the cues) on the perception of painful versus neutral stimuli at late time points (P3 component) over the parietal area (Fan and Han, 2008). Based on these findings, the authors proposed a model in which empathy for pain consists of early emotional sharing and late cognitive evaluation. This report established the foundation for subsequent electrophysiological studies investigating how certain factors may modulate early and/or late event-related potential (ERP) components in the context of pain empathy. Thus, some studies found that age (adolescents vs. adults), sex (men vs. women), occupation (physicians vs. non-physicians) and ethnicity (Chinese observing Asian vs. Caucasian faces) modulate our electrophysiological response to empathic stimuli (Decety et al., 2010; Han et al., 2008; Mella et al., 2012; Sheng and Han, 2012). There is also evidence that there are sex differences in the way we process empathy in terms of neural activation patterns (Rueckert and Naybar, 2008; Schulte-Rüther et al., 2008) and some have found neural but not behavioral sex differences (Derntl et al., 2010). While all these factors are determined by previous experiences or by biological constraints it is not yet known how less permanent variables that affect our daily lives such as acute social stress may influence these ERP components in the appraisal of pain in others.

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Social stress can be caused by several reasons, such as social evaluative threat and uncontrollability, fearing the loss of a loved one or having fear of acting in public (Dickerson and Kemeny, 2004; Miczek, 2010). Owing to the frequency with which most of us experience it, social stress has a profound influence on our social lives and some reports suggest that men and women are distinctively affected. Tomova and colleagues recently demonstrated that men and women under psychosocial stress induced by the Trier social stress test (TSST; Kirschbaum et al., 1993) respond differently to social tasks tackling self-other distinction at the perceptual-motor (mimicry), affective (empathic) and cognitive (mentalizing) modules (Tomova et al., 2014). More specifically, men scored lower in all three self-other distinction paradigms whereas women obtained higher scores in all of them. The authors proposed that, under psychosocial stress, men are more self-oriented, while women become more other-oriented. This is in agreement with the "tend and befriend" hypothesis put forward by Taylor and colleagues, who proposed that whereas men engage in "fight or flight" behavior in response to stress, women's behavioral reaction consists in creating and caring for social networks (Taylor et al., 2000). The findings from the abovementioned study are also supported by another study that found stronger activation in males in brain regions recruited for inhibitory control and sensory awareness when rating and assessing socially stressful situations (Lee et al., 2014). On the other hand, a recent study found that men under psychosocial stress have more emotional empathy, while cognitive empathy remained unchanged (Wolf et al., 2015). Finally, Buruck et al. (2014) recently found that TSST-induced stress resulted in lower pain ratings to the observation of hands or feet in painful circumstances. Most of these studies point to a sex-dependent differential effect of social stress on social attributes although it warrants further replication at the behavioral level since some controversy still exists. Moreover, it is still unknown how this may contribute to changes at the neurophysiological level in men and women.

Thus, the aims of this study were to examine whether social stress affects empathy for pain differently in men and women at the behavioral and electrophysiological levels. More specifically, we compared early (N110 over fronto-central regions) and late (P3 over centro-parietal sites) ERP components, theoretically corresponding to emotional sharing and cognitive evaluation, respectively, in healthy men and women under acute moderate psychosocial stress and a control group when they observed hands in painful and neutral situations. Furthermore, we also considered the potential relationship between ERP components with self-reported empathy and the cortisol response to stress. We hypothesized that acute moderate stress would modulate the late cognitive ERP components but not our emotional perception at earlier time points and that behavioral differences would arise with women being more empathetic.

2. Materials and methods

2.1. Participants

60 healthy participants (30 women) between 18 and 35 were recruited for this study and were randomly assigned to one of two groups (stress vs. control). Participants that took hormonal contraception, smoked, had previous neuropsychiatric disorders or had endocrine or somatic conditions were excluded from the study. We additionally excluded stressed participants who did not show an increase in cortisol and those in the control conditions who had an increase (see below for further details). We also ensured that females were not in their menstrual phase at the time of testing. The study took place between 14:00 and 18:00 at the LWL University Hospital in Bochum, Germany. Participants gave written informed consent and obtained a financial reward upon completion. The study was approved by the ethics Committee of the Medical Faculty of the Ruhr-University Bochum, Germany.

2.2. Procedure

Fig. 1 illustrates the experimental procedure. Participants were first requested to complete the Interpersonal Reactivity Index (IRI), followed by the electrode setup and after that the Positive and Negative Affect Schedule (PANAS) (pre condition), and subsequently they underwent either the stress or the control treatment. They then completed the PANAS (post condition), carried out the pain empathy task while their EEG was being recorded, and filled out the Social Desirability Scale (SDS) at the end of the session. Saliva samples were taken at four distinct time points: before the stress/control condition (baseline), 1 min after (+1), 15 min after (+15) and 30 min after (+30) the treatment.

2.3. Behavioral assessment

2.3.1. Interpersonal Reactivity Index (IRI)

The German version of the IRI (Davis, 1980), the Saarbrücker Persönlichkeits-Fragebogen (SPF; Paulus, 2007) assesses four independent measures (empathic concern, EC; perspective taking, PT; fantasy scale, FS; and personal distress, PD) with 16 items where participants have to select in a 5-point scale how much they agree with each statement, a higher score indicating more empathic skills.

2.3.2. Positive and Negative Affect Schedule (PANAS)

Positive and negative affect before (pre) and after (post) the stress/control treatment was measured with the German version (Krohne et al., 1996) of the PANAS (Watson et al., 1988), which consists of 20 items (ten positive and ten negative affect adjectives) that the participants rated according to how they were feeling "right now" in a 5-point scale (1, not at all; 5, extremely).

2.3.3. Social Desirability Scale-17 (SDS)

The German SES-17 (Soziale-Erwünschtheits-Skala-17; SDS in English) (Stöber, 2001,Stöber, 1999) is a questionnaire containing 16 items that measure the degree to which the participant is socially desirable to others. It consists of statements (e.g. "Sometimes I throw trash on the street") that the participant has to rate as "true" (+1 point) or "false" (−1 point). The total score is determined by the addition of the individual item scores, whereby a higher score indicates that the participant values social desirability more.

2.4. Psychosocial stress manipulation

A slightly modified version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) was employed to induce acute moderate psychosocial stress in half of the participants. The modifications were the number of confederates (two instead of three), the duration of the first preparatory part (5 min instead of 10 min) and the room in which all the parts of the TSST took place (three parts in the same room as opposed to having the first part in a separate room). The procedure lasts 15 min and consists of the following: participants were asked to sit in a separate room in front of a table where two confederates (one man, one woman) sat. They were told that they would be filmed throughout the session and that the two people in the room were psychologists that would analyze their behavior. In the first five-minute period, participants were allowed to take notes on a paper to aid them with a presentation they were asked to give, although they were not allowed to utilize these notes during their talk. In the second five-minute period, participants were requested to describe what personality traits would make them good candidates for their dream job. The last five-minute period consisted of an arithmetic task (counting back in steps of 17). Participants were never told the duration of each period. Furthermore, the two confederates behaved distantly, did not provide social feedback, took notes and made comments such as letting the participant know when they were off topic or they asked them to do the math task faster.

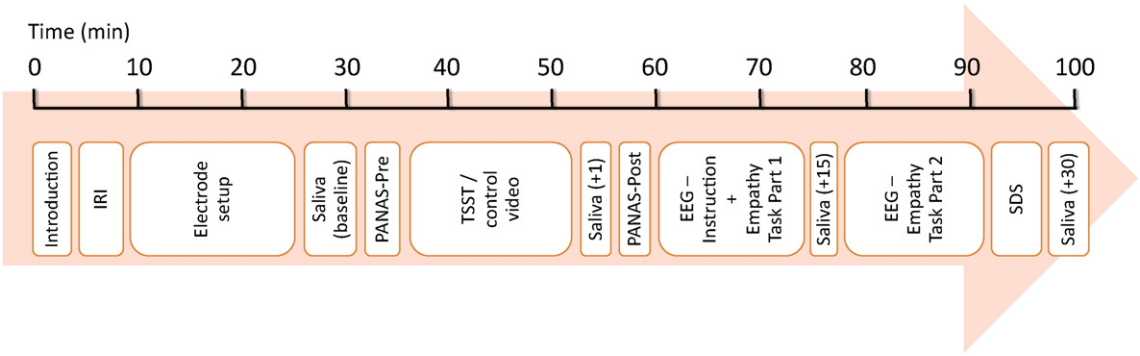

Fig. 1. Illustration of the experimental procedure. The time in minutes is depicted at the top with the approximate corresponding duration of each event shown below. IRI, Interpersonal reactivity index; PANAS, positive and negative affect score; TSST, Trier social stress test; SDS, social desirability scale.

A 15 minute video of a train was used as the control condition. The film clip showed a train ride on the Kootenay Valley Railway from the train driver's cabinet. The video was selected from the Internet platform Youtube (https://www.youtube.com/watch?v=iu7AYYcefUg; the presented section was 00:25:30–00:40:31). This control condition was chosen in favor of other possible control conditions like the Placebo-TSST (Het et al., 2009) or the friendly TSST (Wiemers et al., 2013) in order to avoid increased emotional arousal in response to the control condition.

2.5. HPA axis response

In order to measure the hypothalamic-pituitary-adrenal (HPA) axis response to stress, we collected saliva samples in Salivette collection devices (Sarstedt, Nümbrecht, Germany) at four different time points, which were frozen immediately after the experiment. We additionally calculated the area under the curve with respect to increase (AUC_i) in order to assess the changes of cortisol over time (Pruessner et al., 2003). A negative value indicates a reduction of cortisol over time. Free cortisol concentrations were analyzed without prior extraction using a commercial Chemoluminescence Immunoassay (CLIA; IBL International, Hamburg, Germany) according to the manufacturer instructions. Intra-assay and inter-assay coefficients of variations were below 10%.

2.6. Visual stimuli and design

The stimuli consisted of 14 different photographs of hands, seven in painful and seven in neutral everyday life circumstances. Participants were presented with a fixation cross of variable duration (500–1000 ms) to avoid expectancy, followed by the stimulus (750 ms) and another fixation cross (800–1600 ms), which preceded a final screen where they were requested to rate how unpleasant the pictures made them feel in a scale from 1 (not unpleasant at all) to 9 (very unpleasant). The answer screen was displayed for 2 s if the participants had not yet responded. Participants were instructed to position their index finger on the number 5 of the number keypad and provide an answer by pushing a number, which was equidistant from the starting point where the finger was initially placed. They were additionally told not to push the number 5 to rate the stimuli. The experimental design is illustrated in Fig. 2. The experiment had two blocks, each with 70 trials, and contained a one-minute break within each block and a longer pause in between each block.

2.7. EEG acquisition and analysis

EEG was recorded at a sampling rate of 250 Hz from 32 electrodes mounted according to the international 10–20 EEG system. An electrode placed diagonally of the left eye was used to monitor eye blinks. The EEG was re-referenced to the mastoids, filtered (0.1–100 Hz) and eye and muscle artifacts were removed with independent component analysis (ICA). Trials containing muscle potentials exceeding ±100 μV were removed. The ERPs had a duration of 1000 ms starting at stimulus onset and were computed separately for painful and neutral stimuli, plus an additional 200 ms epoch before stimulus onset that was used for baseline correction. Artifact rejection was performed and ERPs were averaged over trials, separately for each electrode, stimulus type and participant. The mean ERP activity was exported ±30 ms of each peak of interest (Decety et al., 2010), i.e. N110 (early) over fronto-central regions (Fz and Cz), and P3 (late) over the centro-parietal area (Cz and Pz). Offline analysis was carried out with BrainVision Analyzer 2.0 (Brain Products GmbH) and data were subsequently analyzed with SPSS statistical software. Reaction times (RT) were monitored using Presentation® software (Version 16.5, www.neurobs.com).

2.8. Statistical analyses

We checked for assumptions of normality as a preliminary step. Univariate analyses of variance (ANOVAs) with group (stress vs. control) and sex (male vs. female) as between-subjects factors were performed to compare differences in the IRI subscales, the SDS, the percentage of the difference between ratings to painful and neutral stimuli ($100 * [(\text{ratings}[(\text{ratings to the painful stimuli}) - (\text{ratings to the neutral stimuli}]/(\text{ratings to the painful stimuli}))$ and the cortisol level change over time (AUC_i). We conducted one repeated measures ANOVA for the PANAS positive and another for the PANAS negative with time (pre- vs. post-treatment) as the within-subjects variable, and group and sex as between-subjects factors.

2x2x2 ANOVAs were carried out to compare each ERP of interest (N110 over Fz and Cz; and P3 over Cz and Pz) and another $2 \times 2 \times 2$ ANOVA to contrast subjective ratings with stimulus type (painful vs. neutral) as the within-subjects factor, and group and sex as between-subjects variables. Similarly, a $4 \times 2 \times 2$ design was used to contrast cortisol levels across groups and sexes with time (baseline, +1, +15, +30) as the within-subjects factor.

The statistically significant level was appointed at $p < 0.05$. Planned comparisons were conducted for significant interactions and the p value required to reach statistical significance was adjusted (corrected α) implementing the conservative Bonferroni method.

Finally, the relationship among ERPs, cortisol levels and behavior were performed with non-parametric Spearman correlation analyses, which were not adjusted for multiple analyses given the distinct nature of the ERP components and the exploratory nature of this statistical analysis.

3. Results

The stress and the control group did not differ in terms of sex, age, body mass index (BMI) or years of education. We first explored the

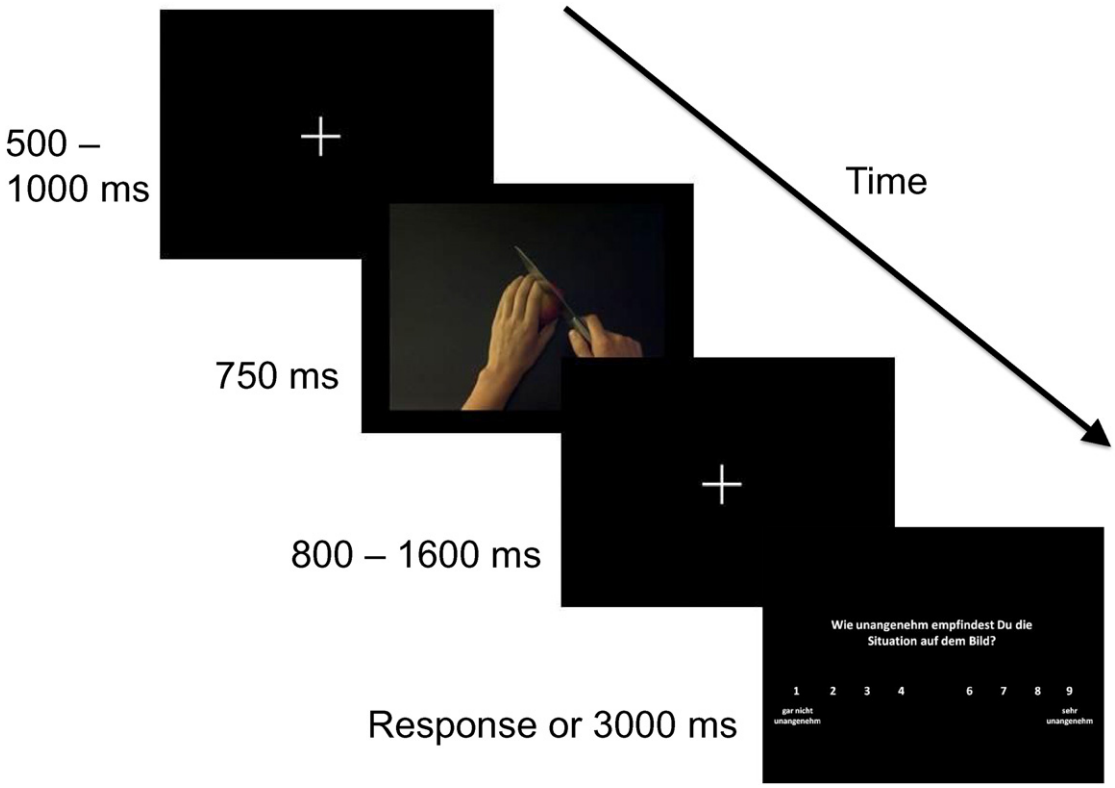

Fig. 2. Experimental design of the pain empathy task.

cortisol response of the participants and we excluded those in the stress condition who did not display an activation of the HPA axis, i.e. showed a decrease in cortisol levels at the +15 time point (n = 2 male and 4 female), as well as those in the control condition who had a stress reaction (n = 1 male) (i.e. a cortisol increase over 2.5 nmol/L at any time point (Petzold et al., 2010; Schoofs and Wolf, 2009; Wolf et al., 2009). We additionally excluded one (female) behavioral outlier who obtained scores over 2SD away from the mean in the IRI. Thus, 52 participants remained for the analysis. Demographical information for the included participants can be found in Table 1.

3.1. HPA axis endocrine response

The cortisol response of both groups is illustrated in Fig. 3. Repeated measures ANOVA showed a strong time by group interaction (F (3.46) = 54.0, $p < 0.001$, $\eta p^2 = 0.779$), as well as a main effect of time (F (3.46) = 40.3, $p < 0.001$, $\eta p^2 = 0.724$) and group (F (1.48) = 28.8, $p < 0.001$, $\eta p^2 = 0.375$), while there were no sex effects. Post-hoc independent t-tests revealed significant differences between groups at all time points ($p < 0.001$ at all time points) except at baseline (t (50) = −0.477, $p = 0.636$). We additionally explored the AUC_i of the cortisol response. Univariate ANOVA found a group effect (F (1.48) = 130.6, $p < 0.001$, $\eta p^2 = 0.731$), suggesting that stressed participants displayed an increase in cortisol over time, but no effect of sex (F (1.48) = 0.13, $p = 0.909$, $\eta p^2 < 0.001$).

3.2. Behavioral assessment

The scores and statistical (ANOVA) results from the behavioral tests are presented in Table 2. Post-hoc tests (corrected $\alpha = 0.0125$) for the PANAS positive indicated that the control group scored lower after watching the video (control condition) (t (25) = 8.55, $p < 0.001$), whereas the stressed group did not show any difference after the TSST. For the PANAS negative, post-hoc tests (corrected $\alpha = 0.0125$) showed that the stressed participants obtained higher scores post-treatment than the control group (t (47) = −5.69, $p < 0.001$), and that both groups showed a significant difference between pre and post scores, albeit in opposite directions (Control, t (25) = 4.30, $p < 0.001$; Stress, t (20) = −3.63, $p = 0.002$) (Fig. 4a). Regarding the Time × Sex interaction in the PANAS negative scores, we did not find any further differences from the post-hoc analyses.

Univariate analysis of the social desirability scores revealed a significant main effect of group (F (1.48) = 5.54, $p = 0.023$, $\eta p^2 = 0.104$), indicating that stressed participants are less socially desirable than their healthy counterparts (Fig. 4b).

We did not find any effects or interactions for the IRI scores.

Table 1
Demographic information of the participants. Values correspond to mean (SD).

	Control		Stress		Statistics
	Male	Female	Male	Female	
Sex	14	15	13	10	$X(1)^2 = 0.349$, $p = 0.554$
Age (yrs)	24.6 ± 3.7	22.7 ± 2.7	25.3 ± 4.1	23.9 ± 3.6	$F(3.48) = 0.135$; $p = 0.270$
BMI	23.6 ± 2.2	23.1 ± 2.7	23.8 ± 2.2	22.1 ± 2.3	$F(3.48) = 1.12$; $p = 0.350$
Years of education	16.5 ± 2.7	16.5 ± 2.0	16.0 ± 2.1	15.5 ± 1.1	$F(3.48) = 0.631$; $p = 0.599$

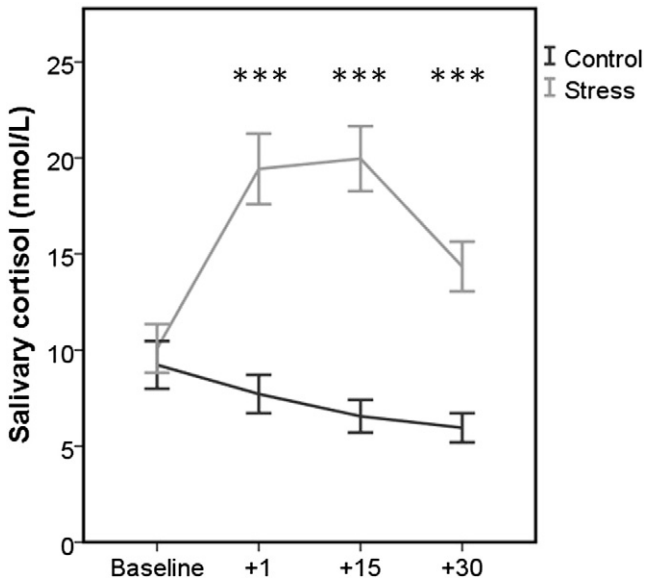

Fig. 3. Cortisol response to the TSST. Graph depicts mean (± SEM) of the cortisol levels at baseline, +1, +15 and +30 min after the stress (TSST) or the control condition. ***$p < 0.001$.

3.3. Subjective ratings of unpleasantness

The scores and reaction times for the subjective ratings of unpleasantness are presented in Table 3. Repeated measures ANOVA only revealed a main effect of pain (F (1.48) = 485.0, $p < 0.001$, $\eta p^2 = 0.910$), whereby painful stimuli elicited higher unpleasantness scores. We then explored group differences in the percentage of the difference between ratings to painful and neutral stimuli, and we found a significant main effect of group (F (1.48) = 5.66, $p = 0.021$, $\eta p^2 = 0.105$) implying that stressed participants rated painful stimuli as more unpleasant and neutral images as less unpleasant (Fig. 5). We also found a main effect of sex that approached but did not reach significance (F (1.48) = 3.75, $p = 0.059$, $\eta p^2 = 0.072$), with females showing a greater percentage of the difference between ratings to painful and neutral photographs, although we did not find any group by sex interaction.

ANOVAs of the reaction times (RT) revealed a two-way pain by group interaction (F (1.47) = 5.1, $p = 0.029$, $\eta p^2 = 0.098$) as well as a significant main effect of pain (F (1.47) = 21.1, $p < 0.001$, $\eta p^2 = 0.310$). Follow-up t-tests (corrected $\alpha = 0.0125$) showed that stressed participants took longer to respond to painful than to neutral photographs ($p < 0.001$), while this difference did not occur in the control group.

3.4. Electrophysiological analysis

The grand average ERPs in response to the painful and neutral stimuli in the stressed and the control groups are depicted in Fig. 6. In agreement with previous accounts we found an initial negative component (80–140 ms after stimulus onset, N110), followed by a positive peak (150–210 ms), a negative wave (210–270 ms), another positive deflection (350–410 ms; P3), a negative one (420–480 ms) and a late positive potential (LPP) over the frontal and central electrodes. The parietal electrode recorded an early positive component (70–130 ms), followed by a negative deflection (120–180 ms), a positive peak (180–240 ms), a negative wave (220–280 ms), a positive one (320–480; P3), a negative wave (400–460) and finally a LPP. We focused on N110 over frontal (Fz) and central (Cz) regions, and P3 over Cz and parietal (Pz) electrodes.

We looked at the role of sex and stress in each of the ERP components of interest. Repeated measures ANOVAs revealed no significant interactions or effects at N110 over Fz and Cz. At P3, we found significant three-way Stimulus type × Sex × Group interactions, one at each electrode site (Cz and Pz) (Fig. 7). Over the central electrode (F (1.47) = 4.49, $p = 0.039$, $\eta p^2 = 0.087$), post-hoc tests revealed a significant difference at P3 between painful and neutral stimuli in control females (t (14) = −3.30, $p = 0.005$) and stressed males (t (12) = −4.26, $p = 0.001$), whereby painful images elicited larger amplitudes than neutral stimuli, but we did not find any difference in control males nor stressed females. We did not observe any other differences when comparing stimulus type between sexes or between groups (all $p > 0.3$). Over the parietal area (F (1.48) = 6.07; $p = 0.017$, $\eta p^2 = 0.112$), post-hoc tests revealed no further differences despite the presence of the three-way interaction.

We additionally obtained a strong main effect of pain at P3 (F (1.47) = 22.1; $p < 0.001$, $\eta p^2 = 0.320$) over Cz, whereby the mean voltage was greater for painful than for neutral stimuli. We did not find any additional effects of pain at the investigated time points and electrodes.

3.5. Correlation analyses

In order to explore the potential association between brain activity to the observation of painful stimuli (i.e. the differential of ERPs to painful minus neutral stimuli) with behavioral performance and cortisol response, we conducted exploratory non-parametric Spearman correlation analyses in all participants pooled together and in each group (stress vs. control) separately in order to distinguish those empathy-related ERP components that were affected by stress from those that were not (Fig. 8). The differential ERPs reflect activity relevant only to the presence of pain. Early differential ERPs (N110 at Cz) were strongly correlated in all participants with the personal distress subscale of the IRI, which was measured before the stress or control treatment (Fig. 8a). A late differential ERP (P3 at Cz) was correlated with the

Table 2
Behavioral assessment. Values represent mean (SD). The statistics column shows the significant interactions and main effects in bold from the repeated measures ANOVAs in the case of the PANAS Positive and Negative scales. In the case of the IRI and the Social Desirability tests, the statistics column depicts the F value from the one-way ANOVA results.

	Control		Stress		Statistics
	Male	Female	Male	Female	
PANAS pos, pre	33.0 ± 6.9	32.6 ± 6.0	29.7 ± 6.3	29.7 ± 5.6	Time: F (1.46) = 49.5; $\eta p^2 = 0.518$; $p < 0.001$
PANAS pos, post	25.5 ± 10.9	23.5 ± 6.6	29.3 ± 6.6	28.7 ± 5.3	Time * Group: F (1.46) = 34.8; $\eta p^2 = 0.431$; $p < 0.001$
PANAS neg, pre	13.3 ± 2.7	14.0 ± 3.7	12.5 ± 2.9	14.9 ± 4.6	Time * Sex: F (1.46) = 5.60; $\eta p^2 = 0.109$; $p = 0.022$
PANAS neg, post	12.2 ± 2.5	10.7 ± 1.3	18.6 ± 5.7	15.4 ± 5.4	Time * Group: F (1.46) = 30.6; $\eta p^2 = 0.400$; $p < 0.001$ Group: F (1.46) = 13.1; $\eta p^2 = 0.222$; $p = 0.001$
IRI — FS	13.3 ± 2.7	14.7 ± 2.4	13.0 ± 2.3	14.0 ± 2.5	F (3.48) = 1.27; $p = 0.294$
IRI — PT	15.0 ± 3.1	15.4 ± 1.7	14.9 ± 1.9	16.2 ± 3.0	F (3.48) = 0.62; $p = 0.606$
IRI — EC	13.9 ± 2.6	15.5 ± 1.6	14.7 ± 2.5	15.4 ± 2.4	F (3.48) = 1.46; $p = 0.238$
IRI — PD	8.4 ± 2.6	10.9 ± 3.3	8.9 ± 2.1	10.3 ± 3.4	F (3.48) = 2.20; $p = 0.101$
Social desirability	11.2 ± 2.4	10.4 ± 2.6	8.2 ± 3.1	9.9 ± 2.7	F (3.48) = 3.09; $p = 0.036$

Fig. 4. Treatment and sex effects of mood and social desirability. (a) Negative mood before (pre) and after (post) treatment. (b) Social desirability post-treatment. Graphs indicate M ± SEM. $^{**}p < 0.01$, $^{***}p < 0.001$.

change in cortisol only in the stressed group ($r = 0.51$, $p = 0.016$) but not in the control participants. Further analysis revealed that the correlation occurred in stressed males ($r = 0.73$, $p = 0.005$) but not in stressed females ($r = 0.13$, $p = 0.732$) (Fig. 8b).

4. Discussion

In this study we examined the neurophysiological and behavioral effects of moderate acute psychosocial stress on empathy for pain and the differential influence in healthy men versus women. More specifically, we investigated early (N110 over frontocentral electrodes) and late (P3 over centroparietal) ERP components of the participants, half of which underwent the TSST before they engaged in a pain empathy task consisting in the presentation of photographs of hands in painful and neutral situations. At the behavioral level, we observed that stress induced an increase in the subjective unpleasantness to painful stimuli and a decrease to neutral stimuli, enhanced negative affect, and reduced the degree to which participants rated themselves as socially desirable to others, independent of sex. At the neurophysiological level, however, we found a sex-dependent differential influence of stress on the ERPs to the pain empathy task at late time points (P3), while early temporal components (N110) were not shaped by stress. Correlation analyses showed a strong association between neural correlates to pain stimuli at N110 over the central electrode and personal distress (a trait marker assessed prior to the stress condition) in all participants, whereas P3 over the central region correlated with the change in cortisol in stressed males. Our results thus suggest that while men and women may respond similarly to stress at the behavioral level, at least in our paradigm, separate neural mechanisms may give rise to such behavior, in agreement with previous reports assessing empathic abilities in both genders under normal conditions (Derntl et al., 2010). Furthermore, our findings imply that stress does not modulate our emotional perception of empathic cues but instead shapes late neural mechanisms possibly corresponding to cognitive evaluation.

The TSST has been experimentally employed in numerous settings in order to induce and investigate moderate acute psychosocial stress in humans (Kirschbaum et al., 1993). As predicted, the participants that undertook the TSST showed an increase in salivary cortisol levels indicating activation of the HPA axis, while the control participants did not, which parallels previous studies and confirms that our stress manipulation was successful (Kelly et al., 2008; Kudielka et al., 2004). Stress also augmented negative affect while the controls showed a decrease, as previously reported (Smeets et al., 2009), and the stressed group rated themselves as less socially desirable to others. It is likely that the increase in negative affect is reflected in our social behavior (Watson and Clark, 1984) and how desirable others perceive us, as well as how we perceive painful stimuli (Buchanan et al., 2010), since the stressed group showed a higher difference in the unpleasantness ratings between painful and neutral photographs, maybe due to an increase in salience, which would be consistent with recent study showing that mineralocorticoid stimulation increased emotional empathy in women (men were not tested) and this could potentially occur through an effect on the stimulus salience (Wingenfeld et al., 2014). Finally, the stressed participants were slower in rating painful than neutral stimuli, while the same did not occur in the controls, suggesting that social stress may impair cognitive performance (Scholz et al., 2009; but see Eysenck et al., 2007) in the response (rating) to painful cues or, alternatively, may delay the affective perception.

Several studies have previously explored the impact of experimentally induced psychosocial stress on social attributes. A recent report documented a lower score in the ratings of the perceived pain of another person in painful circumstances in participants that had undergone the TSST, while no effects of stress emerged regarding the ratings to neutral pictures (Buruck et al., 2014). This is in contrast with our findings showing an increase in the percentage of the difference between painful and neutral stimuli (i.e. higher ratings for painful stimuli and lower ratings for neutral photographs) in the stressed group. This may be due to at least two reasons. First, we asked the participants to judge the unpleasantness and not the pain perceived by the observed person, as the above mentioned study did. And second, we intentionally excluded the cortisol non-responders in the stressed group to ensure HPA axis activation, which the authors of the other study did not. On the other hand, another study recently showed that reducing social stress in mice and humans elicited emotional contagion of pain,

Table 3
Unpleasantness ratings to painful and neutral stimuli. Values represent mean (SD).

	Control		Stress		Statistics
	Male	Female	Male	Female	
Subj ratings neutral	1.91 ± 1.2	1.38 ± 0.36	1.46 ± 0.63	1.15 ± 0.23	
Subj ratings painful	5.94 ± 2.0	5.75 ± 1.7	6.10 ± 1.1	6.28 ± 1.1	
% painful-neutral	67.0 ± 14.6	73.6 ± 10.5	75.1 ± 12.9	81.2 ± 5.4	Group: $F(1.48) = 5.66$, $\eta p^2 = 0.105$, $p = 0.021$
RT neutral	687 ± 164	652 ± 185	730 ± 227	606 ± 159	Pain*Group:
RT painful	749 ± 228	660 ± 183	853 ± 285	691 ± 177	$F(1.47) = 5.10$; $\eta p^2 = 0.098$; $p = 0.029$

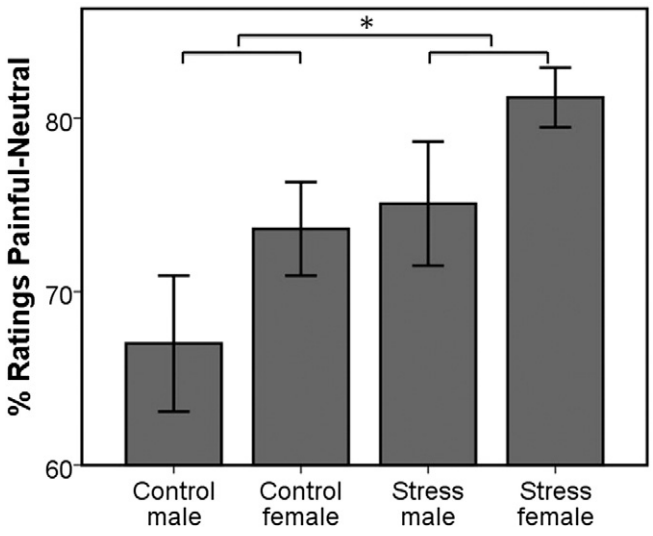

Fig. 5. Ratings of unpleasantness. The percentage of the difference between ratings to painful and neutral stimuli.

although the employed paradigm was quite different (Martin et al., 2015). In evolutionary terms, this makes sense if we consider the perceived safety of the observer. Reducing stress arising from social situations (e.g. by familiarizing ourselves with our social partners) may allow us to consider the other individual's affective state, hence increasing emotional contagion, empathy and prosocial behavior, in line with previous work (Buchanan and Preston, 2014; von Dawans et al., 2012). Similarly, being in a safe environment as in an experimental setting after being exposed to the TSST may let us take notice of another's emotional state (in our case pain), as supported by our results and by a recent study showing increased emotional (although not cognitive) empathy in men exposed to the TSST (Wolf et al., 2015). Being in high levels of (social) stress (e.g. facing strangers in pain) could therefore produce the opposite effect by prioritizing our own safety and preventing us from empathizing with others, as previously suggested by studies in humans and rodents (Buchanan and Preston, 2014; Gonzalez-Liencres et al., 2014; Langford et al., 2006; Martin et al., 2015).

Tomova and colleagues recently found a sex-dependent effect of stress: while women under social stress induced by the TSST were more emotionally and cognitively other-oriented, although their automatic motor mimicry was reduced as compared to the non-stressed females, men presented the opposite pattern, i.e. they were more self-centered and thus did not empathize with others to the same extent and performed worse at taking another individual's visual perspective although their motor mimicry increased under stress (Tomova et al., 2014). Whereas the authors interpreted this as women turning other-oriented and men inward, the role of stress on automatic mimicry suggests that distinct mechanisms operate in men and women under

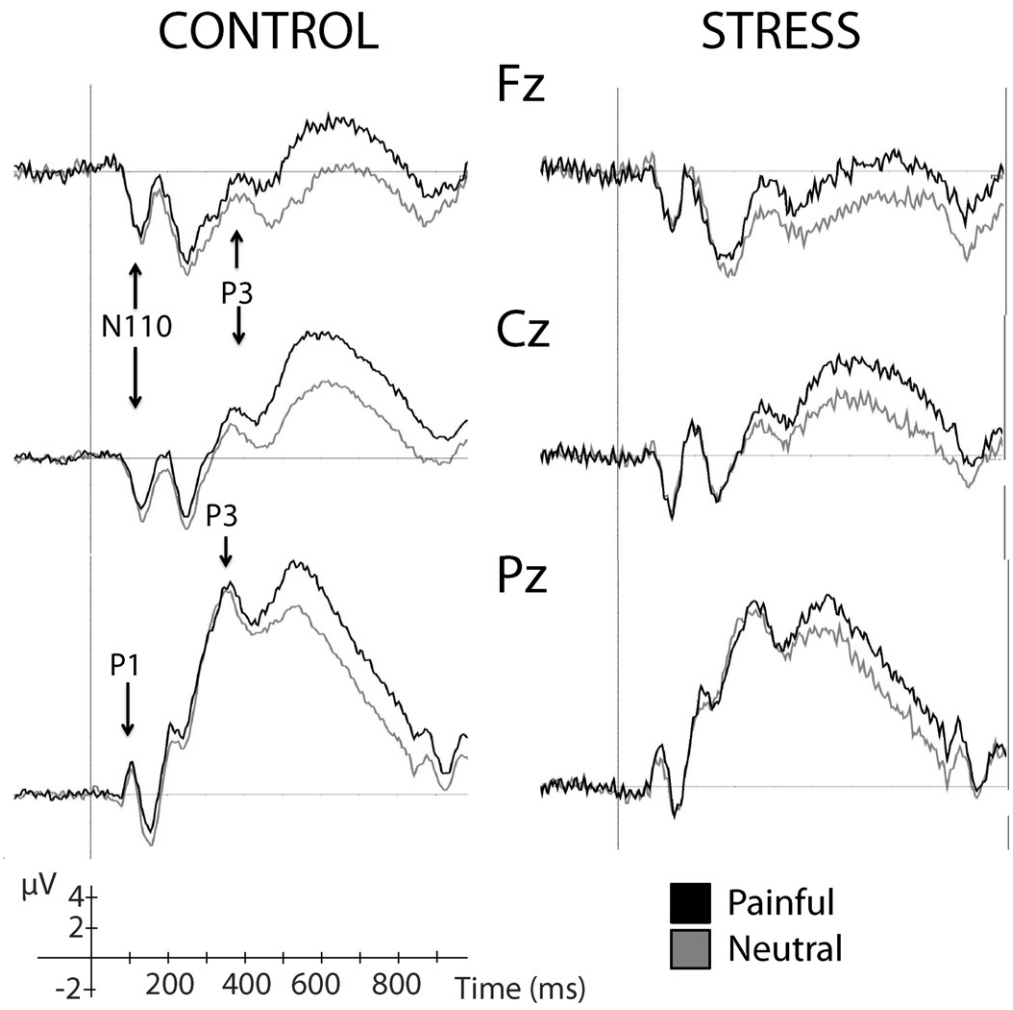

Fig. 6. Grand average ERPs to painful (black) and neutral (gray) hand stimuli in stressed and control participants. The components of interest (N1, P1, and P3) are shown for each electrode (Fz, Cz, Pz).

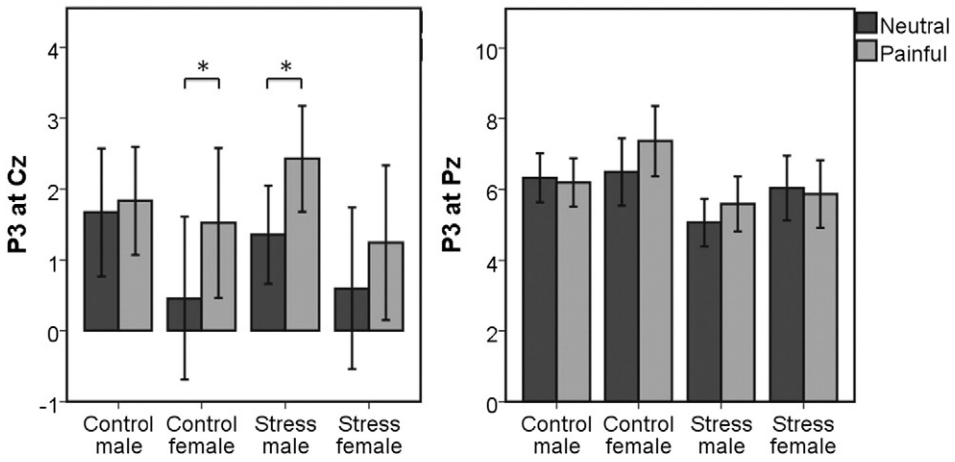

Fig. 7. Effects of treatment and sex on ERPs to hand stimuli at mid-late time points over frontal (Fz), central (Cz) and parietal (Pz) electrodes. Graphs depict M ± SEM. *$p < 0.05$ (corrected).

social stress that produce the resulting behavior. This would be in agreement with our findings showing a sex-dependent effect of stress on the neural correlates when processing empathic stimuli, although we did not find a sex by stress interaction at the behavioral level, which could be due to using a simple empathy task that may not be able to reflect small behavioral changes. Paralleling this sex-dependent distinctive brain activation in response to stress are several studies demonstrating separate coping mechanisms in men and women. For instance, Kelly et al. (2008) observed that women reported more fear, confusion, irritability and less happiness than men after being exposed to the TSST even though their physiological measures remained comparable in both sexes. Taylor and colleagues suggested that, in order to cope with stress, men may engage in fight-or-flight responses (i.e. sympathetic nervous system activation) while women may take part in tend-and-befriend behaviors consisting in being more receptive and understanding of social cues in order to benefit from social support to deal with stressful times (Taylor et al., 2000), which has been proven by some studies (Matud, 2004; Ptacek et al., 1994) and is compatible with a higher oxytocin secretion in response to stress in women (Carter, 2007; Sanders, 1990). Although this is not reflected in our results at the behavioral level, our ERP comparison and correlation analyses imply a sex-specific mechanism. There is, however, evidence that (non-stressed) men and women perform comparably in empathy tasks at the behavioral level even though the underlying neural mechanisms are distinct (Derntl et al., 2010), which raises the possibility that each sex employs separate networks to deal with social situations (Rueckert and Naybar, 2008; Schulte-Rüther et al., 2008).

One of the main findings of this study is the sex-dependent modulation of late (centro-parietal P3) but not early (fronto-central N110) ERPs by stress. A number of reports have previously compared the neural correlates of pain empathy in a variety of human samples. For instance, Decety et al. (2010) found a significant difference between ERPs to painful and neutral stimuli at both early and late time points in a sample of participants, while this difference did not occur in physicians. Similarly, other studies have documented neurophysiological differences at early and late time points when comparing men and women, adolescents and adults, healthy people and schizophrenia patients, and when observing same-race and other-race individuals (Fan and Han, 2008; Gonzalez-Liencres et al., 2016; Mado Proverbio et al., 2009; Mella et al., 2012; Sheng and Han, 2012). Our results suggest that, unlike the stated variables, psychosocial stress seems to modulate later but not early components. This is supported by our correlation findings showing a strong association between early neurophysiological activity relevant to the presence of pain and personal distress assessed at the beginning of the session in all participants, and a robust relationship between P3 over the parietal region and the cortisol response in stressed males but not in stressed females or in the control group. This is remarkable for several reasons. First, the model proposed by Fan and Han (2008) suggesting that empathy for pain consists of early events corresponding to emotional sharing and late mechanisms involved in cognitive evaluation is in agreement with our correlation studies showing a relationship between personal distress and early neural correlates. Moreover, this association implies that the larger the difference of N110 at central sites between painful and neutral stimuli,

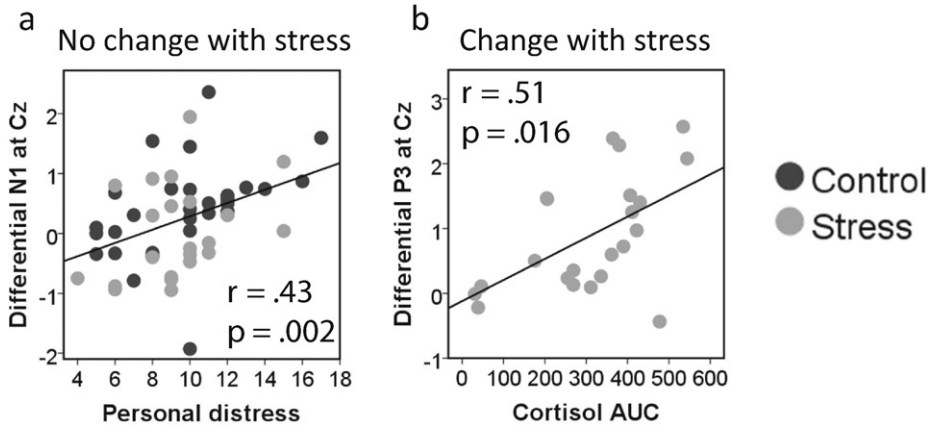

Fig. 8. Correlations between the differential ERP response to painful versus neutral stimuli, behavioral measures and cortisol response. The differential ERP response was calculated as the difference between the ERPs to painful stimuli minus the ERPs to neutral stimuli. (a) Early ERP components were related to personal distress in both stressed and control participants. (b) Mid-to-late components were associated with the change in cortisol over time (AUC_i) only in stressed males.

the higher the personal distress in all participants. In terms of P3 over central regions, we found that the greater the difference in the ERPs between painful and neutral cues, the higher the cortisol response in stressed males. As suggested by other authors, the centro-parietal P3 component seems to be related to recruitment of supplementary motor area (SMA), anterior cingulate cortex and anterior insula (Fan and Han, 2008; Fan et al., 2011; Shackman et al., 2011) and has been proposed to be involved in attentional tasks and stimulus evaluation. Our findings are in agreement with a study that found a positive correlation between the cortisol response to the TSST and social cognitive competence assessed with the movie for assessment of social cognition (MASC) in men but not in women (Smeets et al., 2009). Interestingly, the authors found that the reason high cortisol male responders obtained higher scores in the MASC than the low cortisol responders was due to the diminished tendency of the former to make overly complex inferences, and possibly their turning more emotional and less cognitive. It is therefore plausible that a mild hindrance of cognitive computations after being exposed to the TSST allow for a better perception of others' pain.

It is worth noting that we did not find a main effect of pain or interaction at N110 over the frontal electrode (Fz) although an effect of pain approached significance at N110 over Cz. Interestingly, other authors have obtained similar results. For example, Mella et al. (2012) found a pain effect at N110 over Fz in adolescents but not in adults. On the other hand, other authors have reported distinct N110 responses to painful and neutral stimuli in controls (Decety et al., 2010). While the original electrophysiological recordings in pain empathy paradigms reported differences after 140 ms after stimulus onset, using a different analysis methodology consisting in evaluating time periods and not ERP components (Fan and Han, 2008), it is possible that N110 may not yet reflect these pain-dependent changes in all cases. While our results are discussed in line with previous reports and with the pain empathy model described by Fan and Han (2008) consisting of early emotional sharing and late cognitive evaluation of painful stimuli, caution is warranted for future studies since not all authors have been able to replicate these findings in controls.

Even though we controlled for a number of variables, the present study presents some limitations. First, our sample consisted of young participants between 18 and 35; these findings may thus not apply to older or younger populations. Second, we focused on the effect of moderate psychosocial stress, yet other types of stress or more intense stress may modulate empathic appraisal in distinct ways. Third, we intentionally excluded those participants in the stress group who did not show a cortisol response to stress, thereby limiting the interpretation of our results to those who displayed HPA axis activation. And fourth, we ensured that females were not in their menstrual phase; however, we did not control whether they were in the follicular or luteal phases, which may have influenced our results. Given the final relatively small sample size and the preliminary nature of our correlation analyses, our results should be interpreted with caution and replication of our findings is warranted.

In conclusion, this study provides evidence for a sex-specific differential role of psychosocial stress on empathy for pain at the neurophysiological level, while behavioral attributes in men and women remained comparable in the task we employed. Our results additionally suggest that induced moderate social stress may influence late but not early neurophysiological responses. The findings of the present study have implications for understanding the distinctive effect of psychosocial stress on the perception and neural processing of empathy for pain in men and women as well as for the separate mechanisms that each sex undertakes to cope with socially stressful situations, which may aid in the comprehension of psychopathological conditions characterized by moderate to high levels of social stress.

Acknowledgments

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