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Immediate and delayed neuroendocrine responses to social exclusion in males and females

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ABSTRACT

Social exclusion is a complex phenomenon, with wide-ranging immediate and delayed effects on well-being, hormone levels, brain activation and motivational behavior. Building upon previous work, the current fMRI study investigated affective, endocrine and neural responses to social exclusion in a more naturalistic Cyberball task in 40 males and 40 females. As expected, social exclusion elicited well-documented affective and neural responses, i.e., increased anger and distress, as well as increased exclusion-related activation of the anterior insula, the posterior-medial frontal cortex and the orbitofrontal cortex. Cortisol and testosterone decreased over the course of the experiment, whereas progesterone showed no changes. Hormone levels were not correlated with subjective affect, but they were related to exclusion-induced neural responses. Exclusion-related activation in frontal areas was associated with decreases in cortisol and increases in testosterone until recovery. Given that results were largely independent of sex, the current findings have important implications regarding between-sex vs. within-sex variations and the conceptualization of state vs. trait neuroendocrine functions in social neuroscience.

1. Introduction

Social exclusion threatens the fundamental human need of belonging, with powerful and immediate negative consequences (Williams, 2001, 2007). Commonly operationalized as a virtual ball-tossing game (Cyberball; Williams and Jarvis, 2006), social exclusion leads to increased anger, distress and subjective feelings of 'being hurt'. Moreover, Cyberball reliably activates the anterior insula, the anterior cingulate cortex (ACC) extending to posterior medial frontal cortex (pMFC), and the orbitofrontal cortex (OFC) (Cacioppo et al., 2013) – a network of brain regions associated with the detection, appraisal and regulation of physical pain, rendering 'social pain' more than just a metaphor (Kawamoto et al., 2015). The link between affective and neural responses to social exclusion is reinforced by positive correlations between exclusion-related activation in the ACC/pMFC and self-reported distress (Eisenberger et al., 2003; Masten et al., 2009) and negative correlations between orbitofrontal activation and the 'pain' of being excluded (Eisenberger et al., 2003; Kawamoto et al., 2012).

These *immediate* effects of social exclusion might contribute to short-term motivational reactions, such as seeking affiliation, mobilizing energy for fight-or-flight reactions or exerting aggression (Chester et al., 2014). Hormones are important mediators of social motivational behavior. They tune specific endocrinological responses to external stimuli, which usually unfold later than immediate neural responses

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(Bedgood et al., 2014). Mapping reactions to social exclusion over time therefore requires the integration of multi-level measures (Sleegers et al., 2017). Immediate affective responses while undergoing exclusion might have downstream consequences on later hormonal reactivity and recovery after the exclusion experience.

In particular, progesterone has been proposed to serve the desire to affiliate with others, both as a trait motive (Schultheiss et al., 2003) and when affiliation motivation is aroused, e.g., after watching rejection-themed film clips (e.g., Wirth and Schultheiss, 2006), which may reflect empathy. However, evoking a first-person rejection experience via Cyberball yielded no changes in salivary progesterone (in both females and males; 20–100 min after exclusion; Gaffey and Wirth, 2014), an increase only in females (20 min after exclusion; Seidel et al., 2013) or an increase moderated by individual and situational factors (mixed sample; 15 min after exclusion; Maner et al., 2010). Similarly, whereas real-life rejection appears to elicit cortisol reactivity (Blackhart et al., 2007; but see Linnen et al., 2012; Stroud et al., 2000), Cyberball increased neither cortisol nor testosterone levels at an immediate or a later stage (Gaffey and Wirth, 2014; 15–25 min after exclusion: Geniole et al., 2011; 15 min after exclusion: Peterson and Harmon-Jones, 2012; Seidel et al., 2013; up to 100 min after exclusion: Zoller et al., 2010; 20–25 min after exclusion: Zwolinski, 2012). The absence of strong hormonal reactions to Cyberball has been attributed to its schematic, computer-like appearance, lacking face-to-face contact and the need to prepare for action (Gaffey and Wirth, 2014; Novembre et al., 2015). Using a more naturalistic version of Cyberball, validated for neuroimaging (Novembre et al., 2015), we sought to bridge the gap between behavioral endocrinology and social neuroscience by assessing affective, hormonal and neural responses to social exclusion.

Based on the large body of behavioral and neuroimaging studies, we expected to replicate previous findings of increased anger and distress (e.g., Seidel et al., 2013) after social exclusion as well as increased exclusion-related activation of the anterior insula, the ACC/pMFC and the OFC (e.g., Cacioppo et al., 2013). We also tested for the interplay between these immediate affective and neural responses, focusing on the ACC/pMFC and OFC (in keeping with Eisenberger et al., 2003; Kawamoto et al., 2012).

Despite the more naturalistic look of the Cyberball version used in the current study, it still lacked the necessity to mobilize energy, rendering a cortisol response implausible (Gaffey and Wirth, 2014). Nevertheless, we assessed cortisol as most studies on hormonal reactions to social exclusion have focused on cortisol (e.g., Blackhart et al., 2007; Gaffey and Wirth, 2014; Stroud et al., 2002), which might also interact with progesterone following social rejection (Duffy et al., 2017). Considering the relation between gonadal steroid hormones and social approach motivation (e.g., affiliation or aggression), we hypothesized that the virtually real-life depiction of interaction partners would induce changes in progesterone and testosterone. Conversely, hormonal changes might go hand in hand with changes in subjective affect, as demonstrated for testosterone and anger (Peterson and Harmon-Jones, 2012). Furthermore, endocrine levels influence cortical and subcortical emotion processing, particularly regarding social threat (Radke et al., 2015; van Wingen et al., 2008), so that similar positive associations between sex steroids and neural responses to social exclusion can be anticipated.

Importantly, hormonal effects may vary by sex, as Seidel et al. (2013) showed a progesterone increase only in females (but see Gaffey and Wirth, 2014). In view of sex differences occasionally reported regarding exclusion-related responses (Seidel et al., 2013; Stroud et al., 2002), we investigated a balanced sample of 40 males and 40 females and explored sex differences in affective, hormonal and neural responses to social exclusion.

2. Methods and materials

2.1. Sample

Eighty right-handed healthy students from the University of Vienna (40 females) participated in the study. Students were investigated in order to obtain a homogenous sample concerning age (males: $M = 24.38$ years, $SD = 3.37$, females: $M = 24.69$ years, $SD = 3.85$) and intelligence (IQ; males: $M = 103.82$, $SD = 9.59$, females: $M = 103.15$, $SD = 10.21$); however, psychology students were excluded due to potential suspicions about the deception. Exclusion criteria were history of neurological or psychiatric disorders, chronic illnesses, drug intake, alcohol abuse or addiction, night shift working, competitive sport, oral contraceptive intake or any other hormone treatment, recent or current pregnancy, and MRI contraindications such as metal parts in the body. The presence of psychiatric disorders (according to DSM IV) was excluded on the basis of the German version of the Structured Clinical Interview for DSM (SCID; Wittchen et al., 1997) conducted by trained psychology students with clinical experience. Participants' self-report regarding drug intake and pregnancy was validated by urine screening.

Participants were recruited via advertisements posted at the University of Vienna and the Medical University of Vienna, Austria, as well as via various online student platforms. The study was approved by the local Institutional Review Board. Participants provided written informed consent and were treated according to the Declaration of Helsinki (1964). After participation, all participants were fully debriefed and informed about the study aims, and received €50 as financial compensation.

2.2. Procedure

Participants were asked to abstain from physical exercise and alcohol for 24 h prior to the session, medication, caffeine and drug intake on the test day, as well as from food or drinks other than water for 2 h before the session. All sessions took place at the MR Centre of Excellence at the Medical University of Vienna and were scheduled in the afternoon between 1:30pm and 6:30pm. All sessions consisted of two measurements, i.e., applying two paradigms in two separate fMRI measurements on the same day with at least 60 min break in-between, and in randomized order balanced for sex (Cyberball first: 19 males, 22 females). The other task was a cognitive task without any social interactive component, so that these data are not reported here as such, but were included in post-hoc analyses of order effects (see Section 3.3). Half of the females were tested in mid-luteal phase (in a 28 day cycle: days 18–23) and the other half during early follicular phase (day 1–5). Exploratory analyses showed no significant differences (except for progesterone levels) between these two cycle phases.

2.3. Social exclusion task and cover story

When making the appointment for the testing session, we insisted on participants being punctual (as ostensibly, three participants would be scheduled for the same time). Participants were told that they would engage in a virtual ball tossing game with two other players sitting in other laboratories in the same building. To strengthen credibility of the cover story, we explained where the other laboratories were exactly located in the building, and that participants were not to meet the other players beforehand as first impressions and personal likeability might influence their game play. However, participants were told that they could meet the others afterwards if they wanted to (but they did not have to).

During the game, participants could press one of two buttons of a keyboard in order to throw the ball to either one of the other players (one male, one female) located on the right and on the left side of the screen. The other players were represented by black and white silhouettes, stemming from pre-recorded video clips of real people whose

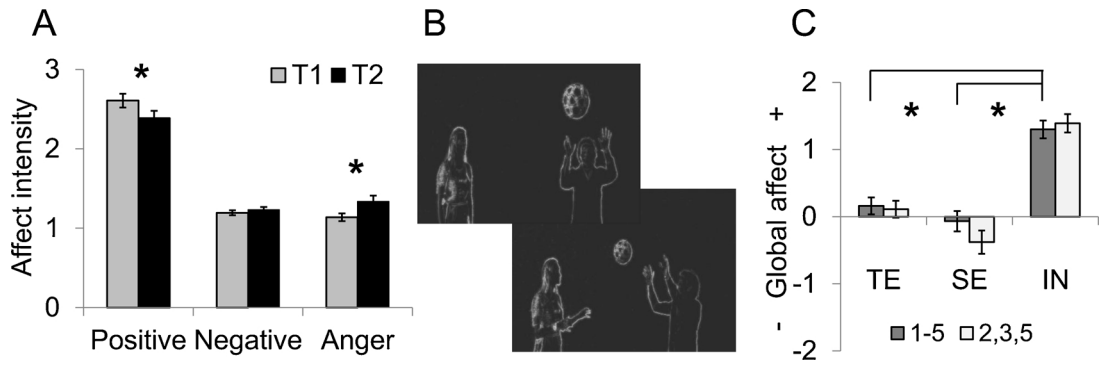

Fig. 1. Affective responses to social exclusion. A) Mean affect ratings before (T1) and after (T2) social exclusion, showing significant changes in positive affect and anger. B) Illustration of the modified Cyberball paradigm C) Mean global affect ratings obtained between blocks. Dark gray columns are based on data from all five blocks, showing significantly more positive ratings after inclusion than after the two exclusion conditions, as reported in section and consistent with all other analyses, * $p < .05$. Light columns show data of blocks 2, 3, and 5, i.e., the blocks in which participants received 0 ball passes during social exclusion and were thus completely excluded. Here, additional differences between the two exclusion conditions emerge, with more negative ratings for social exclusion than for technical exclusion. TE = Technical exclusion, SE = social exclusion, IN = inclusion. Error bars represent standard errors.

gender was recognizable (see Fig. 1B and Novembre et al., 2015; Seidel et al., 2013). Participants themselves were represented by two hands in the lower center of the screen. In reality, there were no other players, but their actions were determined by the computer. To reinforce the cover story, participants had to wait one minute before starting the game as "the others were not ready yet".

The game consisted of 15 separate blocks with 12 passes each. The blocks were equally assigned to three conditions: technical exclusion, social exclusion, inclusion. In the five inclusion blocks, participants received at least one third of the passes. In all exclusion blocks, participants received zero or only two passes. For technical exclusion, participants were told that the network connection was not effective due to technical problems, i.e., they could only watch the other players. As social exclusion, participants were excluded from the game without any explanation, i.e., the other players played exclusively together, and a message was shown that the network connection was effective. The order of the blocks was fixed. The game always started with the technical exclusion blocks in order to increase the credibility of the manipulation. The next three blocks were inclusion blocks, followed by five blocks of social exclusion and two inclusion blocks at the end of the game. Each single block lasted 30–40 s (average duration 33.5s), after which the rating scale was displayed for 4 s (see next section). An interblock interval, during which a fixation cross was presented, followed for 1–3s.

2.4. Psychometric and endocrine measurements

At the end of each block, participants rated their subjective global affect in terms of valence on a 9-point Likert scale, ranging from −4 ('very negative') to +4 ('very positive'). As a manipulation check, participants were informally asked about their game experience at the end of the session before being fully debriefed, e.g., whether they wanted to meet the others. Before (T1) and directly after (T2) the task, subjective affect was assessed by means of the Positive and Negative Affect Scale (PANAS; Watson et al., 1988) and emotional self-ratings (ESR; Schneider et al., 1994).

Three saliva samples (before entering the MR scanner, constituting the baseline: T1, 20 min after the onset of social exclusion: T2, and 40 min after social exclusion, i.e., during recovery: T3) were obtained with SaliCap collection devices (Immuno-Biological Laboratories GmbH, Hamburg, Germany). Samples were stored at less than −20 °C from immediately after the experimental session until delivery to the laboratory. Hormone concentrations (cortisol, testosterone, progesterone) were analyzed by a commercial laboratory (SwissHealthMed, Aying, Germany). Upon arrival to the laboratory, samples were frozen at −20 °C at least overnight. To precipitate mucins, samples were thawed and centrifuged at 3000 – 2000 × *g* for 10 min. Competitive Luminescence Immunoassay kits (LUMI) were used to measure concentrations of hormones (testosterone and progesterone as pg/ml, and cortisol as ng/ml). The LUMI kit is based on the competition principle. These kits have minimal cross-reactivity to other steroid hormones. Measurements were highly reliable, or, for progesterone, acceptable (progesterone: intra-assay CV < 7% and inter-assay CV < 19%, testosterone: intra-assay CV < 4% and inter-assay CV < 7%, cortisol: intra-assay CV < 4% and inter-assay CV < 5%). The lower limit of sensitivity of the immunoassay kits was 2.6 pg/mL for progesterone, 1.8 pg/mL for testosterone and 0.003 µg/dL for cortisol.

2.5. Analyses of psychometric and endocrine data

Global affect between blocks was averaged per condition (technical exclusion, social exclusion, inclusion) and subjected to a repeated-measures ANOVA, with the within-subject factor Condition (technical exclusion, social exclusion, inclusion) and the between-subjects factors Sex (male, female) and Order (first, second).

Positive affect was determined as the mean value for the positive items and negative affect for negative items on the PANAS, respectively. As negative affect scores and all ESR scales (anger, disgust, fear, happiness, sadness, surprise) deviated from normal distribution, these scores were log-transformed. As the disgust ratings were still substantially skewed after transformation (for T1 $sk = 1.44$, and for T2, $sk = 6.67$), this scale was excluded from further analyses. Data from the other scales were subjected to separate repeated-measures ANOVAs, with the within-subject factor Time (T1, T2) and the between-subjects factors Sex (male, female) and Order (first, second). Correcting for the number of comparisons yielded effects with $p < .007$ regarding changes in affect (PANAS, ESR) to be considered significant. Changes in affect (positive, negative, anger) were calculated by subtracting values at T1 from values at T2.

Cortisol levels at T1 could not be determined for one (female) participant. Hormone levels were log-transformed to correct for non-normal distributions and subjected to three repeated-measures ANOVAs for cortisol, testosterone and progesterone, respectively, with the within-subject factor Time (T1, T2, T3) and the between-subjects factors Sex (male, female) and Order (first, second).

Hormonal changes (cortisol, testosterone, progesterone) were evaluated relative to the initial values, using the following formulae: (T2-T1)/T1 and (T3-T1)/T1, respectively. Affective and hormonal change scores (for T2) were correlated using Spearman's rank correlations to account for non-normality (indicated by r_s) and a $p < .005$ (corrected for multiple comparisons).

Post-hoc analyses of order effects were conducted by

complementing and restructuring the affect and hormonal data based on the time course of the entire session including both fMRI tasks. This entailed measurements at four time points for affect and five time points for the assessment of hormones. To get a better understanding of the order effects observed especially for cortisol and testosterone (see Section 3.2), two repeated-measures ANOVAs on the entire data of the session were conducted, with the within-subject factor Time (T1, T2, T3, T4, T5) and the between-subjects factors Sex (male, female) and Task (Cyberball, Cognitive). For these, only significant effects of Task or Time are reported in Section 3.3. Moreover, to delineate whether order effects were attributable to task-related effects or general fatigue, we selected the PANAS items reverse-coding for fatigue, i.e., *attentive* and *active*, and subjected the log-transformed scores to two analogous ANOVAs (Time x Sex x Task).

For the ANOVAs, within-subject effects are reported with partial eta squared as an indication of effect size. Whenever the assumption of sphericity was violated, Greenhouse-Geisser corrected *p*-values are reported. The α-level was set at $p < .05$. Statistical testing was performed with the Statistical Package for the Social Sciences (IBM SPSS 20).

2.6. Image acquisition and processing

Functional and anatomical data were acquired on a 3T TIM Trio scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with the manufacturer's 32-channel head coil. Head motion was restricted with foam padding and a tape spanning from the head coil over the subject's nose to provide movement feedback. Stimuli were projected onto a screen, which participants viewed via a mirror mounted on the head coil. We recorded 23 interleaved slices with a gradient-echo EPI-sequence with distortion correction and the following BOLD imaging parameters: TE/TR = 38/1800 ms, flip angle = 90°, voxel size = 1.5 × 1.5 × 3 mm, bandwidth = 1446 Hz/pixel, slice thickness = 3 mm plus 1.8 mm slice gap. At the beginning of the MR session, a high-resolution anatomical image using an MPRAGE sequence (3-D Magnetization Prepared Rapid Gradient Echo) was acquired with 160 sagittal slices, TR = 2300 ms, TE = 4.21 ms, 1 × 1 × 1.1 mm resolution, flip angle 9°, and inversion time 900 ms.

Preprocessing and analyses of the imaging data was performed with statistical parametric mapping (SPM8, Wellcome Department of Imaging Neuroscience, London) implemented in Matlab (Mathworks Inc., Sherborn, MA, USA) using standard algorithms and parameters unless specified differently. Images were realigned to correct for head movement, slice-time corrected, spatially normalized to MNI (Montreal Neurological Institute) stereotactic space using unified segmentation and finally smoothed with an 8 mm^3 full-width-at-half-maximum Gaussian kernel.

In the GLM-analysis, the three experimental conditions (technical exclusion, social exclusion, inclusion) were modeled block-wise as three task-relevant regressors convolved with the canonical hemodynamic response function. The rating period between blocks was modeled as an additional regressor of no interest to the experimental question. To minimize residual head movement effects, additional regressors were derived from incorporating the realignment parameters as well as signal intensities of white matter and cerebrospinal fluid. Finally, images were high-pass filtered at 128 s, and an autoregressive AR(1) model was used to account for serial correlations in fMRI time series.

2.7. Multiple regression analyses

On the group level, a random effects multiple regression analysis was performed based on participants' task-relevant effects (i.e., three contrast images: technical exclusion, social exclusion, inclusion). The log-transformed hormonal change scores (calculated by means of (T2-T1)/T1 and (T3-T1)/T1, respectively) were z-standardized separately per Sex and Order to take into account the effects of these factors on hormone levels (as reported in Section 3.2). These change scores were simultaneously included in the multiple regression analysis as condition-specific [Sex (male, female) x Condition (technical exclusion, social exclusion, inclusion)] regressors, generating another 6 regressors per hormone (cortisol, testosterone and progesterone) and time period, i.e., a total of 36 regressors.

First, to isolate the neural correlates of social exclusion, we compared social exclusion to technical exclusion, as the two exclusion conditions are perceptually identical. Following other Cyberball studies, we also contrasted social exclusion against inclusion. Second, we extracted parameter estimates (eigenvariates) from the pMFC, OFC and IFG/insula clusters (see Results) to perform correlation analyses with condition-related global affect (i.e., global affect after social exclusion blocks minus technical exclusion blocks, and global affect after social exclusion blocks minus inclusion blocks, respectively). Third, we tested for immediate and delayed neuroendocrine modulations of social exclusion by assessing the differences between social exclusion and technical exclusion on the regressors parametrizing interindividual differences in hormonal changes from T1 to T2 and from T1 to T3. In other words, we tested for correlations of social-exclusion-related brain activation (both social exclusion vs. technical exclusion and social exclusion vs. inclusion) with cortisol, testosterone and progesterone changes from T1 to T2 and T1 to T3. While positive associations were tested directly, negative associations were inferred based on the inverse contrast, e.g., technical exclusion > social exclusion. Finally, we explored sex differences by formally testing for Sex x Condition interactions.

All effects were tested using a whole-brain approach, with $p < .05$ at cluster-level, family-wise-error-corrected for multiple comparisons ($p_{FWE} < .05$), with an underlying voxel-level threshold of $p < .001$, uncorrected. The SPM anatomy toolbox (Version 2.0; Eickhoff et al., 2005) was used for anatomical localization.

3. Results

3.1. Affect

The Condition x Sex x Order ANOVA on the global affect ratings between blocks showed a significant main effect of Condition, F (2, 152) = 57.761, $p < .001$, partial $\eta^2 = 0.43$. This validated the exclusion manipulation as effective since ratings following the inclusion blocks were significantly more positive than following both exclusion conditions (*ps* < .001; see Fig. 1C). There was also a significant Condition x Sex x Order interaction, F (2, 152) = 4.12, $p = .019$, partial $\eta^2 = 0.05$, which was driven by females' increased rating of the technical exclusion condition when Cyberball was administered as the second task. In particular, these ratings were significantly more positive than (i) when Cyberball was the first task, (ii) males' ratings of this condition, and (iii) ratings of the social exclusion condition. Other effects were not significant, *Fs* < 1.55, *ps* > 0.216.

For positive affect, the Time x Sex x Order ANOVA showed a main effect of Time, F (1, 76) = 13.11, $p = .001$, partial $\eta^2 = 0.15$, i.e., a decrease of positive affect from T1 to T2. For negative affect, a Time x Order interaction emerged, F (1, 76) = 8.05, $p = .006$, partial $\eta^2 = 0.10$, evident as an increase in negative affect from T1 to T2 when Cyberball was the first task. For the ESR scale anger, there was a significant effect of Time, F (1, 76) = 10.53, $p = .002$, partial $\eta^2 = 0.12$, showing an increase in anger from T1 to T2 (see Fig. 1A). For fear, there was a significant effect of Order, F (1, 76) = 9.46, $p = .003$, partial $\eta^2 = 0.11$, with higher fear ratings when Cyberball was administered first. Other effects were not significant when correcting for the number of tests.

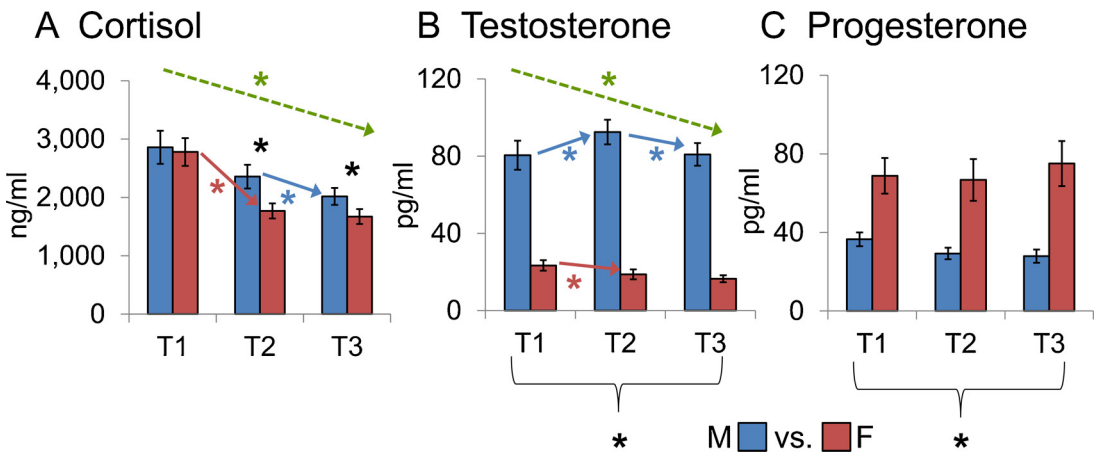

Fig. 2. Hormonal responses to social exclusion. Non-transformed mean levels of A) cortisol B) testosterone C) progesterone are shown per sex (M = male, F = female). Black asterisks indicate significant sex differences; red and blue arrows and asterisks illustrate sex-specific patterns, and effects of time are shown in green. Error bars represent standard errors, * $p < .05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Hormones

3.2.1. Cortisol

The Time x Sex x Order ANOVA on the log-transformed cortisol levels showed a significant main effect of Time, F (2, 150) = 39.54, $p < .001$, partial $\eta^2 = 0.35$, a significant Time x Sex interaction, F (2, 150) = 4.74, $p = .017$, partial $\eta^2 = 0.06$ (see Fig. 2A), and a significant Time x Sex x Order interaction, F (2, 150) = 4.06, $p = .029$, partial $\eta^2 = 0.05$. There was a significant main effect of Order, F (2, 75) = 17.04, $p < .001$, partial $\eta^2 = 0.19$. Other effects were not significant, all $Fs < 2.93$ $ps > 0.09$. The main effect of Time was due to declining cortisol levels throughout the session, i.e., T1 > T2 > T3 (all $ps < 0.006$). The main effect of Order was due to higher cortisol levels when Cyberball was first compared to when it was second. Follow-up analyses of the Time x Sex interaction revealed sex differences in the pattern of declining cortisol levels: In males, there was no significant difference between T1 and T2, whereas in females, there was no significant difference between T2 and T3 (all other $ps < 0.02$). This was also evident in sex differences at T2 and T3, with higher cortisol levels in males than in females ($p = .011$ and $p = .042$, respectively). The Time x Sex x Order interaction can be decomposed as follows: In males undergoing Cyberball first, cortisol levels differed between all time points (i.e., declining levels throughout the session, all $ps < 0.048$), whereas in males undergoing Cyberball second, cortisol levels did not differ between time points. In females, the order did not affect the cortisol effect, as both subgroups showed differences in cortisol between T1 and T2, and T1 and T3 (all $ps < 0.005$). Moreover, higher cortisol levels when Cyberball was first compared to when it was second were evident only at T1 and T2 in males ($p = .002$ and $p = .008$), and at T2 and T3 in females ($p = .002$ and $p = .004$).

3.2.2. Testosterone

The Time x Sex x Order ANOVA showed a significant main effect of Time, F (2, 152) = 4.78, $p = .011$, partial $\eta^2 = 0.06$, and a significant main effect of Sex, F (1, 76) = 122.82, $p < .001$, partial $\eta^2 = 0.62$. There was also a significant Time x Sex interaction, F (2, 152) = 12.44, $p < .001$, partial $\eta^2 = 0.14$ (see Fig. 2B), and a significant Time x Order interaction, F (2, 152) = 5.55, $p = .005$, partial $\eta^2 = 0.09$. Other effects were not significant, all $Fs < 2.25$ $ps > 0.11$. The main effect of Sex was attributable to higher testosterone levels in males than in females. The main effect of Time was due to decreased testosterone levels at T3, compared to T1 ($p = .035$) and to T2 ($p = .021$). The Time x Sex interaction unfolded as follows: In males, testosterone increased from T1 to T2 ($p = .007$), and decreased again from T2 to T3 ($p = .031$), whereas in females, testosterone decreased from T1 to T2 ($p = .002$), along with a decrease from T1 to T3 ($p < .001$). Follow-up analyses of the Time x Order interaction revealed that effects of Time, i.e., decreased testosterone levels at T3 compared to T1 and T2, only emerged when Cyberball was first ($ps < 0.001$), but were not evident when Cyberball was second.

3.2.3. Progesterone

The Time x Sex x Order ANOVA revealed a significant main effect of Sex, F (1, 76) = 11.51, $p = .001$, partial $\eta^2 = 0.13$, with higher progesterone levels in females than in males (see Fig. 2C). There was also a significant effect of Order, F (1, 76) = 6.73, $p = .011$, partial $\eta^2 = 0.08$, due to higher progesterone levels when Cyberball was administered first compared to when it was administered second. Other effects were not significant, $Fs < 2.89$, $ps > 0.061$.

There were no significant correlations between affective and hormonal change scores (all $ps > 0.13$).

3.3. Post-hoc: order effects

The additional ANOVAs on the complete hormone data revealed a main effect of Time, F (4, 300) = 35.55, $p < .001$, partial $\eta^2 = 0.32$ for *cortisol*, and F (4, 304) = 4.23, $p < .001$, partial $\eta^2 = 0.05$ for *testosterone*. No effects or interactions relating to Task were significant, $Fs < 2.0$, $ps > 0.12$. Cortisol levels decreased throughout the session, with all time points significantly differing from each other (all $ps < 0.016$) except for T4 and T5. For testosterone, levels were lowest at T3 and significantly differed from levels at T1 and T2 ($ps < 0.024$).

Similarly, the ANOVAs regarding self-reported fatigue showed a main effect of Time, F (3, 225) = 14.12, $p < 001$, partial $\eta^2 = 0.16$ for *attentive*, and F (3, 225) = 7.47, $p < .001$, partial $\eta^2 = 0.09$ for *active*, but no other significant effects, $Fs < 2.09$, $ps > 0.11$. Irrespective of which task was performed first, participants rated themselves as more *attentive* at T1 than at T2, T3, and T4 (all $ps < 0.002$) and as more *active* at T1 than at T2 ($p < .001$). Taken together, these findings point towards the diurnal decline of especially cortisol, and suggest that fatigue emerged in the course of the session.

3.4. Neural effects of social exclusion

Contrasting social exclusion to technical exclusion yielded increased activation in the right middle frontal gyrus, pMFC, right inferior frontal gyrus (cluster including the right insula) and left insula (see Table 1 and Fig. 3A).

Table 1
Task-related differences in whole-brain activation, all with p < .05 (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and T-values. Only significant effects are listed. For each cluster, the maximum peak in gray matter is reported.

Contrast	k	Side	MNI			T-value
Region			x	y	z	
Social exclusion > Technical exclusion						
Middle Frontal Gyrus	1038	R	34	40	32	4.51
Posterior-medial Frontal	645	R	8	8	52	5.19
Inferior Frontal Gyrus (p. Orbitalis)	762	R	32	24	−6	6.23
Insula	259	L	−28	22	6	5.04
Social exclusion > Inclusion						
Precuneus	1745	L	−10	−56	14	5.60
Rolandic Operculum	1841	R	40	−14	18	5.88
Precuneus	726	R	12	−48	6	4.91
Paracentral Lobule	292	R	8	−28	62	4.28
Middle Orbital Gyrus	206	L	0	44	−12	3.81

Table 2
Neuroendocrine modulations of task-related effects in whole-brain activation, all with p < .05 (FWE-corrected at the cluster level), with cluster size (k), side, MNI coordinates and T-values. Only significant effects are listed. For each cluster, the maximum peak in gray matter is reported.

Contrast	k	Side	MNI			T-value
Region			x	y	z	
Cortisol (T3-T1) modulation of Technical exclusion > Social exclusion						
Inferior Frontal Gyrus (p. Orbitalis)	205	L	−46	32	−10	3.90
Middle Temporal Gyrus	368	L	−56	−48	0	3.95
Testosterone (T3-T1) modulation of Social exclusion > Technical exclusion						
Middle Orbital Gyrus	275	R	38	42	−14	5.09

For social exclusion compared to inclusion, there was stronger activation in bilateral precuneus, right rolandic operculum and the paracentral lobule as well as a cluster peaking in the middle orbital gyrus, extending to the left inferior frontal gyrus (see Table 1 and Fig. 3B). Results for the reverse contrasts are presented in Supplementary Table S1.

Activation in the orbitofrontal cluster [social exclusion > inclusion] was positively correlated with condition-related global affect [social exclusion > inclusion], $r = 0.251$, $p = .025$. There was no analogous correlation between the posterior-medial frontal cluster and condition-related affect for social exclusion > technical exclusion, $r = -0.053$, $p = .64$. Activation in the right IFG and the left insula

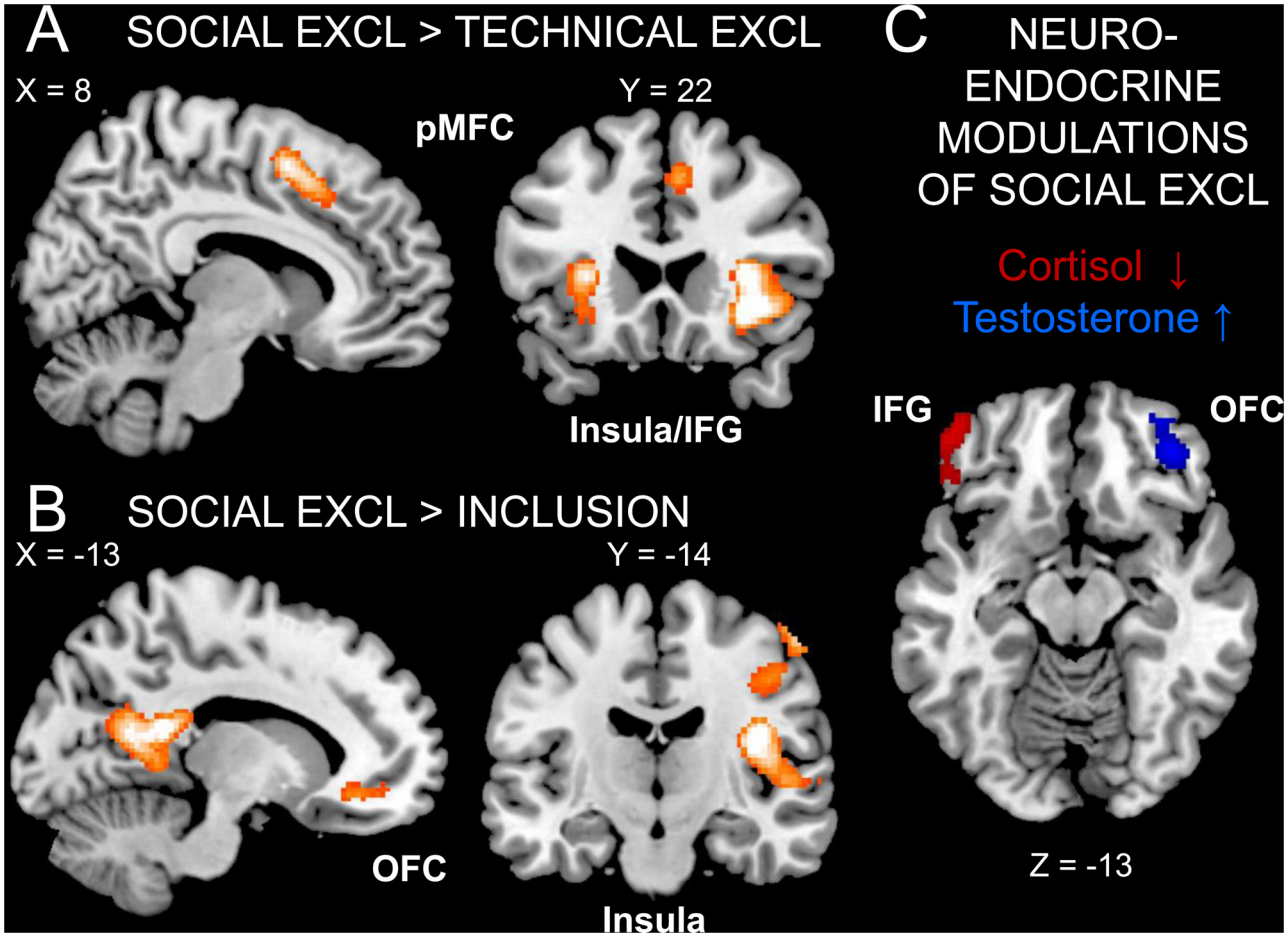

Fig. 3. Neural and neuroendocrine responses to social exclusion. Social exclusion compared to technical exclusion (A) elicited increased activation in the posterior-medial frontal cortex, right inferior frontal gyrus (cluster including the right insula) and left insula. Social exclusion compared to inclusion (B) elicited increased activation in bilateral precuneus, right rolandic operculum and the middle orbital gyrus. Cortisol changes from T1 to T3 (C; in red) modulated the effect of social exclusion [positive association with technical exclusion > social exclusion; depicted as negative association with reverse contrast for visualization purpose] in the left inferior frontal gyrus. Testosterone changes from T1 to T3 (C; in blue) showed a positive association with activation for social exclusion > technical exclusion in the right middle orbital gyrus, all with $p_{FWE} < 0.05$ (FWE-corrected at the cluster level). Excl = exclusion. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

clusters during social exclusion > technical exclusion did not correlate with affect, $r = -0.006$, $p = .96$, and $r = -0.022$, $p = .85$, respectively.

3.5. Neuroendocrine modulations of social exclusion

3.5.1. Cortisol (T3)

Neural effects of social exclusion [technical exclusion > social exclusion] in the left inferior frontal gyrus and middle temporal gyrus were associated with changes in cortisol from T1 to T3 (see Table 2 and Fig. 3C). In other words, exclusion-induced neural responses were associated with a decrease in cortisol.

3.5.2. Testosterone (T3)

There was a positive correlation between activation in the right middle orbital gyrus for social exclusion > technical exclusion and testosterone changes from T1 to T3 (see Table 2 and Fig. 3C). In other words, exclusion-induced neural responses were associated with an increase in testosterone.

There were no significant correlations for cortisol and testosterone changes from T1 to T2, nor for progesterone changes, nor for any comparisons involving inclusion instead of technical exclusion.

3.6. Sex differences

At a threshold of $p_{FWE} < 0.05$, there were no significant effects for either Sex x Condition interaction ([female > male] x [social exclusion > technical exclusion] or [male > female] x [social exclusion > technical exclusion]), neither regarding the main effects nor the neuroendocrine modulations of social exclusion. For within-sex effects, please see Supplementary Tables S2 and S3.

4. Discussion

The current study investigated immediate and delayed effects of social exclusion via various measures: self-reports, hormones, brain activation. As expected, social exclusion elicited well-replicated affective and neural responses, i.e., increased anger and distress, and increased exclusion-related activation of the anterior insula, the pMFC and the OFC, respectively. Interestingly, OFC activation was positively related to global affect, but no analogous effect was observed for the pMFC. Hormonal changes did not represent a classical stress response; instead, when looking at the whole sample, cortisol and testosterone declined over time, albeit with sex-specific patterns, e.g., a testosterone increase from before to after the exclusion experience in males. In contrast, there was no support for a progesterone increase elicited by social exclusion or a relation between hormonal and affective changes. However, exclusion-induced neural responses were associated with a decrease in cortisol and an increase in testosterone until recovery, respectively.

4.1. Affect

According to William's sequential model (2001), *immediate* reactions to social exclusion can manifest as subjective distress, anger and hurt feelings. Indeed, our participants felt worse during and directly after being excluded. Reduced positive mood and a centering around the mean of the bipolar global affect scale suggest a relatively neutral state, as in Zwolinski (2012). Negative affect even increased from before to after Cyberball for those who performed it as the first task. Increased anger replicates previous affective changes, not only from prior to after exclusion, but also from comparison between exclusion and inclusion (Seidel et al., 2013). Moreover, participants felt worse when they were completely excluded in the ostensibly 'social' conditions than when a technical reason was provided. Along with the correlation between global affect and exclusion-related OFC activation (contrasted against inclusion), we can therefore be fairly confident that these changes in subjective affect are not merely due to participating in an experiment per se (e.g., fatigue, boredom). In particular, the contrast between social exclusion and inclusion appears to capture the 'social' nature of social exclusion along with the distress elicited by the violated expectation of being included. In line with Seidel et al. (2013), there were no sex differences in specific affective reactions. However, females' ratings of their global affect after the technical exclusion blocks were increased when Cyberball was the second task, which may represent an unexpected carry-over effect from the previous task.

4.2. Hormones

Despite the unpleasantness of social exclusion, it was not associated with specific endocrine reactivity. Instead, we observed an overall decline in cortisol across the whole sample, which matches previous findings on the lack of a cortisol response after Cyberball at different time points (Gaffey and Wirth, 2014; Geniole et al., 2011; Seidel et al. (2013); Zoller et al., 2010; Zwolinski, 2012). Based on these studies, we had considered an activation of the endocrinological stress axis unlikely, as being excluded during Cyberball is not associated with any demands to mobilize energy (see e.g., Gaffey and Wirth, 2014). Given the additional constraints resulting from the MR environment (e.g., supine body position), physiological/behavioral responses to the exclusion are very limited. Rather than exclusion-specific changes, the overall decline likely reflects the diurnal profile of cortisol, which was evident in the data based on the entire session including both fMRI tasks. This observation ties in with fatigue emerging in the course of the session, irrespective of the order of tasks. Moreover, the adjustment to the potentially stressful MR environment may also play a role. While self-reported *fear* ratings were higher when Cyberball was the first task, possibly indicating stress, we did not systematically assess the perceived stress of the scanning experience and therefore cannot draw conclusions regarding these possible cortisol changes.

Interestingly, however, we observed different hormonal patterns in males and females. In females, cortisol levels decreased from before to immediately after Cyberball, whereas in males, this decline was delayed. In contrast, testosterone increased from before to immediately after the interaction in males (after which it decreased), whereas in females, testosterone directly decreased. Based on the notion that social exclusion poses a threat to an individual's social status, the testosterone increase evident in males might reflect an adaptive response to social challenges (e.g., Bedgood et al., 2014). Notably, progesterone levels did not change throughout the experiment, which is at odds with the punctual increase in females 20 min after exclusion reported by Seidel et al. (2013), yet in line with results from a larger mixed sample where hormonal responses were continuously mapped up to 100 min after exclusion (Gaffey and Wirth, 2014). Taken together, and contrary to our expectations, even the more realistic appearance of the interaction partners was not sufficient to evoke a distinct, sustained response in gonadal steroid hormones. Although the sex-specific patterns of cortisol and testosterone might point towards differential social motivational reactions, effects are likely overshadowed by the diurnal hormonal profiles. Therefore, replication and direct comparison to appropriate control groups (e.g., inclusion, real-life exclusion) are warranted.

4.3. Neural and neuroendocrine mechanisms

In line with a large body of neuroimaging findings, social (vs. technical) exclusion was associated with increased activation in the insula and the pMFC (sometimes referred to as "dorsal ACC") (Bolling et al., 2011; Cacioppo et al., 2013; Eisenberger et al., 2003; Masten et al., 2009; Wagels et al., 2017), which have predominantly been related to the experience of social pain during Cyberball (Eisenberger et al., 2003; Rotge et al., 2015). However, being excluded often also violates the social expectation of being included, which recruits conflict

monitoring functions subserved by the ACC and pMFC (Botvinick et al., 2004). In the current study, comparing social vs. technical exclusion on the one hand and social exclusion vs. inclusion on the other hand allowed disentangling these components on the neural level. Similarly, experiments dissociating exclusion from rule-breaking (both arbitrary and social rules) endorse the role of the pMFC in the detection of social exclusion (Bolling et al., 2011; Kawamoto et al., 2012). Using an event-related approach, Kawamoto et al. (2012) further compared social exclusion to "micro-rejection", i.e., when participants did not receive the ball 1–3 times, and observed increased activation in bilateral insula along with pMFC. We can thus safely assume that the current activation of the social pain network reflects not merely the detection of violated social expectations.

Conversely, the comparison of social exclusion vs. inclusion might rather capture the emotional component of exclusion processing. Here, increased activation was observed in areas associated with self-related processing, such as the precuneus, which might stem from updating one's self-image in the light of exclusion or from reflective thinking about the motives of the other players (Bolling et al., 2011). Moreover, the current findings replicate involvement of the OFC, which prior Cyberball studies linked to social evaluation (Sebastian et al., 2011) and emotional responses (Wagels et al., 2017).

Interestingly, neural reactions to social (vs. technical) exclusion were linked to changes in endocrine levels from before Cyberball to recovery, with changes in cortisol and testosterone being predicted by frontal activation. A stronger exclusion-related recruitment of the left IFG and left MTG yielded lower cortisol levels, which underlines the link between neural and hormonal regulatory processes. It seems plausible that social exclusion may necessitate appraisal and emotion regulation processes subserved by frontal regions, i.e., the IFG (Kohn et al., 2014; see also Maurage et al., 2012). While this is the first study linking exclusion-related IFG activation to cortisol changes, a coupling of regulatory responses has been reported for other frontal areas. For example, Mareckova et al. (2017) found a negative association between OFC activation to negative affective stimuli and the cortisol response. Complimentary, in older adults, higher activation in the ventromedial prefrontal cortex when downregulating negative affect, was coupled with a more adaptive diurnal cortisol pattern, i.e., a steeper cortisol decline (Urry et al., 2006). Likewise, individuals with higher emotion regulation abilities showed lower cortisol levels over the course of a stress task (Quirin et al., 2010). Taken together, these findings suggest that even with little impact on the detection of exclusion, i.e., *immediate* reactions (Williams, 2001, 2007), individual patterns of psychological and neuroendocrine regulation influence recovery from the exclusion experience.

Despite well-documented sex differences in emotional and neural reactivity as well as stress vulnerability (Bangasser and Valentino, 2014; Stevens and Hamann, 2012), exclusion-related brain activation did not differ between women and men, in line with a recent meta-analysis (Rotge et al., 2015). Importantly, sex differences on one level, e.g., in gonadal hormones, may not necessarily manifest as differences on another level, but rather serve to compensate and converge to similar functional outcomes (De Vries, 2004).[1]

Individual differences in endocrine function might further contribute to motivational reactions, such as avoidant or aggressive behavior. For example, increases in testosterone after Cyberball − but not baseline levels − predicted subsequent punishment behavior (Geniole et al., 2011). Based on the notion that testosterone influences aggression via the OFC (e.g., Mehta and Beer, 2009), one may speculate in how far the current association between OFC involvement and changes in testosterone until recovery maps onto motivational reactions to social exclusion. This could be clarified in future studies by assessing subsequent behavior directly (as in, e.g., Chester et al., 2014) and affective reactions, e.g. distress, as well as their appraisal and regulation more continuously. Moreover, as effects of testosterone on social behavior are often modulated by cortisol (Mehta and Josephs, 2010; Montoya et al., 2012), taking into account the balance of these hormones may be informative of potential dual-hormone effects.

4.4. Strengths and limitations

The lack of sex differences in neural and specific affective responses to social exclusion is consistent with meta-analyses (Hartgerink et al., 2015; Rotge et al., 2015), but also raises questions about between-sex vs. within-sex variations in social neuroscience. Importantly, following recent conceptualizations of state and trait neuroendocrine function (Geniole et al., 2011; Juster et al., 2016), our fMRI design accounted for inter- and intra-individual differences in hormone levels in males and females. Yet, testing for linear relations between affective, hormonal and neural responses might not map the underlying, potentially non-linear, functions or interactions between hormones. Along these lines, despite sampling hormones at several time points, the design remains a cross-sectional snapshot, with the absence of a control group undergoing inclusion or a non-social task additionally limiting interpretation of the specificity of our findings. The latter was driven by practical reasons in the context of the fMRI measurement, for which we investigated a respectably large and balanced sample.

Also for practical reasons, another paradigm was applied as a separate fMRI measurement, but within the same session. Although the order of tasks was randomized, only when Cyberball was first, an increase in negative affect from before to after the task became evident. Moreover, the decline of cortisol (for males) and of testosterone was more pronounced when Cyberball was administered first, which further limits interpretation of the hormonal patterns. Future studies need to clarify in how far these changes are due to the time of the day, to having performed another task beforehand, or to an interaction of these factors.

5. Conclusion

Taken together, our multi-level assessment of immediate and delayed reactions to social exclusion extended previous research on its behavioral and hormonal consequences to include neural activation. As expected, social exclusion recruited the social pain network, related to the detection of exclusion, but also frontal areas associated with emotion regulation. Neural reactions to exclusion were correlated with changes in endocrine levels. Our findings also run along the lines of William's sequential model (2001), ranging from *immediate* affective reactions to *delayed* consequences on hormone levels until recovery. Future research could benefit from including behavioral measures to bridge the gap toward social motivational reactions, such as affiliation or aggression.

Author contributions

EMS, BD, EM, IKE and UH designed the study and wrote the protocol. Authors RNB, HM and HT managed literature search and data acquisition. SR undertook statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psyneuen.2018.04.005.

References

Bangasser, D.A., Valentino, R.J., 2014. Sex differences in stress-related psychiatric

[1] Within-sex effects are reported in the Supplementary Material.

disorders: neurobiological perspectives. Front. Neuroendocrinol. 35, 303–319.
Bedgood, D., Boggiano, M.M., Turan, B., 2014. Testosterone and social evaluative stress: the moderating role of basal cortisol. Psychoneuroendocrinology 47, 107–115.
Blackhart, G.C., Eckel, L.A., Tice, D.M., 2007. Salivary cortisol in response to acute social rejection and acceptance by peers. Biol. Psychol. 75, 267–276.
Bolling, D.Z., Pitskel, N.B., Deen, B., Crowley, M.J., McPartland, J.C., Mayes, L.C., Pelphrey, K.A., 2011. Dissociable brain mechanisms for processing social exclusion and rule violation. Neuroimage 54, 2462–2471.
Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn. Sci. 8, 539–546.
Cacioppo, S., Frum, C., Asp, E., Weiss, R.M., Lewis, J.W., Cacioppo, J.T., 2013. A quantitative meta-analysis of functional imaging studies of social rejection. Sci. Rep. 3, 2027.
Chester, D.S., Eisenberger, N.I., Pond, J.R.S., Richman, S.B., Bushman, B.J., DeWall, C.N., 2014. The interactive effect of social pain and executive functioning on aggression: an fMRI experiment. Soc. Cogn. Affect. Neurosci. 9, 699–704.
De Vries, G.J., 2004. Minireview: sex differences in adult and developing brains: compensation, compensation, compensation. Endocrinology 145, 1063–1068.
Duffy, K.A., Harris, L.T., Chartrand, T.L., Stanton, S.J., 2017. Women recovering from social rejection: the effect of the person and the situation on a hormonal mechanism of affiliation. Psychoneuroendocrinology 76, 174–182.
Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25, 1325–1335.
Eisenberger, N.I., Lieberman, M.D., Williams, K.D., 2003. Does rejection hurt? An FMRI study of social exclusion. Science 302, 290–292.
Gaffey, A.E., Wirth, M.M., 2014. Stress, rejection, and hormones: cortisol and progesterone reactivity to laboratory speech and rejection tasks in women and men. F1000Research 3, 208.
Geniole, S.N., Carre, J.M., McCormick, C.M., 2011. State, not trait, neuroendocrine function predicts costly reactive aggression in men after social exclusion and inclusion. Biol. Psychol. 87, 137–145.
Hartgerink, C.H., van Beest, I., Wicherts, J.M., Williams, K.D., 2015. The ordinal effects of ostracism: a meta-analysis of 120 Cyberball studies. PLoS One 10, e0127002.
Juster, R.-P., Raymond, C., Desrochers, A.B., Bourdon, O., Durand, N., Wan, N., Pruessner, J.C., Lupien, S.J., 2016. Sex hormones adjust sex-specific reactive and diurnal cortisol profiles. Psychoneuroendocrinology 63, 282–290.
Kawamoto, T., Onoda, K., Nakashima, K., Nittono, H., Yamaguchi, S., Ura, M., 2012. Is dorsal anterior cingulate cortex activation in response to social exclusion due to expectancy violation? An fMRI study. Front. Evol. Neurosci. 4, 11.
Kawamoto, T., Ura, M., Nittono, H., 2015. Intrapersonal and interpersonal processes of social exclusion. Front. Neurosci. 9.
Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., Habel, U., 2014. Neural network of cognitive emotion regulation-an ALE meta-analysis and MACM analysis. Neuroimage 87, 345–355.
Linnen, A.M., Ellenbogen, M.A., Cardoso, C., Joober, R., 2012. Intranasal oxytocin and salivary cortisol concentrations during social rejection in university students. Stress 15, 393–402.
Maner, J.K., Miller, S.L., Schmidt, N.B., Eckel, L.A., 2010. The endocrinology of exclusion: rejection elicits motivationally tuned changes in progesterone. Psychol. Sci. 21, 581–588.
Mareckova, K., Holsen, L., Admon, R., Whitfield-Gabrieli, S., Seidman, L.J., Buka, S.L., Klibanski, A., Goldstein, J.M., 2017. Neural – hormonal responses to negative affective stimuli: impact of dysphoric mood and sex. J. Affect. Disord. 222, 88–97.
Masten, C.L., Eisenberger, N.I., Borofsky, L.A., Pfeifer, J.H., McNealy, K., Mazziotta, J.C., Dapretto, M., 2009. Neural correlates of social exclusion during adolescence: understanding the distress of peer rejection. Soc. Cogn. Affect. Neurosci. 4, 143–157.
Maurage, P., Joassin, F., Philippot, P., Heeren, A., Vermeulen, N., Mahau, P., Delperdange, C., Corneille, O., Luminet, O., de Timary, P., 2012. Disrupted regulation of social exclusion in alcohol-dependence: an fMRI study. Neuropsychopharmacology 37, 2067–2075.
Mehta, P.H., Beer, J., 2009. Neural mechanisms of the testosterone-aggression relation: the role of orbitofrontal cortex. J. Cogn. Neurosci. 22, 2357–2368.
Mehta, P.H., Josephs, R.A., 2010. Testosterone and cortisol jointly regulate dominance: evidence for a dual-hormone hypothesis. Horm. Behav. 58, 898–906.
Montoya, E.R., Terburg, D., Bos, P.A., van Honk, J., 2012. Testosterone, cortisol, and serotonin as key regulators of social aggression: a review and theoretical perspective. Motiv. Emot. 36, 65–73.
Novembre, G., Zanon, M., Silani, G., 2015. Empathy for social exclusion involves the sensory-discriminative component of pain: a within-subject fMRI study. Soc. Cogn. Affect. Neurosci. 10, 153–164.
Peterson, C.K., Harmon-Jones, E., 2012. Anger and testosterone: evidence that situationally-induced anger relates to situationally-induced testosterone. Emotion 12, 899–902.
Quirin, M., Kuhl, J., Duesing, R., 2010. Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities. Psychoneuroendocrinology 36, 898–904.
Radke, S., Volman, I., Mehta, P.H., van Son, V., Enter, D., Sanfey, A.G., Toni, I., De Bruijn, E.R.A., Roelofs, K., 2015. Testosterone biases the amygdala toward social threat approach. Sci. Adv. 1, e1400074.
Rotge, J.Y., Lemogne, C., Hinfray, S., Huguet, P., Grynszpan, O., Tartour, E., George, N., Fossati, P., 2015. A meta-analysis of the anterior cingulate contribution to social pain. Soc. Cogn. Affect. Neurosci. 10, 19–27.
Schneider, F., Gur, R.C., Gur, R.E., Muenz, L.R., 1994. Standardized mood induction with happy and sad facial expressions. Psychiatry Res. 51, 19–31.
Schultheiss, O.C., Dargel, A., Rohde, W., 2003. Implicit motives and gonadal steroid hormones: effects of menstrual cycle phase oral contraceptive use, and relationship status. Horm. Behav. 43, 293–301.
Sebastian, C.L., Tan, G.C., Roiser, J.P., Viding, E., Dumontheil, I., Blakemore, S.J., 2011. Developmental influences on the neural bases of responses to social rejection: implications of social neuroscience for education. Neuroimage 57, 686–694.
Seidel, E.M., Silani, G., Metzler, H., Thaler, H., Lamm, C., Gur, R.C., Kryspin-Exner, I., Habel, U., Derntl, B., 2013. The impact of social exclusion vs inclusion on subjective and hormonal reactions in females and males. Psychoneuroendocrinology 38, 2925–2932.
Sleegers, W.W.A., Proulx, T., Van Beest, I., 2017. The social pain of Cyberball: decreased pupillary reactivity to exclusion cues. J. Exp. Soc. Psychol. 69, 187–200.
Stevens, J.S., Hamann, S., 2012. Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. Neuropsychologia 50, 1578–1593.
Stroud, L.R., Tanofsky-Kraff, M., Wilfley, D.E., Salovey, P., 2000. The Yale Interpersonal Stressor (YIPS): affective, physiological, and behavioral responses to a novel interpersonal rejection paradigm. Ann. Behav. Med. 22, 204–213.
Stroud, L.R., Salovey, P., Epel, E.S., 2002. Sex differences in stress responses: social rejection versus achievement stress. Biol. Psychiatry 52, 318–327.
Urry, H.L., van Reekum, C.M., Johnstone, T., Kalin, N.H., Thurow, M.E., Schaefer, H.S., Jackson, C.A., Frye, C.J., Greischar, L.L., Alexander, A.L., Davidson, R.J., 2006. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J. Neurosci. 26, 4415–4425.
van Wingen, G.A., van Broekhoven, F., Verkes, R.J., Petersson, K.M., Backstrom, T., Buitelaar, J.K., Fernandez, G., 2008. Progesterone selectively increases amygdala reactivity in women. Mol. Psychiatry 13, 325–333.
Wagels, L., Bergs, R., Clemens, B., Bauchmüller, M., Gur, R.C., Schneider, F., Habel, U., Kohn, N., 2017. Contextual exclusion processing: an fMRI study of rejection in a performance-related context. Brain Imaging Behav. 11 (3), 874–886.
Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54, 1063–1070.
Williams, K.D., Jarvis, B., 2006. Cyberball: a program for use in research on interpersonal ostracism and acceptance. Behav. Res. Methods 38, 174–180.
Williams, K.D., 2001. Ostracism: The Power of Silence. Guilford, New York.
Williams, K.D., 2007. Ostracism. Annu. Rev. Psychol. 58, 425–452.
Wirth, M.M., Schultheiss, O.C., 2006. Effects of affiliation arousal (hope of closeness) and affiliation stress (fear of rejection) on progesterone and cortisol. Horm. Behav. 50, 786–795.
Wittchen, H.U., Wunderlich, U., Gruschwitz, S., Zaudig, M., 1997. SKID-I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft, Hogrefe Göttingen.
Zoller, C., Maroof, P., Weik, U., Deinzer, R., 2010. No effect of social exclusion on salivary cortisol secretion in women in a randomized controlled study. Psychoneuroendocrinology 35, 1294–1298.
Zwolinski, J., 2012. Psychological and neuroendocrine reactivity to ostracism. Aggress. Behav. 38, 108–125.