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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