



# The influence of androstadienone during psychosocial stress is modulated by gender, trait anxiety and subjective stress: An fMRI study



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## ABSTRACT

Androstadienone (ANDR), a bodily secreted steroid compound, is a socially relevant chemosignal that modulates subjective and (neuro)physiological responses, predominantly in females. The impact of ANDR on stress responses in males and females has not been explored. Therefore, this fMRI study aimed to examine psychosocial stress reactions induced by mental arithmetic and social evaluation on behavioral and hormonal levels (46 participants: 15 naturally cycling females in their early follicular phase (EF), 15 females on hormonal contraceptives (HC) and 16 males); and on a neural level (40 participants: 13 EF-females, 13 HC-females and 14 males) in an ANDR and placebo treatment repeated-measures design.

While no gender differences emerged in subjective ratings and performance during stress, neural activation patterns differed significantly. Besides, ANDR attenuated the post-stress increase of negative mood in all participants. Region of interest analyses showed that irrespective of treatment, males showed stronger activation of the dorsolateral prefrontal cortex (DLPFC) than females. At the whole brain level, gender differences emerged indicating stronger fronto-parietal activation in males compared to HC-females on both treatments. Males showed stronger visual and fusiform activation than EF-females under ANDR. Both female groups did not show stronger activation than males. Further, error ratio in the ANDR-stress condition was positively associated with their post-stress cortisol level and increase in subjective stress in males; and male DLPFC activity in the ANDR-stress condition was negatively associated with trait anxiety. Surprisingly, compared to HC-females, EF-female only showed stronger activation of arousal-related areas under placebo treatment.

Taken together, these findings suggest that the male stress reaction under social evaluative threat was stronger than female stress reactions as a function of ANDR. More specifically, this effect on behavioral and neural stress reactions seems to depend on trait anxiety in males only. The study highlights the significance of a chemosignal in enhancing social threat that may facilitate adaptive stress responses.

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## 1. Introduction

A crucial function of chemosignal communication is to convey messages between conspecifics such as potential threat and

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modulate adaptive stress behaviors to promote a better survival outcome. In humans, socially relevant chemosensory signals have been shown to enhance processing of socio-emotional information (Haegler et al., 2010; Prehn-Kristensen et al., 2008) and to improve cognitive performance (Bensafi et al., 2004a; Chen et al., 2006). One of many compounds produced in the human body is a steroid found in male semen and axillary sweat, namely androstadienone (4,16-androstadienon-3-one; ANDR) (Gower and Ruparelia, 1993).

Exposure to ANDR, at an undetectable concentration (250 µM) applied on the skin above the upper lip, has been shown to increase the feeling of attentional focus after viewing a 20-min video clip

low in emotional and arousal variables (Lundström et al., 2003a). Hummer and McClintock (2009) demonstrated that when exposed to ANDR female and male participants directed greater attention to emotional information: reaction time was quicker specifically to emotional information. Also, under ANDR participants spent more time on emotional words in an Emotional Stroop task and findings of higher subjective attentive ratings were replicated. Similarly, processing speed of social threat information was accelerated as indicated by faster reaction times to angry faces in an approach-avoidance task under ANDR (Frey et al., 2012). The improved feeling of being focused was likely due to the sustained attention towards emotional cues (Lundström et al., 2003a). Further support comes from electrophysiological data where ANDR modulated early positive and late positive components (P1 and P3) in electrophysiological cortical responses compared to other odors, suggesting faster sensory and cognitive processing under exposure to ANDR (Lundström et al., 2006b). During human interaction, more attention might be directed to important information such as emotional content as ANDR is likely to be more socially salient than other odors.

Especially the prefrontal cortex (PFC), a region responsible for attentional control, seems to be affected by ANDR. A positron emission tomography (PET) study by Jacob et al. (2001b), including ten females during their mid/late follicular phase in a visual attention task, showed increased activation of PFC, including dorsolateral prefrontal cortex (DLPFC/BA 9, 10), after passively inhaling a low concentration of ANDR. In another PET study, Gulyás et al. (2004) reported stronger activation of DLPFC (BA 8, 10, 25) and other frontal, temporal and occipital regions related to social cognition and attention under exposure to ANDR compared to non-social odors. In other words, ANDR might modulate attention required for the on-going task at hand.

Effects of ANDR were shown to depend on the gender of the receiver. Smelling pure ANDR before viewing emotionally arousing videos (humorous, sad, or erotic videos) led to reduced negative mood, elevated cortisol levels and increase in a range of physiological arousal parameters in females (Wyart et al., 2007), probably as a function of increased hypothalamic activation (Savic et al., 2001). More recent findings indicated increased hypothalamic activation in both genders (Burke et al., 2012), arguing against a sexually dimorphic neural activation of the hypothalamus. However, these effects of ANDR on peripheral arousal and affective processing were mostly reported in females during their periovulatory phase (7–18 days post-menstruation) (Krajnik et al., 2014). Current evidence of behavioral effects of ANDR in males is limited. Males with higher levels of testosterone exhibited increased pro-social behavior under exposure to pure ANDR (Huovalia and Rantala, 2012). In another study, males but not females, showed an increased negative mood to pure ANDR (Bensafi et al., 2004b), while a mixed gender sample showed increased pain perception at a subliminal concentration (250  $\mu$ M) (Villemure and Bushnell, 2007). Thus, there is tentative evidence that ANDR may modulate behaviors in females and males differently (Baum and Bakker, 2013; Krajnik et al., 2014). Fitting to the purpose of chemosensory signal communication (see Lübke and Pause, 2015), ANDR seems to direct social salience in different experimental contexts (Pause, 2004). By such means, ANDR could enhance social evaluative threat in a negative and stressful context.

Confronted with acute psychosocial stress, males and females showed different physiological responses (Cahill, 2006; Kudielka and Kirschbaum, 2005; Taylor et al., 2000) and divergent neural activation patterns (Kogler et al., 2015a; Wang et al., 2007). Compared to early-follicular females (EF-females, with typically low circulating endogenous ovarian hormone concentrations) and females using hormonal contraceptives (HC-females, stable and suppressed/low circulating ovarian hormone concentrations),

males showed stronger stress reactions with significantly higher cortisol responses (Kirschbaum et al., 1999). Previous data also indicated a significant effect of menstrual cycle phase on physiological (Duchesne and Pruessner, 2013; Juster et al., 2015) and neural stress reactions (Andreano and Cahill, 2010; Chung et al., 2016).

The Montreal Imaging Stress Task (MIST, Dedovic et al., 2005), which is commonly used in neuroimaging environments, is a mental arithmetic task incorporated with social evaluative threat elements (Dickerson and Kemeny, 2004) provided by both the program and experimenter (Kogler et al., 2015a; Pruessner et al., 2008). Social evaluative threat is induced in a way similar to the Trier Social Stress Test (TSST) and other mental stress tasks involving mental arithmetics (Wang et al., 2007). The MIST requires trial-by-trial flexibility of attention control as well as regulation of the perceived social evaluative threat. The neural stress network includes fronto-parietal regions (DLPFC and ventromedial prefrontal cortex [VMPFC], middle and inferior frontal gyri and pre-cuneus) associated with executive function, working memory and goal-directed cognitive processes (Cieslik et al., 2013; Dolcos and McCarthy, 2006); and fronto-limbic regions (orbitofrontal cortices, insula, middle and superior temporal sulci) associated with psychosocial stress and regulation of negative emotions (Dedovic et al., 2005; Kogler et al., 2015b; Pruessner et al., 2008). Particularly, the PFC is critical for executive functioning and top-down regulation of attention and has been shown to be influenced by social threat (Bishop et al., 2004, 2007). Attentional resources on the task can be disrupted by potential occurrence or signs of threats, comments, or interpretations of these negative events. Pre-attentive evaluation of threat has been demonstrated to be further modulated by individual differences, in particular trait anxiety, in a response conflict task (Bishop et al., 2007). This function of altering allocation of attentional resources was specific to DLPFC (Bishop, 2009). It has been suggested that amygdala-prefrontal circuitry has a reciprocal relationship in representation and interpretation of social threat, with prefrontal activation exerting inhibitory control over the response to threat-related stimuli. As a result, insufficient attentional resources, as indicated by lower DLPFC activation, would be allocated on the on-going task. Based on these findings we speculated that more anxious participants with higher sensitivity to social threat may have selective attention towards social threat and suffer a lapse of attention and cognitive control during the task, which can be characterized by the failure to recruit the DLPFC. To test our hypothesis that ANDR enhances social threat perception and evaluation, lower DLPFC activation was expected to be observed in more trait-anxious participants.

Gender differences in neural stress reactions under social evaluative threat have been observed previously, with males relying more strongly on fronto-parietal regions while females seem to recruit emotion-related regions such as amygdala more strongly (Kogler et al., 2015a; Wang et al., 2007). Specifically, DLPFC activity has been shown to differ between genders during social evaluative threat: although no gender difference was reported in a sample of 10 females and 8 males (Bishop et al., 2007), Wang et al. (2007) reported stronger right DLPFC activation during social evaluative threat in 16 males vs. 16 females. Therefore, we investigated whether gender and laterality differences existed in stress-related DLPFC activation and whether DLPFC activation was negatively associated with trait anxiety when social threat could be augmented by ANDR. Notably, direct comparisons of neural stress responses between males and females at different stages of the menstrual cycle or taking hormonal contraceptives are missing.

Millions of females worldwide use hormonal contraceptives, but their effects on the behavioral and neural stress reaction are far from understood (Pletzer and Kerschbaum, 2014). Hormonal contraceptives are likely to modulate behavioral, hormonal and neural stress responses (e.g. Merz et al., 2012; Nielsen et al., 2013). Pletzer

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