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Exploring the fMRI based neural correlates of the dot probe task and its modulation by sex and body odor

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ABSTRACT

The dot probe task implicitly cues attention via emotional information, an effect which is especially pronounced for threat-related cues. However, several questions remain unexplored. The first one is whether chemosignals like the androgen-derivative androstadienone can influence such attentional biases. Second, few studies have addressed sex differences regarding attentional biases. Finally, the neural correlates of these potential behavioral effects based on functional magnetic resonance imaging (fMRI) are not known. In two experiments we aimed to answer these questions.

A total of 159 healthy individuals (58 oral-contraceptive-users, 42 luteal women, 59 men) were tested. In experiment 1 (behavioral study) we examined attentional biases behaviorally, while in experiment 2 (fMRI study) the dot probe task was complemented by fMRI.

Our results provide robust evidence that in healthy participants fearful but not angry or happy faces lead to a strong general attentional bias. Elucidating the neural basis of this effects points to an early processing advantage in bilateral thalamus for valid compared to invalid cued fear. However, this finding was limited to those participants with the strongest attentional biases and was not linked to behavioral measures. Furthermore, no consistent sex or group differences existed neither did the putative human chemosignal androstadienone reliably modulate attentional biases or change neural processing.

1. Introduction

Human attention is both stimulus and control driven, i.e. both the salience of stimuli and the motivation/goal of the perceiver have an impact in the control of attention (Yantis and Egeth, 1999; Corbetta and Shulman, 2002). To investigate such attention capture especially with respect to stimulus driven attention, the dot probe task (MacLeod et al., 1986) was developed which assesses attentional biases induced by the presence of emotional and non-emotional stimuli. Commonly, participants have to detect a non-emotional target (dot probe) which is preceded by irrelevant cues. These cues can either be at the same (valid) or at the opposite (invalid) location to the following probe. In previous studies, cues have included aversive words (Mogg et al., 1994; Koster et al., 2004) or faces with different emotional displays (e.g. Pfabigan et al., 2014). The central assumption behind this procedure is that emotional information shifts attention in space, thereby influencing subsequent performance in detecting the target probe. In this regard, Bar-Haim et al. (2007) have pointed out in a meta-analysis including dot probe and Stroop paradigms, that threat-related stimuli lead to stronger attentional biases in clinical samples compared to non-anxious healthy controls. However, the reliability of the dot probe task has been repeatedly disputed claiming either the complete absence of internal and test-retest reliability (e.g. Schmukle, 2005) or that many situational factors including cue presentation time or types of stimuli play a role in determining the magnitude of attentional biases (see van Rooijen et al., 2017 for a review of such influencing factors).

1.1. Neural correlates of the dot probe task

Despite extensive research on the dot probe task, few experiments have addressed the neural correlates underlying attentional biases. Electroencephalography-experiments have tracked the temporal dynamics of theses biases (Pourtois et al., 2004; Kappenman et al., 2014; Pfabigan et al., 2014; van Heck et al., 2017). For example, time-locking event-related potentials (ERPs) to the onset of the dot probe, Pourtois et al. (2004) found an increased P1-amplitude at bilateral occipital

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location when the probe followed a fearful rather than a neutral face, suggesting an early visual processing advantage when no reallocation of attention was needed (valid > invalid location). Furthermore, in an fMRI study, Pourtois et al. (2006) showed a stronger activation of the bilateral intraparietal sulcus during invalid compared to valid fear-cue trials. This adds to other neuroimaging studies (comparing invalid to valid threat/fear) implicating the inferior frontal gyrus in healthy adolescents (White et al., 2016) or the anterior cingulate cortex in youth with anxiety disorder (Price et al., 2014) as the neural basis of reallocating attentional resources. The diversity of such results is somewhat surprising but is often attributed to the heterogeneity of modulatory factors, e.g. the use of differently aged participant samples and emotional displays (van Rooijen et al., 2017).

1.2. Sex-specific effects relating to emotion processing and attentional bias

Also emotional processing seems to be susceptible to the influence of a number of situational factors. Especially within women, hormonal fluctuations have been shown to influence reactions to emotional stimuli: women during their follicular cycle phase (low levels of endogenous female sex hormones) show better general emotion recognition than women during their luteal cycle phase (Derntl et al., 2008, 2013) whereas the intake of oral contraceptives (OCs) may lead to impaired recognition for sad, angry and disgusted faces (Hamstra et al., 2014) and reduced affective responsiveness (Radke and Derntl, 2016). Mechanistically, such associations are far from understood. However, it is known that sex hormones pass the blood brain barrier to act on sex steroid receptors in the brain. For example, progesterone can be metabolized into neuroactive steroids such as allopregnanolone and pregnanolone which potentiate the inhibitory $GABA_A$-receptor comparable to the action of benzodiazepines (Melcangi et al., 2011). Thus, high levels of progesterone can have an anxiolytic effect which speculatively could also spill over and affect the processing of emotional displays.

Yet, despite such theoretical considerations, few previous studies have investigated sex differences in attentional biases using the emotional dot probe task. In one study, Pfabigan et al. (2014) report no behavioral sex differences, whereas in another study, Tran et al. (2013) reported an interaction between sex and the level of individual anxiety. Here, high levels of anxiety favored a stronger attentional bias for angry faces in women, while hindering attentional disengagement from happy faces in men. Still, systematic studies exploring the impact of hormonal fluctuations on attentional biases and their neural underpinnings are missing.

1.3. Specific effects of androstadienone

Next to the potential influence of participant sex or hormonal fluctuations, another modulator of interest especially in social contexts may be the presence of chemosignals. One of such potential human chemosignals is the steroid 4,16-androstadien-3-one (AND) which has been identified in human axillary hair (Nixon et al., 1988; Gower et al., 1994). Thus, being present in human body secretions, AND has been considered a candidate for human pheromones. In this regard, research has revolved around the effects of AND on mood (Grosser et al., 2000; Jacob and McClintock, 2000; Villemure and Bushnell, 2007) and attractiveness of the opposite sex (Saxton et al., 2008; Ferdenzi et al., 2016; Hare et al., 2017). Of note, results of these studies have been mixed, sparking criticism (Wyatt, 2015) and asking for a better understanding of the basic psychological properties of AND. To help with this, a study by Hummer and McClintock (2009) investigated the effects of AND on attentional processes. Results of this study suggest that AND may strengthen attentional biases in an emotional dot probe task including happy and angry faces. In this experiment the authors showed that during the AND session participants took longer in detecting the dot probe when displayed at the invalid location compared to the control session. Thus, attention seemed to be more strongly captured by emotional cues under AND. However, this result has remained singular allowing not to derive a common theoretical background on the action of AND. This is due to the variety of experimental paradigms that have followed since Hummer & McClintock's study. For example, the presence of AND enhanced avoidance of angry faces in an approach and avoidance task (Frey et al., 2012) and, in male participants, it reduced interference-related costs in an emotional Stroop task with angry faces (Hornung et al., 2017). However, the neural underpinnings of these odor-dependent attention effects are almost unknown apart from a recent study by Hornung et al. (2018a) pointing to higher interference related brain activation in areas involved in the detection and resolution of emotional conflicts. In another experiment, Parma et al. (2012) provided a link that also hormonal fluctuations as occurring throughout the female menstrual cycle might have an impact on AND-action: here the authors reported that under AND exposure women during their luteal phase spent more time looking at other women's faces compared to women in their follicular phase. This result provided a potential link to the action of the human chemosignal AND when fertility is high in women.

Experimental questions. With the present set of experiments, we aimed at answering the following two main questions:

Sex and hormonal effects: Do hormonal differences as observed between men and women and within women (e.g. depending on the use of oral contraceptives) have an impact on attentional biases? We do not formulate clear behavioral expectations regarding this question as previous studies are scarce and results provided no consistent pattern. This is true both for sex differences in general and for differences in hormonal states (OC-use, menstrual cycle).

Odor effects: Does the putative human chemosignal AND affect attentional biases? As previous studies had indicated that AND might shift attention to emotional stimuli, we expected AND to increase attentional biases across all emotions in our dot probe paradigm. Importantly, we decided to refine this claim by incorporating participants with different hormonal states, by using various negative and positive emotions and to differentiate between orientation towards and disengagement from emotional cues which no previous experiment has provided. Furthermore, we were interested in the potential neural mode of such AND-action.

2. Methods

2.1. Participants

In two studies, a total of 159 female and male students at the University of Tübingen, Germany were recruited and measured twice (once under AND, once under placebo-exposure on two consecutive days). An initial behavioral study (n = 79, results are partially reported in Hornung et al., 2017) served to establish baseline effects and expectations for a subsequent fMRI study (n = 80). Female participants were either taking combined oral contraceptives (OC-users behavioral study: n = 29, fMRI study: n = 29; combination of ethinyl-estradiol and progestin) or were during their luteal cycle phase without taking any oral contraceptives (luteal women behavioral study: n = 21, fMRI study: n = 21). To maximize hormonal differences between our female groups, experimental dates were scheduled for luteal women between day 18–24 of the standardized 28 day cycle when endogenous female sex hormones are high in contrast to the low endogenous hormone profile that is normally observed during OC-use (Sundström-Poromaa and Gingnell, 2014). Exclusion criteria were any current or past psychiatric or neurological disorders as confirmed via structured clinical interview, SCID (DSM-IV; Wittchen et al., 1997) and depression inventory, BDI-II (Hautzinger et al., 2006). Furthermore, the intake of any other type of hormones or medication were exclusion criteria for both men and women. Both in the behavioral and fMRI study three subjects were excluded due to high depression scores resulting in 77 (fMRI

study) and 76 (behavioral study) available participants for behavioral analyses. Please see Supplementary Material 1 for sociodemographic details of both studies.

2.1.1. A priori power analyses

Our sample size for both studies was determined a priori (GPower, Faul et al., 2007) by targeting a power of 0.80 in the corresponding interactions of interest (Validity x Sex; Validity x Odor: Hummer and McClintock, 2009) and assuming a low-to-moderate retest reliability of our measures (rtt = .50) together with an expected medium effect size (η^2 = 0.10). Based on these parameters, we obtained a total sample size of 74 participants. In an effort to maximize power for behavioral data beyond 0.80, we also collapsed data from both studies resulting in a total of 153 participants (men: n = 55; OC-users: n = 58; luteal women = n = 40; see Supplementary material 2).

Participants received monetary compensation and provided written informed consent prior to participation in accordance with the Declaration of Helsinki. The Ethics Committee of the Medical Faculty of the University of Tübingen approved the experimental protocol of the study.

2.2. Odors

Based on similar procedures performed in our group (Chung et al., 2016a, b; Hornung et al., 2018a, b), 250 µM solution of AND (purity of AND ≥ 99%; Steraloids Inc., Newport, RI, USA) was prepared, diluted in propylene glycol and masked with 1% musk oil (Sigma–Aldrich, Deisendorf, Germany). In contrast to this, the placebo solution was solely a 1% musk oil solution diluted in propylene glycol. We also assessed the sensitivity to smell AND by means of threshold and discrimination tests (e.g. Lundström et al., 2003), performed a general test of olfaction (MONEX-40, Freiherr et al., 2012) and asked for self-reports of intensity, pleasantness and familiarity across both studies to characterize odor properties (see Supplementary material 3 for further details of olfactory testing and Supplementary material 1 for outcome of testing). Both solutions were pipetted on a cotton pad with one-direction permeability and attached on the upper lip directly before the behavioral paradigm (behavioral study) or MRI scanning (fMRI study) started.

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2.3. Emotional dot probe task (emoDot)

Emotional facial expressions of 14 different actors (seven women) from all age categories of the FACES database (Ebner et al., 2010) were selected as stimuli. From each of these actors a neutral, angry, happy, and fearful facial expression was selected. Each trial started with the presentation of a white fixation cross on a black background for 500 ms. Immediately afterwards two faces of the same actor appeared, one on the left and the other on the right side of the screen for 500 ms. Both pictures were replaced by a white dot probe (0.5 × 0.5 cm), which appeared either on the left or the right side of the display. Participants were asked to indicate the position of the dot probe as quickly and accurately as possible by pressing the cursor buttons on a standard keyboard or MR-compatible device. The dot probe disappeared 1500 ms after onset. The trial ended with the presentation of another fixation cross with a random duration of 750–1000 ms (behavioral study) or 2000–3500 ms (fMRI study). In each trial, one of the following pairs of faces was presented: neutral-neutral, angry-neutral, fearful-neutral or happy-neutral. Each pair was presented 28 times leading to a total of 196 trials. The location of the emotional face and the location of the subsequent dot probe were pseudorandomized to ensure that each condition was equally often followed by any other condition. A trial was labeled valid when the dot probe appeared at the location of the emotional face and was labeled invalid when the dot probe appeared at the location of the neutral face (see Fig. 1 for a depiction of the dot probe task). An emotional Stroop task (not reported here, see Hornung et al., 2018a,b for results in the behavioral and fMRI study) was either performed before or after the emoDot. The order of tasks was counterbalanced across subjects.

2.4. Acquisition of anatomical and functional MRI images [fMRI study]

Anatomical and functional MRI images were acquired at a 3 T MRI scanner (Siemens, Erlangen, Germany) using a twenty-channel head coil with foam paddings to limit head movements. A high-resolution anatomical image was taken first using a T1-weighted MPRAGE sequence that consisted of 32 slices (TR = 400 ms, TE = 4.92 ms, 1 × 1 x 1 mm resolution, field of view (FOV) = 192 mm, flip angle (FA) = 60°). During the emoDot functional scanning of the whole brain was performed via a multiband-sequence (number of bands per RF pulse = 3) acquiring 72 axial slices with a T2*-weighted EPI sequence (TR = 1500 ms, TE = 34 ms, resolution = 2 × 2 x 2 mm, FOV = 192 mm, FA = 70°). Images were recorded parallel to the anterior-posterior commissure (AC−PC) line.

2.5. Experimental design and statistical analysis

2.5.1. Data preprocessing of behavioral data

First, error trials (behavioral study M = 2.36 trials, SD = 4.50 trials; fMRI study M = 3.86 SD = 6.43) were discarded. Afterwards, similar to other studies (Koster et al., 2004; Mogg et al., 2004), for the remaining trials outliers were defined on a subject to subject basis as deviating two SDs from the mean reaction time of each condition separately. This outlier handling led to a further exclusion of trials in the behavioral study (M = 9.07 trials, SD = 1.73 trials) and the fMRI study (M = 9.67 trials, SD = 1.99 trials). Thus, in total, 5.8% of trials (behavioral study) and 6.8% of trials (fMRI study) were excluded.

2.5.2. Statistical analysis of behavioral data

Behavioral analyses were conducted with the software SPSS 24 (IBM). The statistical threshold was set to α = .05. In general, Greenhouse-Geisser corrections were applied if the assumption of sphericity was violated in our mixed-design ANOVAs. Post-hoc tests and planned contrasts were Bonferroni-corrected for multiple comparisons to a significance threshold of p = .05. Effect sizes were reported in case of significant results for F-tests (partial η^2 = η^2).

emoDot. Mean reaction times (RT) were first used to calculate the following frequently used attentional bias scores (Salemink et al., 2007; Pfabigan et al., 2014):

Bias Index (BI) = RT (invalid trials) – RT (valid trials)

Orienting Index (OI) = RT (neutral trials) – RT (valid trials)

Disengagement Index (DI) = RT (invalid trials) – RT (neutral trials)

The BI reflects the general tendency to get distracted by emotional information as positive scores indicate overall longer RTs for invalid compared to valid trials. The OI quantifies the tendency to direct attention towards emotional stimuli. Positive scores reflect a stronger orienting to valid emotional stimuli. Finally, the DI measures the difficulty to withdraw attention once an emotional stimulus has caught attention. Positive scores reflect diminished disengagement from invalid stimuli. Each of these attentional bias scores was subject to a 3 × 2 × 3 mixed ANOVA including the within-subject factors Emotion (angry, fearful, happy face) and Odor (AND, placebo) and the between-subjects factor Group (men, OC-users, luteal women).

2.5.3. Statistical analysis of functional MRI images [fMRI study]

Prior to analyses of functional imaging data, further participants were excluded due to head movements (> 2 mm in any direction) (five

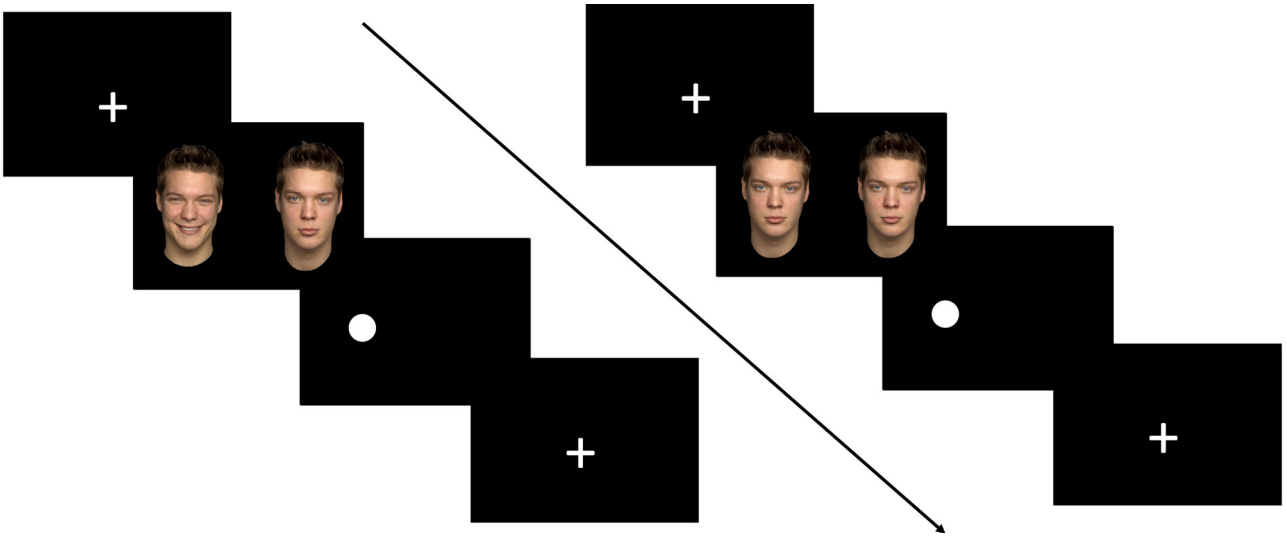

Fig. 1. Procedure dot probe task. Participants were presented either an emotional-neutral or neutral-neutral face pair of the same actor. After 500 ms, the faces disappeared and a dot probe appeared behind one of the faces. Participants were asked to indicate the dot position by pressing left or right as quickly and correctly as possible. An example of a valid trial with a happy cue (left) and a neutral trial (right) is given.

women, three men) and incomplete recording of the whole brain (one women, one men). Thus, a total of 67 participants (43 women) with a mean age of 24.07 years (*SD* = 3.64 years) were included in the final analyses of fMRI data. After discarding the initial four functional scans, data were preprocessed and analyzed using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). For preprocessing, functional images were first slice-time corrected, realigned to the first functional image, co-registered with the mean anatomical image of both sessions, spatially normalized to the standard template of the Montreal Neurological Institute (MNI, Canada) and finally smoothed with a 6 mm FWHM isotropic Gaussian kernel.

2.5.3.1. Whole-brain analyses. For statistical analysis, a General Linear Model (GLM) was specified for each participant. The model included seven regressors of interest (three emotions x valid and invalid trials + neutral trials). Task-related changes in blood oxygen level dependent (BOLD) signal were modelled by convolving the onset of each emotional face pair with the canonical hemodynamic response function (HRF). Three translation and three rotation estimates generated during the realignment step served as further regressors to correct for head motion. To allow for group inferences, another GLM (flexible-factorial model) was created including the within-subject factors Validity (valid, invalid), Odor (AND, placebo) and Emotion (happy, angry, fearful faces) and the between-subjects factor Group (men, OC-users, luteal women). Within this model we were interested in the effects of Validity and the interactions of Validity by Group, Odor and Emotion. To control for inflation of the α-error, whole brain analyses were thresholded at $p < .001$ (cluster-forming threshold at voxel level) and family-wise-error corrected (FWE) for multiple comparisons at the cluster level to a threshold of $p = .05$. The resulting significant voxel coordinates of activation peaks (in MNI-space) were located anatomically by help of the anatomy toolbox (Eickhoff et al., 2005) implemented in SPM12.

2.5.3.2. Region of interest-analyses. Previous fMRI studies using a version of the dot probe task have provided highly heterogenous results. Despite this heterogeneity, we decided to perform specific region of interest analyses on all previously reported putative correlates referring to the comparison of valid vs. invalid trials in studies using a suprathreshold display of emotional faces in the dot probe task (see Table 1). Next to these regions implicated in attentional cueing, we also selected bilateral amygdala as it is related to a variety of processes including olfaction (Gottfried, 2006; Lundström and Olsson, 2010), and processing of emotional faces (Fusar-Poli et al., 2009; Dricu and Frühholz, 2016). To build ROIs, we selected peak coordinates and transformed them to MNI space if necessary by help of the Lancaster-transformation (Lancaster et al., 2007). Afterwards we built a sphere of 5 mm around each peak coordinate and used it to extract beta estimates. Only bilateral amygdala was defined anatomically by help of the Anatomy Toolbox v2 (Eickhoff et al., 2005). In general, parameter estimates for each ROI were extracted via the software Marsbar and included into a mixed ANOVA in SPSS including the within-subject factors Odor, Validity and Emotion and the between-subjects factor Group. Post-hoc tests and planned contrasts were Bonferroni-corrected for multiple comparisons to a significance threshold of $\alpha = .05$, and effects were only further explored if they were below this threshold. For the sake of clarity, we will only report main effects and interactions in connection with the main factor of interest Validity.

3. Results

3.1. Study 1 – behavioral data

3.1.1. Bias index

In general, attention was strongly dependent on the kind of emotional cues as indicated by a main effect of Emotion, $F(2,146) = 17.57$, $p < .001$, $\eta^2 = 0.19$, reflecting an increased attentional bias for fearful compared to angry ($p < .001$) and happy cues ($p < .001$) while no differences existed between angry and happy cues ($p = .54$). In addition, this emotion effect was modulated by our odor intervention as indicated by an Emotion-by-Odor interaction, $F(2,146) = 5.14$, $p = .007$, $\eta^2 = 0.07$. To disentangle this interaction, post-hoc t-tests compared emotions between both odors in a pairwise manner and showed that under AND, fear elicited a stronger attentional bias than under placebo ($p = .012$) while this was not true for angry ($p = .19$) and happy faces ($p = .31$). Comparing each emotion against zero, furthermore showed that only for fear, bias scores differed from zero across both odors ($ts > 3.15$, $ps < .002$). Finally, attentional biases did not differ in general between odors or between sexes as no main effects of Odor or Group ($Fs < 0.41$, $ps > .67$) nor any further interactions were detected ($Fs < 2.66$, $ps > .08$) (see Figs. 2 and 3 for a display of significant effects and Supplementary Material 4 for full

Table 1
All ROIs selected to investigate Validity effects. Indicated are the contrasts of the original publication from which peak coordinates were derived.

Regions of interest	Reported Contrast	X	Y	Z	Volume in mm^3	ROI-definition
L Amygdala	–	−23	−4	−22	2745	anatomical
R Amygdala	–	24	−2	−22	2432	anatomical
Left IPS (Pourtois et al., 2006)	invalid > invalid fear	−36	−42	36	648	5 mm sphere
Right IPS (Pourtois et al., 2006)	invalid > invalid fear	30	−42	48	648	5 mm sphere
dACC (Price et al., 2014)	valid > invalid fear	2	28	16	648	5 mm sphere
L IFG (White et al., 2016)	invalid > valid anger	−25	27	−6	648	5 mm sphere

Note. Center coordinates reflect MNI-space. dACC = dorsal anterior cingulate cortex, IFG = inferior frontal gyrus, IPS = intraparietal sulcus, L = left, R = right.

descriptive data of reaction times in the emoDot).

3.1.2. Orientation index

Orientation (OI) was not affected by the emotion of cues, $F(2,146) = 0.07$, $p = .93$, Odor, $F(1,73) = 0.01$, $p = .91$, or Group, $F(2,73) = 0.27$, $p = .76$, nor were any significant interactions detected ($Fs < 1.58$, $ps > .21$).

3.1.3. Disengagement index

For disengagement (DI), the kind of emotional cues had a strong impact as indicated by a main effect of Emotion, $F(2,146) = 36.99$, $p < .001$, $\eta^2 = 0.34$. This reflects increased difficulty to disengage attention from fearful compared to angry ($p < .001$) and happy facial cues ($p < .001$) while no differences existed between angry and happy cues ($p = 1$). In addition, this emotion effect was modulated by our odor intervention as indicated by an Emotion-by-Odor interaction, $F(2,146) = 7.04$, $p < .001$, $\eta^2 = 0.09$. To disentangle this interaction, post-hoc t-tests compared emotions between both odors in a pairwise manner and showed that under AND fear elicited by trend stronger difficulty to disengage attention than under placebo ($p = .067$) while this was not true for angry ($p = .12$) and happy faces ($p = .40$). Comparing each emotion against zero, furthermore showed that only for fear disengagement scores differed from zero across both odors ($ts > 4.63$, $ps < .002$). No main effects of Odor or Group ($Fs < 0.15$, $ps > .86$) nor any further significant interactions were detected for disengagement ($Fs < 0.65$, $ps > .63$). Supplementary analyses also show that AND administration on the first or second experimental day did not affect any attentional bias index (BI, OI, DI) differently (see Supplementary material 5).

3.2. Intermediate conclusions

Based on the findings of our initial behavioral study, we conducted an fMRI-experiment to explore the neural underpinnings of the above described effects. The general procedure was identical in both studies. Crucially, the dot probe task was administered in the same way as in the behavioral study to allow comparability. Given the results in study 1, we were especially interested in neural contrasts investigating:

a) The neural basis for the general attentional bias for fear.
b) The interaction Emotion-by-Odor, i.e. the neural basis for the specifically higher general attentional bias for fear under AND.

3.3. Study 2 – behavioral data

3.3.1. Bias index

In general, attention was strongly dependent on the kind of emotional cues as indicated by a main effect of Emotion, $F(2,148) = 32.85$, $p < .001$, $\eta^2 = 0.31$, indicating an increased attentional bias for fear compared to anger ($p < .001$) and happiness ($p = .001$) while anger and happiness did not differ ($p = 1$). No main effects of Odor and Group ($Fs < 0.57$, $ps > .57$) or interactions ($Fs < 0.42$, $ps > .66$) were detected (see Fig. 4 for a display of significant effects). Comparing each emotion against zero, furthermore showed that only for fear, bias scores differed from zero across both odors ($ts > 6.18$, $ps < .001$), while this was the case for happiness only under AND ($p = .02$) but not placebo exposure ($p = .09$).

3.3.2. Orientation index

For orientation (OI), attention was dependent on the kind of emotional cues as indicated by a main effect of Emotion, $F(2,148) = 3.28$, $p = .040$, $\eta^2 = 0.042$, pointing to quicker orienting towards fearful

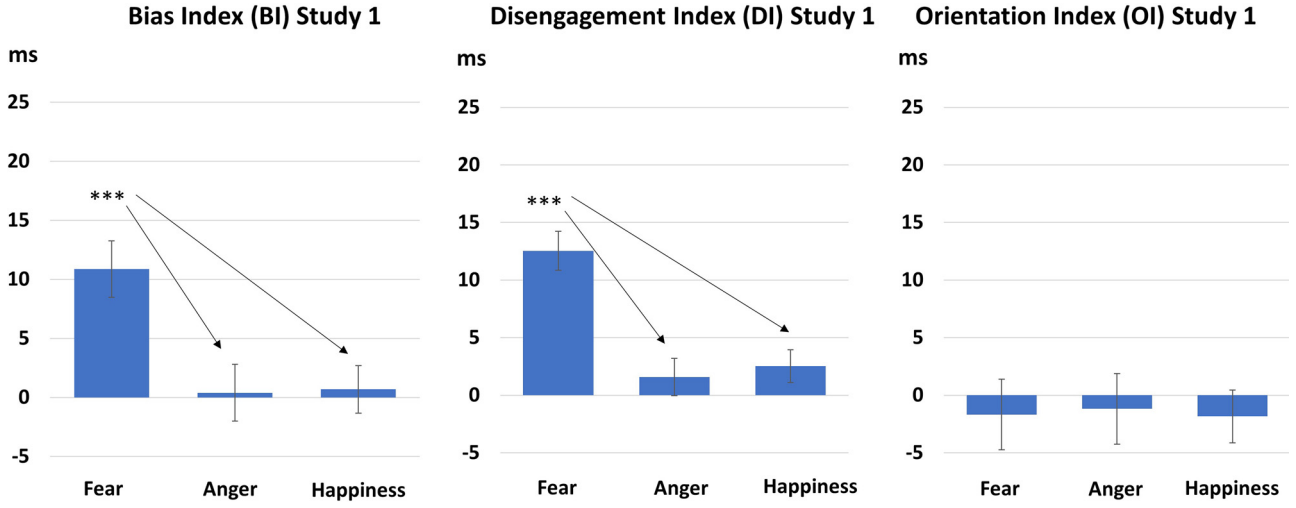

Fig. 2. Attentional biases study 1. Display of the attentional bias (left) and further divided into disengagement (middle) and orientation (right) in study 1. Fear led to a general attentional bias and stronger disengagement difficulty than anger and happiness. *** $p < .001$. Error bars indicate the standard error of the mean (SEM).

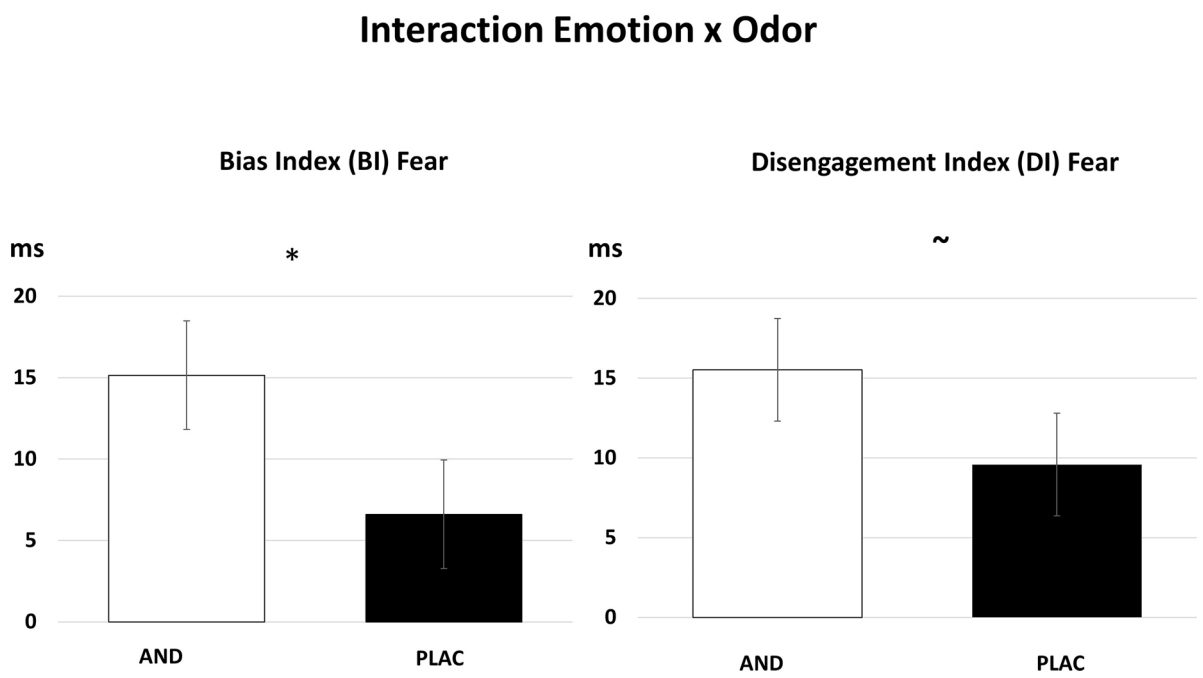

Fig. 3. Interactions for the attentional scores in study 1. Fearful faces elicited a larger general attentional bias and by trend larger disengagement under AND compared to placebo (right). * p < .05; ~p < .10. Error bars indicate the standard error of the mean (SEM).

compared to angry (p = .038) but not compared to happy cues (p = .50). Also, angry and happy cues did not differ (p = 1). No main effects of Odor and Group (Fs < 2.59, ps > .08) nor any significant interactions (Fs < 1.41, ps > .25) were detected.

3.3.3. Disengagement index

For disengagement (DI), attention was strongly dependent on the kind of emotional cues as indicated by a main effect of Emotion, $F(2,148) = 28.97$, p < .001, η^2 = 0.28, indicating increased difficulty to disengage from fearful compared to angry (p < .001) and happy (p < .001) cues while no difference existed between angry and happy faces (p = .83). No main effects of Odor and Group (Fs < 3.20, ps > .08) nor any significant interactions (Fs < 0.43, ps > .65). See Fig. 4 for a display of significant effects.

3.4. Conclusions from behavioral data to motivate fMRI analyses

In summary, behavioral data of two studies consistently pointed to an emotion dependent cueing effect, i.e. a larger attentional bias and stronger difficulty to disengage attention from fear. In addition, results of study 1 suggested that this emotion dependent effect could be further increased depending on exposure to AND. Subsequent fMRI analyses thus especially focused on these fear-related cueing effects.

3.5. fMRI analyses

3.5.1. General impact of odor and sex on validity

Regarding the general effect of emotional bias, across all emotions no significant activation was found both for valid > invalid and invalid > valid trials. Also, no significant clusters emerged when modelling the interaction of Validity x Emotion, Validity x Odor and

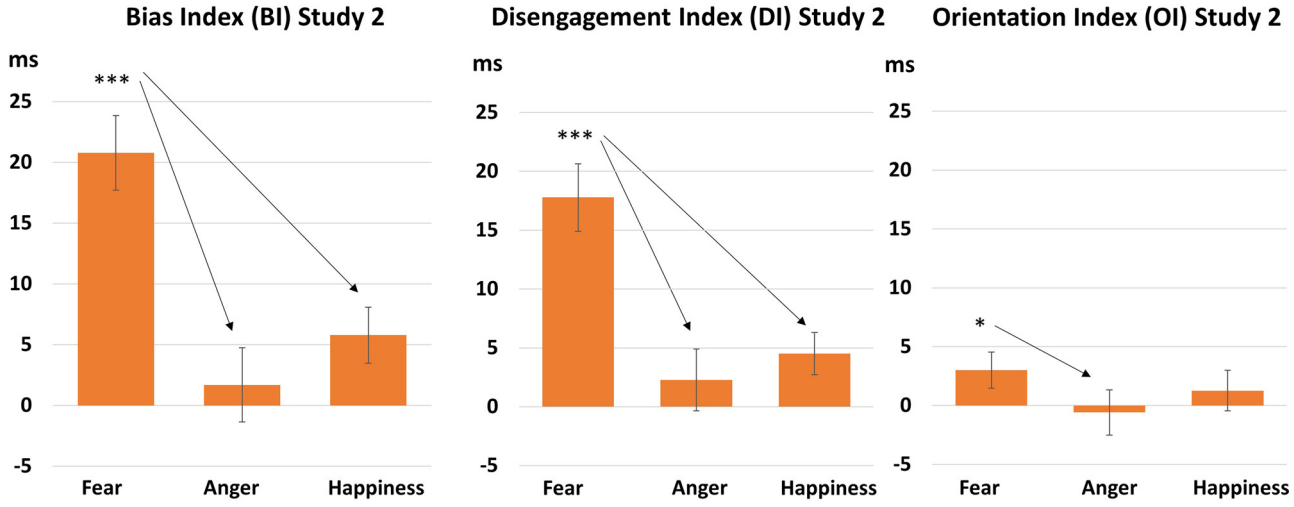

Fig. 4. Attentional biases study 2. Display of the attentional bias (left) and further divided into disengagement (middle) and orientation (right) in study 2. Fear led to a general attentional bias and stronger disengagement difficulty than anger and happiness and to stronger orientation than anger. *** p < .001. * p < .05. Error bars indicate the standard error of the mean (SEM).

Table 2
Whole brain analyses for valid vs. invalid fear only for participants (n = 16) with a strong behavioral attentional bias for fearful faces across both experimental days (FWE-corrected at cluster-level $p < .05$).

Whole brain voxel-wise activations	MNI			Voxels (k)	t-value (cluster-level)
	X	Y	Z		
Valid > invalid fear					
Cluster Thalamus				334	
R Thalamus	10	−30	16		5.31
L Thalamus	−10	−28	12		5.28
Invalid > valid fear	–	–	–	–	n.s.

Validity x Group indicating that validity effects were not specific to any of our three emotions, two odor interventions or three groups (male and female groups).

3.5.2. Investigating participants with a high BI for fear

Given that a strong behavioral attentional bias existed for fear we aimed to increase the sensitivity of our analyses. To do so, we identified subjects who had an above-median attentional bias (BI) for fear on both experimental days. This resulted in 16 participants (4 OC-users, 6 luteal women) with a mean positive BI for fear of 37.55 ms (SD = 14.32 ms). For these subjects a separate whole-brain analysis was conducted comparing valid to invalid fear trials. This yielded one significant cluster spanning bilateral temporal thalamus for the contrast valid > invalid (see Table 2 for MNI coordinates of maxima). To connect this finding to behavioral outcome, parameter estimates were extracted from the spatial extent of this thalamic cluster. Then, brain activation during valid fear trials was subtracted from activation during invalid fear trials to quantify a neural BI for fear. Afterwards this neural difference was correlated with the general attentional bias for fear (reaction times). However, this correlation was not significant, $r = -0.33$, $p = .21$, suggesting no coupling of behavioral measures of the attentional bias for fear and its potential neural correlate (see Fig. 5 for an illustration of thalamic activation).

3.6. Region of interest analyses

More specific region of interest analyses investigated whether an effect of validity could be found in previously identified regions or whether validity was modulated by Odor or Group. Our analyses failed to replicate any previous finding as neither bilateral IPS nor dACC or left IFG showed activation differences between valid and invalid trials (see Table 3). In general, also no interactions of Validity with the factors Group or Odor emerged. Only in the left IPS a significant interaction Odor x Validity was detected. Here, further post-hoc t-tests showed

Table 3
All selected regions for specific analysis. Main effects of Validity and interactions with Validity are reported.

Regions of interest	Main effect Validity	Interactions with Validity
L Amygdala	F(1,64) = 4.31, **p = .04**, $\eta^2 = 0.06$[a]	ps > .13
R Amygdala	F(1,64) = 3.10, p = .08, $\eta^2 = 0.05$[a]	ps > .13
Left IPS	p = .66	Odor x Validity: F(1,64) = 6.66, **p = .012**, $\eta^2 = 0.09$[b]
Right IPS	p = .92	ps > .30
dACC	p = .29	ps > .35
L IFG	p = .52	ps > .08

Note. Center coordinates reflect MNI-space. dACC = dorsal anterior cingulate cortex, IFG = inferior frontal gyrus, IPS = intraparietal sulcus, L = left, R = right. Significant findings are highlighted in bold.
[a] Stronger activation during valid compared to invalid trials.
[b] Stronger activation during invalid compared to valid trials under AND but not under the placebo odor.

that invalid trials led to higher activation than valid trials under AND ($p = .022$) but not under placebo ($p = .26$). Furthermore, in the left amygdala a main effect of validity was detected pointing to higher activation for valid compared to invalid trials ($p = .04$) which was by trend also true for the right amygdala ($p = .08$).

3.6.1. Correlation analyses

To connect the significant findings in left amygdala and IPS to behavior, neural and behavioral BI scores were correlated independent of odor (left amygdala) or separately for both odors (left IPS). For the left amygdala the correlation was not significant, $r = -0.04$, $p = .75$. For the left IPS, a negative association emerged under AND, $r = -0.27$, $p = .03$, but not for the placebo odor, $r = -0.11$, $p = .39$. Direct comparisons between both correlation coefficients (left IPS) revealed no significant difference, $Z = 0.94$, $p = .17$.

3.7. Supplementary material and analyses

In the supplementary material we provide sociodemographic details of our study samples (Supplementary material 1), a pooled analysis of behavioral data from both studies (Supplementary material 2), details about the methods of olfactory testing (Supplementary material 3), reaction time data of both studies (Supplementary material 4) and effects regarding the order of AND-application on the first or second experimental day (Supplementary material 5).

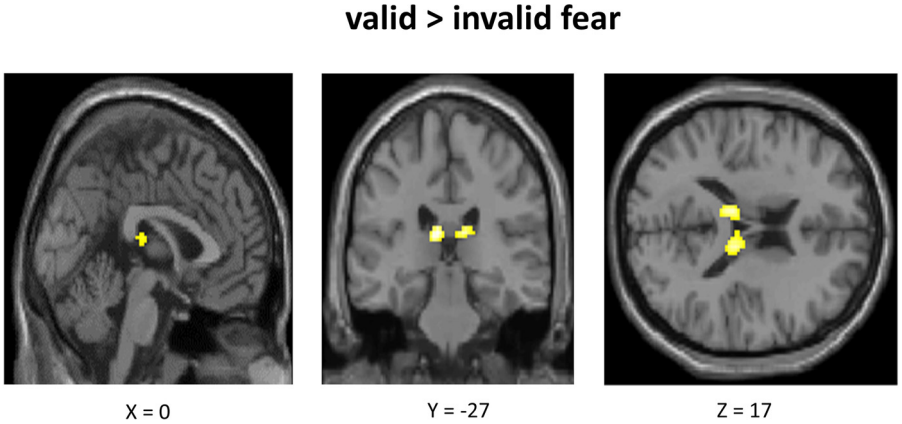

Fig. 5. Thalamic validity effect. During valid compared to invalid fear trials, a cluster in bilateral thalamus was significantly more active. Cluster forming threshold ($p < .001$), FWE-corrected at cluster level ($p < .05$).

3.8. Overall summary of results

Across two studies we provide strong evidence that group measures of attentional biases are very robust. At the same time hormonal fluctuations and an odor intervention do not or only lightly impact these attentional biases. Finally, a corresponding robust neural correlate of the behaviorally pronounced attentional bias for fear was not detected

4. Discussion

In the present set of experiments we aimed at exploring the neural correlates of attentional biases as measured by an emotional dot probe task (experimental question 1). Furthermore, we were interested whether such attentional biases could be modulated by hormonal fluctuations as occurring between men and women and within women, e.g. due to use of oral contraceptives (experimental question 2). Finally, we asked the question whether also a putative human chemosignal like AND would be able to modify attentional biases (experimental question 3).

4.1. Experimental question 1

In the present set of experiments, we found a consistent general attentional bias towards and difficulty to disengage attention from fearful faces. This finding is partially in line with previous reports of increased attentional biases for threat-related stimuli (Bar-Haim et al., 2007). However, threat is an ambiguous concept encompassing both anger and fear. In this regard, anger is believed to signal direct threat for the observer while fear may signal threat only indirectly (Davis et al., 2011; Grillon and Charney, 2011). Given this conceptual distinction, it may come as a surprise that unlike fearful faces, angry faces did not elicit an equally strong attentional bias in the present set of experiments. Still, previous studies tend to be more consistent in finding attentional biases for fearful faces (Pourtois et al., 2004; Carlson et al., 2011) and in reporting no attentional biases for anger (Pfabigan et al., 2014; White et al., 2016). However, it is problematic that many experiments have either used fearful or angry stimuli but not both kinds of emotions in the same experiment, thus reducing the generalizability of emotion-specific effects. Given our robust finding of fear-related attentional biases we expected to detect a neural correlate of this effect by comparing invalid with valid trials specifically for fearful faces. However, as long as participants were not selected depending on the strength of their attentional biases, no significant neural difference was found between valid and invalid fear. As this finding might be confounded by the large heterogeneity of attentional biases across participants, we selected only participants who had an above-median attentional bias for fearful faces on both experimental days. These analyses yielded stronger activation during valid compared to invalid trials in bilateral thalamus. Given the central role of the thalamic lateral geniculate nuclei as a relay for visual input (e. g. Sherman, 2016 for a recent review of thalamic functions) this may speak for an early target amplification when visual attention has been cued validly and thus no reallocation of attention is required.

Although research on the neural correlates of attentional cueing in the dot probe task as measured by fMRI is scarce, previous evidence indeed points to the stronger involvement of visual areas during valid compared to invalid trials. In this respect, Carlson et al. (2011) detected occipital clusters when fearful faces were masked and presented subliminally, while Pourtois et al. (2006) showed a stronger involvement of the right extrastriate cortex during valid compared to invalid fear faces (however, only at a more liberal statistical threshold). This line of results suggests a very early processing advantage for validly cued dot probes when no reallocation of attention is needed. In addition, other fMRI studies by Pourtois et al. (2006) and White et al. (2016) suggested higher order processes as the basis for reallocation of attention (invalid > valid). In this regard, Pourtois et al. (2006) found a bilateral cluster in intraparietal sulcus (invalid > valid fear) while White et al. (2016) detected a small cluster of activation in the left hemisphere encompassing claustrum, insula and inferior frontal gyrus investigating healthy adolescents (invalid > valid anger). Furthermore, Price et al. (2014) observed increased activation in the right anterior cingulate cortex in youth with anxiety disorders (valid > invalid fear). Of note, other fMRI-studies investigating the dot probe task mainly in adolescents (Monk et al., 2006, 2008; Telzer et al., 2008; Fani et al., 2012) did not report brain activation (contrasts: invalid vs. valid) at all and therefore null-findings might be assumed in these studies. For our second study, we also selected regions of interest derived from the coordinates reported in these studies but failed to replicate any of these findings. Only in the left amygdala valid led to stronger activation than invalid trials, however, independent of emotion. At the same time neural and behavioral outcome were not correlated making this finding an unlikely correlate of attentional processes as measured by our version of the dot probe task. Together with the pattern of our whole brain analyses we suggest several methodological issues that makes detecting a neural basis of attentional biases based on fMRI difficult: First, and foremost, the dot probe paradigm has been repeatedly criticized for the alarming lack of both internal and test-rest reliability (e.g. Schmukle, 2005; Chapman et al., 2017). Though effort has been invested in identifying factors that might explain this lack of reliability, only few progress has been made. Chapman et al. (2017) provide some evidence that a short cue-target interval (CTI) of 100 ms could indeed improve reliability, however, not by a large degree. Here the authors suggest that a short CTI allows for an initial capture (selection, orienting) of attention which might be disturbed by longer CTIs potentially adding several other attentional processes like engagement, disengagement and shifting of attention. Due to their limited temporal resolution, many fMRI experiments employ longer CTIs like 500 ms which may pose severe constraints on disentangling the multitude of attentional processes although also EEG studies do not provide a homogenous pattern of activation (Pourtois et al., 2004; Kappenman et al., 2014; Pfabigan et al., 2014; van Heck et al., 2017). Furthermore, due to the often reported lack of internal reliability with regard to behavioral outcome, the question is whether individual trials lead to a reliable neural activation pattern that transfers to a robust validity effect. In view of these considerations there may be hard limits for fMRI to identify a stable correlate of attentional shifts.

4.2. Experimental question 2

We furthermore asked the question whether hormonal differences or fluctuations as observed during OC-use or throughout the menstrual cycle affect attentional biases. A growing literature points to subtle differences in emotion processing between men and women and also within women depending on the menstrual cycle phase. While men indicate stronger emotional experience with anger stimuli than women (Deng et al., 2016), women may have a positivity bias rating subliminally presented happy faces as more positive than men (Donges et al., 2012). Furthermore, women during their follicular cycle phase have been reported to show e.g. better general emotion recognition than women during their luteal cycle phase (Derntl et al., 2008, 2013). In the present set of experiments, no consistent evidence was detected to support group differences as men and women with low levels (OC-users) or generally increased levels of endogenous sex hormones (luteal women) did not differ regarding behavioral and neural attentional bias processing. Thus, our experiments provide initial evidence that no differences regarding attentional biases exist between healthy men and women. Though the above-mentioned reliability issue puts some constraints on the definitiveness of this conclusion, we collapsed behavioral results from study 1 and 2 to maximize statistical power (reported in Supplementary Material 2). These supplementary analyses do not provide evidence in favor of sex effects on attentional biases as measured by the dot probe task.

4.3. Experimental question 3

Finally, regarding the question whether the putative human chemosignal AND is able to modulate attentional biases, one previous study (Hummer and McClintock, 2009) reported an attentional bias across happy and angry faces under AND compared to a placebo odor. In the same study the authors also found that AND slowed reactions to positive and negative words when these words acted as distractors in an emotional Stroop task. More recent studies have more strongly pointed to the emotion-specificity of AND-effects by showing faster reactions to angry cartoon faces in an approach and avoidance task (Frey et al., 2012) and reduced emotional Stroop interference when angry faces were presented to men under AND (Hornung et al., 2017). In the present set ofexperiments, only in the behavioral study AND slightly increased the general attentional bias for fearful faces. As noted above, in general only fear led to robust attentional biases in the first place. Though speculative, it may therefore be assumed that the putative body-odor compound AND can further pronounce this attentional fear bias. However, as no clear theoretical background exists for AND, e.g. as a highlighter of threatening information, we ask to consider this effect with caution and highlight that it can only be small in view of the large collective sample we used for analysis. Furthermore, an interaction effect in the left intraparietal sulcus (IPS) suggested higher activation for invalid compared to valid trials under AND but not placebo while general bias scores were reduced with higher left IPS activation under AND. Again, the nature and importance of this effect remain unclear given that our behavioral findings tended to support AND-effect specifically for fearful faces.

Regarding the question whether men and women differ with respect to AND-action, previous studies had pointed to mood enhancing effects of AND specific to women (Grosser et al., 2000; Jacob and McClintock, 2000; Villemure and Bushnell, 2007) and reported that women during their luteal phase compared to women in their follicular phase spent more time looking at other women's faces in an eye-tracking study under AND exposure (Parma et al., 2012). In the present set of experiments, no odor-dependent group differences were found which is also backed by our own null-findings regarding mood and emotional Stroop interference (Hornung et al., 2018b). All in all, we therefore see no consistent ground to support the claim of attentional bias strengthened by AND neither in general nor in connection with hormonal differences.

5. Conclusions

The present set of experiments provides robust evidence that in young healthy participants fearful but not angry and happy human faces led to a strong general attentional bias which was mainly due to increased difficulty to disengage attention from fearful faces. Elucidating the neural basis of this bias points to a very early visual processing advantage in bilateral thalamus for validly compared to invalidly cued fear but this finding was limited to those participants with the strongest attentional bias plus no correlation existed between this neural finding and behavioral bias scores. Furthermore, when reallocation of attention was required (invalid > valid) no neural correlate was detected. Also region of interest analyses on previously reported areas did not yield a clear correlate of neural validity processing. A number of methodological problems may account for this instability including low temporal resolution of fMRI or the low cognitive demands of the dot probe task. Also, no consistent sex or group differences existed with respect to attentional biases as neither women high in endogenous sex hormones (luteal cycle phase) differed from women low in endogenous sex hormones (OC-users) nor did women in general differ from men. Finally, the putative human chemosignal androstadienone was not reliably able to modulate attentional biases and change neural processing. Overall, our results question the reliability of the dot probe paradigm regarding fMRI based findings and caution the use of further fMRI experiments without additional methodologies like eye tracking and combined EEG.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.08.036.

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