Psychoneuroendocrinology 75 (2017) 15–25

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

A human chemosignal modulates frontolimbic activity and connectivity in response to emotional stimuli

Tom A. Hummer[a,*], K. Luan Phan[b], David W. Kern[c,1], Martha K. McClintock[c,d]

[a] Department of Psychiatry, Indiana University School of Medicine, United States
[b] Department of Psychiatry, University of Illinois at Chicago and Mental Health Service Line, Jesse Brown VA, Chicago, IL, United States
[c] Institute for Mind and Biology and Department of Comparative Human Development, The University of Chicago, United States
[d] Department of Psychology, The University of Chicago, United States

ARTICLE INFO

Article history:
Received 12 April 2016
Received in revised form
23 September 2016
Accepted 28 September 2016

Keywords:
Androstadienone
Pheromone
fMRI
Attention
Emotion
Prefrontal cortex
Amygdala

ABSTRACT

Evidence suggests the putative human pheromone Δ4,16-androstadien-3-one (androstadienone), a natural component of human sweat, increases attention to emotional information when passively inhaled, even in minute amounts. However, the neural mechanisms underlying androstadienone's impact on the perception of emotional stimuli have not been clarified. To characterize how the compound modifies neural circuitry while attending to emotional information, 22 subjects (11 women) underwent two fMRI scanning sessions, one with an androstadienone solution and one with a carrier control solution alone on their upper lip. During each session, participants viewed blocks of emotionally positive, negative, or neutral images. The BOLD response to emotional images (relative to neutral images) was greater during exposure to androstadienone in right orbitofrontal and lateral prefrontal cortex, particularly during positive image blocks. Androstadienone did not impact the response to social images, compared to nonsocial images, and results were not related to participant sex or olfactory sensitivity. To examine how androstadienone influences effective connectivity of this network, a dynamic causal model was employed with primary visual cortex (V1), amygdala, prefrontal cortex, and orbitofrontal cortex on each side. These models indicated that emotional images increased the drive from V1 to the amygdala during the control session. With androstadienone present, this drive to amygdala was decreased specifically for positive images, which drove downstream increases in orbitofrontal and prefrontal activity. This evidence suggests that androstadienone may act as a chemical signal to increase attention to positively valenced information via modifications to amygdala connectivity.

1. Introduction

Mounting evidence suggests that exogenous chemical signals can act as social cues in humans, by providing information or influencing psychological processes during social interaction (McClintock, 2002). One such airborne signal is the human compound Δ4,16-androstadien-3-one (androstadienone), a natural component of human sweat (Gower et al., 1994; Labows, 1988). Passive inhalation of minute amounts of androstadienone induces psychological, typically mood-related, changes in women and men (Bensafi et al., 2004a, 2003, 2004b; Jacob et al., 2002; Jacob and McClintock, 2000; Saxton et al., 2008; Villemure and Bushnell, 2007; Wyart et al., 2007). The nature of these changes, however, is modified by experimental context (Bensafi et al., 2004a; Jacob et al., 2001a), including enhanced pain perception by women in the presence of androstadienone (Villemure and Bushnell, 2007). Additional research has revealed that the compound alters autonomic arousal (Bensafi et al., 2003; Jacob et al., 2001a), potentially related to higher cortisol levels that accompany exposure (Wyart et al., 2007).

A recent investigation examined the effect of passive inhalation of androstadienone during a series of psychological tests (Hummer and McClintock, 2009). Men and women demonstrated increased attention to emotional stimuli during exposure to subthreshold levels of androstadienone. To date, the neurobiological changes underlying this increased attention to emotional information remain unclear.

* Corresponding author at: Riley Outpatient Center, ROC 4300, 705 Riley Hospital Drive, Indianapolis, IN 46202-5225, United States.
E-mail address: thummer@iupui.edu (T.A. Hummer).
[1] Present address: Department of Psychology, Northeastern Illinois University, United States.

http://dx.doi.org/10.1016/j.psyneuen.2016.09.023
0306-4530/

Although neuroimaging techniques have been utilized to investigate the neural effects of androstadienone, these studies have primarily focused on identifying the brain's specific response to smelling the compound, rather than revealing how androstadienone can modify distinct brain processes. For instance, smelling androstadienone may alter hypothalamic activity dependent on sexual orientation and attraction (Burke et al., 2012; Savic et al., 2001, 2005). In addition, subjects presented 5% androstadienone solution, a relatively large amount detectable by most individuals (Lundstrom et al., 2003), had increased blood flow in orbitofrontal cortex, prefrontal cortex, fusiform gyrus and superior temporal cortex (Gulyas et al., 2004), regions consistently involved in both social and emotional processing (Norris et al., 2004; Phan et al., 2002). Finally, with EEG, androstadienone odor presentation has shown quicker cortical responses than chemically and qualitatively similar compounds, indicating a fundamental importance to the compound (Lundstrom et al., 2006).

These studies focused on the direct, immediate neural responses to smelling androstadienone, rather than how the compound modulates brain state over a longer time scale. Jacob and colleagues quantified androstadienone-induced changes in glucose metabolism over 20-min periods on two separate days (Jacob et al., 2001b). During performance of a simple visual task, a variety of regions involved in emotion and attention, including visual cortex, amygdala, prefrontal cortex, parietal cortex, anterior cingulate, and hypothalamus, demonstrated significant changes in glucose utilization between the two solution conditions. This investigation indicated how continuous inhalation of androstadienone can act as a contextual influence on brain activity, but skirted the question of whether rapid neural processes are similarly affected.

To investigate how an airborne social cue can influence brain activity and connectivity during a basic psychological task, we examined whether the presence of androstadienone altered neural responses to viewing blocks of social and emotional images. This study differs from most odor-related fMRI research, in that the primary focus was not the sensory act of smelling a compound, but rather a distinct psychological process (visual attention). Thus, the investigation required a contrast of androstadienone session and control session neural responses, with brain activity measured while images were viewed under each solution condition.

This experimental design did not rely on short olfactory bursts or sniffs; rather, androstadienone was present or absent for an entire session, with each session conducted on a separate day. This design represents a unique approach to examining how odors or chemosignals can alter the immediate neural drivers underlying psychological processes, despite being below the level of detection. While compounds are known to affect systemic neural activity while being below detection threshold (Jacob et al., 2001b; Sobel et al., 1999), it is unclear how the extended presence of a compound may influence rapid neural activity and connectivity between brain regions.

Within this framework, we examined how the response to emotionally valenced social and nonsocial images was influenced by androstadienone. From these contrasts, we established regions of interest (ROIs) to examine how androstadienone modified effective connectivity within brain regions responsible for focusing attention on emotional stimuli. Effective connectivity analysis examines how a pre-selected network of regions interacts, quantifying directional relationships between brain structures and measures how coupling between regions is modulated by experimental context or manipulations (Friston et al., 2003). To assess effective connectivity, we utilized dynamic causal modeling (DCM).

This investigation employed traditional fMRI techniques along with DCM to determine how passively inhaling androstadienone influences the brain during the processing of emotional information. Since behavioral work indicates that androstadienone enhances attention to emotional information (Hummer and McClintock, 2009), we hypothesized an enhanced BOLD response to emotional stimuli in emotion-relevant (orbitofrontal cortex, limbic regions, insula) and attention-related regions (lateral prefrontal cortex). In addition, this experiment examined whether androstadienone's neural effects were confined to emotional stimuli, with no overall visual effects and no influence on social stimuli, as seen in behavioral work.

2. Materials and methods

This study utilized a repeated-measures paradigm. Each participant was scanned on two separate occasions, 2–3 days apart, at the same time of day. The procedure was identical each day, except for the solution and the images. All procedures were approved by the local institutional review board.

2.1. Subjects

Thirty-two subjects (ages 18–36; 16 females) were scanned for this study, recruited via advertisements posted online and around the local university community. However, due to various quality control measures (high motion, inattention, low signal-to-noise ratio, inability to detect menstrual phase; see Section 2.4), data from only twenty-two subjects (11 female) were analyzed.

The sample consisted of individuals reporting that they did not take hormones (including oral contraceptives), were not smokers, and had no history of sinus pathology, drug use, or neurological impairments. All had a self-reported normal sense of smell, verified by olfactory discrimination screening with clove oil. Individuals gave informed consent and received $50 for completing both fMRI sessions.

Female subjects were scheduled to take part during the late follicular phase of the menstrual cycle, based on self-reports of cycle length and onset of menses, due to the potential relationship of menstrual phase with androstadienone effects (Chung et al., 2016), with an initial introductory visit 7–10 days following onset of menstruation and the first scan 10–14 days post-onset. Estrogen levels are high at this time, so intra-gender hormonal differences were maximized. An ovulation testing kit (Unipath Diagnostics, Inc., Waltham, MA) was provided to pinpoint the day of ovulation and verify that women were studied during the late follicular or periovulatory phase of the menstrual cycle. All included subjects had a positive indication of ovulation within seven days of the first scan.

2.2. Androstadienone preparation

The preparation of androstadienone (Steraloids, Inc., Newport, RI) was identical to previous work (Jacob and McClintock, 2000). In order to create a 250 μM solution, the purified crystalline steroid was dissolved in propylene glycol, and clove oil was added to form 1% of the solution. The carrier control solution was identical, without androstadienone. Immediately prior to the scanning procedure, two cotton swabs were each dipped in 130 μL of solution and applied to the upper lip of the individual. Prior research has demonstrated that this procedure leaves approximately 9 nanomoles of androstadienone (in solution) under the nose of subjects (Jacob and McClintock, 2000).

2.3. Procedure

During the introductory session, subjects were instructed on the fMRI paradigm, underwent olfactory testing, and shown images similar to those shown in the scanner. Apart from the presented solution, the two scanning sessions were identical, consisting of a

mood evaluation before and after the fMRI scan, the scan itself, and a post-scan evaluation of attention to presented images. A sole male tester, blind to the solution condition, administered each session.

2.3.1. Olfactory testing

Olfactory screening involved a forced-choice paradigm in which subjects were presented with three 100-mL jars with 20 mL of propylene glycol. One jar contained 1% clove oil, and subjects were required to smell each jar once and identify the unique jar. Correct selection of the distinct jar on at least 6 of 9 trials was required for inclusion.

A brief measure of androstadienone threshold was taken using a similar forced-choice paradigm, with the first odd jar containing a 125 μM concentration of androstadienone in propylene glycol. After an incorrect answer, a higher concentration was provided, until four correct answers in a row were given. Dilution stepped upward to 250, 500 and 1000 μM solution steps. These measures were ruled out as factors influencing androstadienone-induced modulations of BOLD activity (see ROI results).

2.3.2. Psychological state testing

Each participant completed a 22-item version of the Visual Analog Scale (VAS) (Folstein and Luria, 1973) before and after each scan. The VAS entails marking a horizontal scale to mark the degree to which a provided adjective describes how one feels at the current moment ("Not at all" to "Extremely").

2.3.3. Scanning procedure

Prior to each scan (as the subject lay supine on the patient table), the androstadienone solution or vehicle control was applied to the upper lip, with presentation order counterbalanced across subjects. Each fMRI session involved six runs, each containing 12 alternating 20 -s image and fixation blocks (Fig. 1). The six picture blocks contained images from the International Affective Picture System (IAPS) (Lang et al., 1999), a set of color images with normative ratings of pleasantness. The IAPS has been extensively utilized in neuroimaging studies examining the brain's response to positive and negative pictures (Hamann et al., 2002; Lane et al., 1997; Lang et al., 1998). Fixation blocks had a small cross in the center of the screen. Each picture block contained five consecutive images (shown for four seconds each), of a particular valence (positive, negative or neutral) and social category (social or nonsocial). All six different picture types comprised a single block in each run: social positive, social neutral, social negative, nonsocial positive, nonsocial neutral and nonsocial negative. Presentation order of blocks was counterbalanced with a Latin squares design, ensuring that each picture type appeared in each block position once during the six runs, and run order was balanced across subjects as well. The presentation order was identical during a given participant's two fMRI sessions.

The goal of picture blocks was to induce the natural emotional reaction to the images. Therefore, subjects were instructed to attend to the presented images and to "respond mentally and emotionally as you naturally would," but no motor response was required. This procedure was utilized to minimize cognitive effort, as making even simple valence ratings of IAPS pictures can attenuate limbic responses (Taylor et al., 2003). To ensure that attention was paid to the images, subjects were told they would be tested later to determine which they remembered seeing.

2.3.3.1. Picture presentation. All instructions and images were presented via E-prime® software (Psychology Software Tools, Inc., Pittsburgh, PA) and viewed through a back-projection system visible from a mirror placed above the participant's eyes. Each presented image was viewed only once per subject (across both sessions). Images were defined as social if they contain the presence of one or more humans. Normative data on the valence of the images was used to categorize each image as positive, neutral or negative (Lang et al., 1999). Positive pictures were those in the highest third for pleasantness rating, neutral the middle third, and negative the lowest third (Fig. 1). However, an image was only used if in the same valence category for each sex (i.e. both males and females rate the picture similarly).

Arousal ratings of positive and negative images tend to be higher than those of neutral images. However, higher arousal is a natural element of emotionally evocative stimuli (Lang et al., 1999), and controlling for arousal may decrease the natural emotional response that we aimed to examine. In fact, those neutral images that rate high in arousal (e.g. a volcano close-up) are more likely to contain *both* positive and negative elements than to be a purely neutral, emotionless scene. Thus, use of high-arousal neutral images was avoided.

2.3.3.2. Imaging parameters. A 3T GE Signa machine was utilized to implement the scanning procedure, which began with a high-resolution T1 scan to provide precise anatomical localization (3D-MPRAGE, TR of 25 ms, min TE, field of view (FOV) of 24 cm, slice thickness of 1.5 mm). Functional data were acquired with a T2*-weighted reverse-spiral sequence (TE = 30 ms, TR of 2000 ms, frequency of 64 frames, flip angle of 77°, FOV of 24 cm, 30 contiguous 5 mm axial slices approximately parallel to the AC-PC line).

2.3.4. Behavioral testing

After scanning, subjects viewed a series of 54 images on a computer (36 from the scan—one from each 20-s block, and 18 new images) and were required to respond via mouse-click to indicate whether or not the image was seen during the scan. Reaction times (RTs) and accuracy scores were recorded. A computer problem caused data from one participant to be lost. This participant was not included in data analysis.

2.4. Quality control

Imaging data were not analyzed if subjects were inattentive (<75% accuracy on the post-scan test, representing a level of correct responses significantly different from chance at $p < 0.0001$), had excessive head movement (>5 mm at any point), or demonstrated high levels of measurement noise (e.g., "spikes" in the time series likely to be of non-neuronal origin), as identified with whole-brain time-series variance maps. Due to these exclusions, three subjects had poor accuracy, four had high variance, and six had high motion during at least one of the two scans (with overlaps), resulting in 10 excluded subjects.

2.5. Analysis

2.5.1. Imaging analysis

BOLD data were analyzed with the AFNI software package (Cox, 1996). Functional data from each run were concatenated and registered to a single time point based on a least-squares algorithm to diminish effects of small head movements. Each day's functional data were also aligned to the structural T1-weighted brain image from the first session.

Data from each voxel were convolved with an 8-mm full-width-at-half-maximum (FWHM) spatial Gaussian kernel, and a despiking algorithm smoothed large spikes in the BOLD time series. BOLD values for each voxel were then translated into a percent change from the mean for that session, to account for changes in baseline BOLD measurement between days. To determine the relative contribution of each condition to BOLD activity, a general linear model (GLM) was implemented.

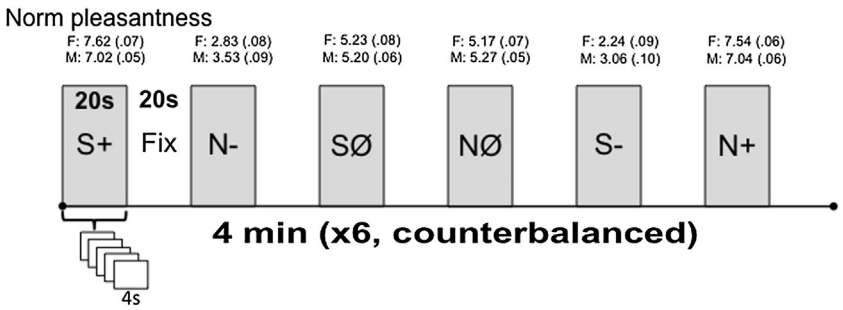

Fig. 1. fMRI block design. Example of a single scanning run. Subjects underwent six runs per session. Each block lasted 20 s, with five images of four seconds each. Gray marks picture blocks: social positive (S+), social neutral (SØ), social negative (S−), nonsocial positive (N+), nonsocial neutral (NØ), and nonsocial negative (N−), along with fixation cross (Fix) blocks. Normative ratings of valence for each picture type are also included for males (M) and females (F).

The design matrix for the ideal GLM was formed by convolving a haemodynamic response function with boxcar functions marking the timing of each condition (factor): fixation, social positive, social neutral, social negative, nonsocial positive, nonsocial neutral and nonsocial negative. Motion regressors were also included in the GLM to account for any signal due to head movement. Regression coefficients were calculated to determine the relative BOLD effect of each factor and were then transformed to a standardized brain (Talairach and Tournoux, 1988) to enable comparisons at the group level.

To examine effects of androstadienone, we first conducted general linear tests to directly contrast BOLD responses between conditions of interest (e.g. emotional vs. neutral, social vs. nonsocial) during individual sessions, to understand the nature of any solution-related differences. Repeated-measures ANOVA tests were utilized to determine how these contrasts differed between solutions (i.e., Androstadienone(Emotion – Neutral) vs. Control(Emotional – Neutral)). To examine the likely subtle effects of androstadienone, an individual voxel alpha level of $p < 0.01$ was used for between-solution contrasts. Monte Carlo simulations of data were performed for all contrasts and ANOVA tests to establish cluster size thresholds to correct for multiple comparisons at $p < 0.05$.

2.5.2. Psychological state

Each VAS descriptor was quantified by the distance from the left end of a scale to the participant's mark. Due to the smaller sample size, factor loadings from prior research were used to define three psychological factors: spacy-discontented, attentive-sharp and calmness (Hummer and McClintock, 2009). A $2 \times 2 \times 2$ repeated measures MANOVA (session by time by sex) was performed to identify potential effects of androstadienone on psychological changes.

2.5.3. Image recognition

For accuracy and RT measures, $2 \times 2 \times 3$ repeated-measures ANOVAs (session by social content by emotional valence) were utilized (no significant effects of sex were present if included as an additional factor, nor were other significant effects altered). To examine true effects on image recognition, only RTs from accurate trials to images shown during the scan were used. RT outliers were removed from analysis, identified as RTs more than three times the interquartile range from the 75th percentile of RTs for each solution condition (6.2% of trials). For each ANOVA, a Greenhouse-Geisser correction was made to reported p values when necessary.

2.5.4. Region-of-interest formation

Regions of interest were formed primarily for DCM analysis, although post-hoc ROI analyses were also performed to examine potential influences of sex or olfactory threshold on significant effects, and to test for social-by-valence-by-solution interactions within these ROIs. Functional ROIs were established using the Talairach coordinates of the peak differences within androstadienone clusters, transformed back to each participant's individual brain. An 8-mm sphere around these points defined ROIs for each subject. In addition, ROIs for right and left amygdala and visual cortex (VC) were established due to their central role in viewing emotional images (Hamann et al., 2002; Lane et al., 1997; Lang et al., 1998). The VC ROI was defined functionally by the Talairach peak of the group Image vs. Fixation contrast (collapsed across both sessions), likewise used as the center of an 8 mm ROI sphere. Amygdala ROIs were set anatomically as a 6 mm sphere around the central point of each amygdala in each subject. Post-hoc repeated-measure ANOVA tests (sex by emotional valence by session) were performed on each ROI with voxel means for the emotional BOLD contrasts (Positive vs. Neutral and Negative vs. Neutral).

2.5.5. Dynamic causal modeling

To model fMRI data with DCM, existing anatomical or functional knowledge informs connections in proposed models, with regions and possible connections defined *a priori*, according to, in this case, the results of fMRI analyses (Friston et al., 2003). The first step in the DCM process is to select ROIs and extract time-series data from these nodes. The principal eigenvariate of each ROI was calculated from the time series of each voxel, using the DCM toolbox in the Statistical Parametric Mapping software package (SPM5, www.fil.ion.ucl.ac.uk/spm5; scripts were modified to use AFNI-extracted data). This eigenvariate represented the time-series output for each region, which the model aimed to predict.

3. Results

Imaging data from 22 subjects (11 males, 11 females, mean (sd) age: 21.4 (4.3)), each scanned during both an androstadienone and a control session, were analyzed. For consistency, behavioral data are only reported from those subjects included in imaging analysis. Of these subjects, two women and two men had detection levels at 125 μM, and one woman and two men had detection levels at 250 μM.

3.1. Psychological state

Derived psychological factors (spacy-discontented, attentive-sharp, and calmness) significantly changed over the course of each session (Supplementary Fig. 1), although there was no discernible effect of androstadienone. MANOVA results indicated a significant effect of time ($F(3,18) = 17.00$, $p < 0.001$), with no other significant effects (all $F < 2.42$, $p > 0.10$). Post-hoc univariate tests revealed that subjects became significantly more spacy-discontented and less attentive-sharp by the conclusion of each session.

3.2. Image recall

Subjects were most accurate at identifying whether post-scan social negative and nonsocial positive presented images were shown in the scanner (valence-by-social interaction: $F(2,20) = 7.018$, $p = 0.004$; Fig. 2). No other significant main effects or interactions were present (all $F < 1.49$, $p > 0.25$). For reaction times (RTs), individuals were slower to accurately recall social images than nonsocial images (main effect of social: $F(1,21) = 8.543$, $p = 0.008$; Fig. 2). In addition, a three-way interaction was present ($F(2,20) = 6.628$, $p = 0.006$), driven in part by relatively slower responses to social negative images and quicker responses to social positive images during the androstadienone session.

3.3. BOLD activation

Consistent with prior research of emotional processing, emotional images elicited greater activity during the control session in visual cortex, medial prefrontal cortex, medial orbitofrontal cortex and left amygdala compared to neutral images (see Table 1 for full results). In contrast, neutral images were associated with greater activity in the right inferior parietal lobule, right medial frontal gyrus and the right lateral prefrontal cortex. During the androstadienone session, there was greater activity in visual cortex, medial prefrontal and thalamic regions for emotional images (Table 1). In addition, increases in lateral prefrontal and parietal regions were also evident.

To determine the effect of androstadienone on the BOLD response to emotional images, activation during these sessions was directly contrasted. The presence of androstadienone significantly enhanced the emotional BOLD response in two notable clusters: right orbitofrontal cortex (rOFC) and right lateral prefrontal cortex (rPFC) (Table 2; Fig. 3). Follow-up tests revealed no significantly different clusters between sessions when testing social and nonsocial conditions separately (e.g., social emotional – social neutral).

Importantly, session differences in these regions were not driven by a differential response to neutral images. Androstadienone did not alter the BOLD response to neutral images, with no significantly different clusters for a Neutral vs. Fixation contrast between the two solution conditions.

3.4. Social images

Collapsing all three emotion conditions together, the BOLD response to social images or nonsocial images was not influenced by androstadienone, and no clusters were significantly different between the two sessions (Supplementary Table 1). Taken together, these two results reveal that androstadienone is specifically associated with a differential BOLD response to emotional images and does not depend on social content.

3.5. Valence-Specific effects

The control session response to positive images revealed a network of regions similar to the overall emotional BOLD response (see Supplementary Table 2 for within-session results), with the androstadienone session associated with a heightened positive BOLD response (relative to the control session) in the parietal cortex and a large cluster in the right frontal lobe, extending from orbitofrontal and prefrontal regions to insula (Table 2; Fig. 3). For negative images, no regions were significantly different between the two sessions.

3.6. ROI results

Functional ROIs were defined for those clusters demonstrating a significant effect of androstadienone on emotional processing (rOFC, rPFC), formed as 8-mm radius spheres around peak differences (Supplementary Table 3), along with their left-side mirrors (flipped over the mid-sagittal axis). A single spherical VC ROI (Supplementary Fig. 2) and bilateral amygdala ROIs were also formed for each participant. Thus, each participant had seven total ROIs, all of which were visually inspected to ensure that the spheres were wholly within the identified regions.

While the establishment of ROIs was necessary for DCM analysis, ROI data could also clarify whether gender, androstadienone olfactory sensitivity, or order of sessions contributed to neural effects. In these ROIs, post-hoc tests revealed that participant sex did not interact with androstadienone or valence effects. In addition, amygdala and VC ROIs did not demonstrate any effects relating to androstadienone or sex, further evidence that the compound did not influence the BOLD response in these regions. Androstadienone detection level or presentation order was not correlated with activity changes in any ROI, for either valence.

Finally, despite image recall effects, no social-by-valence interactions were found in these ROIs, nor did solution presentation interact with these factors. However, because a significant three way interaction was present in post-scan image reaction times, we conducted exploratory analyses to examine whether similar interactions were present with BOLD activity. To do this, we identified clusters with a significant social-by-valence interaction for either solution separately. This analysis revealed three significant clusters during the androstadienone session only: right posterior temporal cortex/middle occipital gyrus, right superior parietal lobule, and right cerebellum (see Supplementary Table 4 and Supplementary Fig. 3). Mean data was extracted from these clusters for each session, and post-hoc ANOVA tests were performed, revealing significant social-by-valence-by-solution interactions in the temperal-occipital ($F(1,21) = 5.285$, $p = 0.03$) and parietal ($F(1,21) = 8.72$, $p = 0.008$) clusters. These interactions were both driven by a greater BOLD response to social positive images during the androstadienone session, with no such relationship during the control condition (Supplementary Fig. 3).

3.7. Dynamic causal modeling

3.7.1. DCM model selection

Multiple DCM models were compared to determine the optimal model for the group (Penny et al., 2004). Each potential model included only bidirectional connections, which may not be statistically optimal compared to strictly feed-forward models, since the Bayesian criteria for choosing the optimal model penalizes for complexity (Penny et al., 2004). However, we chose to only test models with bidirectional connections to allow for feedback to VC and maximize biological plausibility overall. Right and left sides were modeled separately, though the same VC region was used for both sides.

Three possible models were developed to represent the network, based primarily on anatomical connections (Carmichael and Price, 1995; Freese and Amaral, 2005). The Bayesian and Akaike information criteria (BIC and AIC) were computed to evaluate model evidence (Penny et al., 2004). Using a Bayes Factor calculation, pairwise comparisons of each participant's models for the control session were performed. To establish an optimal group model, the product of each pairwise model comparison was calculated, with the highest product indicating the best model. To ensure that outliers did not skew the Bayes Factor product, we counted how many models were significantly better in direct comparisons.

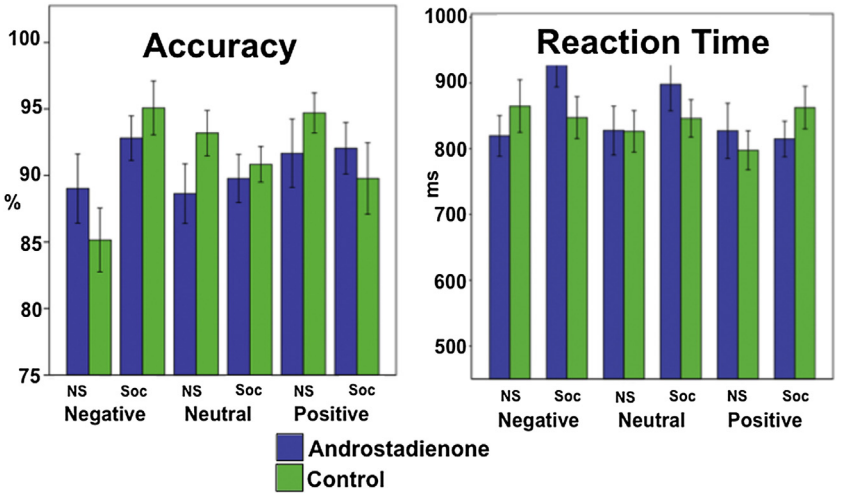

Fig. 2. Post-scan recall performance. Mean ± SEM accuracy and reaction time (to correctly recalled images) are shown for nonsocial (NS) and social (Soc) images. ANOVA tests indicate a significant ($p < 0.05$) social-by-valence interaction for accuracy scores and both a main effect of social and a three-way interaction (social by valence by session) for reaction time.

Table 1
Brain response to emotional images.

Session/Contrast	Region	Talairach Coordinates	Cluster size (mm^3)
Control			
Emotional > Neutral			
	Visual Cortex	(5, −69, 7)	65,680
	mPFC	(0, −54, 10)	4898
	R Thalamus	(15, −27, −7)	1798
	mOFC	(−2, 49, −15)	803
	L Amygdala	(−16, −4, −10)	658
	L Cerebellum	(−19, −74, −26)	525
Neutral > Emotional			
	R Inf Parietal Lobule	(45, −39, 42)	1357
	R vlPFC/OFC	(33, 46, −5)	921
	R Middle Frontal Gyrus	(34, 34, 21)	520
Androstadienone			
Emotional > Neutral			
	Visual Cortex	(1, −68, 9)	56,111
	R/L Thalamus	(3, −27, −1)	2748
	R Inf/Mid Frontal Gyrus	(41, 15, 21)	2179
	mPFC	(3, 48, 25)	876
	L Inf Parietal Lobule	(−57, 27, 29)	351
	R Sup Parietal Lobule	(25, −62, 48)	340
Neutral > Emotional	No significant clusters		

Clusters with significantly different activation between emotional and neutral images listed. Talairach coordinates represent center-of-mass for the cluster. Individual voxel significance defined as $p < 0.001$, with clusters significant at $p < 0.05$ (cluster size >507 mm^3). Abbreviations: right (R) and left (L) sides; medial (m) and ventrolateral (vl) locations; and prefrontal cortex (PFC) and orbitofrontal cortex (OFC).

Table 2
Effect of androstadienone on emotional BOLD response.

Session Contrast	BOLD Contrast	Region	Talairach Coordinates	Cluster size (mm^3)
Androstadienone > Control				
	Emotion – Neutral			
		R Mid Frontal Gyrus/OFC	(31, 47, −6)	3041
		R Mid Frontal Gyrus/PFC	(38, 26, 30)	1466
	Positive – Neutral			
		R Sup Parietal Lobule	(40, −46, 46)	5994
		R Mid Frontal Gyrus/PFC	(41, 22, 24)	3976
		R Mid Frontal Gyrus/OFC	(32, 48, −5)	3402
Control > Androstadienone				
	No significant clusters			

Clusters with significantly different activation in the emotional image BOLD response between sessions listed. Talairach coordinates represent center-of-mass for the cluster. Individual voxel significance was defined as $p < 0.01$, with clusters significant at $p < 0.05$ (>1403 mm^3). Differences were confined to the right (R) side, including prefrontal cortex (PFC) and orbitofrontal cortex (OFC).

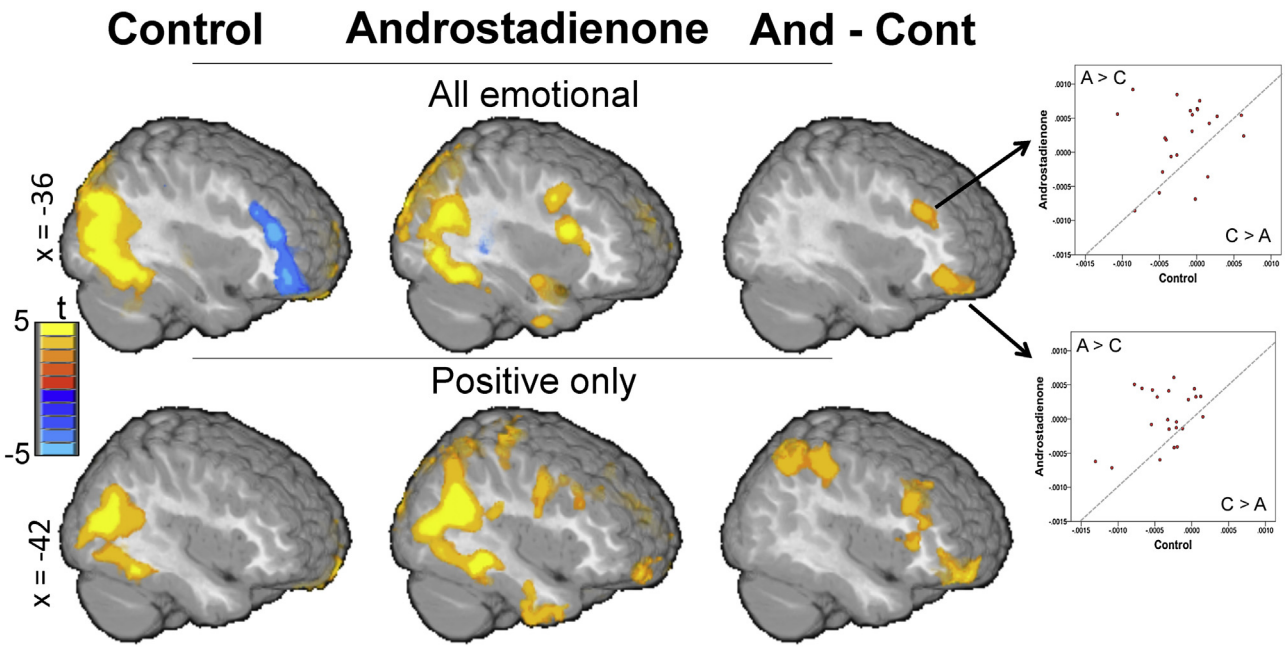

Fig. 3. BOLD response to emotional images. Group differences in BOLD activation for emotion – neutral and positive – neutral contrasts are shown on standardized Talairach brain, along with results for each session. Between-session comparison of this contrast demonstrates significantly more activity in right orbitofrontal and prefrontal cortices for emotional image viewing during the androstadienone session (voxel $p < 0.01$, cluster size < 1403 mm^3 to correct for multiple comparisons at $p < 0.05$), with an additional parietal cluster significantly different during positive images only. No significant differences were present in response to negative images. Scatterplots depict each subject's emotional vs. neutral contrast for significant right OFC and PFC clusters during each session, with unit-slope line.

Both methods identified the same optimal group model, on both sides of the brain.

In this optimal model, visual input entered the model during image blocks via VC, which connected bidirectionally with the amygdala. Although the amygdala does not receive projections directly from primary visual cortex, the amygdala does receive input from other visual cortical sites (Updyke, 1993) and is a target of the ventral visual stream. *Positive* and *Negative* contexts modulated the drive from VC to amygdala, which fed forward to prefrontal and orbitofrontal cortices. This model was a better fit than those with identical connections but with Positive and Negative influencing the drive from amygdala to PFC or OFC.

A repeated-measures ANOVA test measured the influence of *Positive* and *Negative* on the VC-amygdala drive. The ANOVA examined session by emotion by side (right/left) effects, which had the added advantage of determining whether laterality effects were present. A follow-up session-by-emotional valence ANOVA was performed on each side separately. To examine whether the network was influence by androstadienone, a MANOVA test (side by session) was planned using all between-region parameters.

3.7.2. DCM analysis

In the optimal dynamic causal model, activation of VC by images influenced downstream activity in amygdala and OFC, with emotional context mediating the drive from VC to amygdala. One-sample *t*-tests contrasting each model parameter to zero were conducted to improve understanding of the model. For both sessions, there was a strong drive from visual cortex to the amygdala, with a significant connection in the reverse direction as well, for both sides of the brain. Bilateral amygdalae had a significantly negative effect on the OFC ROI. While the amygdala-PFC connectivity was minimal during either condition, OFC-PFC connectivity was generally stronger.

Notably, negative context increased the drive from VC to amygdala during each session (main effect of valence: $F(1, 21) = 10.743$, $p = 0.004$). Positive pictures, meanwhile, increased this drive with the control solution, but no such effect of positive context was present when androstadienone was applied to the upper lip (session-by-valence interaction: $F(1, 21) = 6.150$, $p = 0.022$). No laterality effects were present: when examined separately a significant session-by-valence interaction was present on the right side ($F(1, 21) = 5.577$, $p = 0.028$), with the left side demonstrating a similar trend-level pattern ($F(1, 21) = 2.918$, $p = 0.102$). On both sides, a main effect of emotional valence was present (right: $F(1,21) = 6.723$, $p = 0.017$; left: $F(1, 21) = 9.791$, $p = 0.005$), with negative images more strongly influencing the VC-amygdala drive. MANOVAs revealed no significant overall effect of androstadienone on effective connectivity between regions.

4. Discussion

By investigating how passively inhaled androstadienone modulated the neural response to visual stimuli, we were able to examine how the compound influences the brain during perception of emotionally relevant images, even when present in minute concentrations. We demonstrated that androstadienone is associated with an elevated BOLD response to emotional stimuli in two brain regions: right orbitofrontal cortex and right lateral prefrontal cortex. Moreover, DCM analyses indicate that effects of androstadienone on amygdala connectivity may be the primary driver of these cortical effects. Effects in these regions were not influenced by participant sex or conscious androstadienone olfactory detection sensitivity. Furthermore, androstadienone did not influence the neural response to social images, compared to nonsocial pictures, or to neutral images, relative to a fixation cross.

Androstadienone enhanced activity in regions involved in allocation of attentional resources and in top-down control of emotional information processing, and *it did so only during emotional image presentation*. This finding aligns with previous work indicating that androstadienone enhances attention specifically to emotional information (Hummer and McClintock, 2009), with no overall effects on cognitive performance or processing speed.

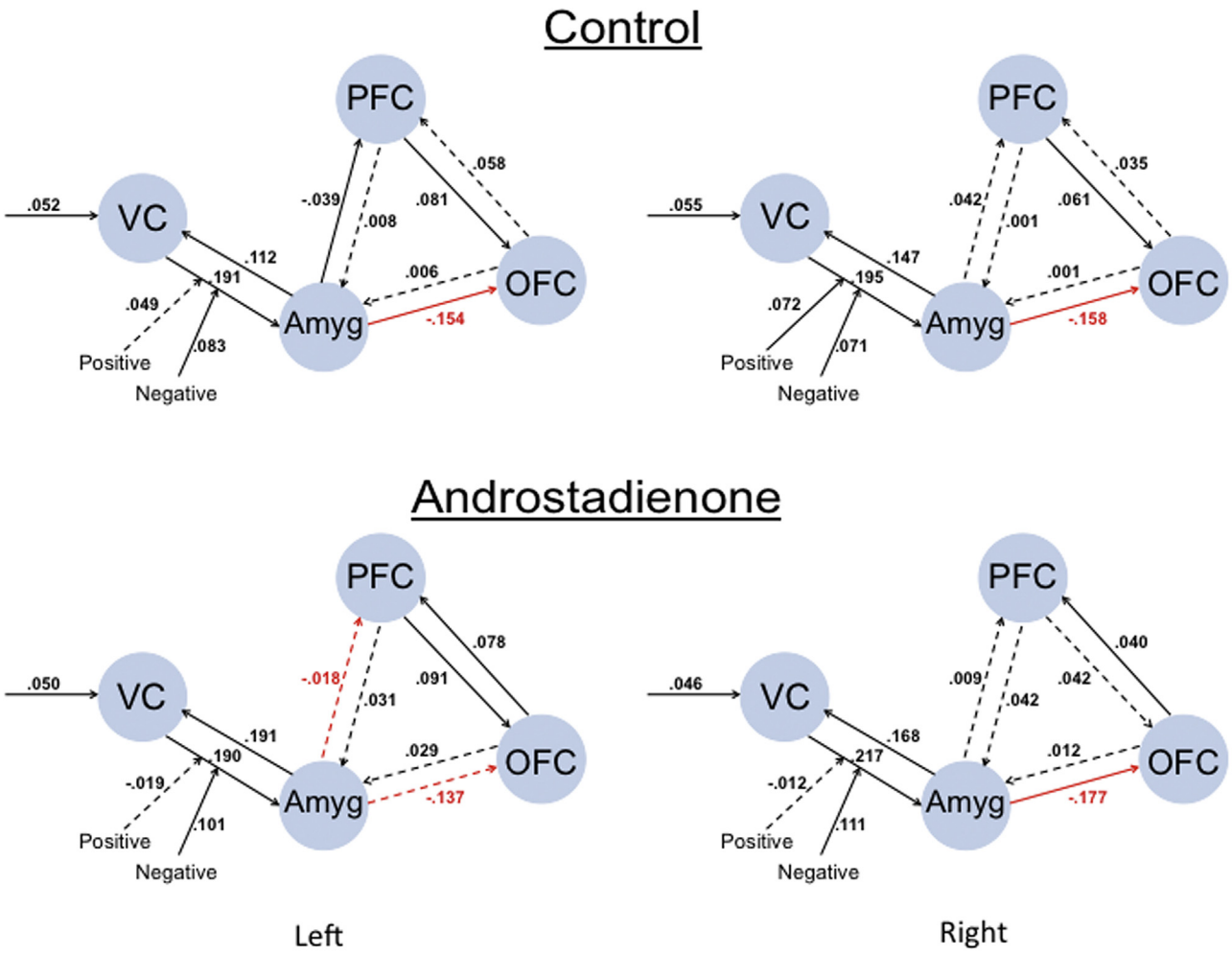

Fig. 4. Dynamic causal models of each session. Left and right sides are separately modeled for VC (visual cortex), amygdala (Amyg), prefrontal cortex (PFC), and orbitofrontal cortex (OFC) regions of interest. Solid lines indicate that parameter significantly differs from zero (one-sample *t*-test, $p < 0.05$, uncorrected), with black for positive connections and red for negative. Positive information had a lower effect on the drive from VC to amygdala, as shown by a significant interaction between session and emotional drive. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

By creating a dynamic causal model, we demonstrated that androstadienone lessens the naturally increased drive from visual cortex to amygdala caused by positive information. Within this model, visual images typically activate a network, starting at VC and projecting to the amygdala, a drive enhanced when images carry emotional valence (positive or negative). The amygdala maintains a negative connection with lateral OFC (Fig. 4), meaning higher activity in the amygdala induces lower lateral OFC BOLD signal. When androstadienone is present, the effect of positive information on VC-amygdala connectivity was lower, leading to a relative increase in frontal activity during positive picture viewing. Based on our DCM analysis, the higher signal present in rPFC and rOFC during the androstadienone session is evidently due to the changes in VC-amygdala connectivity rather than a direct effect on frontal regions. With this effect, it is curious that amygdala activity was not significantly different between sessions. It may be that input to the amygdala from regions not present in the model is also influenced by androstadienone, resulting in no net change in amygdala activity.

In this investigation, emotional images elicited a BOLD response during the control session in a well-characterized emotional network that includes visual cortex, medial PFC and limbic regions (Davidson and Irwin, 1999; Lane et al., 1997; Norris et al., 2004; Phan et al., 2002). Activity in emotion-relevant regions did not change with androstadienone, which may indicate that the compound also induces either a lower drive from amygdala to these emotion-responsive regions or a greater influence of lateral prefrontal "cognitive" regions on mPFC or limbic areas. However, a more complex model, integrating both a larger emotion-sensitive network and a traditional frontoparietal attention network, is difficult to accurately assess with DCM analysis.

Selecting an optimal model to examine effective connectivity within a group often imposes a non-optimal model for specific subjects. While an optimal model is necessary for group comparisons, examining individual variability in emotional processing and effects of androstadienone is more difficult to discern, a problem inherently present when creating simplified physiological models. In DCM models, care must be taken to limit the number of regions and the complexity of the model, as model estimation becomes practically impossible with increasing numbers of nodes (Stephan et al., 2010). Thus, the number of regions included in the model were purposely limited, and this model should not be considered comprehensive, but rather representing how androstadienone impacts frontolimbic interactions. For instance, the hypothalamus, which previous research has found to be impacted by androstadienone (e.g., Savic et al., 2001), was not included in this model because it was not significantly active for any stimuli, and thus did not fit within the DCM input-output framework. However, this

lack of response could have been due to poor signal acquisition of the region, and could be resolved in future research with more suitable functional imaging sequences. Furthermore, our focus on frontolimbic regions left out the thalamus, which has roles in both attentional and emotional processes (Zikopoulos and Barbas, 2012). Future research can further examine how androstadienone affects the drives of these two regions with more focused DCM models and tasks that encompass both attention and emotion domains.

Nonetheless, DCM indicates that neural effects of androstadienone are likely due to altered amygdala connectivity, particularly during positive image presentation. The amygdala typically acts as high-arousal "alert" system (Adolphs et al., 1995; Anderson et al., 2003), integrating attention and emotional processes by strongly engaging sensory and emotion-responsive regions to respond to salient external stimuli (Anderson and Phelps, 2001; Vuilleumier et al., 2004). These actions are carried out in part via bidirectional connectivity with OFC and both medial and lateral PFC (Carmichael and Price, 1995; McDonald et al., 1996). Plus, the amygdala receives direct olfactory input (Carmichael and Price, 1995) and has a fundamental role in processing pheromonal information in other mammals (Meredith and Westberry, 2004). Projections from the amygdala and piriform cortex drive a role for OFC in olfactory processing, noteworthy since any effects of androstadienone purported to be from inhaling the compound (passively or actively) must somehow be influenced by the olfactory system.

The OFC provides an important route through which emotional stimuli influence an attention network (Vuilleumier, 2005). During the control session, viewing emotional images increased medial prefrontal and medial OFC activity while decreasing lateral frontal activity relative to neutral images, likely due to direct or indirect input from the amygdala. The prevalence of this pattern during passive image viewing studies is unclear, as reports of such "deactivation" in past research are inconsistent (Phan et al., 2002), and many studies report only regions where the response to emotional images increases over that to neutral images. Regardless, with androstadienone, the decreased effect of inhibitory drives from the amygdala may reflect a calmer, more cognitive response than during the control session. Dorsolateral PFC has a top-down influence on emotional processing, with a stronger role in the more cognitive aspects of viewing emotional images (attention, goal-directed behavior). This role does not necessarily indicate that lateral prefrontal cortex and emotional regions are inversely related. Rather, emotional and cognitive processes are integrated in lateral PFC (Gray et al., 2002), making the region particularly important for potential increases in attention to emotional information with androstadienone (Hummer and McClintock, 2009).

In this study, there is some indication that androstadienone differentially modulated the BOLD response to positive and negative images, but no solution effects or solution-by-valence interactions on RT or accuracy were present during image recall. This result may indicate a disparity between attention and cognitive recall for emotional images, though it is not clear that the post-scan test was sufficient to detect solution differences. The test was primarily to ensure that attention was paid to images presented in the scanner, and subjects were told that the test measured whether they were paying attention during the scan, which may have put less emphasis on speed to respond than on accuracy.

On the other hand, participants had relatively quicker reactions to recall positive social pictures with androstadienone (compared to neutral or negative social images), and exploratory analyses revealed visual and attention regions had a greater response to positive social images. These results may indicate either a natural biological signal or a conditioned priming mechanism associating androstadienone with positive information. A more extensive study focusing on how androstadienone influences recollection of positive and negative images may help elucidate how emotional valence and social context interact to influence the effects of androstadienone.

Prior behavioral evidence provides mixed clues as to how androstadienone influences the processing of positive and negative information. Androstadienone impairs memory of events from a sad film but not a positive film (Bensafi et al., 2004a), and modifies reaction times to emotional words or faces independent of valence direction (Hummer and McClintock, 2009). Women report a more positive mood after an androstadienone-treated session, particularly with a male experimenter (Bensafi et al., 2004b; Jacob et al., 2001a; Jacob and McClintock, 2000; Lundstrom and Olsson, 2005) or following a happy film (Bensafi et al., 2004a), both potentially robust sources of positive information. Furthermore, with androstadienone women rate men to be more attractive in a complex social interaction (Saxton et al., 2008), and men demonstrate more cooperative behavior (Huoviala and Rantala, 2013). As for negative stimuli, while women report pain to be more intense with androstadienone, they do not report the pain to be significantly more unpleasant, reinforcing the idea that immediate attention to negative stimuli is enhanced while its perception is diminished (Villemure and Bushnell, 2007).

No sex-specific effects of androstadienone were detected in this study. While women are more often the subjects of androstadienone research, men's mood is often affected differently, with androstadienone eliciting a more negative mood or no mood change at all (Bensafi et al., 2004b; Jacob and McClintock, 2000). The enhancement by androstadienone of immediate attention to emotional information does not differ between men and women (Hummer and McClintock, 2009). Here, we carefully controlled the presented images to ensure that, based on normative averages, images were rated similarly pleasant or unpleasant by each sex. The lack of sex-specific effects suggests the effects of androstadienone are due to natural differences in how men and women perceive the emotionality of the environment.

On the other hand, Savic and colleagues reported effects of androstadienone on hypothalamus activity to be related to sex or sexual preference (Savic et al., 2001, 2005), though more recent work found no such sex differences (Burke et al., 2012). These studies, however, focused directly on the effect of smelling androstadienone, rather than how androstadienone influences the BOLD response to visual processes. Thus, any sex differences may be due to odor-related priming or conscious associations of the odor, since the musky odor is more commonly associated with men. To understand the neural mechanisms through which androstadienone or other potential biological chemosignals (Gelstein et al., 2011; Zhou et al., 2011) may be influencing psychological state, research showing direct changes to brain activity due to smelling biological compounds must be integrated with studies examining how continuous passive inhalation modifies environmental context, thus altering the brain's response to social or emotional stimuli.

There are several limitations to this study. First, subjects did not rate pictures, so specific blocks may not have been as strictly positive or negative as designed for a given individual. This procedure was followed to capture the natural response to viewing images, since simultaneous ratings—or the knowledge that ratings were to be performed at a later time—may have influenced this goal. Moreover, despite attempts to induce subjects to respond to images as they naturally would, there were likely individual differences in how much cognitive effort was put forth, given their knowledge that they would be tested later. Next, while placing androstadienone in a solution on the upper lip follows methodology from previous work (Jacob and McClintock, 2000), individual differences may exist in how much androstadienone was passively inhaled. In addition, it is possible that androstadienone or the carrier solution was absorbed transdermally. An olfactometer, to

provide consistent airflow for an fMRI experiment, should help allay these concerns in future research (Burke et al., 2012). Finally, given the physiological changes that may occur, we unfortunately were unable to monitor whether heart rate or breathing differed between the two sessions.

Despite these limitations, this investigation provides strong evidence that passive inhalation of a social chemosignal enhances the brain's response to emotional images in regions involved in general and emotional attention, providing a mechanism for increased attention to emotional stimuli. These results indicate how airborne biological signals can influence the manner in which the environment is perceived. Notably, the consistent presence of androstadienone modifies how the brain responds during a specific psychological process—viewing emotional stimuli—that is distinct from the direct sensory response of smelling the compound.

Conflict of interest

The authors report no conflicts of interest for this study.

Contributors

Tom A. Hummer, K. Luan Phan, David W. Kern, Martha K. McClintock

TAH, KLP, and MKM contributed to design of the study.

TAH conducted investigation and acquired data.

TAH, KLP, DWK, and MKM contributed to the analysis, data interpretation, and writing of the manuscript.

All authors have provided their final approval of the submitted version of the article.

Role of the funding source

This project was supported by a Brain Research Foundation Seed Grant awarded to Dr. McClintock. The funding source had no involvement in the study design; the collection, analysis, and interpretation of data; the writing of the report; and in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.09.023.

References

Adolphs, R., Tranel, D., Damasio, H., Damasio, A.R., 1995. Fear and the human amygdala. J. Neurosci. 15, 5879–5891.

Anderson, A.K., Phelps, E.A., 2001. Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature 411, 305–309.

Anderson, A.K., Christoff, K., Panitz, D., De Rosa, E., Gabrieli, J.D., 2003. Neural correlates of the automatic processing of threat facial signals. J. Neurosci. 23, 5627–5633.

Bensafi, M., Brown, W.M., Tsutsui, T., Mainland, J.D., Johnson, B.N., Bremner, E.A., Young, N., Mauss, I., Ray, B., Gross, J., Richards, J., Stappen, I., Levenson, R.W., Sobel, N., 2003. Sex-steroid derived compounds induce sex-specific effects on autonomic nervous system function in humans. Behav. Neurosci. 117, 1125–1134.

Bensafi, M., Brown, W.M., Khan, R., Levenson, B., Sobel, N., 2004a. Sniffing human sex-steroid derived compounds modulates mood, memory and autonomic nervous system function in specific behavioral contexts. Behav. Brain Res. 152, 11–22.

Bensafi, M., Tsutsui, T., Khan, R., Levenson, R.W., Sobel, N., 2004b. Sniffing a human sex-steroid derived compound affects mood and autonomic arousal in a dose-dependent manner. Psychoneuroendocrinology 29, 1290–1299.

Burke, S.M., Veltman, D.J., Gerber, J., Hummel, T., Bakker, J., 2012. Heterosexual men and women both show a hypothalamic response to the chemo-signal androstadienone. PLoS One 7, e40993.

Carmichael, S.T., Price, J.L., 1995. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J. Comp. Neurol. 363, 615–641.

Chung, K.C., Peisen, F., Kogler, L., Radke, S., Turetsky, B., Freiherr, J., Derntl, B., 2016. The influence of menstrual cycle and androstadienone on female stress reactions: an fMRI study. Front. Hum. Neurosci. 10, 44.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.

Davidson, R.J., Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. Trends Cogn. Sci. 3, 11–21.

Folstein, M.F., Luria, R., 1973. Reliability, validity, and clinical application of the Visual Analogue Mood Scale. Psychol. Med. 3, 479–486.

Freese, J.L., Amaral, D.G., 2005. The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. J. Comp. Neurol. 486, 295–317.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302.

Gelstein, S., Yeshurun, Y., Rozenkrantz, L., Shushan, S., Frumin, I., Roth, Y., Sobel, N., 2011. Human tears contain a chemosignal. Science 331, 226–230.

Gower, D.B., Holland, K.T., Mallet, A.I., Rennie, P.J., Watkins, W.J., 1994. Comparison of 16-androstene steroid concentrations in sterile apocrine sweat and axillary secretions: interconversions of 16-androstenes by the axillary microflora – a mechanism for axillary odour production in man? J. Steroid Biochem. Mol. Biol. 48, 409–418.

Gray, J.R., Braver, T.S., Raichle, M.E., 2002. Integration of emotion and cognition in the lateral prefrontal cortex. Proc. Natl. Acad. Sci. U. S. A. 99, 4115–4120.

Gulyas, B., Keri, S., O'Sullivan, B.T., Decety, J., Roland, P.E., 2004. The putative pheromone androstadienone activates cortical fields in the human brain related to social cognition. Neurochem. Int. 44, 595–600.

Hamann, S.B., Ely, T.D., Hoffman, J.M., Kilts, C.D., 2002. Ecstasy and agony: activation of the human amygdala in positive and negative emotion. Psychol. Sci. 13, 135–141.

Hummer, T.A., McClintock, M.K., 2009. Putative human pheromone androstadienone attunes the mind specifically to emotional information. Horm. Behav. 55, 548–559.

Huoviala, P., Rantala, M.J., 2013. A putative human pheromone, androstadienone, increases cooperation between men. PLoS One 8, e62499.

Jacob, S., McClintock, M.K., 2000. Psychological state and mood effects of steroidal chemosignals in women and men. Horm. Behav. 37, 57–78.

Jacob, S., Hayreh, D.J., McClintock, M.K., 2001a. Context-dependent effects of steroid chemosignals on human physiology and mood. Physiol. Behav. 74, 15–27.

Jacob, S., Kinnunen, L.H., Metz, J., Cooper, M., McClintock, M.K., 2001b. Sustained human chemosignal unconsciously alters brain function. Neuroreport 12, 2391–2394.

Jacob, S., Garcia, S., Hayreh, D., McClintock, M.K., 2002. Psychological effects of musky compounds: comparison of androstadienone with androstenol and muscone. Horm. Behav. 42, 274–283.

Labows, J., 1988. Odor detection, generation and etiology in the axilla. In: Felger, C., Laden, K. (Eds.), Antiperspirants and Deodorants. Dekker, New York, pp. 321–343.

Lane, R.D., Reiman, E.M., Bradley, M.M., Lang, P.J., Ahern, G.L., Davidson, R.J., Schwartz, G.E., 1997. Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia 35, 1437–1444.

Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., Nangia, V., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35, 199–210.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1999. International Affective Picture System (IAPS): Instruction Manual and Affective Ratings. The Center for Research in Psychophysiology, University of Florida.

Lundstrom, J.N., Olsson, M.J., 2005. Subthreshold amounts of social odorant affect mood, but not behavior, in heterosexual women when tested by a male, but not a female, experimenter. Biol. Psychol. 70, 197–204.

Lundstrom, J.N., Hummel, T., Olsson, M.J., 2003. Individual differences in sensitivity to the odor of 4,16-androstadien-3-one. Chem. Senses 28, 643–650.

Lundstrom, J.N., Olsson, M.J., Schaal, B., Hummel, T., 2006. A putative social chemosignal elicits faster cortical responses than perceptually similar odorants. Neuroimage 30, 1340–1346.

McClintock, M.K., 2002. Pheromones, odors and vasanas: the neuroendocrinology of social chemosignals in humans and animals, hormones. Brain Behav.

McDonald, A.J., Mascagni, F., Guo, L., 1996. Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. Neuroscience 71, 55–75.

Meredith, M., Westberry, J.M., 2004. Distinctive responses in the medial amygdala to same-species and different-species pheromones. J. Neurosci. 24, 5719–5725.

Norris, C.J., Chen, E.E., Zhu, D.C., Small, S.L., Cacioppo, J.T., 2004. The interaction of social and emotional processes in the brain. J. Cogn. Neurosci. 16, 1818–1829.

Penny, W.D., Stephan, K.E., Mechelli, A., Friston, K.J., 2004. Comparing dynamic causal models. Neuroimage 22, 1157–1172.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16, 331–348.

Savic, I., Berglund, H., Gulyas, B., Roland, P., 2001. Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. Neuron 31, 661–668.

Savic, I., Berglund, H., Lindstrom, P., 2005. Brain response to putative pheromones in homosexual men. Proc. Natl. Acad. Sci. U. S. A. 102, 7356–7361.

Saxton, T.K., Lyndon, A., Little, A.C., Roberts, S.C., 2008. Evidence that androstadienone, a putative human chemosignal, modulates women's attributions of men's attractiveness. Horm. Behav. 54, 597–601.
Sobel, N., Prabhakaran, V., Hartley, C.A., Desmond, J.E., Glover, G.H., Sullivan, E.V., Gabrieli, J.D., 1999. Blind smell: brain activation induced by an undetected air-borne chemical. Brain 122 (Pt. 2), 209–217.
Stephan, K.E., Penny, W.D., Moran, R.J., den Ouden, H.E., Daunizeau, J., Friston, K.J., 2010. Ten simple rules for dynamic causal modeling. Neuroimage 49, 3099–3109.
Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging. Thieme, Stuttgart.
Taylor, S.F., Phan, K.L., Decker, L.R., Liberzon, I., 2003. Subjective rating of emotionally salient stimuli modulates neural activity. Neuroimage 18, 650–659.
Updyke, B.V., 1993. Organization of visual corticostriatal projections in the cat, with observations on visual projections to claustrum and amygdala. J. Comp. Neurol. 327, 159–193.
Villemure, C., Bushnell, M.C., 2007. The effects of the steroid androstadienone and pleasant odorants on the mood and pain perception of men and women. Eur. J. Pain 11, 181–191.
Vuilleumier, P., Richardson, M.P., Armony, J.L., Driver, J., Dolan, R.J., 2004. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. Nat. Neurosci. 7, 1271–1278.
Vuilleumier, P., 2005. How brains beware: neural mechanisms of emotional attention. Trends Cogn. Sci. 9, 585–594.
Wyart, C., Webster, W.W., Chen, J.H., Wilson, S.R., McClary, A., Khan, R.M., Sobel, N., 2007. Smelling a single component of male sweat alters levels of cortisol in women. J. Neurosci. 27, 1261–1265.
Zhou, W., Hou, P., Zhou, Y., Chen, D., 2011. Reduced recruitment of orbitofrontal cortex to human social chemosensory cues in social anxiety. Neuroimage 55, 1401–1406.
Zikopoulos, B., Barbas, H., 2012. Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. J. Neurosci. 32, 5338–5350.