

The putative pheromone androstadienone activates cortical fields in the human brain related to social cognition

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Received 9 October 2003; accepted 9 October 2003

Abstract

Using ¹⁵O-butanol positron emission tomography (PET), we measured regional cerebral blood flow changes in five healthy young women during exposure to androstadienone, a putative human pheromone, as well as pleasant (γ -methyl-ionone), unpleasant (methyl-thio-butanoate), and neutral (dipropylene glycol; vehicle compound) odours. Compared with the odorous substances, androstadienone activated a widely distributed neuronal network. Two large cortical fields exhibited consistent activation in each contrast: the anterior part of the inferior lateral prefrontal cortex (PFC) and the posterior part of the superior temporal cortex (STP). Intriguingly, these areas were deactivated by γ -methyl-ionone and methyl-thio-butanoate. These brain regions can be identified as cortical fields underlying other than olfactory functions, including various aspects of social cognition and attention.

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Keywords: Olfaction; Human pheromones; Social cognition; Prefrontal cortex; Superior temporal cortex; PET

1. Introduction

In recent years human pheromones have become subjects of intense investigation in neurochemistry, due to their direct effects on the human brain (Savic et al., 2001). Pheromones are unique volatile chemosignals secreted into the environment (in sweat, urine) by one individual of a species and releasing specific behavioural patterns or physiological changes in individuals of the same species (Karlson and Luscher, 1959). In the majority of mammals pheromones are transduced in the vomeronasal organ to signals that, via the accessory olfactory bulb, the medial amygdala, and stria terminalis, reach the anterior hypothalamus (Keverne, 1999).

Recent studies have suggested that pheromone-like compounds activate directly the human brain (Sobel et al., 1999; Savic et al., 2001; Jacob et al., 2001). Using oestra-1,3,5(10),16-tetraen-3-yl acetate, Sobel et al. (1999) found activation in the inferior frontal gyrus and anterior medial thalamus. Savic et al. (2001) suggested that the

patterns of activation are different with respect to gender and putative pheromones, and they are focused to the sexually dimorphic hypothalamic nuclei. Whereas smelling of 4,16-androstadien-3-one (androstadienone), a putative pheromone primarily produced in male axillary secrete, activates the preoptic and ventromedial nucleus in heterosexual females, the oestrogen-resembling oestra-1,3,5(10),16-tetraen-3-ol engages the paraventricular and dorsomedial nuclei in heterosexual males (Savic et al., 2001). In addition, Savic et al. (2001) found activation in several brain areas that do not comprise classic olfactory structures, including the fusiform gyrus and anterior cingulate cortex. It has also been shown that exposure to androstadienone may modify regional cerebral glucose metabolism in several neocortical regions not directly related to olfaction (Jacob et al., 2001). Some of these areas may be related to social cognition and attention that are involved in behavioural effects of pheromones.

These studies regularly compared pheromone related brain activation to air as a baseline. However, in everyday circumstances pheromones appear in an odorous environment containing several non-pheromone odours. The

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relationship between brain activity elicited by pheromones and non-pheromone odorous substances has not been investigated yet, despite the fact that in our everyday life the human brain is regularly exposed to both odours of various origin and pheromones of human origin. In order to explore this question, we set out to investigate the direct effects of androstadienone on regional cerebral blood flow (rCBF) in the female brain. Exposure to androstadienone was contrasted with exposure to pleasant, unpleasant and neutral odours, while the subjects' rCBF changes were measured with ^{15}O -butanol positron emission tomography (PET). Our hypothesis was that androstadienone activates cortical fields related to social cognition and attention when contrasted with non-pheromone odours. Based on the results of previous studies using non-olfactory stimuli on social cognition tests (Frith and Frith, 1999; Adolphs, 2002), we expected pheromone-related activation in lateral and medial prefrontal cortex (PFC), superior temporal cortex (STP), amygdala, and fusiform gyrus.

2. Methods

2.1. Subjects

Five, regularly menstruating healthy women (aged between 40 and 45 years) participated in the study. At the time of the PET measurements they were in the first week of their menstrual cycle. The study was approved by the Ethics Committee and the Isotope Committee of the Karolinska Institute. All participants gave their written informed consent. The study was conducted in line with the recommendations of the Declaration of Helsinki.

2.2. Behavioural procedure

The participants were placed supine on the bed of a PET-scanner and were asked to avoid body movements and speaking. The room temperature was kept constant at 23 °C. The subjects were blindfolded during the study. Four PET measurements were made on each subject. In each condition the subjects smelled androstadienone, γ -methyl-ionone (pleasant odour), methyl-thio-butanoate (unpleasant odour), or dipropylene glycol (control). The various compounds were presented in a randomised order during the four measurements. Dipropylene glycol was used as vehicle compound for the substances, including androstadienone (5% solutions). After the PET session, subjects rated the pleasantness of stimuli using a -10 to $+10$ analogue scale. The participants were blind to the aim of the experiment and the type of substance they smelled.

The putative pheromone and the odorous substances were put in jars, which were prepared in a separate room and brought into a funnel in the vicinity of the subject about 4 cm from the nostrils. At the beginning of the exposure, the tracer was injected. One block of PET measurements de-

voted to a particular substance took 90 s. After an interval of 20 min without olfactory stimulation, the whole session was repeated with the next substance. A constant negative airflow through a hood above the gantry of the scanner provided the quick removal of airborne substances.

The electroencephalogram (EEG) of the subjects was recorded during the experiment, using 4 scalp electrodes. The EEG measurements revealed signs of relaxation, but not sleep in the participants.

2.3. Brain scanning

During the high-resolution magnetic resonance imaging (Siemens Magnetom, 1.5T) and PET recordings, individually moulded plastic head fixation helmets were used which kept the head in identical positions in both scanners and restricted head movements. For the PET measurements, a Scanditronix 2048-15B camera was used (Knoop et al., 1989). The ^{15}O -butanol tracer was given in a bolus injection in the cubital vein (65 ± 5 mCi dissolved in 7 ml solution of physiological saline (90%) and ethanol (10%)). Data were obtained for a total of 90 s in 18 subsequent scans. The acquisition of rCBF measurements and stimulus presentation started simultaneously. During image reconstruction, attenuation correction was made on each image using a rotating solid gamma-radiation source (^{68}Ge).

2.4. Data analysis

The statistical parametric mapping software (version 1999 (SPM99), Wellcome Department of Cognitive Neurology, London, UK) was used, which was implemented in a MATLAB package (Mathworks Inc., Sherborn, MA) in an Octane-2 Silicon Graphics workstation. T1-weighted structural magnetic resonance images were coregistered to the PET images. Scans were realigned using the first scan for reference. Images were stereotactically transformed to the Montreal Neurological Institute template space (Friston et al., 1995). Images were smoothed with an isotropic Gaussian kernel of 8 mm FWHM. Statistical parametric maps were calculated according to the general linear model and the theory of Gaussian fields (Friston et al., 1994). Condition and subject effects were calculated at each voxel. Analysis of covariance (ANCOVA) was used, including global brain activity as covariate of no interest (fixed at 50 ml/100 g/min). Contrasts between brain activities obtained for the three odorous substances were calculated. For each contrast, the voxel values constitute a statistical parametric map of t -statistics (SPM(t)), which was then transformed to the unit of normal distribution (SPM(Z)). The voxel-size used during the statistical analysis was 2 mm \times 2 mm \times 2 mm. The location of brain areas (putative Brodmann areas, BA) was given using the Talairach–Tournoux coordinates (Talairach and Tournoux, 1988). The level of significance was $P < 0.001$, uncorrected (30 contiguous voxels extending threshold).

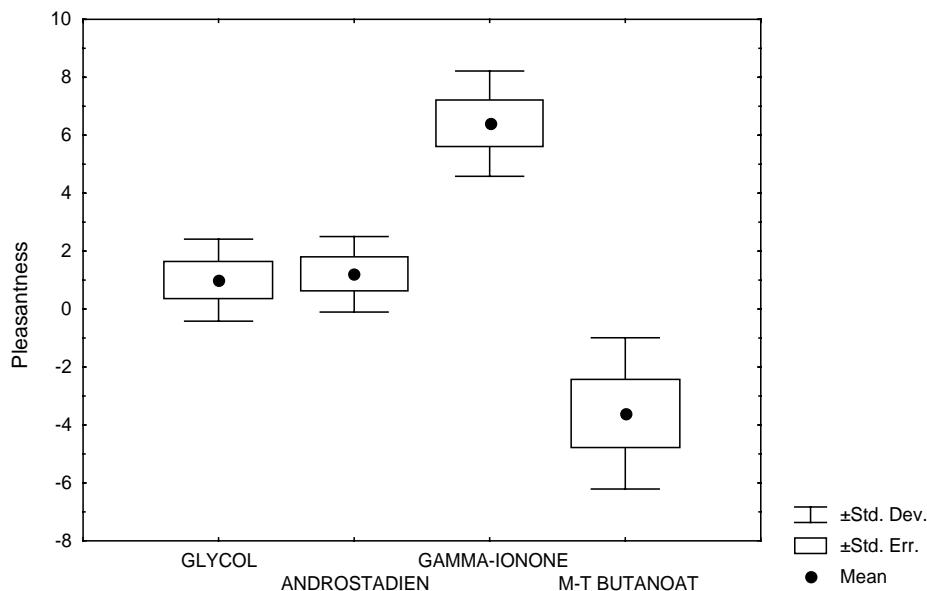


Fig. 1. Scores of pleasantness of substances used, rated by the subjects on a $-10/+10$ analogue scale (mean ($n = 5$), S.D. and S.E.M.).

3. Results

3.1. Behavioural data

Fig. 1 shows the participants' judgments about the pleasantness of the substances used. Friedman analysis of variance (ANOVA) indicated that the participants judged γ -methyl-ionone more pleasant than androstadienone (ANOVA $\chi^2 = 5.0$, d.f. = 1, $P < 0.05$) and judged methyl-thio-butanoate more unpleasant than androstadienone (ANOVA $\chi^2 = 4.0$, d.f. = 1, $P < 0.05$).

3.2. Brain activation

First, we contrasted androstadienone with the vehicle compound dipropylene glycol. Androstadienone activated several areas, including the orbitofrontal cortex, inferior prefrontal cortex, and the fusiform gyrus (Table 1). In the inverse contrast (not shown in the table), we observed a large effect in the inferior occipital gyrus (BA 18; $x = -32$,

$y = -90$, $z = 0$; $Z = 4.66$, $P < 0.001$, uncorrected; 61 contiguous voxels extending threshold).

Second, we investigated the effect of androstadienone in an odorous environment with either unpleasant or pleasant odours. When compared with methyl-thio-butanoate (an unpleasant odour), androstadienone activated the inferior and superior prefrontal cortex, superior temporal areas, and the inferior temporal gyrus (Table 2, Fig. 2). Significant brain activation in the androstadienone > γ -methyl-ionone contrast (pleasant odour) was observed in the inferior prefrontal cortex, as well as in the superior and inferior temporal regions (Table 3, Fig. 2).

Only few areas were engaged by odours as compared with androstadienone. These included the brainstem ($x = -16$, $y = -26$, $z = -42$; $Z = 5.23$; $P < 0.001$, uncorrected; 38 contiguous voxels extending threshold) and the inferior frontal gyrus (BA 45) ($x = 58$, $y = 20$, $z = 6$; $Z = 3.87$; $P < 0.001$, uncorrected; 35 contiguous voxels extending threshold).

When androstadienone was compared with the odorous substances altogether, two extensive cortical fields showed

Table 1

Significant brain activation in the 4,16-androstadien-3-one > dipropylene glycol contrast

Brain region	Coordinates (x, y, z)	Z value
Gyrus rectus (BA 11)	-6, 32, -24	5.02
Inferior frontal gyrus (orbital part) (BA 47)	44, 14, -22	4.71
Fusiform gyrus (BA 21)	62, -10, -24	4.45
Middle frontal gyrus (BA 10)	32, 60, -8	4.32
Paracentral lobule (BA 5)	8, -24, 52	4.30
Superior temporal cortex (BA 39)	54, -66, 28	4.13
Parahippocampal gyrus (BA 36)	56, -26, -24	4.13

$P < 0.001$, uncorrected; 30 contiguous voxels extending threshold. BA: Brodmann area.

Table 2

Significant brain activation in the 4,16-androstadien-3-one > methyl-thio-butanoate contrast

Brain region	Coordinates (x, y, z)	Z value
Superior temporal cortex (BA 39)	54, -66, 28	4.90
Superior frontal gyrus (BA 6)	-20, 10, 64	4.87
Middle frontal gyrus (BA 10)	30, 54, 4	4.70
Precentral gyrus (BA 4)	48, -4, 50	4.61
Superior frontal gyrus (BA 8)	34, 40, 44	4.40
Inferior temporal gyrus (BA 20)	50, -12, -34	3.85

$P < 0.001$, uncorrected; 30 contiguous voxels extending threshold. BA: Brodmann area.

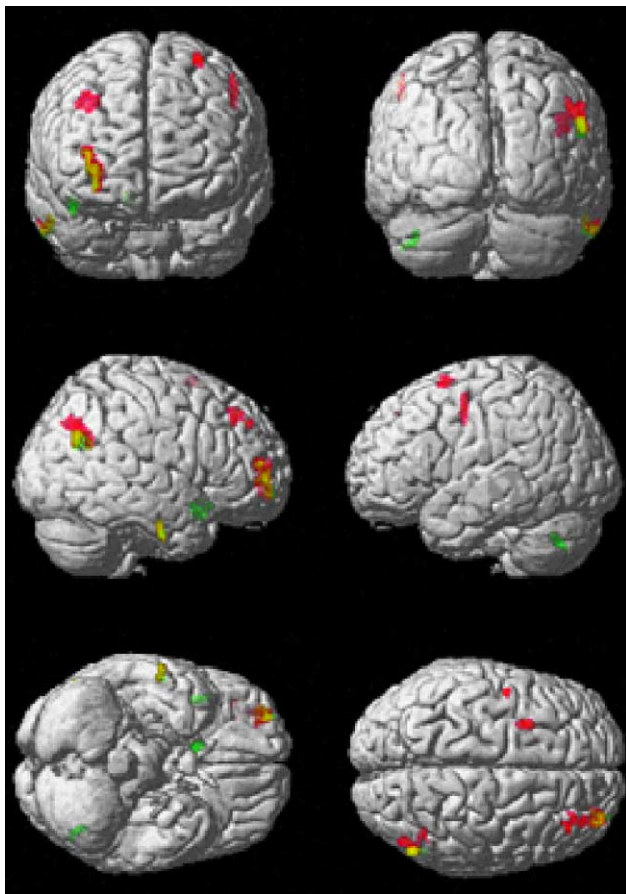


Fig. 2. Three dimensional rendering (shown from six different perspectives) of the significantly activated regions obtained when androstadienone was contrasted with methyl-thio-butanoate (red) and γ -methyl-ionone (green). Yellow shows overlapping brain areas between the two contrasts. All significantly activated voxels are shown here; for details regarding 30 or more contiguous voxels, see Tables 2 and 3.

common activation: the inferior anterior prefrontal cortex (BA 10, $x = 30$, $y = 54$, $z = 4$; 138 contiguous voxels) and the superior temporal cortex (BA 39, $x = 54$, $y = -66$, $z = 28$; 84 contiguous voxels).

It is remarkable that although these cortical areas exhibited significant activation even in the androstadienone (dissolved in dipropylene glycol) > dipropylene glycol contrast

(BA 10: 48 contiguous voxels; BA 39: 31 contiguous voxels, see also Table 1), the extent of this activation was much larger when androstadienone was compared with the odours. A possible explanation of this finding is that the odours deactivated these cortical areas. To test this hypothesis, we contrasted the vehicle compound dipropylene glycol with the odours. We found that the anterior prefrontal cortex and the superior temporal cortex were indeed deactivated ($x = 36$, $y = 52$, $z = 14$; $Z = 4.06$; 43 contiguous voxels and $x = 54$, $y = -66$, $z = 28$; $Z = 4.84$; 46 contiguous voxels, respectively).

4. Discussion

In this study, we specifically investigated brain activation related to exposure to androstadienone as compared with non-pheromone odours. We were able to demonstrate a considerable overlap among the three contrasts (androstadienone versus vehicle compound, pleasant and unpleasant odours), comprising the anterior part of the inferior lateral prefrontal cortex (BA 10) and the posterior part of the superior temporal cortex. Interestingly, these areas were more pronouncedly activated when androstadienone was compared with pleasant and unpleasant odours than with the neutral vehicle compound. Additional analysis indicated that parts of the inferior PFC and STP were deactivated by the pleasant and unpleasant odours. In other words, pheromone and non-pheromone odorous have an opposite effect: androstadienone activates these cortical areas, whereas non-pheromone odours have a deactivating effect. Contrary to our initial hypothesis, no activation was found in the medial prefrontal cortex and amygdala, possibly because of the small sample size and low statistical power.

When androstadienone was compared with the neutral vehicle compound, several brain areas showed increased activity. A number of these areas were similar, but not identical to that found in our earlier study (Savic et al., 2001). The cingulate gyrus (BA 23; $x = 0$, $y = -58$, $z = 14$; $Z = 4.45$; $P < 0.001$, uncorrected) and the hypothalamus ($x = -14$, $y = -2$, $z = -4$; $Z = 3.56$ and $x = -10$, $y = 0$, $z = -12$; $Z = 3.18$; $P < 0.001$, uncorrected) were also activated, although in a less extensive manner (<30 voxels). There are several factors that may contribute to this discrepancy. First, the participants in this study were older (40–45 years) than those included in the Savic et al. (2001) study (20–28 years). Second, in the Savic et al. (2001) study the pheromone was compared with air, while in the present study it was compared with dipropylene glycol (although this was the vehicle compound for the pheromone similarly to the odours). Third, the concentration of the pheromone was different in the two studies. Fourth, different methods were used for data analysis. Another limitation of this study is that familiarity and intensity were not rated, which may have important effects on the results.

Table 3

Significant brain activation in the 4,16-androstadien-3-one > γ -methyl-ionone contrast

Brain region	Coordinates (x , y , z)	Z value
Superior temporal cortex (BA 39)	54, -66, 28	5.09
Inferior frontal gyrus (orbital part) (BA 47)	44, 14, -22	4.83
Medial frontal gyrus (BA 25)	12, 12, -16	4.55
Middle frontal gyrus (BA 10)	34, 56, 2	4.31
Inferior temporal gyrus (BA 20)	56, -12, -28	4.12
Cerebellum	-42, -68, -42	4.19

$P < 0.001$, uncorrected; 30 contiguous voxels extending threshold. BA: Brodmann area.

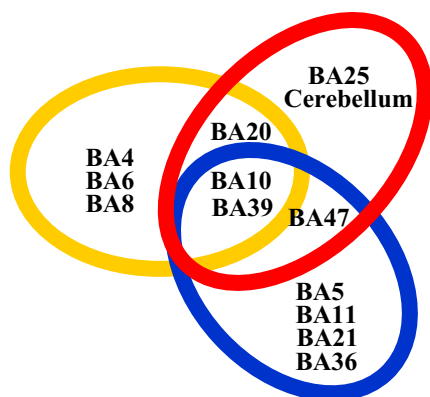


Fig. 3. The diagram indicating the activated regions (as Brodmann areas, BA) in all three tasks; two tasks; and single tasks. Yellow: 4,16-androstadien-3-one > methyl-thio-butanoate contrast; red: 4,16-androstadien-3-one > γ -methyl-ionone contrast; blue: 4,16-androstadien-3-one > dipropylene glycol contrast.

Two of the activated regions (PFC or BA 10 and STP or BA 39) were present in all three contrasts in which androstadienone as compared with non-pheromone odours. Two regions were present in two contrasts (BA 20 and BA 47), whereas the other regions were found in single contrasts (Fig. 3). Because of the small sample size and low statistical power, only the two most robust and overlapping activations (PFC and STP) will be discussed here.

The cortical areas activated by androstadienone do not belong in the narrowly defined olfactory or human pheromone system (Zatorre et al., 1992; Savic et al., 2001). Evidence suggests that the STP cortex participates in the recognition of facial features such as emotional expression and gaze (Haxby et al., 2000). The STP cortex is sensitive for biological motion and it may play an important role in the representation of others' actions, contributing to our ability to understand mental states in social interactions (Frith and Frith, 1999).

The fusiform gyrus was significantly activated by androstadienone, similarly to our previous study (Savic et al., 2001). Extended neuronal populations in the fusiform gyrus are participating in the recognition human faces (Kanwisher et al., 1999; Hadjikhani and de Gelder, 2002). The fusiform face region has strong connections with several cortical areas, including the ventral PFC and their concerted actions may contribute to complex decision processes about human faces (Druzgal and D'Esposito, 2001). The ventral and inferior anterior PFC (BA 10) is also involved in several aspects of social cognition and emotional processing (Adolphs, 2002). Rogers et al. (1999) found activation in BA 10 in a task which included reward-related decisions, while others suggested its role in episodic memory processes (MacLeod et al., 1998) and abstract rule learning (Strange et al., 2001). Jacobs et al. (2001) demonstrated that in this area the synaptic density and the size of dendritic arborizations are larger than anywhere else in the neocortex, suggesting its importance in the phylogenetic specialisation of the human brain.

According to Allman et al. (2002), area 10 "compares the current state with past experience, calculates reward probabilities, formulates strategies, and makes choices based on these calculations (p. 343)". It is notable that PFC activation was observed in each study investigating the effects of pheromones on brain functions, although the extent and localization of activation varied across studies (Sobel et al., 1999; Savic et al., 2001; Jacob et al., 2001).

In the present study, we used a reliable blood flow tracer, ^{15}O -butanol (Berridge et al., 1991), to measure and localise regional cerebral blood flow changes in the brain, underlying regional neuronal activity changes due to a dual sensory stimulation by both odour and pheromone. Even the present exploration could indicate that in the measurable blood flow changes both regional neuronal activation and inhibition may play significant roles. However, the analysis of regional blood flow changes cannot reveal in detail the intricate balance between neuronal excitation and inhibition. In the future, PET with specific receptor radioligands (Halldin et al., 2001a,b) may provide a unique opportunity to investigate the role of the major excitatory and inhibitory neurotransmitter systems, including the GABA-benzodiazepine system (Halldin et al., 1992; Pike et al., 1993) and the major monoamine systems (serotonin (Farde et al., 1997; Nishisawa et al., 1999), norepinephrine (Gehlert et al., 1995) and dopamine (Farde et al., 1987; Hall et al., 1992)) in the mediation of pheromone effects in both normal and pathological conditions.

In conclusion, this is the first functional neuroimaging study showing that androstadienone, a putative gender-specific human pheromone, activates inferior PFC and STP in the human brain when compared with pleasant and unpleasant non-pheromone odours. These activated brain areas are, by several other investigations, shown to be heavily involved in other than olfactory functions, including various aspects of attention, visual perception and recognition and social cognition.

Acknowledgements

During the preparation of this manuscript, Szabolcs Kéri was supported by the Wenner-Gren Foundation, Stockholm, Sweden. The authors express their gratitude to Dr. Ivanka Savic for participation in the experiments, data analysis and for her advice during the preparation of the manuscript.

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