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Research report

Sniffing human sex-steroid derived compounds modulates mood, memory and autonomic nervous system function in specific behavioral contexts

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Abstract

We asked whether the effects of exposure to two human sex-steroid derived compounds were context dependent. The effects of sniffing 4,16-androstadien-3-one (AND) and 1,3,5(10),16-estratetraen-3-ol (EST) on mood, memory, and autonomic nervous system responses were explored in 72 participants. Subjects were tested with AND, EST, or a Control compound within four mood contexts: neutral, sexually aroused, sad and happy. These moods were successfully induced using selected film segments ($P < 0.0001$). During the neutral context, none of the compounds affected mood or autonomic nervous system function. However, compound effects were significantly increased within arousing contexts. During the sexually arousing context, both compounds increased sexual arousal ($P < 0.029$). During the sad context, AND maintained positive mood in women ($P < 0.050$) and increased negative mood in men ($P < 0.031$). Memory for events during the sad context was impaired by AND in women ($P < 0.047$) but not in men. Finally, effects of AND on physiology were observed during the sexually arousing context whereby AND increased skin temperature in both sexes ($P < 0.022$) but reduced abdominal respiration rate in men only ($P < 0.034$). These results suggest that sex-steroidal compounds modulate mood, memory and autonomic nervous system responses and increase their significance within specific behavioral contexts. These findings lend support to a specific role for these compounds in chemical communication between humans.

Keywords: Olfaction; Mood; Memory; Human psychophysiology; Context effects; Androstadienone; Pheromones

1. Introduction

The ability of chemical messages, often referred to as pheromones, to modulate behavior and hormonal state in mammal and insect conspecifics has been extensively explored [4,6,9–11,14,15,20,25,28,30,32,33,42,49,54,62,63,66,71,72,82,87,92,93]. Recent studies of chemical communication in humans focused on sex-specific effects on behavior and autonomic nervous system responses to sex-steroid derived compounds such as 4,16-androstadien-3-one (AND) and 1,3,5(10),16-estratetraen-3-ol (EST) [38,44–46]. The results of these studies, however, were not always consistent. For example, in women, AND reduced autonomic arousal in one study [38], but increased it in others [7,45], and decreased negative feelings in one study [38], but had no effects on negative mood yet increased positive mood in a different study [46]. The time course of these effects was also varied, from 6 min [46], to 30 min [38], to 40 min [7], to more than 2 h after exposure [46]. Moreover, sex-specificity of AND was also not systematically observed. AND effects were specific to women in some studies [38,45,46], but equal for men and women in others [44]. When observed, effects of EST on autonomic nervous system function [45] and mood [46] were in the same direction as those of AND.

The disagreements in the above studies may reflect various methodological differences such as different compound source. In turn, as suggested by Jacob et al. [45], these disagreements may reflect altered responses due to contextual settings that differed across studies. Context may affect

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sensory processing and behavior at perceptual [2], semantic [52], social [69] and emotional [12] levels. Context may play a particularly strong role in the perception of chemical messages as these usually pertain to very specific behaviors such as aggression and reproduction, and a relevant chemical message may be far less potent when out of its appropriate context. To place this distinction within the framework of chemical communication terminology, these compounds may be functioning as primers rather than releasers [46]. In other words, the role of AND and/or EST in chemical communication between humans may be to shape behavior only within the appropriate context, rather than create or release a behavior de novo. To address this possibility, here we set out to examine the autonomic nervous system and mood responses to AND and EST within controlled contextual settings. The effects of AND and EST were measured first during a neutral context and then again following the induction of positive, negative, or sexually arousing moods. These moods were induced with videotapes [1,77], a method sufficient to induce context-dependent pain perception [88]. To further address the possibility that the effects of AND and EST were specific to contextual setting, we also examined memory for events within each context as a function of exposure to the different compounds.

2. Materials and methods

2.1. Subjects

Seventy-two University of California Berkeley graduate and undergraduate students (36 women, mean age 23.5 ± 5.8 and 36 men, mean age 22.05 ± 3.08) of mixed ethnic backgrounds participated in this experiment. Participants were randomly assigned to each sub-group. Exclusion criteria included history of head or nasal passage trauma, history of neurological disease, history of repeated or current sinus infection, chronic use of medication including oral contraceptives, and alcohol, drug, or tobacco abuse. All subjects described themselves as heterosexual. The analysis of the demographic information from a questionnaire revealed that there were no significant sex-by-compound interaction for age ($F[1, 63] = 0.146$, $P = 0.8641$), height ($F[1, 63] = 0.077$, $P = 0.926$) or weight ($F[1, 63] = 0.524$, $P = 0.5950$), and no significant differences between groups for laterality ($\chi^2(2)$, $P = 0.699$). Women's olfactory acuity may vary across the menstrual cycle [27,57,70]. We aimed to minimize the variance in this respect by having all women participants begin testing at around the 14th day of their menstrual cycle, counting forward from the first day of menstruation as day 1 to determine the appropriate experimental start date. It is acknowledged that this verbal report by subjects is an inaccurate assessment of the menstrual phase in women, but was considered helpful towards minimizing experimental variance.

2.2. Compounds

Steroidal compounds were obtained from Steraloids Inc. (Newport, RI, USA). Both AND and EST were employed in this experiment. Fifty milligrams of AND and EST were each deposited in crystal form into identical 60 ml (4.5 cm in diameter at the opening; 5 cm high) opaque jars. Baking powder served as the control substance and 50 mg of this was placed into a third identical jar.

2.3. Autonomic nervous system parameters

In previous studies, sex-steroid derived compounds induced changes in electrodermal response, heart rate, respiratory rate and skin temperature [7,38,45]. Here, we tested whether the effects on autonomic nervous system responses of sex-steroid derived compounds would be more prominent within arousing contexts. Therefore, the following 7 autonomic nervous system parameters were simultaneously and continuously recorded and displayed during the experiment: skin conductance response (SCR), electrocardiogram (ECG), finger pulse (FP), ear pulse (EP), skin temperature (ST), abdominal respiration (AR) and thoracic respiration (TR). All parameters were sampled and recorded at 1 kHz. Data were converted and amplified via a 16-channel amplifier (PowerLab 16SP, ADInstruments, NSW, Australia), and displayed, stored, reduced, and analyzed with the Chart 4.1.1 software package (ADInstruments, NSW, Australia).

2.3.1. Skin conductance (SCR)

SCR was obtained through two bipolar finger Ag/AgCl electrodes (surface: 1 cm^2), placed on the second phalanx of the index and the third digit of the non-dominant hand, attached with Velcro® strap. SCR was measured by applying a 0.5 $\mu A/cm^2$ ac current. The SCR amplifier used was fully isolated with low voltage, 75 Hz (~40 mV) ac excitation. The variables reduced were: (i) during compound exposure, SCR mean (expressed in microsiemens), and (ii) during the films, the non-specific skin conductance response (NS-SCR), expressed in number of events per minute. NS-SCR has been described as the appropriate SCR measure for continuous non-event-dependent SCR [23]. The threshold for an event was a 0.5% deflection from the tracked mean that yielded an average of 3.06 (S.D. = 3.88) NS-SCR events per minute throughout this experiment.

2.3.2. Electrocardiogram (ECG)

ECG was obtained through 3 circular Ag/AgCl conductive adhesive electrodes (0.9 cm diameter). Skin surface was cleaned with alcohol before electrode placement. Electrodes were placed on both the left and the right sides of the abdomen (just under the thoracic cage), and a ground electrode was placed on the left leg. The data were reduced to ECG rate expressed in beats per minute (BPM).

2.3.3. Finger and ear pulse (FP/EP)

Finger and ear pulses were recorded with IR plethysmographs (size: 15 mm × 15 mm × 6.3 mm) placed on the fifth finger of the non-dominant hand (finger pulse), and the ear on the side of the non-dominant hand (ear pulse). These devices used an infrared photoelectric sensor to detect changes in tissue blood volume. They were attached with either a Velcro® strap (for finger), or a clip (for ear). The data were reduced to pulse rate in BPM.

2.3.4. Skin surface temperature (ST)

A small ceramic-encapsulated metal oxide semiconductor (9.5 mm in length, 2 mm in diameter) was used to measure skin surface temperature. The thermistor, designed to operate from 0 to 50 °C was placed directly below the axilla. The data were reduced to temperature change: the difference between ST maximum and ST minimum values.

2.3.5. Abdominal and thoracic respiration (AR and TR)

Two respiratory belt transducers (30 cm rest length, 10 cm maximum elongation, 4.5 cm in width) were used to measure changes in thoracic and abdominal circumference due to respiration. They contained a piezo-electric device that responded linearly to changes in length (sensitivity: 4.5 ± 1 mV/mm). The data were reduced to abdominal and thoracic respiration rates.

2.4. Mood ratings

A 16-item test was used to measure compound and sex effects on mood. Subjects rated how strongly they were experiencing each of 16 different moods on a 9-point scale with 1 corresponding to "not at all" and 9 corresponding to "very strongly." This mood test was devised to tap into mood rather than more transient emotional feelings [31,55]. It is well validated and consists of the following variables: afraid, amused, angry, annoyed, anxious, bored, calm, confident, content, contemptuous, disgusted, embarrassed, happy, interested, sad, and stressed. Sexually aroused was also added to this test and used as a descriptor.

2.5. Mood-induction videos

Three excerpts from different popular movies were used to induce mood. To induce a happy mood we used excerpts from "The Best Bits of Mr. Bean" (PolyGram Entertainment, 1999), to induce a sad mood we used excerpts from "The Champ" (Metro Goldwyn Mayer, 1979), and to induce sexual arousal we used excerpts from "9 1/2 weeks" (Metro Goldwyn Mayer, 1986). The excerpts from both "Mr. Bean" and "The Champ" have been used extensively to induce happy and sad moods, respectively [37,48,56]. The sexually arousing film was selected through a pre-study of 10 subjects (5 women) who viewed numerous films concurrently with physiological recording and questionnaires. The selected excerpt was chosen because it was equally arousing to both men and women. Film presentation order was counterbalanced across subjects according to a Latin square.

2.6. Experimental design

A between-subjects design (Fig. 1) was used such that each subject underwent testing with one of the three compounds (AND, EST or Control). Thus, this study contains data from 72 recording sessions, each lasting about 120 min (from subject arrival at the lab to subject departure). All testing was performed in a temperature and humidity controlled, stainless steel coated, 11 × 8 foot room equipped with HEPA and carbon filtration. This room was designed specifically for olfactory experiments and prevents odor con-

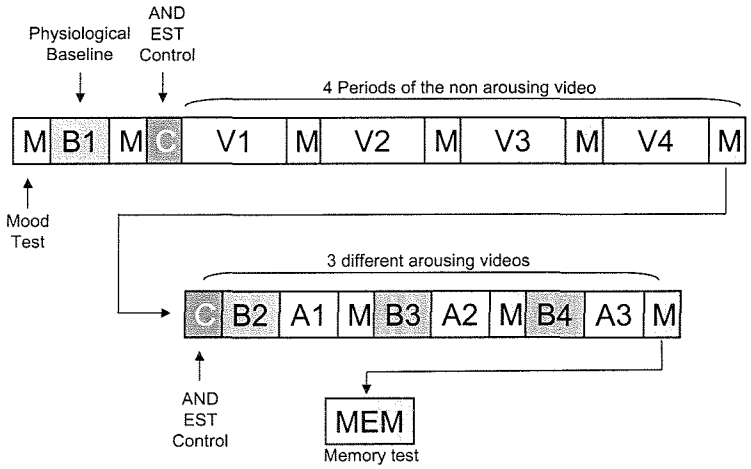

Fig. 1. Experimental design. Each subject was tested with one compound (AND, EST or Control) in a between subjects design. "M" corresponds to the mood tests; "B1" to "B4" corresponds to the physiological baselines; "C" corresponds to compound presentation; "V1" through "V4" corresponds to the ensuing four 10-min epochs of the non-arousing video; "A1" through "A3" corresponds to the three arousing videos; "MEM" corresponds to the memory test.

tamination across conditions. Subjects were left alone in the room during the experiment, and activity in the room was continuously monitored from the adjacent control room via a one-way mirror and video monitor. A same-sex experimenter completed all interactions with participants except compound presentation, which was performed by an opposite sex experimenter. Presentation of the mood scale, video clips, compound sampling instructions, and recording of autonomic nervous system data, were all time-locked through one central computer.

After completing a demographics questionnaire and providing written informed consent, subjects were taken into the testing room and seated in front of a computer monitor. A keypad was positioned in front of them and they were instructed to answer the questions that would appear on the monitor after the experimenter had left the room. At this point the first baseline mood scale was administered via the monitor. Upon completion of the baseline scale, the experimenter re-entered the room and fitted the autonomic nervous system recording equipment to the subject. Once autonomic nervous system measures stabilized, recording was then initiated to obtain a 5-min peripheral physiological baseline. During this time, participants watched a video of the ocean that is commonly employed for its non-arousing contents [73]. This baseline recording was followed by the second administration of the mood scale.

Next, an opposite-sex experimenter entered the room and held the appropriate experimental jar under the participant's nose for each of 6 sniffs that were timed and cued by computer-generated digitized voice instructions. The digitized voice prompted the subject to sniff at a tone following a countdown (e.g. "three, two, one, sniff"). After each sniff, subjects rated compound intensity, pleasantness and familiarity on a 1–9 point scale presented on the monitor. There was no verbal interaction between experimenters and subjects during compound presentation. The experimenter then left the room and participants watched four consecutive 10-min segments (V1 through V4) of a non-arousing nature video, answering the mood scale again in between each segment. The nature video was chosen and edited to be emotionally neutral.

After this non-specific baseline, the same experimenter re-entered in the room and re-presented the appropriate compound to the subject's nose for each of 6 sniffs that were also timed and cued by computer-generated digitized voice instructions. Here again, the participants had to rate compound intensity, pleasantness and familiarity. Next, participants watched three different emotional videos inducing either happiness ("happy film"), sadness ("sad film"), or sexual arousal ("erotic film"), answering the mood scale again in between each video. Each video lasted around 5 min and was preceded by a video of the ocean used for the first peripheral physiological baseline [73]. Autonomic nervous system data were recorded throughout the experiment. The order of presentation of the three videos was counterbalanced across subjects.

After completion of the last mood scale that corresponded to the last arousing video, the experimenter entered the room and disconnected all autonomic nervous system recording devices. Memory for the arousing films was then tested using a multiple-choice recognition test. Here, subjects had to complete a memory questionnaire consisting of 21 questions related to the three arousing films (seven multiple-choice questions per film). From this, we derived a memory score for each arousing film (minimum value: 0; maximum value: 7).

2.7. Data reduction and analysis

Autonomic nervous system data during compound exposure were analyzed in an event-related design in which a baseline of 6 s preceding compound presentation was subtracted from the 6 s period following compound exposure. Data were then expressed as z-scores in order to compare across subjects. Here AR and TR were not analyzed given that participants were asked to sniff the content of the jar, thus inducing artifacts in these two measures.

Autonomic nervous system data during the videos were also first expressed as a change score for each period of interest by subtracting the corresponding baseline value (for the non-arousing video: B1; for the arousing videos: B2, B3 and B4) from that period (for the non-arousing video: during V1, V2, V3 and V4; for the arousing videos: during A1, A2 and A3). They were then expressed as z-scores in order to compare between subjects. Due to technical difficulties in data acquisition, TR for one subject was unavailable.

Mood data were also expressed as change scores for each period of interest by subtracting the baseline value from that period (for the non-arousing video: after V1, V2, V3 and V4; for the arousing videos: after A1, A2 and A3).

Separate ANOVAs for each autonomic nervous system measure and each mood descriptor were performed, including sex (men and women) and compounds (AND, EST and Control) as between factors, and time (V1, V2, V3 and V4) as a within factor (for the non-arousing film). On the basis of previous results, we expected that AND, but not EST, would increase autonomic nervous system arousal (increased in NS-SCR, ECG, EP, FP, AR, TR, and decreased in ST) in women, whereas the reverse pattern would be observed in men [7]. Regarding mood effects, both AND and EST were reported to maintain positive mood [46] and to decrease negative mood [38] in women, and to decrease positive mood in men [46]. Here, we expected that compound effects on mood would occur in the same direction. Moreover, we hypothesized that effects on mood and autonomic nervous system function would be more prominent within arousing contexts. Considering these specific predictions for both autonomic nervous system and mood, planned comparisons (using two-tail t-tests) between AND, EST and Control separately for men and women were conducted when significant interactions (sex-by-compound-by-time, or sex-by-compound) were observed.

Fig. 2. Means and standard errors of intensity, pleasantness and familiarity ratings of AND, EST and the Control in men and women before the non-arousing video (a) and before the arousing videos (b).

3. Results

3.1. Effects in a non-arousing context

3.1.1. During compound presentation

3.1.1.1. Perceived intensity, pleasantness and familiarity. To ask whether the compounds differed significantly in perceived intensity, pleasantness, and familiarity, three separate two-way ANOVAs with sex and compound as between factors were performed on each estimate.

A significant effect of sex was observed for pleasantness ($F[1, 66] = 6.198$, $P < 0.02$), but not for intensity or familiarity ($P > 0.05$), reflecting that men ($m = 5.04 \pm 1.41$) rated the compounds as more pleasant than did women ($m = 4.18 \pm 1.58$). No significant compound effect or sex-by-compound interactions were evident ($P > 0.05$ in all cases). In other words, the three compounds did not differ in intensity, pleasantness, or familiarity (Fig. 2a).

3.1.1.2. Effects on autonomic nervous system function. To ask whether the compounds differently affected autonomic nervous system measures in men and women during compound presentation, all parameters were entered into separate ANOVAs with sex and compounds as between factors. Significant sex effects were observed for FP ($F[1, 66] = 4.629$, $P < 0.04$) and ST ($F[1, 66] = 4.532$, $P < 0.04$) reflecting an increase of FP and ST in men (FP: $m = 0.247 \pm 1.21$; ST: $m = 0.249 \pm 1.03$) relative to women (FP: $m = -0.247 \pm 0.66$; ST: $m = -0.249 \pm 0.92$).

Moreover, a significant compound effect was observed for EP ($F[2, 66] = 6.192$, $P < 0.004$), indicating that AND ($m = 0.54 \pm 0.93$) increased EP relative to EST ($m = -0.31 \pm 0.91$; $t(46) = 3.203$; $P < 0.0025$) and the Control ($m = -0.23 \pm 0.95$; $t(46) = 2.842$; $P < 0.0067$). No sex or compound effects were observed for the remaining autonomic nervous system measurements ($P > 0.05$ in all cases). No sex-by-compound interactions were observed during compound exposure. In other words, compared to the Control and EST, AND increased ear pulse rate in both men and women (Fig. 3a).

3.1.2. Post-compound presentation

3.1.2.1. Effects on mood. To ask whether AND, EST and the olfactory control, differently affected mood in men and

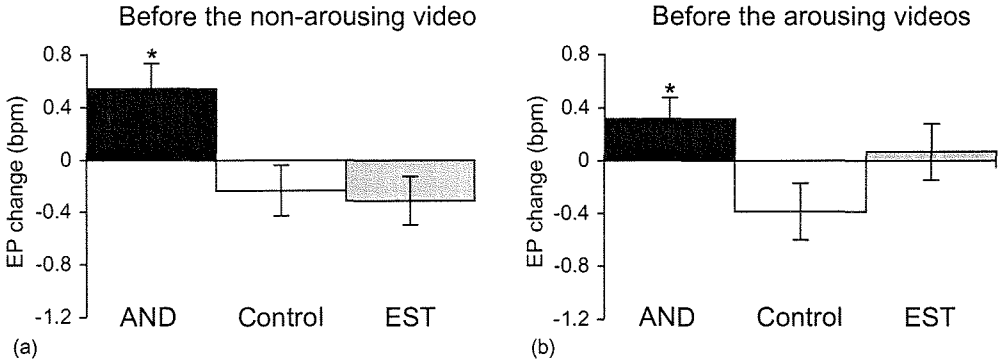

Fig. 3. Means and standard errors of normalized EP rate data obtained during compound presentation before the non-arousing video (a) and before the arousing videos (b), in response to each compound.

women over time, we conducted ANOVAs with sex and compounds as between factors and time as a within factor. A significant sex-by-compound-by-time interaction was evident for "happy" ($F[6, 198] = 2.776$, $P < 0.013$), but comparisons performed separately for men and women revealed no differences between AND, EST and the Control ($P > 0.05$ in all cases). In other words, compared to the Control, AND and EST did not affect mood in men and women during the non-arousing context.

3.1.2.2. Effects on autonomic nervous system function. To ask whether AND, EST and the olfactory control, differently affected autonomic nervous system responses in men and women over time, we conducted ANOVAs with sex and compounds as between factors and time as a within factor. No significant sex or compound effects, or sex-by-compound and sex-by-compound-by-time interactions were evident for any of the autonomic nervous system measurements ($P > 0.05$ in all cases). In other words, in comparison to an olfactory Control, AND and EST did not affect autonomic nervous system responses in men and women during the non-arousing context, regardless of time since stimulation.

3.2. Effects in arousing contexts

3.2.1. During second compound presentation

3.2.1.1. Perceived intensity, pleasantness and familiarity. To ask whether the compounds differed significantly in perceived intensity, pleasantness, and familiarity, three separate two-way ANOVAs with sex and compound as between factors were performed on each estimate. A significant effect of sex was observed for pleasantness ($F[1, 66] = 9.604$, $P < 0.003$), but not for intensity or familiarity ($P > 0.05$), reflecting that men ($m = 5.22 \pm 1.39$) rated the compounds as more pleasant than did women ($m = 4.04 \pm 1.79$). A compound effect was observed for intensity ($F[2, 66] = 5.902$, $P < 0.005$), but not for pleasantness or familiarity ($P > 0.05$), reflecting that AND ($m = 4.96 \pm 1.92$; $t(46) = 2.404$, $P < 0.0203$) and EST ($m = 5.29 \pm 1.49$; $t(46) = 3.404$, $P < 0.0015$) were rated as more intense than the Control ($m = 3.67 \pm 1.80$; Fig. 2b). No difference in perceived intensity was observed in the contrast between AND and EST ($t(46) = -0.673$, NS). No significant sex-by-compound interactions were found ($P > 0.05$). In other words, AND and EST were rated as more intense than the olfactory Control (Fig. 2b).

3.2.1.2. Effects on autonomic nervous system function. To ask whether the compounds differently affected peripheral physiological measures in men and women during compound presentation preceding the arousing videos, all parameters were entered into separate ANOVAs with sex and compounds as between factors. A significant compound effect was observed for EP ($F[2, 66] = 3.221$, $P < 0.05$) reflecting that AND ($m = 0.31 \pm 0.79$) increased EP relative to the Control ($m = -0.38 \pm 1.05$; $t(46) = 2.603$, $P < 0.0125$) in both men and women. No significant sex or compound effects were observed for the remaining autonomic nervous system measurements. No sex-by-compound interactions were observed during compound exposure ($P > 0.05$ in all cases). In other words, compared to the Control, AND increased ear pulse rate in both men and women (Fig. 3b).

3.2.2. Post-compound presentation

3.2.2.1. Induction of moods. In order to test whether the films induced the intended contexts ("happiness," "sadness" and "sexual arousal"), separate ANOVAs for "happy," "sad" and "sexual arousal," including videos ("happy film," "sad film," and "erotic film") as a within factor were performed. The statistical analysis revealed significant video effects for the three descriptors ("happy": $F[2, 142] = 38.909$, $P < 0.0001$; "sad": $F[2, 142] = 77.441$, $P < 0.0001$; and "sexual arousal": $F[2, 142] = 128.641$, $P < 0.0001$). These effects reflected that:

(i) the "happy film" significantly increased "happiness" ("happy film" ($m = 1.24 \pm 1.72$) compared to the "erotic film" ($m = 0.52 \pm 1.79$; $t(71) = 3.705$, $P < 0.0005$), and the "sad film" ($m = -0.39 \pm 1.63$; $t(71) = 8.410$, $P < 0.0001$)) (Fig. 4a);
(ii) the "sad film" significantly increased "sadness" ("sad film" ($m = 2.24 \pm 2.11$) compared to the "erotic film"

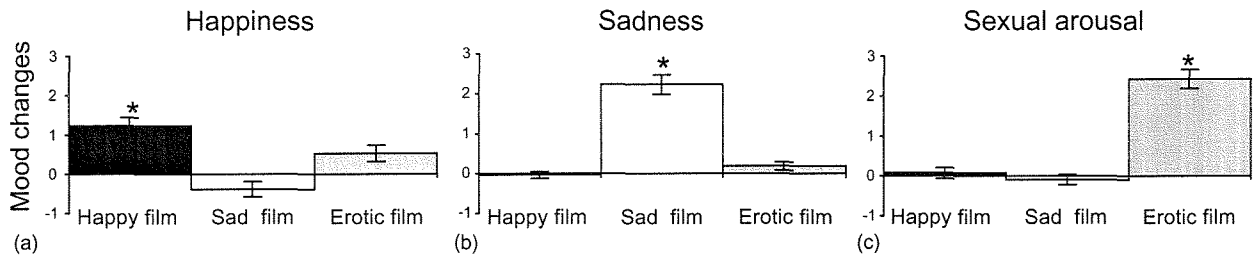

Fig. 4. Induction of moods by the different arousing videos. (a) "Happiness" was greater during the "happy film" than during the "sad film" and the "erotic film." (b) "Sadness" was greater during the "sad film" than during the "erotic film" and the "happy film." (c) "Sexual arousal" was greater during the "erotic film" than during the "happy film" and the "sad film." * $P < 0.0001$.

($m = 0.18 \pm 0.91$; $t(71) = 8.818$, $P < 0.0001$), and the "happy film" ($m = -0.04 \pm 0.70$; $t(71) = 9.459$, $P < 0.0001$)) (Fig. 4b);

(iii) the "erotic film" significantly increased "sexual arousal" ("erotic film" ($m = 2.43 \pm 1.98$) compared to the "sad film" ($m = -0.10 \pm 1.10$; $t(71) = 11.816$, $P < 0.0001$), and the "happy film" ($m = 0.07 \pm 1.10$; $t(71) = 11.919$, $P < 0.0001$)) (Fig. 4c).

These results indicated that the films successfully induced the intended contexts.

3.2.2.2. Effects on mood. To ask whether the compounds differently affected mood of men and women during the arousing videos, a two-way ANOVA with sex and compounds as between factors, for each arousing video and each mood was performed. Fig. 5 illustrates changes in "happiness," "sadness" and "sexual arousal" after each arousing video ("happy film," "sad film" and "erotic film"), in men and women for AND, EST and the Control. During the "happy film," no significant sex or compound effects, or sex-by-compound interaction were observed for any of the mood descriptors ($P > 0.05$ in all cases) (Fig. 5a). During the "sad film," a significant sex-by-compound interaction was observed for "happy" ($F[2, 66] = 4.084$, $P < 0.03$), reflecting that AND ($m = 0.08 \pm 1.62$), relative to the Control ($m = -1.33 \pm 1.72$), maintained happy in women ($t(22) = 2.074$, $P < 0.0500$). Moreover, a significant interaction was also observed for "sad" ($F[2, 66] = 4.726$, $P < 0.02$) reflecting that, compared to the Control ($m = 0.92 \pm 2.15$), AND ($m = 2.83 \pm 1.90$; $t(22) = 2.314$, $P < 0.0305$) increased sad in men (Fig. 5b).

During the "erotic film," a compound effect was observed for "sexual arousal" ($F[2, 66] = 4.285$, $P < 0.02$), reflecting that, compared to the Control ($m = 1.50 \pm 2.06$), AND ($m = 3.00 \pm 1.71$; $t(46) = 2.735$, $P < 0.0089$) and EST ($m = 2.79 \pm 1.88$; $t(46) = 2.262$, $P < 0.0285$) increased sexual arousal, in both men and women (Fig. 5c). Moreover, a significant sex-by-compound interaction was observed for "sad," ($F[2, 66] = 3.358$, $P < 0.05$), but comparisons separately for men and women revealed no differences between AND, EST and the Control ($P > 0.05$ in all cases).

3.2.2.3. Effects on autonomic nervous system function. To ask whether the compounds differently affected autonomic nervous system responses of men and women during the arousing videos, a two-way ANOVA with sex and compounds as between factors, for each arousing video and each parameter was performed. During both the "happy film" and "sad film," no significant sex or compound effects or sex-by-compound interactions were observed in autonomic nervous system measures. During the "erotic film," a compound effect was observed for ST ($F[2, 66] = 3.168$, $P < 0.05$) reflecting that AND ($m = 0.32 \pm 0.65$) increased ST compared to the Control ($m = -0.39 \pm 1.31$; $t(46) = 2.385$, $P < 0.0213$) (Fig. 6a).

Moreover, a significant sex-by-compound interaction was found for AR ($F[2, 66] = 3.421$, $P < 0.04$), reflecting a decrease of AR following AND ($m = -0.42 \pm 1.059$) relative to the Control ($m = 0.64 \pm 0.952$; $t(22) = -2.593$,

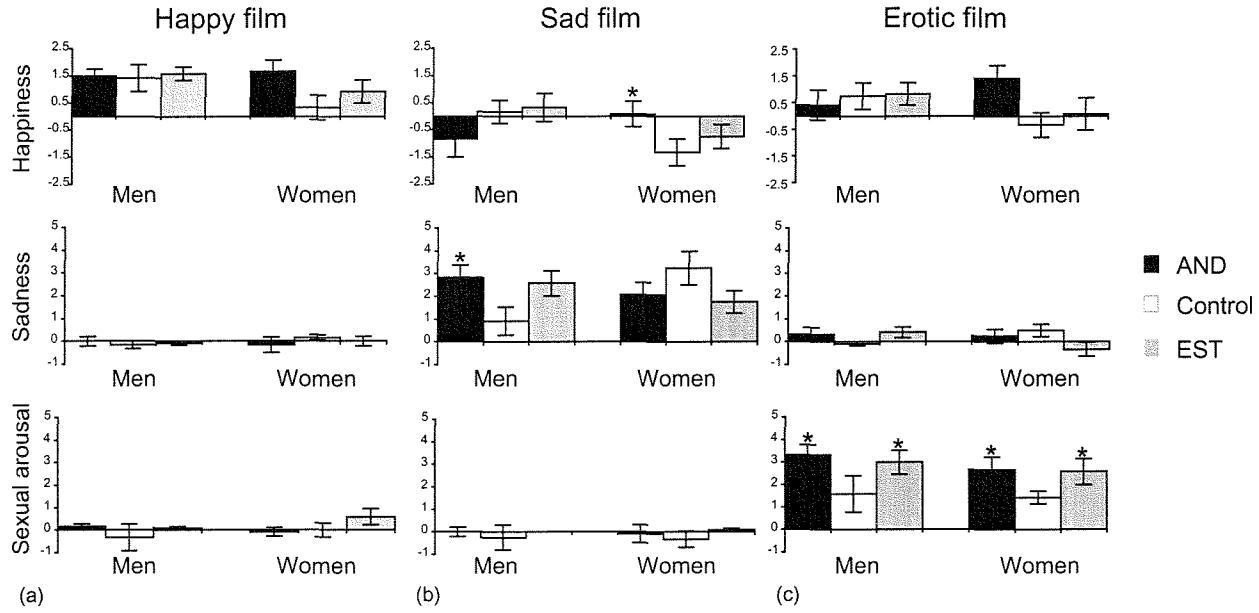

Fig. 5. Means and standard errors of differences in "happiness," "sadness" and "sexual arousal" after each arousing video ("happy film" (a), "sad film" (b), and "erotic film" (c)), in men and women for AND, EST and the Control. During the "sad film" (b), AND maintained "happiness" in women and increased "sadness" in men. During the "erotic film" (c), AND and EST increased "sexual arousal" in both men and women. $^*P < 0.05$.

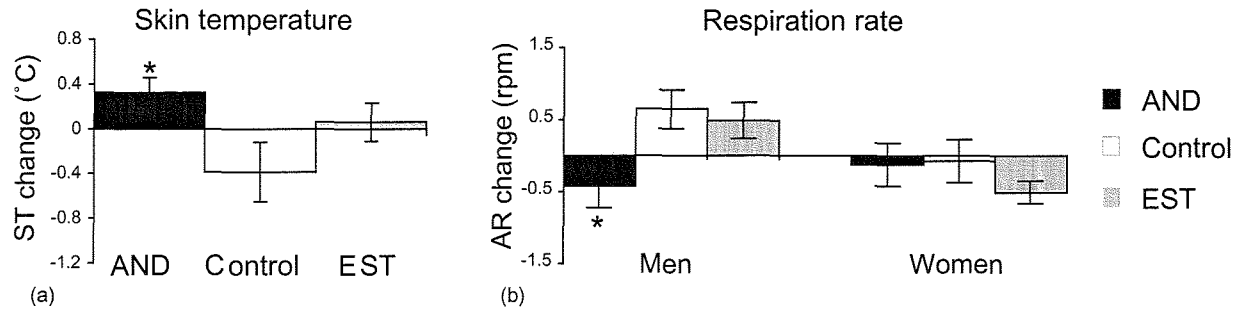

Fig. 6. Means and standard errors of changes in normalized ST range (a) and AR rate (b) in men and women for AND, EST and the Control during the sexually arousing context ("erotic film"). A compound effect was observed for ST and a sex-by-compound interaction was observed for AR reflecting that (i) compared to the Control, AND increased ST in both men and women, and (ii) AND significantly decreased AR compared to EST and the Control in men, but not in women. $^{*}P < 0.05$.

$P < 0.0167$), and EST ($m = 0.49 \pm 0.87$; $t(22) = -2.288$, $P < 0.0330$) in men, but not in women (Fig. 6b). No significant sex or compound effects, or sex-by-compound interactions were evident in the remaining psychophysiological channels. In other words, AND, but not EST, modulated autonomic nervous responses during the sexually arousing context.

3.3. Effects on memory

To ask whether memory for events within each context was differently affected by the compounds in men and women, we performed separate two-way ANOVAs including sex and compounds as between factors for each arousing video.

A sex effect was observed for memory of the "happy film" ($F[1, 66] = 6.117$, $P < 0.02$), reflecting that memory was better in men ($m = 3.89 \pm 0.92$) than in women ($m = 3.31 \pm 1.04$). Furthermore, a compound effect was observed for the "sad film" ($F[2, 66] = 3.530$, $P < 0.04$), reflecting that following exposure to AND ($m = 3.79 \pm 0.93$), there was a decrease in memory of events relative to the "sad film" compared to the Control ($m = 4.63 \pm 1.61$; $t(46) = -2.195$, $P < 0.0333$) and to EST ($m = 4.67 \pm 1.24$; $t(46) = -2.765$, $P < 0.0083$) (Fig. 7b). No sex-by-compound interactions were observed whatever the emotional film. In other words, AND specifically impaired memory for events during the sad context.

4. Discussion

The purpose of the present experiment was to explore potential context-dependence in the effects of two human sex-steroid derived compounds, AND and EST. Within a neutral context, both compounds did not affect mood and autonomic nervous system function. However, the effects of both compounds were increased within arousing contexts. Both AND and EST significantly increased sexual arousal during the sexually arousing context. Within the unpleasant context, AND increased negative mood in men, and maintained positive mood in women. In addition, memory for events during that same negative context was specifically impaired by AND. Effects on autonomic nervous system responses were observed during the sexually arousing context whereby AND, but not EST, decreased respiration rate specifically in men and increased skin temperature in both men and women. Thus, and in answer to the main question of this study, AND, and at a least degree EST, increased their significance within arousing contexts.

That AND specifically impaired memory for events during the sad context is a novel finding. One may ask by what route did AND effect memory? One possibility is a direct pharmacologic type effect of the compound (e.g. via transdermal diffusion) on neural activity in brain regions involved in memory encoding and/or retrieval. Such an effect has been postulated for endogenous testosterone and estradiol whose levels serve to predict verbal memory performance in women

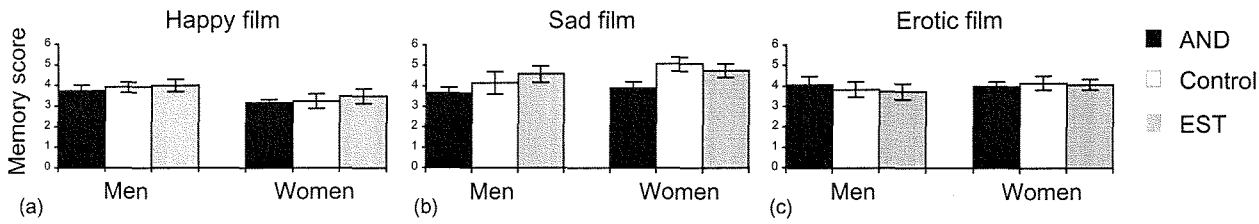

Fig. 7. Effects of AND, EST and the Control on memory related to arousing events during the "happy film" (a), the "sad film" (b), and the "erotic film" (c) in men and women. AND significantly decreased the recall of events during the "sad film."

[91]. A second possibility also entails direct effect on neural activity in the substrates of memory, but mediated by the olfactory system. Such a path would reflect the privileged relationship between the neural substrates of olfaction and regions of the brain involved in processing emotional memories [3,17–19,24,34,35,40,41,53,58,68,78,81,84,94,95].

A third possible explanation for the AND-induced decrease in recall of events linked to the sad context may be explained by the "mood-congruent" memory theory [13,29,51]. Accordingly, mood congruent memory bias predicts superior recall of presented material congruent with the mood state at the time of encoding, and inferior recall of presented material incongruent with that mood. Here the maintenance of a positive mood induced by AND, associated with the negative content of the sad film, represented an incongruent context which induced a decrease in recalled events. However, considering that during the sad context AND's effect on mood was positive for women and negative for men, it was paradoxical that AND impaired memory for sad events in both sexes. Although the overall ANOVA (Fig. 7b) did not point to a significant sex-by-compound interaction, a post hoc analysis (Scheffe test) indicated that AND ($m = 3.92 \pm 0.99$), compared to the Control ($m = 5.08 \pm 1.16$), decreased memory related to the sad context in women ($P = 0.046$), but not in men ($P = 0.702$). No significant differences were observed in Scheffe tests for AND versus EST, or EST versus the Control in both men and women. Thus, the sex specificity in the effects on memory was not incongruent with the effects on mood.

During the non-arousing baseline period of the present experiment both compounds did not significantly affect autonomic nervous system responses. This null finding can be considered to contradict a previous study where we did see autonomic effects of AND within a non-arousing context [7]. We explain this difference between studies as reflecting reduced power in the current study regarding this particular question. Specifically, the study that found effects of AND in a non-arousing context was conducted as a within-subjects design. The current study could not be conducted as a within-subjects design because repeated presentation of films would significantly reduce their efficacy in mood induction. Thus, we opted for a between-subjects design despite a loss in power. This loss was considered acceptable because the question of interest in the current study was a magnitude of difference question. In other words, we were interested in the difference between the arousing and non-arousing contexts, and assume that greater power would have revealed some effects in the non-arousing context, but would have also equally increased the effects in the arousing context. Nevertheless, because of the use of a between-subjects design, one may raise the concern that individual differences in personality and physiology could explain compound effects within each sex. Despite the fact that it is difficult to control for all potential variables that could alter the present results, this possibility is, however, weakened for the following reasons. First, subjects were randomly assigned to the different sub-groups. Second, participant's selection was based on strict exclusion criteria. Third, variables such as sexual preferences, age, height, weight, laterality could not contribute to the observed effects given that no differences were observed between groups (see Section 2). Thus, and in answer to this concern, we think that the compound effects observed in the present experiment were mainly due to the compounds themselves and not to individual differences across participants.

One may ask how specific changes in autonomic nervous system responses that were evident in the arousing contexts may be related to specific changes in mood. Relating autonomic nervous system measures to specific moods is a topic of some complexity and controversy [7,38,45]. Here, there was a significant increase in skin temperature only with increased sexual arousal in both men and women. Considering that such a relationship has been previously reported [43], the positive link between increased sexual arousal and skin temperature appears concrete. In contrast, respiration rate in that same context was significantly decreased only in men. Because a decrease in happiness in men following exposure to AND was observed in this context (Fig. 5c), the relative decrease in respiration rate for AND may have reflected decreased happiness rather than increased sexual arousal in men. The insignificant mean comparisons, however, merit caution in accepting this interpretation.

One may raise the concern that the effects of AND were related to perceived compound intensity. During the second compound presentation, AND and EST were rated as more intense than the Control regardless of sex. We therefore cannot rule out the possibility that this intensity difference underlies some of the effects on autonomic nervous system responses, mood and memory seen here. However, AND decreased memory compared to both the Control and EST, but there was no difference in perceived intensity between AND and EST. Furthermore, if perceived differences in intensity underlie the observed effects, one would expect greater differences between AND and EST versus the olfactory Control when this percept was most prominent, namely during and immediately following compound exposure. The effects, however, were mostly observed only after a considerable delay. These considerations render unlikely the possibility that the slight difference in perceived intensity between AND and EST versus the Control underlies the observed effects of these compounds.

Another concern that may be raised is the fact that it is likely that after corrections, some of the effects observed here would not reach a significant level. Usually, corrections for multiple comparisons are performed when no a priori hypotheses are made. Nevertheless, here, previous findings [7] enabled us to make a priori comparisons. Therefore, the use of direct comparison using *t*-tests was adequate for the present study.

In previous studies, AND and EST were reported to have sex-specific effects on the electrical surface-potential at the epithelium of the vomeronasal organ (VNO) [38,64,65]

(however, see [61] for a critical review of the existence of a human VNO). Furthermore, AND and EST induce sex-specific patterns of brain activity as measured with PET [80]. In contrast, this dissociation was not observed when effects of AND and EST on mood and autonomic nervous system responses were considered. Indeed, Jacob and coworkers reported that both compounds increased positive stimulated mood state in women and decreased it in men [46], and had similar effects in autonomic nervous system responses [45]. Here, both sex-steroid derived compounds modulated sexual arousal in the same direction, but effects on positive and negative moods, memory and autonomic nervous system responses were restricted to AND. That EST may play a smaller role as a chemical signal in humans is consistent with that there is no evidence for EST in human sweat. In contrast, AND is the most prevalent androstene in human male secretions [67], and is more than twice as prevalent in the peripheral blood plasma of men than women [16]. EST is certainly a derivative of estrogen as AND is a derivative of testosterone, but the only evidence of it in humans is in the urine of pregnant women only during the third trimester of pregnancy [86].

Finally, one may ask how the current results reflect on the ongoing debate regarding human pheromones. Chemical communication plays an important role in the reproductive function and sexual behavior of insects [20,42,63] and mammals [4,6,9,14,49,71,82]. The existence of such communication in humans has been considered for some time [8,21,22,39,50] and has received some experimental support. For example, McClintock [59] observed that the menstrual cycles of women who were roommates in dormitories, but with no previous social contact, became synchronized over time. This phenomenon of human menstrual synchrony was later observed solely by wiping compounds from the underarms of "donor" women on to the upper lips of "recipient" women [75,79]. Stern and McClintock [85] found that contact with sweat alone, without social interaction, was sufficient to alter the timing and the length of the menstrual cycle in other women. Given that a similar phenomenon occurs in mice, and is considered as pheromonal in that species [90], Stern and McClintock argued that their results describe a pheromonal effect in humans [89]. Recently, Preti et al. [76] showed that human male axillary extracts contain one or more compounds that influence pulsatile secretion of luteinizing hormones and modulate positive and negative mood in women, and thus may act as primer and modulator pheromones. Since AND was reported to be present in human male axillary hair [36,67], to modulate positive and negative mood in women [38,44–46], to affect specifically autonomic nervous system responses in women [7], and to induce specific brain activation in women [45,80], one may make the assumption that AND was one of those constituents. However, some studies fail to detect AND in male axillary extracts [74], suggesting additional or other components in axillary extracts may underly the above effects.

Whereas it is now widely accepted that chemical communication plays a role of some sort in human behavior and performance, the application of the term pheromones to these chemical signals remains highly controversial [60,61,83]. This is due at least in part to the lack of consent as to the actual definition of what a pheromone is [5,26]. Karlson and Lüscher [47] originally defined pheromones as "substances which are secreted to the outside by an individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process." Here we choose to avoid this now largely semantic debate as to whether AND is a human pheromone, but conclude by stating that AND releases a set of specific reactions (e.g. sex-specific modulation of mood, memory and peripheral physiologic activity) and increases its significance in specific behavioral contexts. These findings suggest a role for AND in chemical communication in humans.

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