PROCEEDINGS OF THE ROYAL SOCIETY B

Proc. R. Soc. B (2006) **273**, 471–478
doi:10.1098/rspb.2005.3342
Published online 29 November 2005

The human brain is a detector of chemosensorily transmitted HLA-class I-similarity in same- and opposite-sex relations

Bettina M. Pause[1,*], Kerstin Krauel[2], Claudia Schrader[1], Bernfried Sojka[1], Eckhard Westphal[3], Wolfgang Müller-Ruchholtz[3] and Roman Ferstl[1]

[1]*Institute of Psychology, Christian-Albrechts-University Kiel, Olshausenstrasse 62, 24098 Kiel, Germany*
[2]*Department of Child and Adolescent Psychiatry, Otto-von-Guericke-University Magdeburg, Emanuel-Larisch-Weg 17-19, 39112 Magdeburg, Germany*
[3]*Institute of Immunology, Christian-Albrechts-University Kiel, Michaelisstrasse 5, 24105 Kiel, Germany*

Studies on subjective body odour ratings suggest that humans exhibit preferences for human leucocyte antigen (HLA)-dissimilar persons. However, with regard to the extreme polymorphism of the HLA gene loci, the behavioural impact of the proposed HLA-related attracting signals seems to be minimal. Furthermore, the role of HLA-related chemosignals in same- and opposite-sex relations in humans has not been specified so far. Here, we investigate subjective preferences and brain evoked responses to body odours in males and females as a function of HLA similarity between odour donor and smeller. We show that pre-attentive processing of body odours of HLA-similar donors is faster and that late evaluative processing of these chemosignals activates more neuronal resources than the processing of body odours of HLA-dissimilar donors. In same-sex smelling conditions, HLA-associated brain responses show a different local distribution in male (frontal) and female subjects (parietal). The electrophysiological results are supported by significant correlations between the odour ratings and the amplitudes of the brain potentials. We conclude that odours of HLA-similar persons function as important social warning signals in inter- and intrasexual human relations. Such HLA-related chemosignals may contribute to female and male mate choice as well as to male competitive behaviour.

Keywords: human leucocyte antigen; body odour; event-related potential; HLA-related chemosignals

1. INTRODUCTION

Several experimental studies have demonstrated that the individual body odour in many vertebrates is associated with their allelic profile of the major histocompatibility complex (MHC; reviewed by Singh 2001). Due to these MHC-related chemosignals individuals prefer to mate with a conspecific that differs at the MHC (reviewed by Penn 2002). However, while most studies indicate female mate choice (Potts *et al.* 1991), some also point to the possibility of male mate choice (Yamazaki *et al.* 1976; Olsson *et al.* 2003). As female mice prefer MHC-similar females as nest mates (Manning *et al.* 1992), kin recognition also seems to be mediated by the MHC type.

MHC-associated chemosignals have been proposed to affect sexual selection in order to preserve MHC polymorphism. The extreme polymorphism in MHC genes is assumed to have an evolutionary advantage in most vertebrates (e.g. heterozygote and rare allele advantage, inbreeding avoidance; reviewed by Brown & Eklund 1994 and Penn & Potts 1999). However, while sexual selection is traditionally considered to include inter- and intrasexual components (Moshkin *et al.* 2000; Moore *et al.* 2001; Olsson *et al.* 2003), it has not been shown whether the MHC also contributes to male competitive behaviour.

*Author and address for correspondence: Institute of Experimental Psychology, Heinrich-Heine University, Düsseldorf Universitätsstraße l, 40225 Düsseldorf, Germany (bettina.pause@uni-duesseldorf.de).

In humans, the MHC is referred to as human leucocyte antigen (HLA). Subjective rating studies, using T-shirts as the odour source, indicate that odours of people with a low (Wedekind & Füri 1997) or intermediate (Jacob *et al.* 2002) number of HLA allele matches are preferred, compared to odours of people with a high number of HLA matches. In investigating same- and opposite-sex relations between odour donors and perceivers, the strongest correlation between HLA-dissimilarity and odour pleasantness was unexpectedly observed in the intra-sexual male condition (Wedekind & Füri 1997). Generally, the behavioural consequences of these HLA-related odour preferences in humans are considered to be related to mate choice (Ober *et al.* 1997), and to the degree of acquaintance between unrelated people (Eggert *et al.* 1999*a*). Again, the strongest HLA effects on the degree of acquaintance were found in male-to-male relations.

In order to understand how HLA-related chemosignals influence human information processing, the present study employed chemosensory event-related potentials (CSERPs; Kobal & Hummel 1988) as an objective indicator of the neuronal activity associated with the perception of HLA-related chemosignals. CSERPs are the averaged epochs of the electroencephalogram (EEG) that occur time-locked to the chemosensory stimulus. Latency and amplitude of the CSERP components can provide information as to whether differences between HLA-related chemosignals are already reflected in early,

Received 8 August 2005
Accepted 21 September 2005

exogenous components (*N1*, ~400 ms post-stimulus) or only influence late, endogenous components (*P3*, ~1000 ms post-stimulus; see Pause & Krauel 2000). Exogenous potentials such as the early negative deflection (*N1*) reflect mainly pre-attentive processing of external stimulus characteristics (quality, intensity; Pause *et al.* 1996, 1997). Endogenous potentials such as the late positive deflection (*P3*) occur in response to rare (unexpected) stimuli and increase in amplitude with the subjective meaning of a stimulus, e.g. when the rare stimulus has to be responded to or is of subjective importance to the perceiver. These components can be elicited in course of the well established oddball paradigm (Donchin & Coles 1988). Within the oddball paradigm, rare stimuli are interspersed among frequent standard stimuli. In the current paradigm, the rare odour stimuli either served as the target stimulus, subjects had to detect and respond to, or served as the distractor stimulus, in order to study evaluative processes independent of task demands.

Summarizing, the aim of the present study was to investigate whether human electrical brain responses to body odour depend on the HLA class-I compatibility between sender and perceiver. In order to investigate HLA effects in same- and opposite-sex relations, CSERPs of male and female subjects in response to odours of male and female donors were analysed. In separating early from late CSERP components, it was addressed whether HLA-associated chemosignals are processed pre-attentively and/or consciously.

2. MATERIAL AND METHODS

(a) *Subjects*

Forty subjects reporting no history of neurological or endocrine diseases, or diseases related to the upper respiratory tract participated in the study. Due to missing EEG data, two subjects were excluded from further analysis (S12 and S33, see table 1). The final subject sample (mean age = 26.9, s.d. = 4.7, range = 20–41, no group differences (ANOVA): $F(3,34) = 1.27$, $p > 0.20$) included three smokers (no group differences (Craddock-Flood): $\chi^2_3 = 3.77$, $p > 0.20$), and 29 dextrals, six sinistrals and three ambidexters (no group differences (Craddock-Flood): $\chi^2_6 = 4.53$, $p > 0.20$). Thirty-six subjects described themselves as heterosexual and two (one male) as bisexual. A screening for olfactory sensitivity (mixture of citral, eugenol, linalool, menthol and isoamyl acetate) at the beginning of the experiment revealed no group differences (Craddock-Flood: $\chi^2_6 = 2.73$, $p > 0.20$). All female subjects were investigated at the beginning of their menstrual cycle (mean cycle day = 3.5, s.d. = 1.8) and 11 of them used oral contraceptives (no group differences (Craddock-Flood): $\chi^2_1 = 0.38$, $p > 0.20$). The subjects participated voluntarily in the study, gave written, informed consent and were paid for participation.

(b) *Body odours and odour presentation*

Odour samples (axillary hair) from 61 donors were collected (table 1). As some donated for more than one experimental session, the number of odour donors for each experimental group varied between 18 and 24. The final donor sample had a mean age of 27.7 years (s.d. = 5.7; no group differences (ANOVA): $F(3,82) = 1.01$, $p > 0.20$) and seven of them described themselves as regular smokers (no group differences (Craddock-Flood): $\chi^2_3 = 0.167$, $p > 0.20$). The donating subjects declared that they did not suffer from any endocrine disorder and were asked to refrain from using deodorants and to wash their armpits exclusively with water 2 days before the axillary hair was collected. Furthermore, they were requested to refrain from eating onions, garlic or asparagus and had to keep nutrition and hygiene diaries. All subjects cut their axillary hair in the morning, immediately after waking up. The females were additionally asked to cut their hair in the follicular phase of the menstrual cycle, within a few days after the end of menstruation (mean cycle day = 6.1, s.d. = 1.8). Axillary hair samples were stored at −20 °C until use (mean storage time = 48 days, s.d. = 42). All donors were paid for their cooperation.

For the EEG sessions, the axillary hairs were placed in odour chambers (mean = 33.3 mg hairs in each chamber, s.d. = 9.6) of a constant-flow (2 × 3-) olfactometer (Burghart Company, Wedel, Germany). Odours were presented birhinally by independent airstreams (100 ml s^{-1}) for 600 ms each with an interstimulus interval of 18–22 s (mean = 20 s). During stimulus presentation, subjects performed the velopharyngeal closure technique (Pause *et al.* 1999*a*). Thereby, the soft palate closes the connection between the oral and the nasal cavity, and because the subjects are breathing through their mouth, the odour presentations do not interfere with the nasal breathing cycle.

(c) *Design*

In our study, all subjects and odour donors (donation of samples of axillary hair) were serologically tissue-typed for their A- and B-loci (HLA-class I). Three odour donors were individually assigned to each of 40 (20 males) subjects (table 1). Whereas two of the donors shared none of the detected HLA class I alleles with the perceiving subject (standard stimulus and deviant stimulus 1, condition: HLA-dissimilar), one of them shared at least three alleles (deviant stimulus 2, condition: HLA-similar). As the subjects perceived the foreign body odours always in the context of their own body odour, it might have been more difficult to detect of the deviant stimulus 2 (HLA-similar). In order to obtain a similar context odour for the deviant stimulus 1 (HLA-dissimilar), the standard stimulus was chosen to be similar to the deviant stimulus 1.

A three-stimulus oddball design was used to differentiate HLA effects on automatic (pre-attentive) and on controlled (conscious) stimulus processing. Within the oddball paradigm, the standard odours were presented with an occurrence probability of 60% and the two deviant stimuli with a probability of 20% each. During four blocks of 50 trials, the deviant stimuli were alternatively presented as targets or distractors. The subjects' task was to detect the target odour by lifting their right index finger (response initiation by a 160 Hz tone, 3–4 s after odour onset). However, they were not informed about the occurrence of the distractor odour.

At the beginning of each 50-trial block, standard and target odours were introduced to the subjects. They were asked whether they disliked or liked the odour and whether they could imagine having a partner with such a body odour (seven-point scale for each rating: −3 to +3). Both ratings were highly correlated ($r = +0.86$, $p < 0.001$). However, further analyses of the subjective data were exclusively based on the ratings for partner preferences, because they were closer to a normal distribution than the ratings for general odour valence (Kurtosis analysis).

Table 1. Design and specification of HLA class I types.

				donors (D)					
		subjects (S)		standard stimulus HLA-dissimilar		deviant stimulus 1 HLA-dissimilar		deviant stimulus 2 HLA-similar	
sex of subject	sex of donor	no.	HLA-type	no.	HLA-type	no.	HLA-type	no.	HLA-type
female	same sex	S1	A2,3 B7,62	D1	A1,24 B8,35	D2	A1,24 B8,44	D3	A2,3 B7,60
		S2	A2,2 B44,62	D4	A3,11 B35,47	D5	A3,11 B35,35	D6	A2,2 B44,62
		S3	A1,25 B8,18	D7	A2,11 B35,39	D8	A2,11 B18,35	D9	A1,25 B18,57
		S4	A1,25 B18,57	D10	A3,24 B35,51	D11	A3,24 B35,61	D12	A1,25 B8,18
		S5	A2,24 B7,62	D13	A1,25 B18,57	D12	A1,25 B8,18	D14	A2,24 B7,62
		S6	A3,24 B35,61	D15	A2,29 B44,44	D16	A2,29 B44,56	D10	A3,24 B35,51
		S7	A2,26 B37,44	D17	A1,24 B8,58	D1	A1,24 B8,35	D18	A2,26 B7,44
		S8	A1,1 B8,8	D19	A2,26 B7,44	D18	A2,26 B7,44	D20	A1,1 B8,8
		S9	A3,11B 35,35	D21	A2,2 B44,62	D6	A2,2 B44,62	D4	A3,11 B35,47
		S10	A1,25B 18,57	D22	A2,3 B7,7	D23	A2,3 B7,62	D9	A1,25 B18,57
	opposite sex	S11	A1,2 B8,60	D24	A3,3 B35,44	D25	A3,3 B27,35	D26	A1,2 B8,60
		S12	A2,3 B7,7	D27	A1,1 B35,57	D28	A1,1 B8,35	D29	A2,3 B7,7
		S13	A3,3 B18,35	D26	A1,2 B8,60	D30	A1,2 B37,60	D25	A3,3 B27,35
		S14	A1,24 B8,35	D31	A2,2 B60,60	D32	A2,2 B7,60	D33	A1,24 B8,51
		S15	A2,3 B7,60	D28	A1,1 B8,35	D34	A1,11 B8,35	D35	A2,3 B7,60
		S16	A1,1 B8,8	D36	A2,30 B27,51	D37	A2,2 B27,51	D28	A1,1 B8,35
		S17	A2,3 B35,60	D33	A1,24 B8,51	D38	A1,24 B7,8	D39	A2,3 B13,35
		S18	A1,11 B35,44	D32	A2,2 B7,60	D40	A2,2 B7,7	D34	A1,11 B8,35
		S19	A3,3 B7,44	D41	A1,24 B8,62	D33	A1,24 B8,51	D24	A3,3 B35,44
		S20	A1,24 B8,44	D42	A2,3 B35,51	D39	A2,3 B13,35	D38	A1,24 B7,8
male	same sex	S21	A24,25 B18,62	D26	A1,2 B8,60	D43	A1,3 B8,60	D44	A24,25 B18,18
		S22	A1,1 B8,35	D35	A2,3 B7,60	D29	A 2,3 B7,7	D34	A1,11 B8,35
		S23	A2,3 B27,62	D38	A1,24 B7,8	D33	A1,24 B8,51	D45	A2,3 B62,62
		S24	A1,11 B8,35	D32	A2,2 B7,60	D31	A2,2 B60,60	D28	A1,1 B8,35
		S25	A2,2 B60,60	D24	A3,3 B35,44	D25	A3,3 B27,35	D32	A2,2 B7,60
		S26	A2,2 B27,51	D41	A1,24 B8,62	D38	A1,24 B7,8	D36	A2,30 B27,51
		S27	A1,3 B7,8	D36	A2,30 B27,51	D37	A2,2 B27,51	D43	A1,3 B8,60
		S28	A2,2 B7,7	D28	A1,1 B8,35	D34	A1,11 B8,35	D29	A2,3 B7,7
		S29	A2,3 B13,35	D46	A24,25 B18,62	D44	A24,25 B18,18	D42	A2,3 B35,51
		S30	A3,3 B7,7	D47	A1,2 B8,51	D26	A1,2 B8,60	D48	A3,3 B7,7
	opposite sex	S31	A 25,33 B7,18	D10	A3,24 B35,51	D11	A3,24 B35,61	D49	A2,25 B7,18
		S32	A 1,1 B35,57	D50	A2,24 B39,44	D51	A2,24 B27,44	D52	A1,1 B8,57
		S33	A3,3 B35,44	D53	A2,11 B50,60	D54	A2,11 B38,60	D55	A3,3 B7,44
		S34	A1,2 B8,60	D56	A3,3 B18,35	D57	A3,30 B18,35	D58	A1,2 B8,60
		S35	A2,3 B7,7	D9	A1,25 B18,57	D12	A1,25 B8,18	D22	A2,3 B7,7
		S36	A1, 24 B8,51	D59	A2,25 B18,62	D49	A2,25 B7,18	D1	A1,24 B8,35
		S37	A2,3 B7,60	D60	A1,24 B8,27	D1	A1,24 B8,35	D3	A2,3 B7,60
		S38	A2,24 B7,62	D13	A1,25 B 18,57	D9	A1,25 B18,57	D61	A2,24 B7,62
		S39	A24,25 B18,18	D62	A1,2 B8,57	D63	A1,2 B8,57	D64	A24,25 B18,51
		S40	A1,3 B8,60	D16	A2,29 B44,56	D15	A2,29 B44,44	D65	A1,3 B7,60

(**d**) ***EEG recording and analysis***

The EEG was recorded unipolarly from seven electrode positions (*F3*, *Fz*, *F4*, *Cz*, *P3*, *Pz*, *P4*) in reference to linked mastoids (bandpass: 0.016–30 Hz) and grounded at the position *Oz*. The recording time was 6 s for each trial, including 1 s baseline (sample rate = 128 Hz). Eye movements were corrected off-line (Elbert *et al.* 1985). For peak detection (maximum amplitudes) the bandpass was set to 0.053–4.7 Hz.

Within the averaged potential, four peaks (*N1*, *P2*, *P3-1*, *P3-2*) were detected in relation to the averaged baseline (Pause *et al.* 1996). However, only those peaks which represented early exogenous or late endogenous stimulus processing were considered for further analysis. Therefore, CSERPs in response to the detected and rejected standard odours were compared with the CSERPs in response to the detected and rejected target odours (three-way ANOVA: detection (correct rejection, false alarms, hits, misses), anterior/posterior and hemisphere (left, central, right)). As the standard stimuli exclusively belonged to HLA-dissimilar donors, these analyses were carried out for odour stimuli from HLA-dissimilar odour donors only. Exogenous potentials were considered not to vary with the subjective stimulus significance, whereas endogenous potentials should be larger in response to subjectively meaningful (detected) stimuli.

The main statistical analysis was performed by means of a six-way ANOVA, including the factors HLA (similar/dissimilar), odour donor (same sex, opposite sex), subject (female, male), detection (hits, correctly rejected distractors), anterior/posterior and hemisphere. In case of significant interactions including the HLA factor, further analyses were carried out by isolating simple HLA effects within selected interactions, according to Levine (1991). By analysing the nested effects within selected interactions, multiple testing of

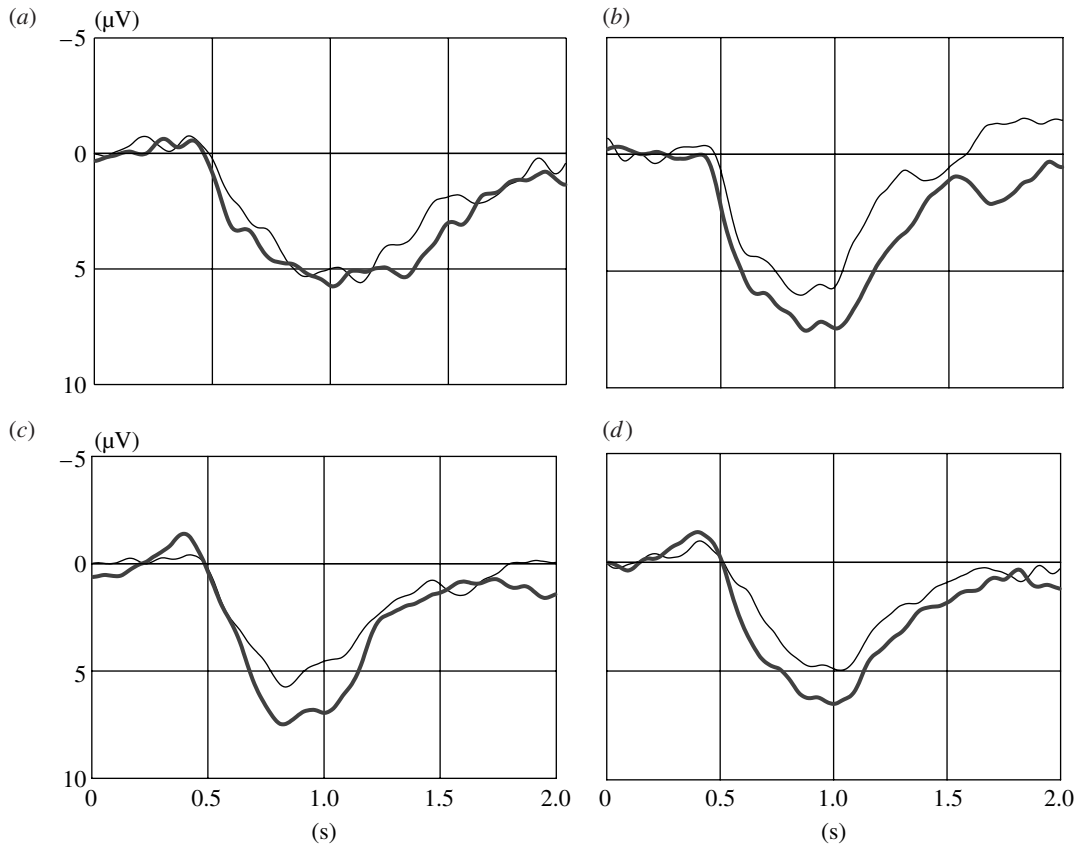

Figure 1. Grand averages across all subjects in response to body odours from HLA-similar donors (bold lines) and HLA-dissimilar donors (thin lines). (*a*) Females smelling females. (*b*) Females smelling males. (*c*) Males smelling males. (*d*) Males smelling females. All recordings from *Pz*; at time point 0 the odorous flow was activated.

single comparisons is avoided. As the standard odours did not vary in terms of HLA similarity, the main analysis was carried out for the deviant odours only.

3. RESULTS

(a) *Detection performance*

Across all conditions, 50.3% of the targets were correctly detected, and 74.6% of the standards and 52.6% of the distractors were correctly rejected. The subjects' detection performance was independent of HLA-related differences.

(b) *CSERPs in response to detected and undetected odour stimuli*

The amplitude of the *N1* was generally larger in response to rare (hits: 2.01 μV, misses: 1.84 μV) than to frequent stimuli (correct rejections: 1.17 μV, false alarms: 1.10 μV; $F(3,845)=8.50$, $p=0.004$). However, the *N1* was unaffected by the subjective task relevance of the odours. On the contrary, the amplitude of the *P3-2* did vary with the subjective stimulus meaning ($F(3,845)=5.61$, $p=0.019$): it was larger in response to detected odours (hits: 4.17 μV, false alarms: 4.27 μV) than to undetected odours (correct rejections: 3.55 μV, misses: 3.10 μV). Additionally, the *P3-2* showed a parietal maximum ($F(1,845)=219.44$, $p<0.001$; anterior: 2.05 μV, posterior: 5.5 μV) and was largest above the midline ($F(2,845)=22.50$, $p<0.001$; left: 3.04 μV, central: 4.86 μV, right: 3.42 μV). As the *P2* and the *P3-1* were neither affected by the level of detection nor by the probability of stimulus occurrence, they were not considered in further analyses.

(c) *CSERPs in response to odours of HLA-similar and HLA-dissimilar donors*

The CSERP analyses show that across all subjects body odours of HLA-similar donors were processed faster than those of HLA-dissimilar donors (Main effect of HLA-similarity on *N1* peak-latency: $F(1,34)=7.45$, $p=0.010$, power=0.755; HLA-similar: 384.5 ms, HLA-dissimilar: 407.7 ms). However, the speed of late, evaluative odour processing (*P3-2*) was not affected by the degree of HLA similarity between subject and odour donor.

Additionally, HLA-related differences between odour donors and perceivers affected the strength of the neuronal brain response during late, evaluative stimulus processing (see figure 1*a–d*). Odours of HLA-similar persons evoked larger *P3-2* potentials than odours of HLA-dissimilar donors (HLA×anterior/posterior×hemisphere: $F(2,68)=7.52$, $p=0.010$, power=0.935). Analyses of the simple main effects revealed that HLA-related differences were most prominent above medial posterior scalp areas (*Pz*; $F(1,37)=7.58$, $p=0.009$, power=0.765).

The local distribution of the HLA-effects on the *P3-2* potential was modulated by the sex of the odour donors and of the subjects. Generally, in same-sex smelling conditions (men smelling male odour or females smelling female odour), potentials evoked by odours of HLA-similar donors were larger than the cortical evoked responses to odours of HLA-dissimilar donors at medial parietal electrodes (HLA×odour donor×anterior/posterior×hemisphere: $F(2,68)=5.03$, $p=0.032$, power=0.800; nested effect for *Pz*: $F(1,37)=8.29$, $p=0.007$, power=0.801). However, analysing female

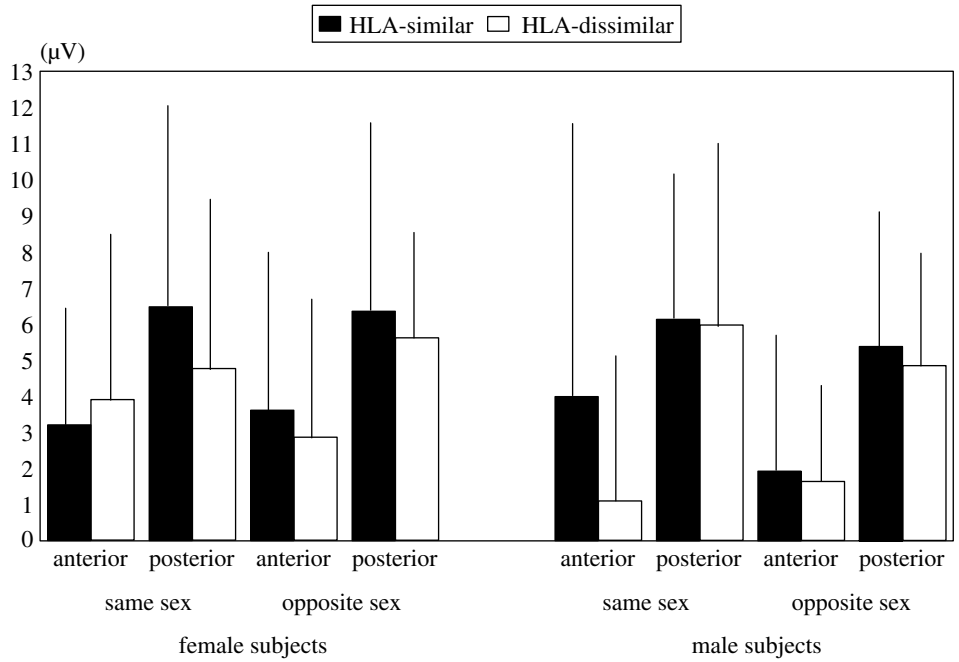

Figure 2. *P3-2* amplitudes (means and standard deviations) in response to HLA-similar and dissimilar odour donors: separation for anterior and posterior electrode positions and for the sex of the subjects and of the odour donors (HLA×odour donor×subject×anterior/posterior; $p=0.008$).

and male subjects separately (HLA×odour donor×subject×anterior/posterior: $F(1,34)=8.08$, $p=0.008$, power=0.789) it could be found that males show larger *P3-2* amplitudes in response to odours of HLA-similar males above frontal scalp areas ($F(1,37)=7.90$, $p=0.008$, power=0.782), whereas females show larger potentials to odours of HLA-similar females above parietal scalp areas ($F(1,37)=5.88$, $p=0.020$, power=0.656; see figure 2).

(d) *Subjective ratings*

Group mean differences of subjective rating data indicate that subjects tended to reject body odours of donors with a similar HLA-type more than those with a dissimilar HLA-type (table 2). Moreover, correlations (Pearson) between the ratings for the potential partner preference and the *P3-2* amplitude (μV; table 2) revealed significant results: high correlations were solely observed when subjects smelled odours from HLA-similar persons of the same sex ($p<0.05$). In females, the *P3-2* amplitude increased, the more negatively the body odours were evaluated. In males, the *P3-2* amplitude was larger, the more positively the body odours were judged.

Table 2. Mean ratings for the potential partner preferences and correlations with the *P3-2* amplitude. (Note: Ratings varied between −3 (least preference) and +3 (highest preference). Correlations were performed across all six electrodes (*F3*, *Fz*, *F4*, *P3*, *Pz*, *P4*). Level of significance: $^*p<0.05$.)

design			rating	correlation
subject	donor	HLA	(mean)	(Pearson)
females	same sex	similar	−0.05	−0.67*
		dissimilar	+0.25	−0.35
	opposite sex	similar	+0.22	−0.30
		dissimilar	+0.33	−0.20
males	same sex	similar	−0.70	+0.75*
		dissimilar	−0.35	+0.02
	opposite sex	similar	−0.11	−0.01
		dissimilar	−0.11	+0.24

4. DISCUSSION

First, the CSERP results as well as the correlation analyses of the subjective ratings reveal that odours of HLA-similar persons convey significant information, whereas odours of HLA-dissimilar persons are perceived as less relevant. Second, both analyses point to the conclusion that males and females process HLA-related chemosignals of the same sex differently.

The CSERP results are related to two components, which reflect exogenous (*N1*) and endogenous (*P3-2*) stimulus processing (Donchin & Coles 1988). The *N1* component did not vary with the subjective task relevance but was larger in response to the rare than to the frequent stimuli. This result is in accordance with the observation that the chemosensory *N1* amplitude is prone to show strong (stimulus-specific) effects of habituation (see Pause 2002). On the contrary, the *P3-2* component was larger in response to detected than to undetected odours and, additionally, showed a parietal maximum. This result is in line with a number of studies which demonstrate that the chemosensory *P3-2* component represents the features of the traditional *P3* component (reviewed by Pause & Krauel 2000). As the chemosensory *P2* might be related to exogenous stimulus processing and the *P3-1* to novelty detection (Pause *et al.* 1996), their functional significance could not be fully explained with the present data set and they were not considered for the HLA analyses.

In general, and independent of the sex of the odour donor and smeller, CSERPs were larger (*P3-2*) and appeared with a shorter latency (*N1*) when the subjects processed body odours from HLA similar donors. We suggest that the HLA effect on the *N1* latency is related to the precise neuronal timing within the primary (Spors & Grinvald 2002) and secondary (Lorig 1999)

olfactory cortex, which is important for pre-attentive odour quality discrimination. Since the *P3-2* is related to cognitive-emotional stimulus evaluation, our results indicate that more attentional resources are activated in response to body odours of HLA-similar donors than to odours from HLA-dissimilar sources.

However, one could argue that the *P3-2* in response to HLA-similar donors was larger, because the deviant stimulus 2 (HLA similar) was more different than the deviant stimulus 1 (HLA-dissimilar) from the standard stimulus (HLA-dissimilar, see table 1). However, this interpretation would indicate that HLA-related body odour differences between two people could be detected in general, without relating them to one's own HLA-type. As so far, all evidence in humans points solely to the ability of humans to detect HLA-related body odours in relation to their own HLA-type (Ober *et al.* 1997; Wedekind & Füri 1997; Jacob *et al.* 2002) it is argued strongly that the HLA-related differences in brain activity, reported here, are due to the immunogenetic relatedness between the odour donor and the perceiver. Moreover, the *N1* effect, which is independent of the oddball design, also refers to the fact that HLA-similarity is processed and is thus in line with the interpretation of the *P3-2* effect stated herein.

The fact that information about genetic similarity has a processing advantage in speed as well as in recruitment of neuronal resources is in line with findings on chemosensory and visual self-perception. As the processing of one's own body odour is faster than the processing of non-self chemical signals (Pause *et al.* 1999*b*) and as the perception of one's own face activates a distinct and unique neuronal network, including limbic and prefrontal brain areas (Kircher *et al.* 2001), the existence of a self-detecting neuronal assembly within the human brain seems to be likely. It is proposed that the detection of genetic similarity might be associated with this self-detection system, which, however, might become functional during a sensitive period in ontogenesis (see Yamazaki *et al.* 1988).

It is further concluded that the behavioural impact of chemosensory signals related to HLA-similarity is stronger than of signals related to HLA-dissimilarity. As the HLA loci are the most polymorphic loci in the human genome (Parham & Ohta 1996), the probability of meeting unrelated individuals with a dissimilar HLA-type is extremely high. Therefore, the development of a preference for potential partners with a dissimilar HLA type might be related to other factors than to chemosensory cues, whereas the rejection of potential partners with a similar or identical HLA type might be most effectively determined by the rarely occurring chemosignals of self. Furthermore, it has been proposed that MHC-regulated inbreeding avoidance might lead to higher fitness benefits than MHC-heterozygosity (Penn 2002). Accordingly, inbreeding avoidance could be successfully achieved if MHC similarity is transmitted as an avoidance behaviour activating signal.

In same sex conditions, the specific brain areas involved in the processing of HLA-related body odours are different in male and female perceivers. In males, large HLA-related potential differences occur above anterior scalp areas and in females above parietal scalp areas. The prefrontal cortex is assumed to play a key-role in the integration of valenced information (Davidson 2002; Anderson *et al.* 2003), while activity in the parietal cortex seems to be related to emotion-related arousal (Nitschke *et al.* 2000). It is, therefore, postulated that males process chemosensory signals from HLA-similar males primarily as hedonic information, while females process according signals primarily as arousing information. In line with these considerations, the most negative ratings were given by males responding to same sex odours, whereas in females, the hedonic ratings were less pronounced (table 2; group mean differences might not have reached the significance level, because the number of subjects in our electrophysiological study was much smaller than in studies designed to investigate subjective ratings). Thereby, the positive sign of the correlation in males indicates that emotionally positive odours of HLA-similar males were perceived as unexpected (average ratings are negative) and correspondingly elicited larger potentials. In contrast, females might have responded with larger potentials to odours of other HLA-similar females with an unexpected negative valence (inverse correlation; average ratings are indifferent).

As the CSERPs of females and males, responding to HLA-related body odour signals of opposite sex donors, showed similar features, it remains possible that not only females but also males are involved in human mate selection (Yamazaki *et al.* 1976; Potts *et al.* 1991; Olsson *et al.* 2003). The effect that females also responded to HLA-similarity in same sex conditions, might be equivalent to the effects of kin recognition in female mice, demonstrating that females nest communally and appear to nest with MHC-similar females when siblings are unavailable (Manning *et al.* 1992). However, the HLA-effect on the chemosensory male–male communication raises the intriguing possibility that competitive behaviour in males may be modulated by HLA-associated chemosignals. So far, it is known that competition in male behaviour and sperm production can be initiated through chemosensory signals of conspecifics (Rich & Hurst 1998; DelBarco-Trillo & Ferkin 2004), and that male competitive behaviour can facilitate female mate choice (Lenington *et al.* 1992; Candolin 1999). Furthermore, the reduced fitness in inbred mice is related to the reduced survivorship of males in competitive conditions (Meagher *et al.* 2000). Thus, male competitive behaviour could have evolved secondary to female mate choice (Moore *et al.* 2001) on the basis of the same MHC-related regulatory mechanisms.

The limitations of our study are related to the unknown relative contribution of the HLA-A and -B loci to the described effects. While so far no study in humans allows us to decide which of the different HLA genes contributes most to the individual body odour, in rats it has been shown that class I as well as class II regions of the MHC are responsible for the individuality of body odours (Brown *et al.* 1989). However, due to the fact that class I genes are expressed on the surface of all nucleated somatic cells, and that class II genes have a much more restricted expression pattern, most animal research on MHC-related body odours has focused on MHC-class I genes (see Penn 2002). In humans, the HLA-C region is the phylogenetically youngest among the classical class I genes (Kelley *et al.* 2005), and might, therefore, contribute less to chemosensory communication than the A- and B-region. We and others (Wedekind & Füri 1997) have,

therefore, focused the research on HLA-related chemoperception on the A- and B-region.

While HLA-related body odours can be differentiated by rodents (Ferstl *et al.* 1990) and via analytic technologies (Eggert *et al.* 1999*b*; Montag *et al.* 2001), so far, the signalling properties of these chemosignals have exclusively been reported in human rating studies (Wedekind & Füri 1997; Jacob *et al.* 2002). In contrast to the latter, our CSERP results show that body odours from HLA-similar sources have a processing advantage and thus may convey more significant information than those from HLA-dissimilar donors. Therefore, in humans, HLA-related signals seem to be associated to a negative selection bias in mating behaviour. Moreover, HLA-associated odour signals from same-sex persons are processed differently in males and females, pointing to different behavioural functions in male-to-male (competition) and female-to-female (communal behaviour) relations.

We thank B. Schaal, A. N. Gilbert and T. Elbert for their helpful comments on earlier drafts of the manuscript and F. Eggert for fruitful discussions throughout the experiment. Special thanks to B. Gottsmann, A. Krischer and K. Rogalski for their technical help during data acquisition. The study was supported by a grant from the Volkswagen foundation.

REFERENCES

Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D. E. & Sobel, N. 2003 Dissociated neural representations of intensity and valence in human olfaction. *Nat. Neurosci.* **6**, 196–202. (doi:10.1038/nn1001)

Brown, J. L. & Eklund, A. 1994 Kin recognition and the major histocompatibility complex: an integrative review. *Am. Nat.* **143**, 435–461. (doi:10.1086/285612)

Brown, R. E., Roser, B. & Singh, P. B. 1989 Class I and class II regions of the major histocompatibility complex both contribute to individual odors in congenic inbred strains of rats. *Behav. Genet.* **19**, 659–674. (doi:10.1007/BF01066029)

Candolin, U. 1999 Male–male competition facilitates female choice in sticklebacks. *Proc. R. Soc. B* **266**, 785–789. (doi:10.1098/rspb.1999.0706)

Davidson, R. J. 2002 Anxiety and affective style: role of prefrontal cortex and amygdala. *Biol. Psychiatry* **51**, 68–80. (doi:10.1016/S0006-3223(01)01328-2)

DelBarco, J. & Ferkin, M. H. 2004 Male mammals respond to a risk of sperm competition conveyed by odours of conspecific males. *Nature* **431**, 446–449. (doi:10.1038/nature02845)

Donchin, E. & Coles, M. G. H. 1988 Is the P300 component a manifestation of context updating? *Behav. Brain Sci.* **11**, 357–374.

Eggert, F., Ferstl, R. & Müller-Ruchholtz, W. 1999*a* MHC and olfactory communication in humans. In *Advances in chemical signals in vertebrates* (ed. R. E. Johnston, D. Müller-Schwarze & P. W. Sorensen), pp. 181–188. New York: Kluwer Academic Press.

Eggert, F., Luszyk, D., Haberkorn, K., Wobst, B., Vostrowsky, O., Westphal, E., Bestmann, H. J., Müller-Ruchholtz, W. & Ferstl, R. 1999*b* The major histocompatibility complex and the chemosensory signaling of individuality in humans. *Genetica* **104**, 265–273. (doi:10.1023/A:1026431303879)

Elbert, T., Lutzenberger, W., Rockstroh, B. & Birbaumer, N. 1985 Removal of ocular artifacts from the EEG—a biophysical approach. *Electroencephalogr. Clin. Neurophysiol.* **60**, 455–463. (doi:10.1016/0013-4694(85)91020-X)

Ferstl, R., Pause, B., Schüler, M., Luszyk, D., Eggert, F., Westphal, E. & Müller-Ruchholtz, W. 1990 Immune system signaling to the brain: MHC-specific odors in humans. In *Psychiatry: a world perspective* (ed. C. N. Stefanis, C. R. Soldatos & A. D. Rabavilas), pp. 751–755. Amsterdam: Elsevier.

Jacob, S., McClintock, M. K., Zelano, B. & Ober, C. 2002 Paternally inherited HLA alleles are associated with women's choice of male odor. *Nat. Genet.* **30**, 175–179. (doi:10.1038/ng830)

Kelley, J., Walter, L. & Trowsdale, J. 2005 Comparative genomics of major histocompatibility complexes. *Immunogenetics* **56**, 683–695. (doi:10.1007/s00251-004-0717-7)

Kircher, T. T. J. *et al.* 2001 Recognizing one's own face. *Cognition* **78**, B1–B15. (doi:10.1016/S0010-0277(00)00104-9)

Kobal, G. & Hummel, C. 1988 Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalogr. Clin. Neurophysiol.* **71**, 241–250. (doi:10.1016/0168-5597(88)90023-8)

Lenington, S., Coopersmith, C. & Williams, J. 1992 Genetic basis of mating preferences in wild house mice. *Am. Zool.* **32**, 40–47.

Levine, G. 1991 *A guide to SPSS for analysis of variance*. Hillsdale: Lawrence Erlbaum.

Lorig, T. S. 1999 On the similarity of odor and language perception. *Neurosci. Biobehav. Rev.* **23**, 391–398. (doi:10.1016/S0149-7634(98)00041-4)

Manning, C. J., Wakeland, E. K. & Potts, W. K. 1992 Communal nesting patterns in mice implicate MHC genes in kin recognition. *Nature* **360**, 581–583. (doi:10.1038/360581a0)

Montag, S., Frank, M., Ulmer, H., Wernet, D., Göpel, W. & Rammensee, H.-G. 2001 "Electronic nose" detects major histocompatibility complex-dependent prerenal and postrenal odor components. *Proc. Natl Acad. Sci. USA* **98**, 9249–9254. (doi:10.1073/pnas.161266398)

Meagher, S., Penn, D. J. & Potts, W. K. 2000 Male–male competition magnifies inbreeding depression in wild house mice. *Proc. Natl Acad. Sci. USA* **97**, 3324–3329. (doi:10.1073/pnas.060284797)

Moore, A. J., Gowaty, P. A., Wallin, W. G. & Moore, P. J. 2001 Sexual conflict and the evolution of female mate choice and male social dominance. *Proc. R. Soc. B* **268**, 517–523. (doi:10.1098/rspb.2000.1399)

Moshkin, M. P., Gerlinskaya, L. A. & Evsikov, V. I. 2000 The role of the immune system in behavioral strategies of reproduction. *J. Reprod. Dev.* **46**, 341–365. (doi:10.1262/jrd.46.341)

Nitschke, J. B., Heller, W. & Miller, G. A. 2000 Anxiety, stress, and cortical brain function. In *The neuropsychology of emotion* (ed. J. C. Borod), pp. 298–319. Oxford: Oxford University Press.

Ober, C., Weitkamp, L. P., Cox, N., Dytch, H., Kostyu, D. & Elias, S. 1997 HLA and mate choice in humans. *Am. J. Hum. Genet.* **61**, 497–504. (doi:10.1017/S0003480097006532)

Olsson, M., Madsen, T., Nordby, J., Wapstra, E., Ujvari, B. & Wittsel, H. 2003 Major histocompatibility complex and mate choice in sand lizards. *Proc. R. Soc. B* **270**(Suppl.), S245–S256.

Parham, P. & Ohta, T. 1996 Population biology of antigen presentation by MHC class I molecules. *Science* **272**, 67–74.

Pause, B. M. 2002 Human brain activity during the first second after odor presentation. In *Olfaction, taste, and*

cognition (ed. C. Rouby, B. Schaal, D. Dubois, R. Gervais & A. Holley), pp. 309–323. Cambridge: Cambridge University Press.

Pause, B. M. & Krauel, K. 2000 Chemosensory event-related potentials (CSERP) as a key to the psychology of odors. *Int. J. Psychophysiol.* **36**, 105–122. (doi:10.1016/S0167-8760(99)00105-1)

Pause, B. M., Sojka, B., Krauel, K. & Ferstl, R. 1996 The nature of the late positive complex within the olfactory event-related potential (OERP). *Psychophysiology* **33**, 376–384.

Pause, B. M., Sojka, B. & Ferstl, R. 1997 Central processing of odor concentration is a temporal phenomenon as revealed by chemosensory event-related potentials (CSERP). *Chem. Senses* **22**, 9–26.

Pause, B. M., Krauel, K., Sojka, B. & Ferstl, R. 1999*a* Is odor processing related to oral breathing? *Int. J. Psychophysiol.* **32**, 251–260. (doi:10.1016/S0167-8760(99)00020-3)

Pause, B. M., Krauel, K., Sojka, B. & Ferstl, R. 1999*b* Body odor evoked potentials: a new method to study the chemosensory perception of self and non-self in humans. *Genetica* **104**, 285–294. (doi:10.1023/A:1026462701154)

Penn, D. J. 2002 The scent of genetic compatibility: sexual selection and the major histocompatibility complex. *Ethology* **108**, 1–21. (doi:10.1046/j.1439-0310.2002.00768.x)

Penn, D. J. & Potts, W. K. 1999 The evolution of mating preferences and major histocompatibility genes. *Am. Nat.* **153**, 145–164. (doi:10.1086/303166)

Potts, W. K., Manning, C. J. & Wakeland, E. K. 1991 Mating patterns in seminatural populations of mice influenced by MHC genotype. *Nature* **352**, 619–621. (doi:10.1038/352619a0)

Rich, T. J. & Hurst, J. L. 1988 Scent marks as reliable signals of the competitive ability of mates. *Anim. Behav.* **56**, 727–735. (doi:10.1006/anbe.1998.0803)

Singh, P. B. 2001 Chemosensation and genetic individuality. *Reproduction* **121**, 529–539. (doi:10.1530/rep.0.1210529)

Spors, H. & Grinvald, A. 2002 Spatio-temporal dynamics of odor representations in the mammalian olfactory bulb. *Neuron* **34**, 301–315. (doi:10.1016/S0896-6273(02)00644-X)

Wedekind, C. & Füri, S. 1997 Body odour preferences in men and women: do they aim for specific MHC combinations or simply heterozygosity? *Proc. R. Soc. B* **264**, 1471–1479. (doi:10.1098/rspb.1997.0204)

Yamazaki, K., Boyse, E. A., Mike, V., Thaler, H. T., Mathieson, B. J., Abbott, J., Boyse, J., Zayas, Z. A. & Thomas, L. 1976 Control of mating preferences in mice by genes in the major histocompatibility complex. *J. Exp. Med.* **144**, 1324–1335. (doi:10.1084/jem.144.5.1324)

Yamazaki, K., Beauchamp, G. K., Kupniewski, J., Bard, J., Thomas, L. & Boyse, E. A. 1988 Familial imprinting determines H-2 selective mating preferences. *Science* **240**, 1331–1332.

As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.