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A predicted interaction between odour pleasantness and intensity provides evidence for MHC social signalling in women

Claus Wedekind
Department of Ecology and Evolution, Biophore, University of Lausanne, Lausanne, Switzerland

MHC social signalling has been found in over 20 vertebrate species so far and is "… *likely the basis for a vertebrate-wide chemosensory communication system*" [1]. Numerous further examples of MHC social signalling have been published since Ruff et al.'s [1] exhaustive review, both demonstrating female reactions to MHC sharing with males [e.g. 2, 3] and male reactions to MHC sharing with females [e.g. 4, 5, 6, 7]. When concentrating on experimental studies in humans, 15 papers so far claimed to provide evidence for MHC-linked odours and/or odour preferences (Supplementary Table S1), and a recent meta-analysis concluded that MHC-linked preferences are "… *likely conserved across primates*" [8]. Well worked-out cases of absent MHC social signalling would therefore be interesting exceptions of what seems to be a general rule, and it is important to find and document such exceptions to learn more about the principles of social signalling. However, as easy as it is to miss an existing effect (e.g. because of problematic experimental protocols or low statistical power), it is just as challenging to demonstrate that an effect does not exist.

Probst et al. [9] argue that they found an example of absent MHC social signalling. They studied men's preferences of women's body odours, following an experimental design that is largely analogous to the one Wedekind et al. [10] had used when they found women's preferences for men's odours to be MHC linked. Probst et al. [9] collected armpit odours from donors and presented 8 of them to raters, with 4 of them being very MHC-dissimilar, and the other 4 very MHC-similar (i.e. testing only the extremes; Wedekind et al. [10] had presented 3 of the extremes each). Both groups studied Swiss students and tried to make sure that their samples were ethnically closely defined (ethnicity can be a confounding factor in studies of MHC social signalling [11, 12]). However, there are important differences between the two studies that can lead to wrong conclusions.

First, if evidence for MHC social signalling is found [10], with preferences depending on MHC sharing, it is possible to conclude that there are effects of the MHC (or linked genes) on both sides of the communication, i.e. the donors' body odours contain MHC-linked signals and the raters' odour preferences are linked to their own MHC. If there were indeed no evidence for MHC social signalling, it remained unclear whether there is no influence of the MHC on the production of odours (donor effects) or on the perception of odours (rater effects), or on both. Probst et al. [9] proposed that the "… *HLA has no effect on men's odour preferences*" (their Abstract; the human's MHC is called human leukocyte antigen, HLA). However, it is still possible that men have MHC-linked preferences and that, in Probst et al. [9], women's body odours did not contain MHC-linked signals, or that these signals were too weak to be detected. Wedekind and Füri [13] tested for MHC-linked odour preferences and found evidence for MHC-linked odour preferences in both, men and women. They recorded the preferences of 121 male and female raters of the same 6 odours (from 2 female and 4 male donors) and found the amount of variance (r^2) in pleasantness scoring that was explained by the sharing of MHC antigens between

donors and raters to vary between nearly 0 and 22.6%. The highest r^2 was found when male raters evaluated the odour of a male donor, while the r^2 turned out to be low for the 2 female donors, i.e. the question whether women signal their MHC was not solved yet (see also Table S1). A further consequence of the low number of odour donors in their study was that possibly confounding effects of non-MHC linked stimuli could not be sufficiently excluded. However, evidence for MHC-linked preferences in both, men and women, was again found in another study on body odours [12], when studying preferences for traditional perfume ingredients [14], or in electroencephalograms of subjects smelling human odour samples (axillary hairs) [15] (Table S1). Male preferences for MHC-dissimilar females have also been found in other species [e.g. 4, 5, 6, 7]. Given these repeated accounts of MHC-linked preferences in men or males, the most parsimonious explanation for the non-significant findings of Probst et al. [9] is that the odours of their donors did not contain strong MHC-linked signals. However, it would also be premature to conclude that there is no MHC social signalling in women. This is because of the second important deviation from previous studies.

In previous studies [10, 13], all donors except one had unshaved armpits, while all donors in Probst et al. [9] were asked to shave their armpits shortly before collection of odours because "… *axillary hair might affect perceived quality of the axillary odour …*" (their Supplementary Material 1). Indeed, odours of shaved armpits are typically perceived as less intense than odours of unshaved armpits [16]. Moreover, the density of apocrine glands is highest in the armpit and few other regions, including the genitoanal regions, and the microbial processing of apocrine secretions that plays an important role in producing body odours is enhanced by axillary and pubic hair [17]. This may be some of the reasons why shaving armpits and using anti-microbial deodorants have become social norms among women in many parts of the world. If the functional significance of armpit hair is to enhance social signalling [15], shaving them reduces this type of signalling. We would then predict that odour intensities and the statistical link to MHC would be reduced. Indeed, the raters in Probst et al. [9] stated in 37 cases that they "… *cannot smell the sample*" [9] while this never happened in the analogous study that allowed for axillary hairs [10]. Moreover, the odours that could be perceived were on average rated as less intense in Probst et al. [9, 18] than in the analogous study that allowed for axillary hairs [10, 19] (mean ± S.E. = 49.7 ± 0.1 vs 60.5 ± 0.1 on a scale from 0-100; $F_{1,1000}$ = 37.0, $p < 0.0001$). A reduced signal intensity could be responsible for the apparent absence of MHC social signalling [9]. However, Probst et al. [9] did not yet test all hypotheses about MHC social signalling that can be derived from previous studies.

Numerous psychophysical studies demonstrate that the relationship between mixtures of volatile chemicals and their perception can be complex and difficult to predict [20]. Empirical observations may therefore be required to obtain testable predictions. Wedekind et al. [10] observed that odour pleasantness correlated negatively with odour intensity if donors and raters were MHC dissimilar ($p = 0.01$) but not if they were MHC similar ($p = 0.98$; see their Fig. 3). The causalities behind this link to MHC sharing is still unclear, but the observation [10] leads to the testable prediction that MHC social signals affect the perception of odour pleasantness in combination with odour intensity.

I used mixed models (in Jmp®; www.jmp.com) to test this hypothesis with the data provided by Probst et al. [18], predicting odour pleasantness by the two (fixed) factors odour intensity and MHC sharing (similar or dissimilar) while controlling for effects of rater identity or donor identity (random factors; controlling for donor

identity is predicted to provide more statistical power than controlling for rater identity [21]). This reanalysis revealed an overall negative correlation between pleasantness and intensity of odours (as reported before [9]) that was, however, dependent on whether donors and raters were similar or dissimilar on their MHC (see significant interactions in Table 1). As predicted [10], the link between pleasantness and intensity was significantly more pronounced in MHC-dissimilar pairs than in MHC-similar pairs (Supplementary Fig. S1). This finding seemed independent on whether the mixed model controlled for rater or for donor identity (Table 1). When combining the datasets of Probst et al. [18] and Wedekind et al. [10] in one statistical model, the effects of intensity and MHC sharing did not seem to change (Supplementary Table S2). There were study differences in mean pleasantness scorings and interaction effects on pleasantness (Table S2) that tended to be stronger when controlling for donor identity than for rater identity. Importantly, however, the three-way interactions (study x intensity x MHC sharing) did not explain pleasantness, i.e. both studies found a similar intensity x MHC interactions on pleasantness (Table S2).

In summary, Probst et al.'s [9] conclusions about MHC social signalling in humans were premature. Their experimental set up would not allow to distinguish between an absence of MHC-linked odour preferences in men and an absence of MHC social signalling in women (while evidence for both types of MHC effects had been found before in humans and other vertebrates). Moreover, their protocol reduced the chances of finding MHC-linked signals, because women were asked to shave their armpit hair that are expected to enhance signals based on body odours. Nevertheless, a reanalysis of Probst et al.'s data [18] revealed a weak but statistically significant interaction between odour intensity and MHC sharing on odour pleasantness in the predicted direction [10]. The link between odour intensity and pleasantness was significantly stronger in MHC-dissimilar pairs than in MHC-similar pairs. Therefore, Probst et al.'s data [18] provide evidence for both, MHC social signalling in women and MHC-linked odour preferences in men.

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Table 1: Mixed-effects analyses of pleasantness scorings in Probst et al. [18] testing the effects of the sharing of MHC antigens between donor and rater (dissimilar versus similar; "MHC") and odour intensity ("intensity") as fixed factors, and rater identity or donor identity ("ID") as random factors. The proportions of the total variance explained are based on REML variance component estimates (unbounded). Significant p-values are marked in bold.

	Pleasantness[1]		Pleasantness[2]	
Fixed factors	*F*	*p*	*F*	*p*
MHC	0.4	0.55	1.5	0.23
Intensity	60.7	**<0.001**	35.0	**<0.001**
MHC x intensity	4.4	**0.04**	4.4	**0.04**
Random factors				
ID	4.4%		7.4%	
ID x MHC	0.6%		0%	
ID x intensity	43.8%		0%	
ID x MHC x intensity	17.8%		51.8%	
Residual	33.5%		40.8%	

[1] with rater identity as random factor; [2] with donor identity as random factor

Electronic Supplementary Material 1

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C. Wedekind, Department of Ecology and Evolution, Biophore, University of Lausanne, Lausanne, Switzerland

Supplementary Table S1. Studies that tested experimentally for MHC-linked body or urinary odours and/or odour preferences in humans, based on a search in Web of Science *(www.webofknowledge.com),* starting with the keywords "HLA" and "odour", and examining studies that cited, or were cited by, the papers that matched the search criteria. The table summarizes the conclusions drawn by the authors of the respective paper, with "yes" = the authors concluded that they had found evidence for MHC-linked effects on odours or odour perception; "(yes)" = both sexes were included and analyses were not sex-specific; "." = link to MHC was not tested; "?" = the role of the MHC remained unclear because there was no statistically significant link. The column "Critique & authors' reply" refers to commentary papers that specifically addressed aspects of the respective paper.

Study	MHC-linked odours		MHC-linked odour perception		Comments	Critique & authors' reply
	men	women	men	women		
Gilbert et al. (1986) [1]	.	.	(yes)	(yes)	Humans evaluating odours of MHC-congenic mice.	
Ferstl et al. (1992) [2]	(yes)	(yes)	.	yes	Human urinary odours evaluated by rats; women reporting peculiar odour perception phenomena.	
Wedekind et al. (1995) [3]	yes	.	.	yes	Users of contraceptive Pill had different preferences than non-Pill users.	[4], [5]
Wedekind & Füri (1997) [6]	yes	?	yes	yes	No significant sex differences in MHC-linked preferences; strongest MHC-linked preference for one male odour ($r^2 = 0.23$).	
Eggert et al. (1999) [7]	yes	yes	.	.	Human odours evaluated by rats and in gas chromatography.	
Milinski & Wedekind (2001) [8]	.	.	yes	yes	MHC-linked preferences for some traditional perfume ingredients.	
Jacob et al. (2002) [9]	yes	.	.	yes	Preferences tested in a group of low genetic diversity.	[10], [11]
Thornhill et al. (2003) [12]	yes	yes	yes	yes	Preferences of male odours linked to MHC heterozygosity, preferences of female odours linked to MHC similarity.	
Santos et al. (2005) [13]	yes	?	?	yes	Potential effects of the contraceptive pill not included in analyses.	
Pause et al. (2006) [14]	yes	yes	yes	yes	Analysing electroencephalograms with axillary hairs as odour samples.	
Wedekind et al. 2007 [15]	yes	.	?	yes	Descriptions of body odours by a female perfumer.	
Roberts et al. (2008) [16]	yes	.	.	yes	Odour preferences shifted towards MHC similarity with use of the contraceptive Pill (as predicted in [3])	
Janes et al. (2010) [17]	?	?	(yes)	(yes)	MHC-linked preferences to artificial scents, no significant link to body odours (the authors discuss ethnic diversity as potentially confounding).	
Natsch et al. (2010) [18]	?	?	.	.	Testing for MHC effects on N-acylglutamine conjugates of volatile carboxylic acids secreted in the axilla.	
Hämmerli et al. (2012) [19]	.	.	(yes)	(yes)	MHC-linked preferences for some traditional perfume ingredients	
Milinski et al. (2013) [20]	.	.	.	yes	Supplementation of own body odour by synthesized MHC peptides.	[21], [22]
Verhulst et al. (2013) [23]	?	.	.	.	Testing MHC effects on attractiveness of odours to mosquitoes.	
Probst et al. (2017) [24]	.	?	?	.		present paper
Present reanalysis of Probst et al.	.	yes	yes	.		

The table only lists studies that tested for potential MHC effects on odours or odour preferences in humans. It does not list studies that tested for links between MHC and facial or skin characteristics [e.g. 25, 26, 27] or that tested for potential MHC effects on mate choice, sexual responsivity, or fertility in humans for which some studies did not find significant MHC effects [e.g. 28, 29] while others found statistically significant links to the MHC [e.g. 30, 31, 32-34].

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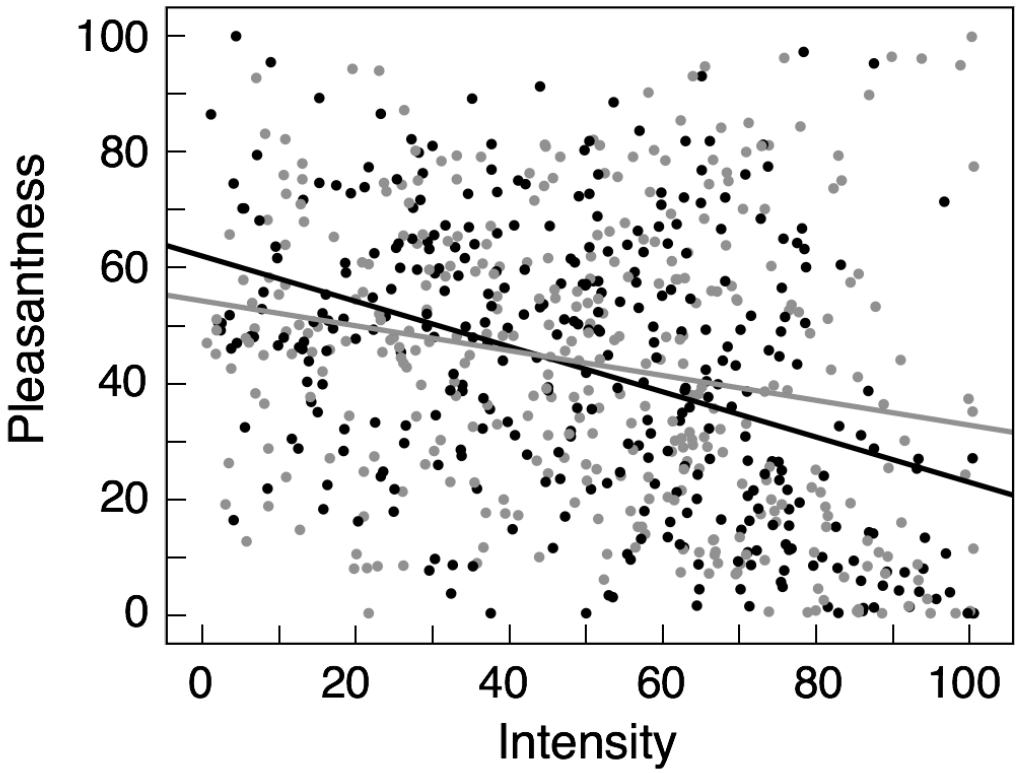
Electronic Supplementary Material 2

A predicted interaction between odour pleasantness and intensity provides evidence for MHC social signalling in women

C. Wedekind, Department of Ecology and Evolution, Biophore, University of Lausanne, Lausanne, Switzerland

Supplementary Figure S1. Pleasantness versus intensity of body odour of MHC-dissimilar (black symbols and line) and MHC-similar pairs (grey symbols and line) of odour donor and rater in Probst et al. [1]. The lines show the regressions. See Table 1 for statistics.



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Electronic Supplementary Material 3

A predicted interaction between odour pleasantness and intensity provides evidence for MHC social signalling in women

C. Wedekind, Department of Ecology and Evolution, Biophore, University of Lausanne, Lausanne, Switzerland

Supplementary Table S2: Mixed-effects analyses of pleasantness scorings in the combined datasets of Probst et al. [1] and Wedekind et al. [2], testing the effects of the sharing of MHC antigens between donor and rater (dissimilar versus similar; "MHC"), odour intensity ("intensity"), and "study" (Probst et al. [1] versus Wedekind et al. [2]) as fixed factors, and rater identity or donor identity ("ID") as random factors. The proportions of the total variance explained are based on REML variance component estimates (unbounded). Significant p-values are marked in bold.

	Pleasantness[1]		Pleasantness[2]	
Fixed factors	*F*	*p*	*F*	*p*
MHC	2.0	0.16	1.0	0.33
Intensity	120.2	**<0.001**	64.5	**<0.001**
MHC x intensity	4.1	**0.05**	5.2	**0.02**
Study	35.0	**<0.001**	15.2	**<0.001**
Study x MHC	5.3	**0.02**	5.6	**0.02**
Study x intensity	2.2	0.14	5.3	**0.03**
Study x MHC x intensity	0.1	0.72	0.01	0.91
Random factors				
ID	0%		5.7%	
ID x MHC	1.9%		0%	
ID x intensity	0%		0%	
ID x MHC x intensity	54.9%		0%	
ID x study	2.9%		0%	
ID x study x MHC	0%		4.9%	
ID x study x intensity	37.3%		45.4%	
ID x study x MHC x intensity	0%		40.7%	
Residual	3.0%		3.3%	

[1] with rater identity as random factor; [2] with donor identity as random factor

Literature cited

1. Probst F., Fischbacher U., Lobmaier J.S., Wirthmüller U., Knoch D. 2017 Data from: Men's preferences for women's body odours are not associated with HLA. In *Dryad Digital Repository* (10.5061/dryad.270h8)
2. Wedekind C., Seebeck T., Bettens F., Paepke A.J. 1995 Data from: MHC-dependent mate preferences in humans. In *Dryad Digital Repository* (10.5061/dryad.r87pq)