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A predicted interaction between odour pleasantness and intensity provides evidence for major histocompatibility complex social signalling in women

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Major histocompatibility complex (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. [4–7]). When concentrating on experimental studies in humans, 15 papers so far claimed to provide evidence for MHC-linked odours and/or odour preferences (electronic supplementary material, 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, 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 eight of them to raters, with four of them being very MHC-dissimilar, and the other four very MHC-similar (i.e. testing only the extremes; Wedekind *et al*. [10] had presented three 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 & 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 six odours (from two female and four male donors) and found the amount of variance (r^2) in

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 italic.

	pleasantness[a]		pleasantness[b]	
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 × intensity	4.4	*0.04*	4.4	*0.04*
random factors				
ID (%)	4.4		7.4	
ID × MHC (%)	0.6		0	
ID × intensity (%)	43.8		0	
ID × MHC × intensity (%)	17.8		51.8	
residual (%)	33.5		40.8	

[a]With rater identity as random factor.
[b]With donor identity as random factor.

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 two female donors (i.e. the question of whether women signal their MHC was not solved yet; see also electronic supplementary material, 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] (electronic supplementary material, table S1). Male preferences for MHC-dissimilar females have also been found in other species (e.g. [4–7]). 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 the perceived quality of the axillary odour' (their electronic supplementary material S1). 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 a 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]. These 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 $\pm$ s.e. $= 49.7 \pm 0.1$ versus 60.5 ± 0.1 on a scale from 0 to 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 (electronic supplementary material, figure S1). This finding seemed independent of 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 (electronic supplementary material, table S2). There were study differences in mean pleasantness scorings and interaction effects on pleasantness (electronic supplementary material, table S2) that tended to be stronger when controlling for donor identity than for rater identity. Importantly, however, the three-way interactions (study × intensity × MHC sharing) did not explain pleasantness (i.e. both studies found a similar intensity × MHC interaction on pleasantness; electronic supplementary material, 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. 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.

Data accessibility. This article has no additional data.

Competing interests. I declare I have no competing interests.

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