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points, but was not seen at earlier time points or in the two unexposed control birds. This may be indicative of antigen or viral exposure or an abortive infection.

These data show that the TG-D5 chickens did not efficiently transmit infection to birds housed with them, but the specific mechanism underlying this effect is not known. Polymerase decoys may disrupt replication by direct binding to polymerase or indirectly by influencing the level of expression of the recently discovered, putative regulatory small viral RNA molecules (14, 15) (which may also have a role in innate immunity). Although decoy 5 suppressed polymerase activity in cell culture, this did not translate into a quantitative reduction in virus shedding from infected birds (Fig. 2) (nor have we found any effect in ovo or in fibroblast cell culture). Polymerase-RNA interactions may be involved in the virus packaging process, but after passage through TG-D5 chick embryo fibroblasts in cell culture, we have not found any effect on the genome:plaque-forming unit ratio of the virus to support the hypothesis that the decoy induced the formation of defective virus particles. The standard intravenous pathogenicity index of the virus shed from one of the TG-D5 chickens (#4457, dpi = 2) was determined after a single passage in embryonated hens' eggs and found to be unaltered, indicating that passage through TG-D5 chickens does not rapidly select for a stable genetic change that reduces the virulence of the shed virus.

Our goal was a proof-of-principle demonstration that genetic modification can be used to prevent avian influenza infection in chickens. The TG-D5 birds exhibited a marked absence of onward transmission of infection, even to unprotected (nontransgenic) chickens housed in direct contact with them. This property could have a major impact on susceptibility and propagation of infection at the flock level and supports the concept of genetic modification for controlling AIV infection in poultry. Our strategy offers substantial potential benefits over vaccination. Although conventional AIV vaccines can achieve strain-specific clinical resistance to primary challenge, sterile immunity is not achieved (3). Such vaccination can allow the cryptic circulation of virus in flocks, facilitating antigenic drift and posing a risk to unvaccinated birds and humans that come into contact with them. In contrast, onward transmission and circulation at the flock level are absent in the TG-D5 chickens. The decoy 5 RNA corresponds to an absolutely conserved sequence that is essential for the regulation of viral transcription, replication, and packaging of all subtypes of influenza A virus, offering pan-subtype A protection, whereas vaccination offers no protection against unmatched viral strains. Unlike proposed micro-RNA-based strategies (4, 5), the development of resistant virus is intrinsically unlikely, requiring mutations in the polymerase and the promoter of all eight genome segments simultaneously, a statistically highly improbable event.

The control of avian influenza by genetic modification brings obvious health benefits to consumers and producers, as well as welfare and productivity benefits to the birds. Nevertheless, it is important to assess any genetic modification for potential hazards. Here, the transgene encodes an innocuous decoy RNA, expressed at steady-state levels that are barely detectable by conventional methods and unlikely to present a risk to consumers, birds, or the wider environment. There are no apparent ill-effects on uninfected transgenic birds, which are phenotypically normal and show no significant deviation from the expected Mendelian frequency or differences in hatch weights (fig. S4 and table S2). The transgene is not expected to alter susceptibility to other pathogens, although this has yet to be confirmed. Transgenes can be introduced into multiple founder lines as discrete traits without affecting other genetic properties of the lines. This will facilitate the permanent introduction of novel disease-resistance traits into the mass population of production birds via conventional breeding techniques, with little impact on genetic diversity or valuable production traits. Our approach is technically applicable to other domestic species that are hosts of influenza A, such as pigs, ducks, quail, and turkeys. Further development of transgenic disease resistance in poultry and other farm animals will undoubtedly stimulate debate about the application of this technology in food production.

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Supporting Online Material

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Methods
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Human Tears Contain a Chemosignal

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Emotional tearing is a poorly understood behavior that is considered uniquely human. In mice, tears serve as a chemosignal. We therefore hypothesized that human tears may similarly serve a chemosignaling function. We found that merely sniffing negative-emotion-related odorless tears obtained from women donors induced reductions in sexual appeal attributed by men to pictures of women's faces. Moreover, after sniffing such tears, men experienced reduced self-rated sexual arousal, reduced physiological measures of arousal, and reduced levels of testosterone. Finally, functional magnetic resonance imaging revealed that sniffing women's tears selectively reduced activity in brain substrates of sexual arousal in men.

Charles Darwin suggested that expressive behaviors initially served emotion-relevant functions, before evolving to serve as emotion-signals alone (1, 2). Thus, the behavior of emotional tearing, considered uniquely human

(3), is a paradox: Whereas tears clearly serve as an emotional signal (4), tears were not related to any emotionally relevant function. Despite psychological theories on the meaning of tears (5, 6) and biological theories describing tears as an adaptation related to their eye-protective nature (3) or a mechanism for expelling toxic substances (7), the functional significance of emotional tears remains unknown (8).

Tears are drops of liquid produced by the lacrimal, accessory lacrimal, and Meibomian glands, which contain proteins, enzymes, lipids, metabo-

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lites, electrolytes, and traces of drugs (9). In mice, tears contain a chemosignal or pheromone (10–12). Because the chemical makeup of human emo-

tional tears differs from that of reflexive eye-protective tears (13), we hypothesized that human tears may similarly convey a chemosignal.

We first asked whether emotional tears have a discernable odor. We obtained negative-emotion tears from two donor women (ages 30 and 31)

Fig. 1. Emotional tears are odorless. (A) To obtain tears, donor women watched sad films in isolation, using a mirror to capture tears into a vial. A typical donation contained ~1 ml. (B) For continuous exposure, tears deposited onto a pad allowed ongoing nasal airflow exposure but not transdermal diffusion. (A) and (B) are illustrations. (C) Accuracy of discrimination of tears from saline. (D to F) Scatterplots of (D) intensity, (E) pleasantness, and (F) familiarity estimates of tears and saline in all experiments. Within-participants comparisons [(D) to (F) here and in all other figures] are presented in scatterplots along a unit slope line ($x = y$), where each point reflects a participant. If data accumulate under the line, then values were greater for tears; if data accumulate above the line, then values were greater for saline. If data accumulate on the line, then there was no difference between tears and saline. (Insets) Bars reflect the number of participants on each side of the unit slope line (left ordinate), and the horizontal dashed line reflects the mean values and standard error (right ordinate).

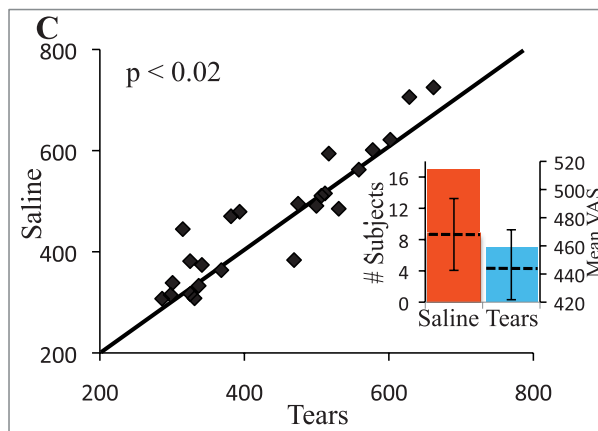
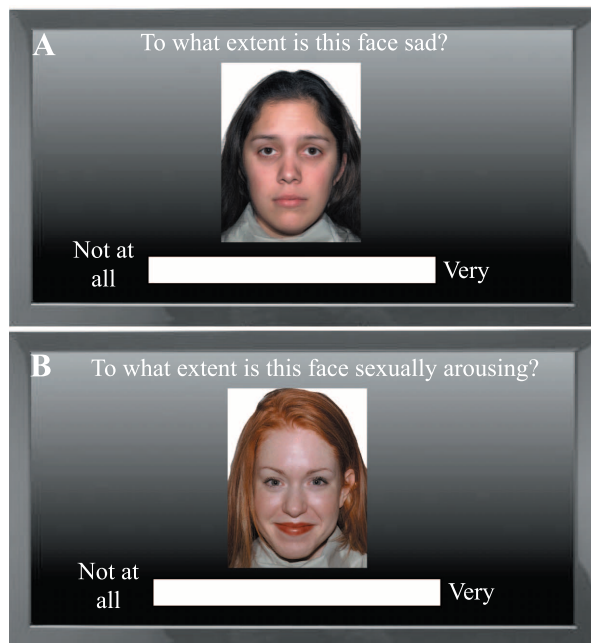
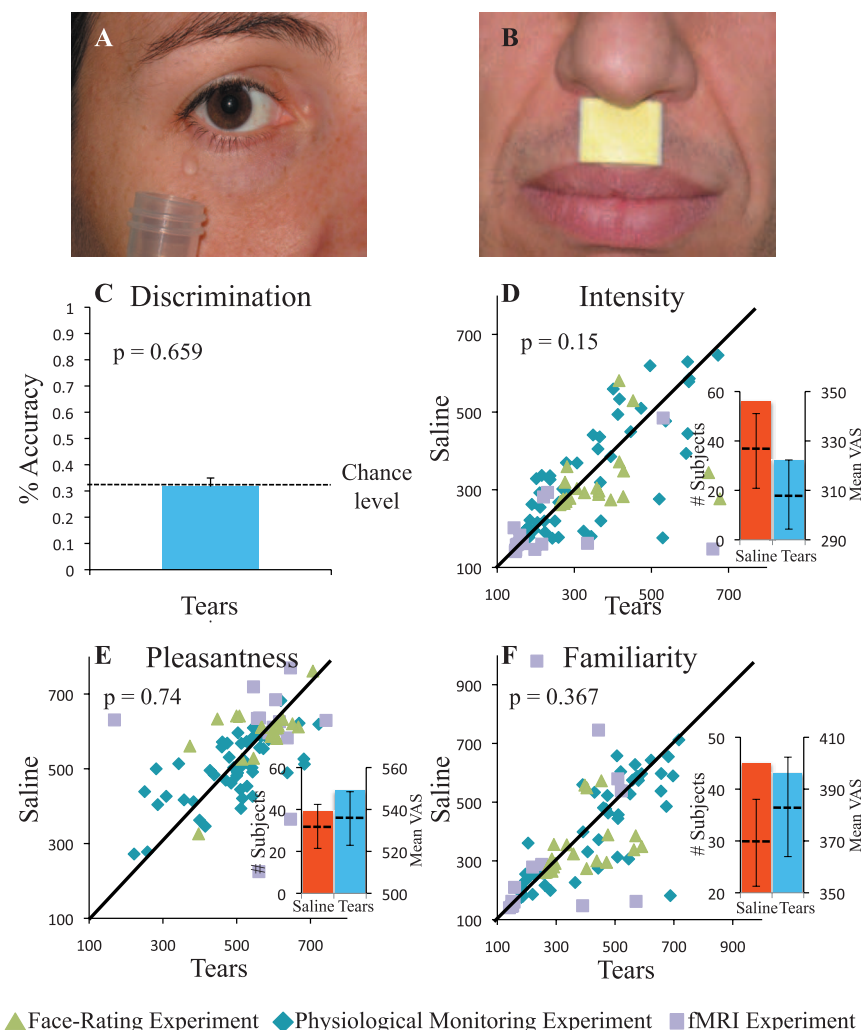


Fig. 2. Sniffing tears reduces attributed sexual attraction. (A) and (B) Typical VAS questions from the face-rating experiment. (C) Attributed sexual attraction by 24 men. Data accumulated above the line, indicating reduced attributed sexual attraction after sniffing tears. (Inset) Bars reflect the number of participants on each side of the unit slope line (left ordinate), and the horizontal dashed line reflects the mean values and standard error (right ordinate).

who watched sad films in isolation [Fig. 1A and supporting online material (SOM)]. We then tested whether 24 men (mean age 28.12 ± 4.05 years) could smell a difference between these fresh tears and saline. The saline was first trickled down the cheek of the donor women to account for any skin-bound odor sources. Participants failed to discriminate the smell of tears from the smell of saline [mean correct = $31 \pm 14\%$, $t(23) = 0.81$,

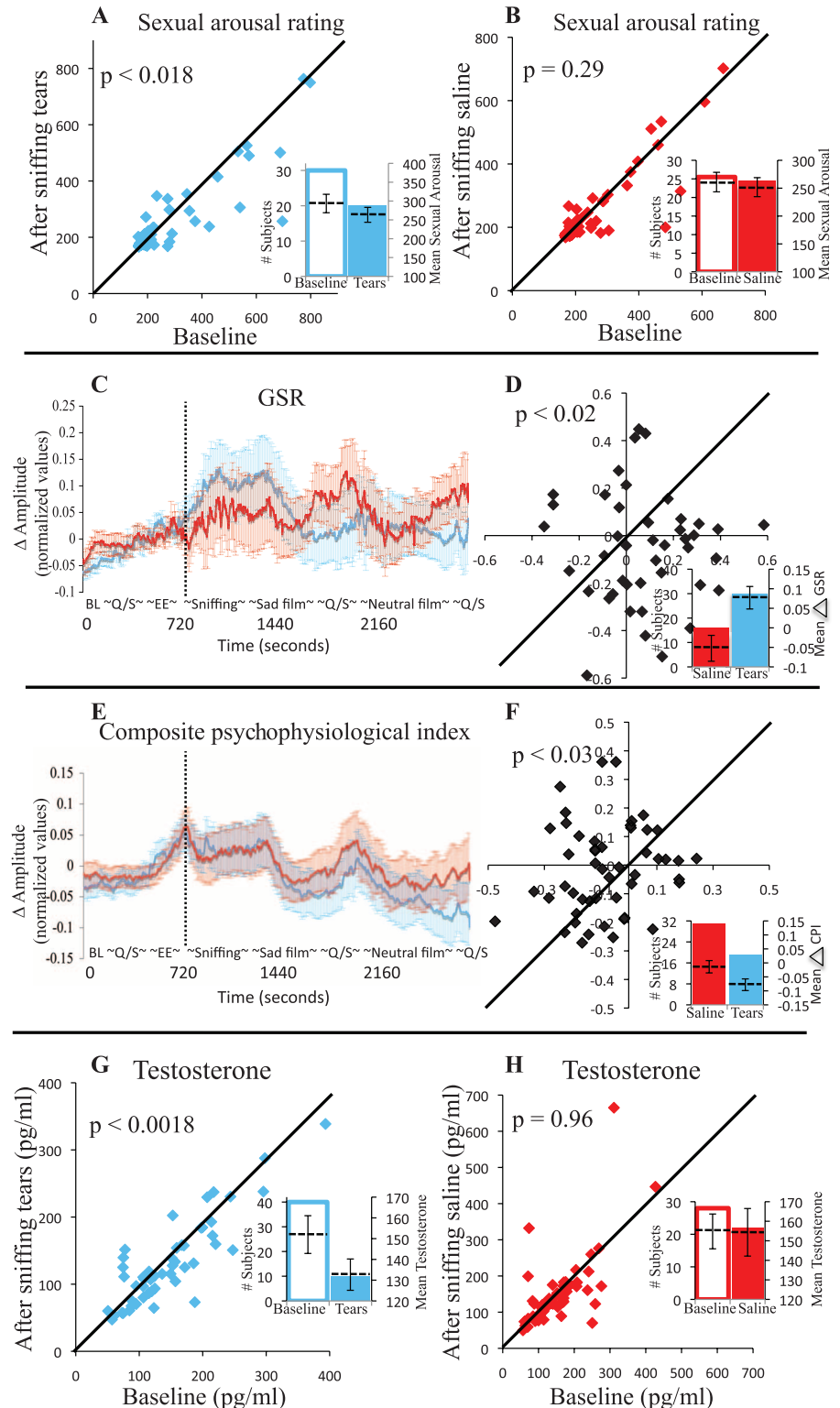
$P < 0.659$; Fig. 1C], indicating that emotional tears did not have a discernable odor.

We next asked whether sniffing such odorless tears influences perception. We compared two alternative hypotheses: (i) Tears may contain a chemosignal related to their typical context of sadness (14). Indeed, seeing tears on faces renders the faces sadder in appearance (4). (ii) Alternatively, human tears may function like mouse

tears, where they signal information related to sociosexual behavior (10–12).

Twenty-four men (mean age 26.92 ± 3.13 years) first sniffed a jar containing a compound (fresh tears or trickled saline; tears were from three donor women, mean age 30.33 ± 0.5 years) and then rated the compound's intensity, pleasantness, and familiarity. To keep study participants exposed to the compound for the rest of

Fig. 3. Sniffing tears reduces arousal. **(A)** Shift in self-rated sexual arousal from baseline to ~5 min after sniffing tears, indicating a drop in arousal. **(B)** Shift in self-rated sexual arousal from baseline to ~5 min after sniffing saline, indicating no change. **(C and E)** Timeline of psychophysiological data. Data were aligned in time to the first sniff (dashed vertical line). The abscissa lists the time in seconds and the experimental phases. BL, baseline; Q/S, VAS mood questionnaire, followed by a saliva sample; EE, experimenter enters room. Experimental phases are approximately (~) accurate in time, because participants differed in questionnaire latency, resulting in a shift of a few seconds. Error bars reflect between-participants variance, here displayed only to give a better sense of the data. The statistically relevant variance is the within-participants variance displayed in scatterplots **(D)** and **(F)**. **(C)** Timeline of ongoing GSR amplitude, indicating greater GSR response for tears during sniffing only. **(D)** GSR change from sniffing to the end of a sad movie, indicating greater change for tears. **(E)** Timeline of the CPI, indicating reduced arousal after sniffing tears. **(F)** CPI at the final stage of the study, indicating significantly lower arousal after sniffing tears versus saline. **(G)** Shift in salivary levels of testosterone from baseline to last saliva collection after sniffing tears, indicating a drop from baseline. **(H)** Shift in salivary levels of testosterone from baseline to last saliva collection after sniffing saline, indicating no change. (Insets) Bars reflect the number of participants on each side of the unit slope line (left ordinate), and the horizontal dashed line reflects the mean values and standard error (right ordinate).



the experiment, 100 μ l of the compound was deposited onto a pad pasted onto the participant's upper lip, directly under his nostrils (Fig. 1B). The jar was presented by an additional, non-crier female experimenter who was blind to the jar's contents (15). Participants next viewed on-screen emotionally ambiguous pictures of women's faces and used a visual-analog scale (VAS) to rate the sadness (24 faces, Fig. 2A) and sexual attraction (18 faces, Fig. 2B) attributed to each face. Interleaved with these ratings were 40 VAS questions from a standardized questionnaire that assesses empathy (16). Each man participated twice, on consecutive days, once with tears and once with saline, counterbalanced for order across participants, and double-blind as to compound identity.

Tears did not differ from saline in perceived intensity, pleasantness, or familiarity [$F_{1,23} = 1.26, P = 0.27$] (Fig. 1, D to F). However, VAS ratings of faces differed after sniffing tears or saline [$F_{1,23} = 7.46, P < 0.02$]. This difference did not reflect a shift in sadness attributed to the faces [mean VAS tears = 572 ± 118 , mean VAS saline = $592 \pm 94, t(23) = 1.2, P = 0.23$] but rather a shift in sexual attraction attributed to the faces, whereby the faces appeared less sexually attractive after sniffing tears than after sniffing saline for 17 of the 24 participants [mean VAS tears = 439 ± 118 , mean VAS saline = $463 \pm 125, t(23) = 2.5, P < 0.02$] (Fig. 2C). Sniffing tears did not

influence empathy [mean VAS tears = 593 ± 56 , mean VAS saline = $587 \pm 56, t(23) = 1.2, P = 0.24$].

Tears may have failed to influence sadness or empathy because the experimental context was not explicitly sad. We therefore studied 50 men (mean age 28.2 ± 3.8 years) using a paradigm that generates negative emotions (15, 17). We measured psychophysiological arousal [galvanic skin response (GSR), heart rate, respiration rate, and skin temperature], VAS self-ratings of mood (18), and salivary levels of testosterone, before (baseline), during, and after participants sniffed either tears (from five donor women, mean age 29.2 ± 2.3 years) or saline. After sniffing, participants watched a sad film. Each man participated twice, on consecutive days, once with tears and once with saline, counterbalanced for order across participants, and double-blind (see SOM) as to compound identity.

Tears did not differ from saline in perceived intensity, pleasantness, or familiarity [$F_{1,49} = 0.36, P = 0.55$] (Fig. 1, D to F). The paradigm successfully reduced positive mood [tears and saline combined, positive mood VAS change from baseline = $-69.81 \pm 99, t(49) = 4.95, P < 0.0001$] and increased negative mood [negative mood VAS change from baseline = $50.57 \pm 58.5, t(49) = 4.95, P < 0.0001$]. Despite this negative emotional setting, VAS self-ratings of mood did not differ after sniffing tears as compared to saline

[$F_{1,49} = 0.1, P = 0.74$]. However, observation of the response within each session revealed a modest effect whereby tears reduced self-ratings of sexual arousal [baseline mean VAS rating = 293.48 ± 173.3 ; after sad film, mean VAS rating = $263.44 \pm 140, t(49) = 2.46, P < 0.01$] (Fig. 3A), yet saline did not [baseline mean VAS rating = 260.96 ± 124 ; after sad film, mean VAS rating = $251.8 \pm 120.4, t(49) = 0.81, P = 0.29$] (Fig. 3B).

Whereas the effect on subjective self-rated sexual arousal was modest (19), the effects on objective psychophysiology and hormonal expression were pronounced [all measures: $F_{1,49} = 4.27, P < 0.05$]. During sniffing, there was an increase in GSR, greater for tears than for saline [mean tears = 0.08 ± 0.03 , mean saline = $-0.05 \pm 0.04, t(42) = 2.68, P < 0.02$] (Fig. 3, C and D), yet after sniffing there was a progressive reduction in arousal, greater for tears than for saline. This was evident in several independent measures (fig. S1), as well as in a conservative composite index (CPI) (17, 20) that equally weighted all recorded measures [end of experiment: CPI mean tears = -0.08 ± 0.02 , mean saline = $-0.01 \pm 0.02, t(49) = 2.29, P < 0.03$] (Fig. 3, E and F). Finally, and critically, levels of salivary testosterone were progressively lower after sniffing tears as compared to the baseline period [baseline testosterone = 151.96 ± 76 pg/ml, last testosterone = 132.66 ± 63.1 pg/ml, $t(49) = 3.3, P < 0.001$] (Fig. 3G), an

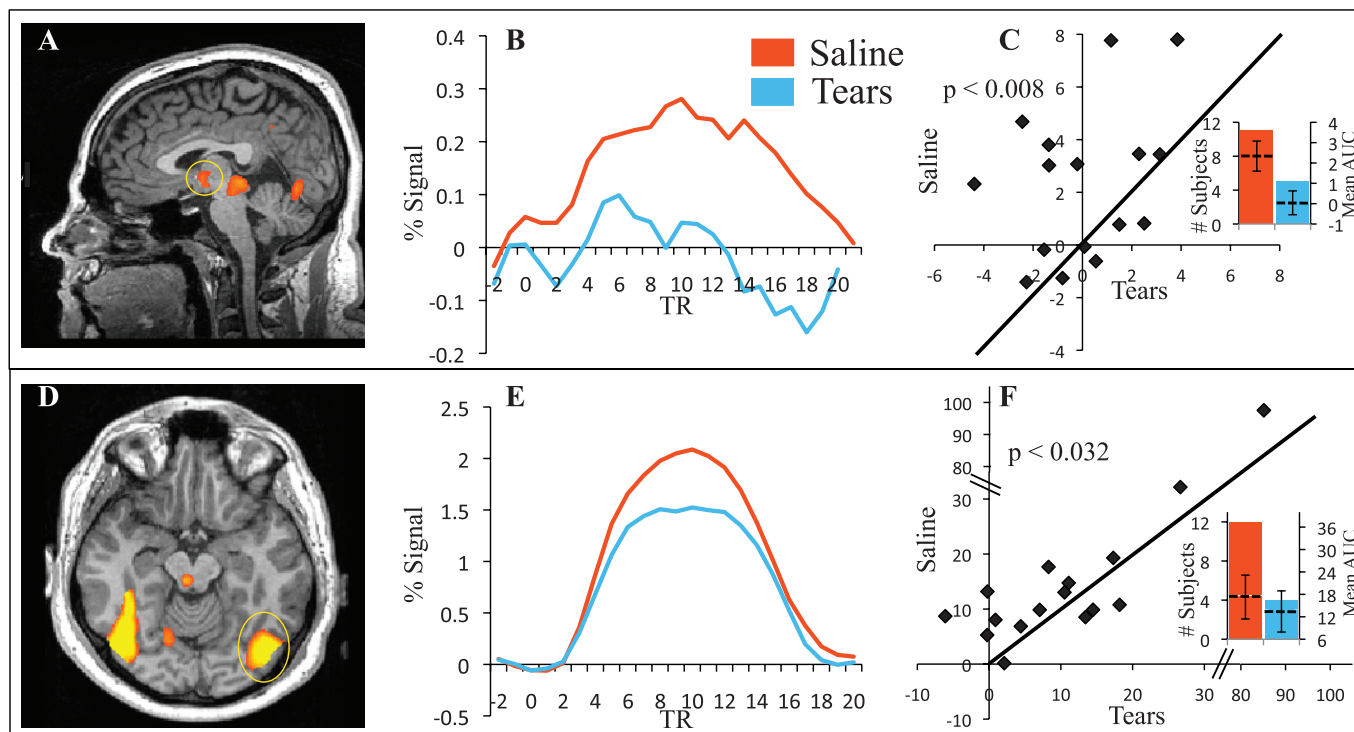


Fig. 4. Sniffing tears reduces brain activity in substrates of sexual arousal. (A) Activity induced by an erotic film generated a region of interest (ROI) in the hypothalamus. (B) Average activity time-course from 16 men within the previously identified hypothalamic ROI. This activity was induced by a sad film clip after sniffing either tears (blue) or saline (red). (C) Area under the curve of activation from (B), providing a measure of variance across participants. (D) Activity induced by an erotic film generated an ROI in the left fusiform gyrus.

(E) Average activity time-course from 16 men within the previously identified fusiform gyrus ROI. This activity was induced by a sad film clip after sniffing either tears (blue) or saline (red). (F) Area under the curve of activation from (E), providing a measure of variance across participants. (Insets) Bars reflect the number of participants on each side of the unit slope line (left ordinate), and the horizontal dashed line reflects the mean values and standard error (right ordinate).

effect not evident for saline [baseline testosterone = 154.8 ± 74.4 pg/ml, last testosterone = 154.34 ± 101.8 pg/ml, $t(49) = 0.81$, $P = 0.96$] (Fig. 3H). Reductions in testosterone are a significant indicator of reductions in sexual arousal in men (21).

Brain imaging has uncovered brain activity associated with human chemosignals (22–24). Because sniffing women's odorless tears consistently reduced sexual arousal in men in a non-sexual setting (viewing pictures of faces and sad or neutral films), we next used functional magnetic resonance imaging to ask whether this was reflected in brain activity. We first presented sexually arousing pictures and movies in order to delineate sexual arousal-related brain structures, and then separately measured the response within these regions to sad, happy, and neutral movies after sniffing either tears or saline. Each of 16 male participants (mean age 28 ± 2.67 years) participated twice, on consecutive days, once with tears and once with saline (from five donor women, mean age 33.6 ± 7.5 years), counter-balanced for order across participants, and double-blind as to compound identity. In order to ensure that participants sniffed the compound, they were asked to provide estimates of intensity, pleasantness, and familiarity, which revealed no perceptible odor for tears [$F_{1,15} = 0.02$, $P = 0.88$] (Fig. 1, D to F).

Sexually arousing stimuli outlined a brain network consistent with that previously implicated in brain imaging studies of sexual arousal (25) (table S1; see fig. S2 for activity induced by tears alone), most notably the hypothalamus (Fig. 4A) and left fusiform gyrus (Fig. 4B). Within these regions, activity induced by the sad film was significantly lower after sniffing tears than after sniffing saline [hypothalamus, area under the curve (AUC) % change tears = 0.04 ± 2.26 , AUC % change saline = 2.33 ± 2.86 , $t(15) = 3.05$, $P < 0.008$ (Fig. 4, B and C); left fusiform gyrus, AUC % change tears = 13.42 ± 21.33 , AUC % change saline = 17.27 ± 22.7 , $t(15) = 2.38$, $P < 0.031$ (Fig. 4, E and F)].

Subjective ratings of attributed sexual appeal, together with objective measures of psychophysiological arousal, testosterone expression, and brain activity, jointly suggest that women's emotional tears contain a chemosignal that reduces sexual arousal in men. We have thus identified an emotionally relevant function for tears.

These effects materialized despite the fact that participants did not see a woman cry, nor were they aware of the compound source. Moreover, in Western culture, exposure to tears is usually in close proximity. We hug a crying loved one, of-

ten placing our nose near teary cheeks, typically generating a pronounced nasal inhalation as we embrace. Such typical behavior entails exposure equal to or greater than that experienced here, hence the effects we observed in the laboratory are relevant to human behavior.

All mammals, including humans, use chemosignals. The most commonly studied carrier of human chemosignals is sweat (25–27), yet most mammals don't sweat like humans do. Although cursory observation of nonhuman mammalian behavior suggests that most chemosignals are carried by urine or anal/vaginal secretions, careful observation reveals that mammals investigate facial chemosignals as well (28). Indeed, specific chemosignals have been identified in the lachrymal secretions of mice (10, 12), that is, in the mouse equivalent of tears. Thus, although it is commonly stated that only humans shed emotional tears, our findings may serve to tie human emotional crying to tear-shedding in other species (7, 29).

The action of mammalian chemosignals can range from “releasers” that generate a response de novo (such as lordosis), to “primers” that modify a long-term process (such as sexual maturation), to “signalers” that provide information (for example, about kinship), and “modulators” that modify an ongoing response (30). In our view, “modulator,” a term coined primarily to describe the action of human pheromones (31), best fits the effects of tears as measured here. Here, women's tears modulated (reduced) sexual arousal, physiological arousal, testosterone levels, and brain activity in men.

These findings pose many questions: What is the identity of the active compound/s in tears? Do chemosignals in women's tears signal anything else but sexual disinterest, and is this signaling restricted to emotional tears alone? Moreover, could the emotional or hormonal state (menstrual phase/oral contraceptives) of the crier/experimenter influence the outcome? In turn, what if any are the signals in men's tears (see SOM) or children's tears, and what are the effects of all these within, rather than across, gender? Despite these open questions, the current results conclusively demonstrate a chemosignal in human tears. In this, we illustrate a previously unknown functional role for crying.

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Materials and Methods

Figs. S1 and S2

Table S1

References

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