

of ORs might still use a rearrangement mechanism: although there is no evidence for this, these two studies only analyzed two of more than 1,000 expressed ORs.

An unresolved issue, which may be technical and/or biological in nature, is that no clones have yet been reported using direct transfer of a neuronal nucleus into an oocyte (Fig. 2), despite expert attempts to do so with nuclei from other neuronal populations^{9,11}. Even with the use of an ES cell intermediate, the overall success rate of cloning with neuronal nuclei seems to be ~1%. Neuronal nuclear 'reprogramming' (might it also include some forms of DNA repair?) seems to require the ES cell intermediate step, although precisely what this step might do to the clonability of neuronal nuclei is currently unclear. The state of the remaining 99% of neuronal nuclei that cannot be cloned remains unknown. It is conceivable that DNA rearrangements exist in

some of these neurons, although the nature of such rearrangements remains purely speculative and, as noted above, might not be expected to hamper cloning. By contrast, this 99% most certainly contains nuclei with global changes in chromosome number (aneuploidy) that exist among developing and postmitotic neurons^{11,13–15}. Although the function and total extent of this aneuploidy have yet to be clarified, it could in part account for the low percentage of successful clones. It could also account for the developmental failures observed by Eggen *et al.* and Li *et al.*, as well as place limits on the percentage of totipotent neurons identified by Eggen *et al.*

That said, none of these considerations detracts from these first glimpses into a single OR neuronal genome, and these impressive technical and scientific achievements will no doubt yield further insights into both olfaction and other neural systems in the near future.

1. Reed, R.R. *Cell* **116**, 329–336 (2004).
2. Jung, D. & Alt, F.W. *Cell* **116**, 299–311 (2004).
3. Buck, L. & Axel, R. *Cell* **65**, 175–187 (1991).
4. Kratz, E., Dugas, J.C. & Ngai, J. *Trends Genet.* **18**, 29–34 (2002).
5. Lane, R.P. *et al. Proc. Natl. Acad. Sci. USA* **98**, 7390–7395 (2001).
6. Zhang, X. & Firestein, S. *Nat. Neurosci.* **5**, 124–133 (2002).
7. Eggen, K. *et al. Nature* **428**, 44–49 (2004).
8. Li, J., Ishii, T., Feinstein, P. & Mombaerts, P. *Nature* **428**, 393–399 (2004).
9. Wakayama, T., Perry, A.C., Zuccotti, M., Johnson, K.R. & Yanagimachi, R. *Nature* **394**, 369–374 (1998).
10. Hochedlinger, K. & Jaenisch, R. *Nature* **415**, 1035–1038 (2002).
11. Osada, T., Kusakabe, H., Akutsu, H., Yagi, T. & Yanagimachi, R. *Cytogenet. Genome Res.* **97**, 7–12 (2002).
12. Serizawa, S. *et al. Science* **302**, 2088–2094 (2003).
13. Rehen, S.K. *et al. Proc. Natl. Acad. Sci. USA* **98**, 13361–13366 (2001).
14. Kaushal, D. *et al. J. Neurosci.* **23**, 5599–5606 (2003).
15. Yang, A.H. *et al. J. Neurosci.* **23**, 10454–10462 (2003).

Imaging gender differences in sexual arousal

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Men tend to be more interested than women in visual sexually arousing stimuli. Now we learn that when they view identical stimuli, even when women report greater arousal, the amygdala and hypothalamus are much more strongly activated in men.

"A man falls in love through his eyes, a woman through her ears," wrote Woodrow Wyatt in 1918. In this issue, Hamann and colleagues¹ use functional magnetic resonance imaging to test whether males and females indeed differ in their brain responses to sexually arousing images. The authors find greater activation in males than females in the amygdala, a brain region involved in emotional arousal, and in the hypothalamus, a brain region central to reproductive functions. What distinguishes this study from a previous effort² is that the investigators went to great lengths to select stimuli and subjects that would ensure similar degrees of self-reported arousal in both sexes. Thus, the observed brain differences are less likely to reflect sex differences in arousal; instead they

reflect sex differences in the processing of sexually arousing stimuli.

Hamann and colleagues scanned 28 healthy, heterosexual volunteers, an equal number of males and females. Participants passively viewed neutral images of couples interacting in nonsexual ways (such as weddings, dancing or therapeutic massage), nude photographs of opposite-sex individuals in modeling poses (opposite-sex stimuli) and photographs of couples engaged in explicit sexual acts (couples stimuli), as well as a fixation cross condition to establish brain activation at baseline. Participants subsequently rated their sexual attraction and physical arousal in response to each image on a three-point scale. Analysis of the imaging data contrasted brain activation to the couples stimuli versus activation to neutral or fixation stimuli, thus revealing regions of significant activation for each sex separately, as well as significant differences between, and commonalities across, the sexes (Fig. 1).

Both sexes reported comparable sexual attraction and physical arousal in response to the images; both groups found the couples stimuli to be the most attractive and arousing. The most sensitive direct comparison

between males and females looked at the contrast in brain activation between the couples and neutral stimuli. Both classes of stimuli depicted couples interacting, differing only in the sexual aspect of the interaction. In this contrast, males showed significantly greater activation than females in the amygdala. This differential activation in the amygdala stands in striking contrast to many brain regions that were commonly activated for both males and females—regions associated with visual processing, attention, motor and somatosensory function, emotion and reward.

Several additional observations are noteworthy. First, brain activation data remained unchanged when the one female subject who reported low sexual arousal was excluded from the analysis. Removal of this subject caused the average arousal of the females to significantly exceed that of the males, yet it was the males who exhibited greater amygdala activation. This is perhaps the strongest indicator that amygdala activation is not related to sexual arousal *per se*.

Second, the average differences between the sexes were striking. Not only did men show greater activation than women in response to sexually explicit couple images in

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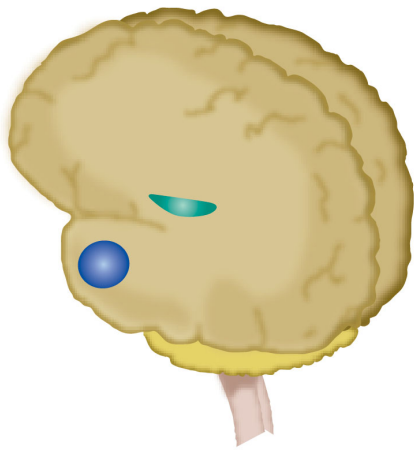


Figure 1 Gender differences in sexual arousal. When viewing sexually arousing visual stimuli, men show greater activation in the amygdala (blue), a brain region involved in emotional arousal, and in the hypothalamus (green), a region involved in reproductive function. Men showed greater activation in these regions even when women reported equal or greater sexual arousal.

the left amygdala, right amygdala and hypothalamus, but also women did not show any greater activation in these regions for the sexually explicit stimuli than for the neutral scenes. It is unclear, therefore, which neural system mediates the sexual arousal reported by the women in this study.

Third, males, but not females, showed significant activation in another region associated with sexual behavior, the hypothalamus, when viewing neutral stimuli depicting couples (albeit at a lower level of statistical significance). The authors speculate that this may represent the male's propensity to view even neutral interactions with females as vaguely sexual, a point that is unlikely to be missed by late-night comedians.

Fourth, males and females differed greatly in their amygdala responses to couples and opposite-sex stimuli. Males showed greater activation for those stimuli that generated the greatest arousal: there was no significant activation to the nudes depicted in the opposite-sex set, but highly significant activation to the sexually explicit couples, relative to the neutral pictures. Females showed the opposite pattern: they had significantly greater activation to the less arousing opposite-sex stimuli, but no significant activation to the copulating couples. The authors speculated that greater amygdala activation in males may represent their propensity for varied, explicit sexual activity, but the paper offers no explanation for women's amygdala responses. The distinction between males' and females' amygdala reactivity appears to map onto that of 'hard' versus 'soft' pornography and is likely to invite commentary from many different schools of thought on human sexuality.

The benefit of recruiting males and females matched in their ability to experience and express sexual arousal comes at the cost of differential recruitment across the sexes. For example, participants were pre-screened

to respond similarly to sexually explicit material. Intuition (and general life experience) suggests that this process generated a greater yield for males than females. Indeed, none of the males reported lack of arousal to visual erotica, whereas 16% of the female prospects were excluded because of insufficient self-reported arousal. This suggests that the data reported here may not necessarily generalize to all women.

Another noticeable sex difference that emerged during the screening of prospective participants was related to self-reported same-sex desire or experience. Only 12% of prospective males, but 36% of prospective females, were excluded from the study for this reason. The basis of this difference remains unclear.

The only other study to directly compare brain responses to sexual images between males and females failed to detect any sex difference². In that study, males reported greater sexual arousal than females, and no significant activation differences were noted when controlling for arousal. Two other studies looking only at males reported conflicting data^{3,4}. It is possible that the extent to which males show amygdala activation to sexually explicit stimuli varies as a function of other factors, such as personality. Indeed, amygdala activation to positive stimuli such as pleasant scenes or happy faces varies as a function of the personality trait of extraversion^{5,6}. Whether this trait may also predict individual differences in amygdala activation to sexual stimuli is unknown.

Asymmetries in left versus right amygdala function are of interest, but poorly understood at present. Hamann and colleagues report greater activation in the left than right amygdala of males for the explicit images. The only other study to report male amygdala activation to sexual stimuli observed it in the right hemisphere³. Consistent with the results of Hamann *et al.*¹, left amygdala activation has been reported to be a function of emotional arousal to non-sexual emotional stimuli^{7,8}, although one of these experiments involved highly negative stimuli⁸. Studies of the encoding of emotional scenes into long-term memory have consistently reported a stronger relation between successful encod-

ing and left amygdala activation for females versus right amygdala activation for males^{8,9}. Although the specific patterns of laterality are difficult to synthesize, amygdala activation often seems to depict some sort of sex difference in the context of emotionally provocative visual stimulation.

It is natural to question whether such brain activation differences reflect genetic or social influences on the human brain and mind. That is a question, however, that brain imaging cannot answer. Men and women are, by definition, genetically different. Men and women are also powerfully socialized into gender roles, a socialization that begins shortly after birth. Both genetic and social influences shape brain function and its consequent behavior, so imaging differences could arise from either nature or nurture or both.

Hamann *et al.*¹ have reported a thoughtfully controlled study of one aspect of human sexuality. Human sexuality, however, would remain unfulfilled without a climax. Psychologists have long distinguished between 'appetitive' and 'consummatory' sexual behaviors, that is, those that lead up to, and those that conclude the sexual act. One imaging study went right to the point, imaging the male brain during ejaculation¹⁰. The authors of this study were not only intrepid in their choice of research topic and subject participation, but they were also undeterred by concerns about motion artifacts. Remarkably, ejaculation in males was associated with decreased amygdala activation. Thus, the appetitive phase of sexual arousal seems to coincide with increased amygdala activation that is then reversed during the consummatory phase. This activation change parallels the rise and rapid fall in sexual excitement from one phase to the other. It remains to be seen whether decreased amygdala activation associated with ejaculation is causally linked to males' subsequent unwillingness to snuggle.

1. Hamann, S., Herman, R.A., Nolan, C.L. & Wallen, K. *Nat. Neurosci.* **7**, 411–416 (2004).
2. Karama, S. *et al. Hum. Brain Mapp.* **16**, 1–13 (2002).
3. Bearegard, M., Levesque, J. & Bourgouin, P. *J. Neurosci.* **21**, RC165 (2001).
4. Redoute, J. *et al. Hum. Brain Mapp.* **11**, 162–177 (2000).
5. Canli, T. *et al. Behav. Neurosci.* **115**, 33–42 (2001).
6. Canli, T., Sivers, H., Whitfield, S.L., Gotlib, I.H. & Gabrieli, J.D. *Science* **296**, 2191 (2002).
7. Hamann, S.B., Ely, T.D., Hoffman, J.M. & Kilts, C.D. *Psychol. Sci.* **13**, 135–141 (2002).
8. Canli, T., Desmond, J.E., Zhao, Z. & Gabrieli, J.D.E. *Proc. Natl. Acad. Sci. USA* **99**, 10789–10794 (2002).
9. Cahill, L. *et al. Neurobiol. Learn. Mem.* **75**, 1–9 (2001).
10. Holstege, G. *et al. J. Neurosci.* **23**, 9185–9193 (2003).