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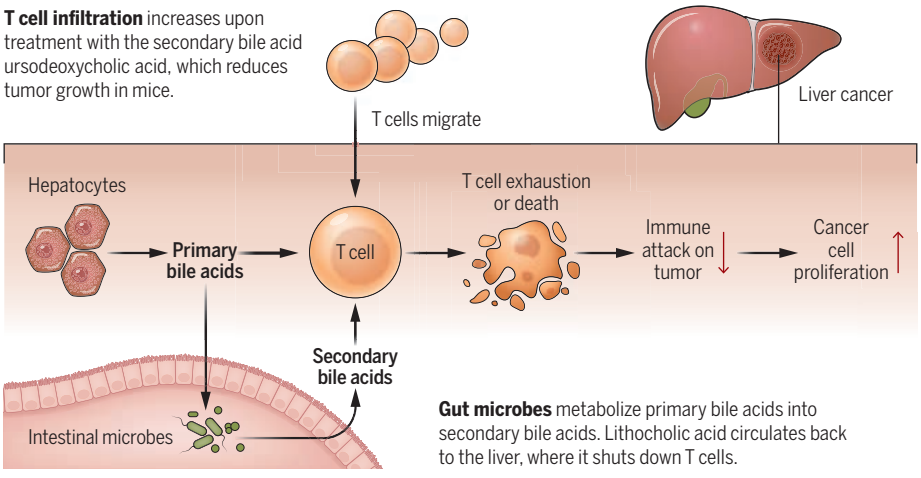
## Bile acids stoke cancer

In cancerous liver tissue, expression of the enzyme bile acid–CoA:amino acid *N*-acyltransferase increases, which boosts the conjugation of primary bile acids. These, along with the secondary bile acid lithocholic acid, impair T cells and tumor immunosurveillance and increase tumor growth.




(a constituent of bile) have been known for their physicochemical properties (*7*). Therapeutically, bile acids were initially used to dissolve gallstones, hardened deposits of cholesterol or bilirubin in the gall bladder, where bile is stored (*8*). Today, ursodeoxycholic acid is mainly used to treat primary biliary cholangitis, an autoimmune condition that destroys small bile ducts and leads to a backup of bile in the liver (*9*).

More recently, bile acids have emerged as important signaling molecules because they bind to and activate nuclear receptors (farnesoid X receptor, pregnane X receptor, and vitamin D receptor) and Takeda G protein–coupled receptor 5 at the cell surface, which all affect lipid and glucose metabolism and energy homeostasis (*10*). In this capacity, bile acids can contribute to liver carcinogenesis (*11*). Bile acids also play a role in T cell homeostasis and differentiation (*12*, *13*). Treating mice with the primary bile acid chenodeoxycholic acid boosted natural killer T cell activity and immunosurveillance of liver tumors (*14*). The bile acid metabolite isoallolithocholic acid enhances regulatory T cell differentiation through NR4A1 (*15*), the same nuclear receptor that responds to the secondary bile acid lithocholic acid and contributes to T cell exhaustion (*5*). Collectively, these findings highlight the importance of bile acids as immunomodulators. The study of Varnasi *et al.* persuasively connects local differences in bile acid production and concentration in liver tumors to the demise of tumor-specific T cells and impaired immunosurveillance.

Not all secondary bile acids produced in the intestine are the same. Lithocholic acid is more hydrophobic and generally considered to be toxic, whereas ursodeoxycholic acid is more hydrophilic and used therapeutically (*9*). Therefore, the different effects of these two bile acids on liver cancer growth and immune cell infiltration are not necessarily surprising. However, the demonstrated impact of ursodeoxycholic acid on liver tumor initiation and growth is an advance that could improve the treatment of hepatocellular carcinoma. Direct inhibition of BAAT or the bile acid receptors could diminish liver cancer growth, as might changing the gut microbiome with antibiotics to alter secondary bile acid composition. Given the decades-long use of ursodeoxycholic acid and its compelling safety profile combined with the low overall response rates in hepatocellular carcinoma patients treated with immune checkpoint inhibitors, there should be an immediate appetite to test ursodeoxycholic acid in these patients in combination with immunotherapy. ■

### REFERENCES AND NOTES

1. D. Q. Huang, H. B. El-Serag, R. Loomba, *Nat. Rev. Gastroenterol. Hepatol.* **18**, 223 (2021).
2. K. A. McGlynn, J. L. Petrick, H. B. El-Serag, *Hepatology* **73** (suppl. 1), 4 (2021).
3. J. M. Llovet *et al.*, *Nat. Rev. Clin. Oncol.* **19**, 151 (2022).
4. S. K. Varanasi *et al.*, *Science* **387**, 192 (2025).
5. X. Liu *et al.*, *Nature* **567**, 525 (2019).
6. L. R. Hagey *et al.*, *J. Lipid Res.* **34**, 1911 (1993).
7. J. T. Nguyen, R. P. H. Shaw, S. Anakk, *Endocrinology* **163**, bqac155 (2022).
8. R. G. Danzinger, A. F. Hofmann, L. J. Schoenfield, J. L. Thistle, *N. Engl. J. Med.* **286**, 1 (1972).
9. U. Leuschner, W. Kurtz, *Lancet* **330**, 508 (1987).
10. A. Perino, H. Demagny, L. Velazquez-Villegas, K. Schoonjans, *Physiol. Rev.* **101**, 683 (2021).
11. F. Yang *et al.*, *Cancer Res.* **67**, 863 (2007).
12. S. Hang *et al.*, *Nature* **576**, 143 (2019).
13. X. Song *et al.*, *Nature* **577**, 410 (2020).
14. C. Ma *et al.*, *Science* **360**, eaan5931 (2018).
15. W. Li *et al.*, *Cell Host Microbe* **29**, 1366 (2021).

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NEUROPHYSIOLOGY

# Stress drives a switch in sex preference

## Distinct brain circuits control sex preferences in mice

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To date, much of the focus in social neurobiology research has been on characterizing the motivational importance of a social stimulus—for example, how an encounter with an individual presents a threat or a potential mate. However, understanding the absolute (fixed) features of a social stimulus has lagged. On page 155 of this issue, Wei *et al.* (*1*) report the distinct sexually dimorphic neural circuits that encode a switch in absolute sexual preference in mice that allow both sexes to prefer interacting with females under normal conditions but change to preferring male interactions when exposed to threatening stimuli. These findings point to a shared flexible control function for social preference with distinct mechanisms for implementation in males and females.

When animals navigate the physical landscape, two types of spatial representations are used: allocentric cognitive maps that are based on the absolute spatial relationships between objects in the environment, and egocentric cognitive maps that are centered around the navigator's relative position and orientation (*2*). Analogous to this, animals may also navigate the social landscape by using relative or absolute maps. Although the neural mechanisms that underpin this are poorly understood, multiple circuits determine how the brain responds to the emotional importance of stimulus (processing positive or negative valence) (*3*), whereas motivational importance can be shifted by context, internal state, or prior experiences.

Wei *et al.* investigated the neural mechanisms that underlie social preference for male or female interactions in mice. The authors operationalized sex preference as a concept distinct from that of sexual orientation, describing which mice a given mouse

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wants to be near rather than which mice it is sexually attracted to. As with physical navigation, sex preference can be framed in relative or absolute terms. For example, a mouse may identify a mouse of the opposite sex as a mate, in relative terms. At the same time, a mouse can be male in absolute terms, regardless of its sex, status, or age. In humans, these two frameworks exist seamlessly in the mind, and the psychology of sex preference, identity, and orientation has a rich, rapidly evolving literature and vocabulary to navigate between relative and absolute paradigms.

Social preference can be influenced by absolute characteristics (such as size or strength) and relative ones, such as familiarity, social hierarchy, and environmental contexts (such as threat or safety). Wei *et al.* discovered that a threat-associated stimulus changes the social preference from females to males for both sexes—a universal shift in absolute sex preference. Male and female mice preferred to socialize with female mice under normal conditions. However, when presented with threats such as predator odor (2,4,5-trimethylthiazoline), preference shifted to male mice over female mice for both sexes. This phenomenon also applied to learned threats, such as a shock-paired cue in which a neutral stimulus (cue) becomes associated with a stimulus (a shock) through repeated pairing, leading to a conditioned response (fear) when the cue is presented alone. Notably, sex preferences were measured by time spent with both male and female mice, or bedding from male or female cages, which allowed for rigorous discrimination of representations of sex preference rather than of sexually dimorphic movement patterns, such as those associated with mating (*4*).

In exploring what neuronal circuitry accounts for this switch in sexual preference, Wei *et al.* found that the sexually dimorphic effect was caused by changes in projections from dopamine-expressing neurons in the ventral tagmental area ($VTA^{DA}$) to the nucleus accumbens (NAc) or the medial preoptic area (mPOA) of the hypothalamus. The NAc processes pleasure, reward, and motivation, whereas the mPOA is implicated in movement associated with mating in mice. Wei *et al.* observed that in male mice, the $VTA^{DA}$-mPOA circuit mediates male preference, whereas the $VTA^{DA}$-NAc projection regulates female preference. Also, steady, regular (tonic) firing of neurons drives male preference, whereas firing in bursts (phasic) promotes female preference (see the figure).

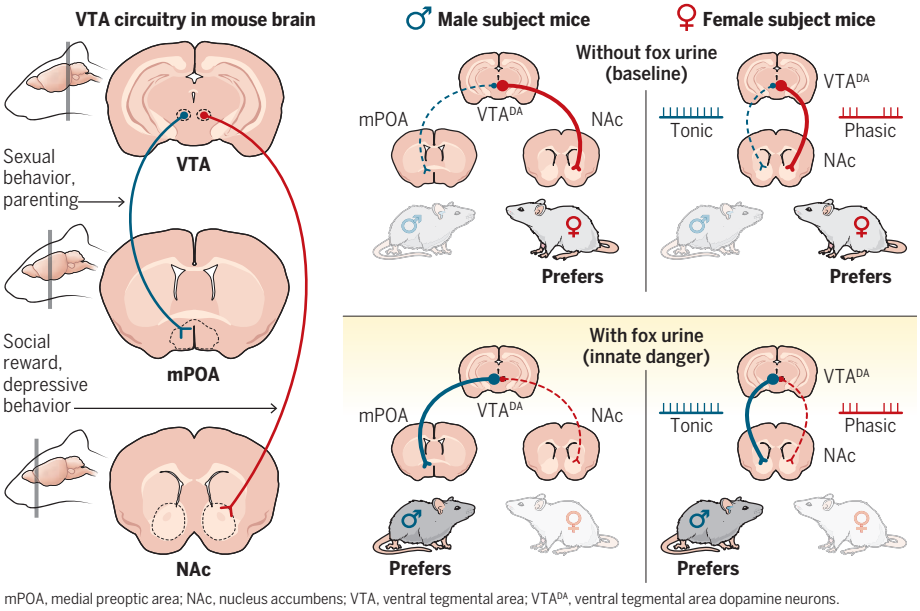
Notably, the universal expression of sex preferences across males and females requires an absolute representation rather than a relational representation. Prior studies in mice have shown $VTA^{DA}$ neurons can promote or suppress social behavior depending on their stimulation or inhibition, and that activation of the VTA-NAc circuit increases social interaction (*5*). However, these comparisons were not made across sexes, leaving a gap in understanding how males and females differentially operate these mechanisms.

One possible explanation for the observations of Wei *et al.* is that the mPOA regulates mating and parenting behaviors. Optogenetic activation of mPOA induces male mounting behavior as well as pup retrieval behavior in both sexes (*6*). A subset of neurons in the mPOA that secretes the neuropeptide galanin elicits male and female parenting behavior, and activation of these neurons reduces aggression and increases pup grooming in males (*7*). In female mice, estrogen receptor (Esr1)–expressing neurons in the mPOA ($mPOA^{Esr1}$) mediate pup approach and retrieval, and $mPOA^{Esr1}$-VTA projections drive maternal behaviors (*6*, *8*). Another possibility is that stress recruits the $VTA^{DA}$-NAc circuit given its role in counteracting stress-induced depressive behaviors in rodents (*9*, *10*). Phasic firing of $VTA^{DA}$ neurons underlies place preference, a condition in which a particular environment is associated with a rewarding experience (*11*). Phasic firing also rescues stress-induced depression-like phenotypes and escape-related behaviors (*9*). Furthermore, female hamsters find female social interactions more rewarding than do males, and receptors in the VTA for the hormone oxytocin regulate social reward in both sexes (*12*). These observations support the hypothesis that male and female mice may have different set points for social reward. For female mice, interactions with other females could exert a stress buffering, antidepressive effect, whereas encountering male mice might serve as a hedonic reward, signaled by phasic bursts of $VTA^{DA}$ neurons.

Whether absolute sex preference, preference shifts, and distinct but shared underlying neural circuits found by Wei *et al.* apply in humans—given their more complex representations of sex, sexuality, and preference—remain to be determined. The degree to which these mechanisms are conserved across species and the independent evolution of sociability calls for further investigation. ■

## Sexually dimorphic neural circuits in mice drive sex preference

The VTA circuitry has been implicated in different social behaviors in mice (left). In males (middle), the VTA-NAc circuitry governs female preference at baseline (top middle), whereas VTA-mPOA circuitry governs male preference when under threat (bottom middle). Only the VTA-NAc circuitry shapes preference in females (right), with phasic firing driving female preference at baseline (top right) and tonic firing mediating male preference when under threat (bottom right).




mPOA, medial preoptic area; NAc, nucleus accumbens; VTA, ventral tegmental area; $VTA^{DA}$, ventral tegmental area dopamine neurons.

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### REFERENCES AND NOTES

1. A. Wei *et al.*, *Science* **387**, eadq7001 (2024).
2. C. Freksa *et al.*, Eds., *Spatial Cognition*, vol. 1404 (Springer, 1998), Lecture Notes in Computer Science.
3. K. M. Tye, *Neuron* **100**, 436 (2018).
4. T. Karigo *et al.*, *Nature* **589**, 258 (2021).
5. L. A. Gunaydin *et al.*, *Cell* **157**, 1535 (2014).
6. Y.-C. Wei *et al.*, *Nat. Commun.* **9**, 279 (2018).
7. Z. Wu *et al.*, *Nature* **509**, 325 (2014).
8. Y.-Y. Fang *et al.*, *Neuron* **98**, 192 (2018).
9. K. M. Tye *et al.*, *Nature* **493**, 537 (2013).
10. D. Chaudhury *et al.*, *Nature* **493**, 532 (2013).
11. H.-C. Tsai *et al.*, *Science* **324**, 1080 (2009).
12. J. M. Borland *et al.*, *Neuropsychopharmacology* **44**, 785 (2019).



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