Sexual orientation and its basis in brain structure and function

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Current evidence indicates that sexual differentiation of the human brain occurs during fetal and neonatal development and programs our gender identity—our feeling of being male or female and our sexual orientation as hetero-, homo-, or bisexual. This sexual differentiation process is accompanied by many structural and functional brain differences among these groups (1). In previous studies (2, 3), the Savic laboratory detected a sex-differentiated activation of the anterior hypothalamus in heterosexual men (HeM) and heterosexual women (HeW) and a sex-atypical, almost reversed, pattern of activation in homosexual men (HoM) and homosexual women (HoW). The hypothalamus (Fig. 1) is a small brain area located under the anterior commissure that is involved in many different functions, including reproduction. These observations raised several questions, one of which was whether the sexual dimorphisms described could be sex-atypical in homosexual subjects even with respect to factors not directly associated with reproduction. In a recent issue of PNAS, Savic and Lindström (4) reported that hemispheric ratios, as well as patterns of amygdala connectivity, were sex-atypical in homosexual individuals, with HoM exhibiting more female patterns than HeM and HoW showing more male-like features than HeW. Whether the observed sex-atypical characteristics are the result of processes that occur during the fetal or neonatal periods, as is the case with gender identity and sexual orientation, is an open question. The excellent imaging research of Ivanka Savic's group in past years has provided strong evidence for structural and functional brain differences related to gender and sexual orientation. The study of these differences has emerged from an era of prejudice and fear such as I experienced 20 years ago (5).

In 1990, we described the first brain difference related to sexual orientation in the suprachiasmatic nucleus (SCN)—the brain's "clock"—which in HoM is twice the size that it is in HeM (6). We later induced a similar brain difference in rats by pharmacologically disturbing the interaction between testosterone and the developing brain, using the aromatase inhibitor ATD in the neonatal period (7). This experiment yielded bisexual adult rats that had a larger-than-normal number of vasopressin neurons and total cells in their SCNs. The difference in the SCN of HoM was, therefore, not caused by a difference in sexual behavior, as was suggested at the time, but by an atypical interaction between sex hormones and the developing brain. In 1991, LeVay (8) reported that HoM, like HeW, have a smaller area in the frontal part of the hypothalamus (the INAH-3) than do HeM. In 1992, Allen and Gorski (9) found that the anterior commissure (Fig. 1) of HoM is larger than that of HeM. This structure, which is larger in women than in men, connects the left and right temporal cortexes and is thus involved in sex differences related to cognitive abilities and language. This difference may be related to the sex-atypical hemispheric asymmetries in HoM and HoW as seen by Savic and Lindström (4). The first functional scanning paper by Kinnunen *et al.* (10), which described differences in the hypothalamus in relation to sexual orientation, received little scientific or public attention, although the results may have had clinical relevance. The hypothalamus of HoM, it turned out, was not as responsive to a classic antidepressant (fluoxetine) as that of HeM, which points to a difference in the activity of the serotonergic system. Subsequently, Savic *et al.* (2) studied the effect of scent—in particular, a pheromone derived from progesterone and excreted in perspiration in concentrations 10 times higher in men than in women. Although pheromones influence sexual behavior and stimulate activation in the hypothalamus of HeW and HoM in the same way, this pheromone did not elicit a response in the hypothalamus of HeM. Pheromones thus may play a part in our behavior related to sexual orientation. A follow-up study (3) showed that HoW reacted in a sex-atypical, almost reciprocal, way to pheromones as compared with HeW, again indicating that some hypothalamic circuits function in relation to sexual orientation. Kranz and Ishai (11) expanded this observation to cortical areas. Functional MRI was used to measure activity changes in the brain when pictures of men and women were shown to subjects. Viewing a female face produced a strong reaction in the thalamus and medial prefrontal cortex of HeM and HoW, whereas in HoM and HeW these structures reacted more strongly to the face of a man.

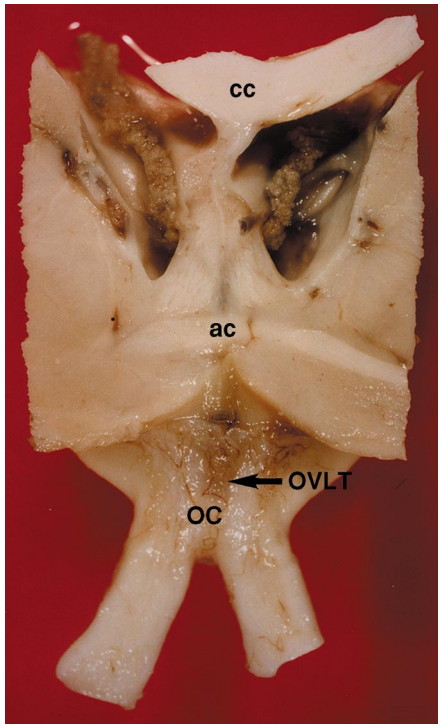

Fig. 1. The human hypothalamus is a small (4 cm^3) brain structure between the anterior commissure (ac) and the optic chiasma (OC) and behind the organum vasculosum of the lamina terminalis (OVLT). Under the corpus callosum (cc), the lateral ventricles are visible.

Savic's previous studies raised the question of whether certain sexually dimorphic features in the brain that are unlikely to be directly involved in reproduction may differ between homosexual and heterosexual individuals. The article by Savic and Lindström (4) provides the answer. The authors measured hemispheric asymmetry with MRI volumetry

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and functional connectivity of the amygdala with PET scans of cerebral blood flow. In HeM and HoW, volumetric measurements showed a rightward cerebral asymmetry, whereas the volumes of the cerebral hemispheres were symmetrical in HoM and HeW. Moreover, homosexual subjects also showed sex-atypical amygdala connections. In HoM, as in HeW, the connections were more widespread from the left amygdala. In HoW and HeM, on the other hand, they were more widespread from the right amygdala. Furthermore, in HoM and HeW the connections were primarily displayed with the contralateral amygdala and the anterior cingulate; in HeM and HoW, they were displayed with the caudate, putamen, and prefrontal cortex. Savic and Lindström describe sex-atypical cerebral asymmetry and functional connections in homosexual subjects that cannot be primarily linked to reproduction and suggest a link between sexual orientation and neurobiological entities. Further research is needed on the putative influence of testosterone on the same parameters (e.g., in individuals with complete androgen-insensitivity syndrome). Neurobiological research related to sexual orientation in humans is only just gathering momentum, but the evidence already shows that humans have a vast array of brain differences, not only in relation to gender, but also in relation to sexual orientation.

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