

# The Interstitial Nuclei of the Human Anterior Hypothalamus: An Investigation of Variation with Sex, Sexual Orientation, and HIV Status

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The interstitial nuclei of the human anterior hypothalamus (INAH1–4) have been considered candidates for homology with the sexually dimorphic nucleus of the preoptic area of the rat. Volumetric sexual dimorphism has been described for three of these nuclei (INAH1–3), and INAH3 has been reported to be smaller in homosexual than heterosexual men. The current study measured the INAH in Nissl-stained coronal sections in autopsy material from 34 presumed heterosexual men (24 HIV– and 10 HIV+), 34 presumed heterosexual women (25 HIV– and 9 HIV+), and 14 HIV+ homosexual men. HIV status significantly influenced the volume of INAH1 (8% larger in HIV+ heterosexual men and women relative to HIV– individuals), but no other INAH. INAH3 contained significantly more neurons and occupied a greater volume in presumed heterosexual males than females. No sex difference in volume was detected for any other INAH. No sexual variation in neuronal size or density was observed in any INAH. Although there was a trend for INAH3 to occupy a smaller volume in homosexual men than in heterosexual men, there was no difference in the number of neurons within the nucleus based on sexual orientation. © 2001 Academic Press

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Examination of the human hypothalamus for morphological sex differences comparable to those described in animals (Bleier *et al.*, 1982; Commins and Yahr, 1984; Gorski *et al.*, 1978; Hines *et al.*, 1985; Tobet *et al.*, 1986) has produced discrepant results. Swaab and Fliers (1985) examined a hypothalamic cell group previously designated as the intermediate nucleus (Brockhaus, 1942) and found it to be larger in males than in females. They suggested that the nucleus may correspond to the sexually dimorphic nucleus of the preoptic area (SDN-POA) of the rat (Gorski *et al.*, 1978). Consequently, they redesignated it as the SDN-POA or, more simply, the sexually dimorphic nucleus (SDN) (Swaab and Hoffman, 1988, 1995). Allen *et al.* (1989) were unable to verify a sex difference in that nucleus; however, they identified two other nuclei which they called the second and third interstitial nuclei of the anterior hypothalamus (INAH2 and INAH3), both of which they found to be larger in males. They designated the SDN of Swaab and Fliers as the first interstitial nucleus of the anterior hypothalamus (INAH1). Thus, the terms intermediate nucleus, SDN-POA, SDN, and INAH1 correspond to a single cell group in the human. Allen *et al.* (1989) also described a nucleus which they called INAH4 for which they found no sexual dimorphism. Like Allen *et al.* (1989), LeVay (1991) found INAH3 to be larger in males than in females and found no sex difference in

INAH1 or INAH4. LeVay (1991), however, found no sex difference in the volume of INAH2.

To address the discrepancies in the literature regarding sexual dimorphism of the INAH, we assessed the volume of each of the INAH in serial sections from postmortem specimens obtained at autopsy and also examined each nucleus for sex differences in neuronal density, total neuronal number, and mean neuronal size. In agreement with two prior studies (Allen *et al.*, 1989; LeVay, 1991), we found INAH3 to be sexually dimorphic, occupying a significantly greater volume in males than females. In addition, we determined that the sex difference in volume was attributable to a sex difference in neuronal number and not in neuronal size or density (Byne *et al.*, 2000). We found no evidence for sexual dimorphism of any other INAH.

LeVay (1991) examined the volumes of the INAH for variation with sexual orientation in men. He found the volume of INAH3 in homosexual men to be smaller than that of presumed heterosexual men and comparable in size to that of presumed heterosexual women. On the basis of that result, he hypothesized that INAH3 is dimorphic, not only with sex, but also with sexual orientation, at least in men (LeVay, 1991). LeVay's characterization was done only for volume and not for cell number.

We now report our examination of the INAH for possible variation with sexual orientation in men. Sexual orientation was determined from a review of medical records available at autopsy. No information regarding sexual orientation was available for subjects that died from causes unrelated to HIV infection. In the absence of such information, all individuals who were not known to be HIV positive (HIV+) at the time of death were classified as heterosexual because of the low rate of homosexuality in the population (Hamer *et al.*, 1993; Michael *et al.*, 1994). Specimens were obtained from HIV+ men only if the autopsy record listed a single HIV risk factor (i.e., intravenous drug use or homosexual behavior). Those for whom intravenous drug use was the only known risk factor were presumed to be heterosexual. Those for whom homosexual behavior was listed as the risk factor were presumed to be homosexual. Thus, as in the study of LeVay (1991), all specimens from homosexual men came from individuals who died from opportunistic infections associated with HIV infection. It has, therefore, been necessary to examine possible effects of HIV infection on the INAH. To date, we have examined all four INAH for volumetric variation with sexual orientation and HIV status. In addition, we have examined INAH3 for such variation in neuronal number,

size, and packing density. In the absence of a source of brains from women of known sexual orientation, it has not been feasible to address the possibility that one or more of the INAH exhibit variation with sexual orientation in women.

The present sample includes the specimens from HIV-negative (HIV-) individuals who were included in our earlier study (Byne *et al.*, 2000) in which all of the morphometric methods were fully described. Throughout the text, data are presented as mean  $\pm$  standard error of the mean (SEM). The mean age of subjects did not differ significantly across groups: HIV+ presumed heterosexual males  $47.1 \pm 10$ ,  $n = 10$ ; HIV- presumed heterosexual males  $49.5 \pm 2.9$ ,  $n = 24$ ; HIV+ presumed heterosexual females  $40.6 \pm 3.2$ ,  $n = 9$ ; HIV- presumed heterosexual females  $49.9 \pm 2.5$ ,  $n = 25$ ; and HIV+ homosexual males  $41.8 \pm 2.5$ ,  $n = 14$ .

#### *HIV Influence on INAH1 and Sexual Influence on INAH3*

For the initial analysis (Table 1), HIV+ and HIV- heterosexual males and females were analyzed in a two-way ANOVA for the volumes of INAH1-4. Only INAH3 revealed a significant influence of sex. There was a highly significant effect of sex ( $P < 0.0001$ ), with no influence of HIV status [ $F(1, 61) = 1.61$ ,  $P > 0.20$ ]. Only INAH1 revealed a significant influence of HIV status, as there was a statistically significant effect on volume ( $P = .047$ ). Volume was increased in HIV+ males and HIV+ females by about 8% ( $0.369 \pm 0.012$  vs  $0.401 \pm 0.017$ ). Since there was no significant influence of HIV status on INAH3, the influence of sexual orientation was analyzed by a one-way ANOVA collapsing across HIV status to yield three groups: male heterosexual, female heterosexual, and male homosexual subjects. This analysis yielded a significant effect of group:  $F(2, 76) = 13.95$ ,  $P < 0.0001$ , with the majority of the effect due to the male-female difference. The size of INAH3 in homosexual males ( $0.096 \pm 0.007$ ,  $n = 14$ ) was intermediate between the heterosexual males ( $0.121 \pm 0.007$ ,  $n = 31$ ) and females ( $0.073 \pm 0.005$ ,  $n = 34$ ), but the differences did not reach statistical significance relative to either group ( $P > 0.05$ , post hoc Tukey-Kramer HSD) (Fig. 1).

#### *Influences on Brain Weight*

Excluding the homosexual male group, there were significant sex ( $P < 0.001$ ) and HIV ( $P < 0.05$ )

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