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Short communication

A lack of dimorphism of sex or sexual orientation in the human anterior commissure[1]

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Abstract

Four studies have examined the cross-sectional area of the anterior commissure (AC) for variation with sex, with conflicting results. One also reported the AC to be larger in homosexual as opposed to heterosexual men. We examined the cross-sectional area of the AC in postmortem material from 120 individuals, and found no variation in the size of the AC with age, HIV status, sex, or sexual orientation.

Theme: Other systems of the CNS

Topic: Limbic system and hypothalamus

Keywords: Anterior commissure; Sex difference; Sexual orientation; HIV; Human

A variety of lines of converging evidence suggests sex differences in hemispheric specialization and in the symmetry of hemispheric functioning [10,15,16]. A general sex difference in the connectivity between the two cerebral hemispheres has been suggested as the neural substrate of those differences [1]. Accordingly, it has been suggested that the neural structures that bridge the two hemispheres (i.e., the commissures and massa intermedia) may be sexually dimorphic [1,2,6]. More specifically, since women tend to exhibit less hemispheric specialization and greater symmetry of hemispheric functioning on particular tests [15], they might be expected to also exhibit relatively larger commissures than men [1,6]. More than three dozen studies have assessed the morphology of the largest interhemispheric commissure, the corpus callosum (CC), but have failed to provide compelling support of that hypothesis (for review see Bishop and Wahlsten [4]). In contrast only four studies, all on post mortem specimens, have looked for sex differences in the human anterior commissure (AC) [1,2,7,11], an interhemispheric fiber bundle primarily connecting homotopic targets in the inferior temporal lobes [8]. The first study [7] detected a statistical trend for the cross-sectional area of the AC in the midsagittal plane to be larger in men ($P=0.05$); however, two subsequent studies from a single laboratory employed larger sample sizes and found the cross-sectional area to be statistically significantly larger in women [1,2]. The second of those studies [1] also reported that the cross-sectional area of the AC was larger in homosexual as opposed to heterosexual men, a finding that was interpreted as support for the hypothesis [9,14] that sexual orientation reflects the sexually differentiated state of the brain. The fourth study [11] found no significant sex difference in cross-sectional area, but did find differences in fiber number and type. Studies in rats have also produced discrepant results regarding possible sexual dimorphism of the AC [3,13].

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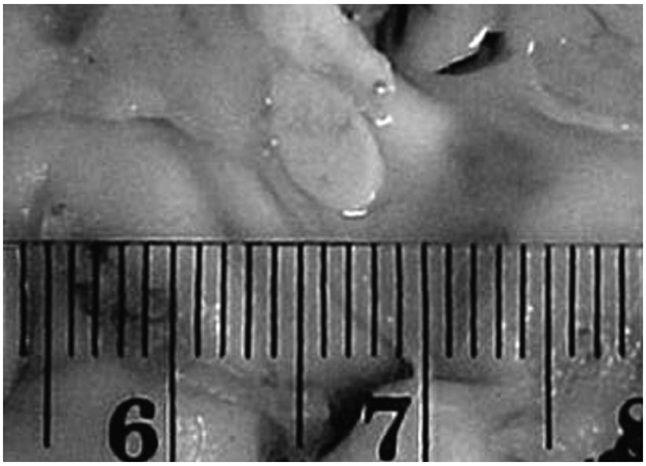

Fig. 1. The midsagittal cross-section of the AC with ruler (centimeters) for scaling.

The aim of the present study was to test the human AC for variation with sex and sexual orientation in an independent sample of specimens (n=120) obtained at autopsy (43 presumed heterosexual women, nine of whom were HIV+; 57 men with no known history of homosexual behavior, 18 of whom were HIV+; 20 HIV+ men with a history of homosexual behavior documented in the medical record (Table 2). All subjects were between the ages of 18 and 65 at the time of death, with no known psychiatric, endocrinological or neurodegenerative disorders. At autopsy, all brains were free of any gross pathological alterations or focal brain lesions. Specimens were excluded from HIV+ individuals if the HIV risk factor was not stated unambiguously in the medical record or if the medical record mentioned more than one risk factor (i.e., i.v. drug abuse and homosexual behavior). All specimens were obtained, and medical records reviewed in accordance with procedures approved by internal review boards at the participating institutions (Mount Sinai Medical Center, New York, NY; Cornell Medical Center, New York, NY; University of California, Davis Medical Center; and Jackson Memorial Medical Center, Miami, FL).

All brains were removed from the calvarium within 48 h of death, fixed for approximately 2 weeks by immersion in buffered neutral formalin, and bisected in the midsagittal plane to reveal the AC. The cross-sectional area of the AC in the midsagittal plane (Fig. 1) was measured with the assistance of a Bioquant TCW Image Analysis System (Nashville, TN). All measurements were made without knowledge of HIV status, sex or sexual orientation of the specimen. Images of the AC and a ruler in the same focal plane were relayed directly to the image analysis system by a video camera fitted with a macrolens, or photographic images were uploaded from disc. Images were viewed on a 21″ monitor. The imaging system was calibrated to account for differences in the magnification of different images, the perimeter of the midsagittal cross-section of each AC was traced, and Bioquant software calculated the cross-sectional area of the cut surface of the AC. Five measurements were made of each AC and the average of those measurements was used for statistical analyses. Data are reported as mean±S.D. Statistical analyses employed the Statistica 5.1 software package. All probabilities are two-tailed with α=0.05.

In the midsagittal plane, the AC has clearly defined boundaries, and thus is not subject to the same variability in measurement as the subdivisions of the corpus callosum (CC). Intraclass correlation for repeated tracings of the AC was 0.98. There was, however, marked variability in AC cross-sectional area between subjects, ranging from 2.49 to 18.18 mm^2 (Fig. 2). This observation is similar to the 7-fold between-subjects variation in AC cross-sectional area reported previously [10].

The cross-sectional area exhibited no significant correla-

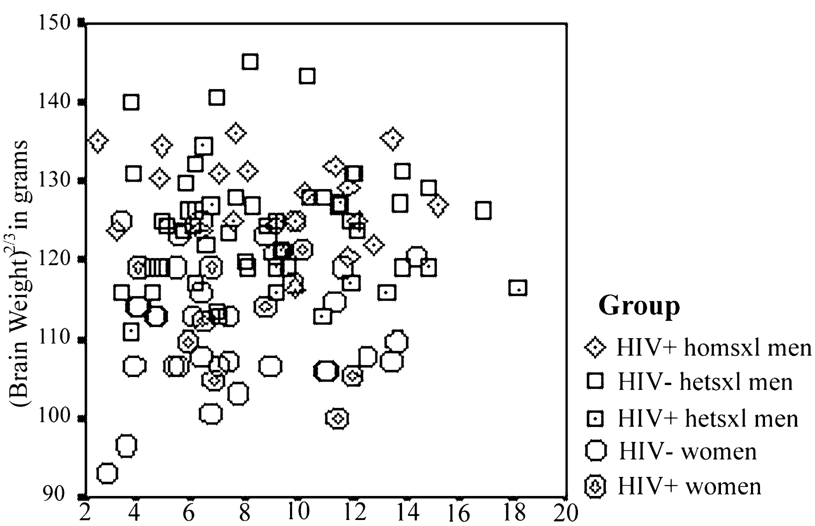

Fig. 2. Scatterplot showing the variability of midsagittal AC measurements by group.

Table 1
Data for presumed heterosexual men and women

	Males (n)	Females (n)
HIV−:		
Age (years)	50.66±10.92 (39)	50.71±12.23 (34)
Brain weight (g)	1416±129 (38)[a]	1187±129 (34)
AC (mm^2)	8.57±3.40 (39)	7.62±3.26 (34)
AC/brain weight (mm^2/g)$\times 10^3$	6.10±2.38 (38)[a]	6.43±2.75 (34)
HIV+:		
Age (years)	42.55±6.38 (18)*	37.66±7.57 (9)**
Brain weight (g)	1328±106 (17)[a]	1183±118 (9)
AC (mm^2)	9.20±3.71 (18)	8.00±2.70 (9)
AC/brain weight (mm^2/g)$\times 10^3$	7.08±3.12 (17)[a]	6.92±2.78 (9)

Details of the ANOVAs are given in the text. *Significantly different from HIV− males, $P=0.036$; **significantly different from HIV− females, $P=0.007$.
[a] BW was not available for one individual.

tion with the age of the subjects ($r=0.11$, $F(1,118)=1.57$, $P=0.212$). Analysis of age by two-way ANOVA (sex× HIV status) in which the homosexual males were excluded, revealed no sex difference ($F(1,96)=0.99$, $P=0.320$); however, the mean age of HIV+ subjects was significantly less than that of subjects without HIV ($F(1,96)=18.40$, $P=0.0000$) on age (Table 1). Follow-up testing with Tukey's honest significant difference (HSD) revealed this was due to HIV+ subjects of both sexes being, on average, younger than HIV− subjects (Table 2). AC area was not correlated with brain weight ($F(1,116)=1.13$, $P=0.289$). Because AC area is a two-dimensional variable and brain weight is proportional to brain volume (a three-dimensional variable), AC area was regressed on the square of the cubed root of brain weight (brain weight)$^{2/3}$, as suggested by Bishop and Wahlsten in their studies of rats and mice [3]. This gave a significant correlation ($r=0.979$, $F(1,116)=2650$, $P=0.212$) replicating the findings from rats and mice in our human sample.

Two-way (sex×HIV status) ANOVA in which the homosexual males were excluded revealed that the brains of men were significantly larger than those of women ($F(1,94)=39.84$, $P=0.0000$), but that there was no effect of HIV status on brain size ($F(1,94)=2.44$, $P=0.121$). In order to assess possible variation in brain size with sexual orientation, a one-way ANOVA was run on three groups: presumed heterosexual males (combined across HIV status), presumed heterosexual females (combined across HIV status) and homosexual males (all HIV+). This analysis revealed a significant effect of group ($F(1,115)=42.18$, $P=0.0000$). Follow-up testing by HSD revealed that this was due to both homosexual men (1448±92 g) and heterosexual men (1384±131 g) having greater brain weights than women (1187±127 g). The difference in brain weight between homosexual and heterosexual men was not statistically significant ($P=0.128$).

To examine the AC for sex differences and HIV effects, a two-way (sex×HIV status) ANOVA was run in which data from homosexual males was excluded. There was no main effect of sex ($F(1,96)=1.84$, $P=0.178$) or HIV status ($F(1,96)=0.41$, $P=0.522$) and no interaction ($F(1,96)=0.025$), $P=0.874$). The same results were seen when (brain weight)$^{2/3}$ was included as a covariate to control for variation with brain size: there was no significant effect of sex ($F(1,93)=0.92$, $P=0.338$) or HIV status ($F(1,93)=0.483$, $P=0.488$) and no interaction ($F(1,93)=0.049$, $P=0.823$).

The AC of homosexual men might theoretically differ from that of heterosexual individuals for reasons unrelated to sexual differentiation of the brain. Therefore, in order to assess possible variation in AC size with sexual orientation, a one-way ANOVA was run on three groups: presumed heterosexual males (combined across HIV status), presumed heterosexual females (combined across HIV status) and homosexual males (all HIV+). This analysis revealed no group effect ($F(2,117)=2.14$, $P=0.122$). Similarly, when (brain weight)$^{2/3}$ was employed as a covariate, no group differences were seen ($F(1,114)=1.65$, $P=0.197$).

In summary, in contrast with Allen and Gorski [1,2], we failed to detect any variation in the size of the AC with either sex or sexual orientation. Thus, to date five studies have examined the cross-sectional area of the AC for sexual variation. Of these, two studies from a single laboratory found it to be larger in women than in men [1,2], one found a trend for it to be increased in men [7], and the present study and one other [11] detected no difference. Findings by Highley et al. [11], suggest that the cross-sectional area of the AC is a poor predictor of the number of fibers it conveys. Accordingly, the number of fibers conveyed by the AC might vary as a function of sex or sexual orientation in the absence of variation in its cross-sectional area.

In light of the uncertainty regarding a sex difference in the size of the AC, any speculation regarding the role of

Table 2
Comparison of homosexual men with presumed heterosexual men and women

	Homosexual men (n)	Heterosexual men (n)	Women (n)
Age	45.90±9.14 (20)	48.29±10.34 (58)	47.81±12.64 (43)
Brain weight	1448±92 (20)	1384±131 (56)[a]	1187±127 (42)*
AC area	8.96±3.49 (20)	8.85±3.51 (58)	7.70±3.02 (43)
AC/brain weight$\times 10^3$	6.25±2.52 (20)	6.50±2.72 (56)[a]	6.41±2.63 (42)

Details of the ANOVAs are given in the text. *Significantly smaller than homosexual men ($P=0.0001$) and heterosexual men ($P=0001$).
[a] BW was not available for two individuals.

such a sex difference in apparent sex differences in hemispheric functioning must be regarded as premature. Furthermore, while it is widely believed that homosexual men may exhibit some brain features similar to those of heterosexual women (e.g., Refs. [2,5,12,14]), in the absence of a sex difference, the distribution of AC cross-sectional areas cannot be hypothesized to be sex reversed in homosexual men.

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