are, roughly 20–30% of the way to the masculine end. The SDN-POA and mounting behavior are the same in this respect. Thus, the effect of estrogen on the SDN-POA reflects not feminization, but the graded effects of hormones (Collaer & Hines 1995) on a masculine trait.

Finally, an update is needed on when sex differences in visuospatial abilities appear. Although Maccoby and Jacklin (1974) suggested that they appear at puberty, this has proved incorrect. Meta-analyses (Linn & Peterson 1985; Voyer et al. 1995) indicate that only certain aspects of visuospatial ability show sex differences, but that they do so in very young children. Sex differences seemed to appear at puberty, because different visuospatial tests were used for different age groups, with younger children generally tested on measures that do not show sex differences and adolescents and adults on measures that do.

Relative size of the human corpus callosum redux: Statistical smoke and mirrors?

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Abstract: Data do exist to support the fact that the corpus callosum is relatively larger in women than in men. The corpus callosum is an integral part of the brain, and contrary to Fitch & Denenberg's examples of "pseudostatistics," is not an extrinsic structure when determining its relative size.

I have no comments to offer on the findings regarding ovarian hormones and sexual differentiation of the brain, as that is out of my area of competence, and a valuable contribution by Fitch & Denenberg (F&D). However, I do wish to discuss the matter of sexual dimorphism in the human corpus callosum, and to respond in particular to the unfair characterization of our work as "pseudostatistics." My comments relate to two areas: (1) the issue of relative size of the corpus callosum in humans and (2) the meta-analysis of the corpus callosum by Bishop and Wahlsten (1997).

First, I think it is very unwise to rely on a statistical technique such as factor analysis to decide whether there are any correlations between the size of the corpus callosum and the brain of which it is a part. It is difficult to understand what is happening to a division of the corpus callosum into 99 measures, particularly in an animal as small as the rat. In all factor analytic studies that I have seen, a size component always comes out in the first factor. If I understand F&D, it does not appear until factor 8. It would seem to me most logical to simply run a Pearson correlation between brain size and corpus callosum size measures, including area and perimeter first, and then to try a factor analysis. I do not understand why this was not done, and instead the authors relied on what amounts to a very complex and relatively little used multivariate statistical technique, which most statisticians would prefer to stay away from, to "prove" a lack of correlation between brain size and the corpus callosum.

Nevertheless, whether rat brain size correlates with the corpus callosum area strongly or weakly, the size of the human brain and its corpus callosum *does* have some considerable empirical basis. We find in Tables 6 and 7 in Holloway et al. (1993, p. 488) a veritable sexual dimorphism of the correlation between brain size and corpus callosum area, in respectable sample sizes of roughly 45 each sex. Males had a correlation of 0.5031 (p = 0.0005), whereas in females the correlation was 0.1638, with a significance of 0.27. Just before these two tables, we had shown from Table 5 that when the sexes were combined, the correlation between brain size and corpus callosum area was 0.3482, with a p-value of 0.0008 (N = 90, p. 487).

I cannot understand why F&D have ignored these findings. As I recall, the Berrebi et al. (1988) paper never tested whether there was any correlation between brain size and corpus callosal measures, nor did the Denenberg et al. (1989) paper provide such a simple test, prior to their use of factor analysis. Perhaps there is no significant correlation between brain size and the corpus callosum in rats, but I doubt that factor analysis is the only way to demonstrate such a lack. In any event, humans do show such a correlation.

We pointed out in our 1993 paper (p. 483) that both Denenberg et al. (1991) and Demeter et al. (1988) claimed there was no correlation between brain size and corpus callosum area, and thus brain size could be ignored. However, because neither ever published the full statistics on brain size (the Demeter et al. study suggested large differences of brain size between human females and males), it begs the question of how strong or weak the correlation was. Surely it is contrary to intuitive wisdom to believe that a structure such as the corpus callosum would have no correlation with the size of the cerebral hemispheres it was connecting, the cerebral hemispheres being some 76% of total brain weight in humans. In any event, as our Tables 5, 6, and 7 (Table 1 here) show, there is indeed a significant correlation within males, and certainly as would be expected given brain size dimorphism, in a combined male and female sample. Particularly strong are the correlations between corpus callosum area and posterior one-fifth area, being on the order of 0.8 for both sexes, separately and combined. Let me recall with a quote from Holloway et al. (1993, p. 495) on the range of human brain sizes from the Demeter et al. (1988) study:

> Brain weights for males cluster between 1,300 and 1,700 cc. Female brain weights cluster between 1,050 and 1,200 cc, and *do not overlap male values* [emphasis mine]. Six male values are above 1,500 cc.

The sample size comprised 22 males and 12 females, hardly enough to draw profound conclusions that brain size could safely be ignored. Those are rather extraordinary and large differences in

Table 1 (Holloway). *Pearson correlation for brain size, corpus callosum area (CCAREA), posterior one-fifth (splenium) area (POST 1/5), and dorsovental splenial distance (SPLNDV)**

Brain weight	CCAREA	POST 1/5	SPLNDV
Total sample, N = 90	0.3482 (0.0008)	0.2127 (0.0442)	−0.0516 (0.6291)
Males only, N = 44	0.5031 (0.0005)	0.3238 (0.0320)	0.0374 (0.8098)
Females only, N = 45	0.1638 (0.2767)	0.2928 (0.0483)	0.1189 (0.4313)

Based on Tables 5, 6, and 7 in Holloway et al. (1993, 487–88).
Significance level in parentheses.
Note the lack of significance and low correlations between brain size and those variables we suggested as particularly dimorphic (i.e., Post 1/5 and SPLNDV).

brain sizes, which do overlap in most populations. It seems strange intuitively that with brain size dimorphism such as this, the mean corpus callosum area would be slightly larger in males, but that the splenial dimension would be almost identical (11.8 mm in males, 11.6 mm in females). I simply cannot understand why a study with those measures would ignore brain size and fail to consider the very simple proposition that relative to the size of the brain, females had larger splenia than males, or that given such large differences between brain sizes, there might be a relative size difference of the corpus callosum.

In that regard, let us examine F&D's statistical arguments for obviating the need for testing the very simple proposition that relative to brain size, the size of the corpus callosum shows sexual dimorphism in humans. F&D write:

> As an example, women weigh on average less than men, and women score lower on average than men on certain tests of spatial ability. . . . One cannot draw any conclusion concerning an association between these two variables from such data. That can only be done if a significant correlation exists between weight and spatial scores within each gender.

I could not agree more! However, that is *not* the hypothesis that we have been trying so hard to test; nor is it even analogous (or homologous) to the structure of our argument that relative to the total size of the brain, a brain structure, namely, the corpus callosum, is larger in females. We have not been discussing body and brain weights and spatial tests; and nowhere have we suggested that spatial ability is a part of body or brain weight, or vice versa.

Elsewhere, we discover under section 6.3.1.1, "Pseudostatistics," a similar argument:

> On average, there is no sex difference between men and women on IQ tests. However, female brains are smaller than male brains, and weigh less. One could obtain an estimate of brain size from cranial measurements or neuroimaging, divide this number into the person's IQ score, and obtain a score that measures "IQ per unit brain tissue." On such a measure females would be significantly superior to males. The reason we do not use such a statistic is that research has established that there is no within-group correlation between IQ and brain size.

Again, I would agree, but this too is rather far removed from what we have done. Nowhere did we attempt any such correlations or any dividing of the data extraneous to the brain by brain size. IQ is simply not a part of the brain; nor is body weight! On the other hand, the corpus callosum is an integral part of the brain, and, like the whole brain, it has a size, albeit an extremely difficult one to calculate, as it is the largest fiber system in the human brain. It is hard to imagine why there should be no correlation worthy of study between the corpus callosum and brain size, when in fact the corpus callosum is a part of brain size. Hence the simple hypothesis that the relative size of the structure differs between males and females is hardly "pseudostatistics." Three recent studies (Andreason et al. 1993; Reiss et al. 1996; Willerman et al. 1991) have demonstrated significant correlations between brain size and various behavioral test scores, so the issue is not quite moot.

Physical anthropologists and other comparative morphologists routinely use ratio data. If we wish to divide the weight of the brain by the weight of the body, we often do so because an extremely interesting set of facts emerges: the relative size of the brain, that is, its part of the total animal's weight, does show sexually dimorphic differences (Holloway 1980) and they vary considerably within the mammalia, and primates in particular. Encephalization quotients and a whole range of allometric analyses depend on such data. It has recently been shown by Semerdeferi et al. (1997) that the proportion of frontal lobe in humans is exactly what we would expect for a primate of our brain size, a fact shown by von Bonin back in 1948, and several others before by the simple expedient of asking how much of the brain was frontal lobe.

I would like to propose the following challenge: Let F&D (or anyone else) explain our finding in Tables 9, 10, and 11 of Holloway et al. (1993, p. 489) that whenever the sexes are compared by dividing the cerebellum, rhombencephalon, ventricles, hippocampus, amygdaloid, thalamus, cortex, or any other part of the brain (except the corpus callosum) by total brain weight, there are no significant statistical differences between human males and females, whereas for each of those absolute measures there is a significant difference. Why is it that the corpus callosum, a part of the brain just like the structures mentioned above, shows the opposite effect when divided by brain size (i.e., a statistically significant difference between human females and males, but no significant difference in absolute size)? Both the Wesseley (1970) and Zilles (1972) data were published well in advance of the simple hypothesis that relative to the size of the brain, one of the brain's structures was larger in females than in males, so we can be reasonably certain their data are unbiased. For all of the structures mentioned above there are indeed positive correlations between their size and the size of the brain.

Last, I wish to address the Bishop and Wahlsten (1997) meta-analysis cited by F&D but not yet in our library. I remember being asked by those authors to provide our original data for the meta-analysis. At the time I refused, because I simply could not understand why mixing two such different approaches in the same statistical analysis could be meaningful. Please recall that part of the controversy over the corpus callosum involves two basic approaches: (1) the study of autopsy data where brain size is available and (2) magnetic resonance imaging (MRI) studies where brain size has largely been ignored, until only recently, when algorithms for adding sections together provide a close approximation to actual brain size. F&D (like Fausto-Sterling 1992) describe how many studies supported our hypothesis and how many did not, as if all the studies were somehow of equal force or merit. Let me give but one interesting example from our 1993 paper. We found that the Byne et al. (1988) study was frequently placed in the category of not supporting our hypothesis. I quote from Holloway et al. (1993, p. 495):

> Magnetic resonance imaging, 15 males, 22 females; dimorphism reported as not significant. Mean CC area was 519 (M) 601 (F). Brain size was not studied. Both CCAREA and posterior one-fifth (splenium) were absolutely larger in females. The splenium was 160 mm^2 for men, and 168 for women in the age > than 40 sample. In the total sample, posterior one-fifth was 170 in females and 160 in males. Given these findings, and the usual dimorphism of brain size being larger in males, these results are fully consistent with our findings.

Here there were absolute size differences in corpus callosum area and splenial area that were larger in females! I can certainly understand how such differences might not be statistically significant using t-tests, but it surprises me that it would not appear important to consider brain size in such analyses. In fact, in almost all the papers we reviewed, the absolute differences between males and females were seldom if ever significant and were very close. Our paper concluded by suggesting that no fewer than 16 of 25 studies reporting no significant differences actually did have results consistent with our findings, if the relative size of the corpus callosum was considered. Bishop and Wahlsten's "meta analysis" is particularly flawed given the mix of studies they combine, and the others that they avoid. Almost all of the earlier published MRI studies that claimed a lack of sexual dimorphism in the corpus callosum simply failed to include the size of the brain in their analyses, and some of the autopsied studies that similarly claimed no dimorphism never provided brain weight data for independent analysis. MRI has advanced to the point where total brain volume is now readily calculable.

Finally, for whatever it is worth, we have found no apparent sexual dimorphism in relative measures of the corpus callosum in other primate species (Holloway & Heilbroner 1992), including, most recently, the chimpanzee (Broadfield et al. 1997, which did suggest some minimal dimorphism in the abstract). We believe, and always have, that more microscopic analyses must be done with types of fibers (myelinated and nonmyelinated) and their distributions (both within the cortex and the corpus callosum) before meaningful functional statements can be made about any

dimorphism between human male and female brains. Nevertheless, it is possible that humans have evolved some species-specific repertoire in their cognitive evolution that includes ethological differences between males and females and have some underlying neural basis. The possibility that the *relative size* of the corpus callosum is larger in females than in males remains to be fairly tested.

The corpus callosum: More than a passive "corpus"

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Abstract: Fitch & Denenberg provide excellent evidence for the existence of dynamically complex interactions between the structural and functional development of the nervous system. They are to be congratulated for showing how subtle social variables (e.g., handling) may not only influence hormonal "cascade effects" on the developing nervous system, but may also alter the structure of brain tissue, such as the corpus callosum.

My commentary is focused on the sections of the target article that deal with the corpus callosum and sexual dimorphism (sects. 5 and 6). I would like to congratulate Fitch & Denenberg (F&D) for presenting a coherent discussion of several lines of research on the complex functions of the corpus callosum. Although the target article pertains mainly to the effects of gonadal hormones on callosal development, it also deals with several other important aspects of the behavioral significance of the corpus callosum.

I agree that the frequent use of relative measures (and the strong pressure from the "scientific community" to do so) can sometimes result in the typical type II error of "throwing out the baby with the bath water." Unfortunately, however, the "statistical" solution F&D advocate – that there should be "a significant association between two variables *within a group* before one needs to make an adjustment" (sect. 5.2) – may likewise lose the baby. The problem is not that there should be a significant association or correlation between the target variable and a covariate, but that the association should also have a *theoretical* foundation. The example F&D provide in section 5.2 – that women weigh less than males and have lower scores on certain spatial ability tests – does not warrant the conclusion that their spatial scores are related to their weight unless there is a "significant correlation . . . between weight and spatial scores within each gender" (sect. 5.2). The problem is that women and men differ on a variety of variables, of which some may correlate spuriously with the target variable by chance alone.

The finding that testosterone propionate treatment must be associated with handling in order to significantly enlarge the female's callosum is indeed intriguing. As F&D quite correctly state, "this effect is more complex than simple exposure of the female to androgen" (sect. 5.4.1). This finding also points to a few other possible interactions with callosal development and functioning. "Individual variation" is ignored in many neurobiological subfields. Traditionally this is treated as "error variance." However, it is quite possible that behind the differential handling effect on callosal development is a complex interaction of individual variation in susceptibility to the social environment, which in turn affects callosal morphology. Such variation could well have a hormonal basis.

The finding by Aboitiz (1992), as well as by others (e.g., Cowell et al. 1992), that there are regional differences along the callosal axis in area size and fiber density and that they interact with "general" functions such as gender and age, is an example of what I would call a "hardware/software" interaction. Aboitiz's conclusion, with which F&D seem to agree (sect. 6.2), was that the callosal regions connecting primary sensory motor areas have large-diameter myelinated fibers. The other callosal regions at the borders of the large-fiber areas consist of small-diameter fibers with a more "diffuse" spatial orientation. My argument is that optimal transfer of information across the callosum, including greater interhemispheric connectivity, may not be exclusive to the large-fiber areas (as both Aboitiz and F&D seem to believe). I would like to argue for a "two-stage" model of callosal transfer in which the small-diameter, diffusely spread fibers reflect "cognitive gating" that may dynamically enhance or inhibit primary sensory transfer depending on the cognitive "set" of the subject or patient. Some dichotic listening data from my own laboratory can be used as an example of the relationship between interhemispheric transfer and callosal size. This suggests a "two-channel" threshold model of callosal transfer that would also include transfer of attentional resources and the gating of sensory transfer (e.g., by attention).

In a recent study on hemispheric asymmetry for auditory stimuli in multiple sclerosis (MS) patients (Reinvang et al. 1994) we specifically examined callosal sector size and left ear performance. The left ear performance in dichotic listening is thought to involve transfer across the corpus callosum (see Hugdahl 1995 for further details about the dichotic listening technique). The corpus callosum often shows atrophic changes in MS patients and measures of the corpus callosum are often included in the diagnosis. In our study we had magnetic resonance imaging measures of callosal sector size. The study involved three conditions, one in which the patients were requested to report both ear inputs, as well as possible, and two conditions in which they were instructed to monitor (attend to) the left or right ear input only. The results showed the expected right ear advantage (better recall from the right than left ear) in both the MS patients and a healthy control group during the nonattention condition. When the subjects were instructed to focus their attention to the left ear, however, the correlations between left ear performance and callosal size were clearly significant, particularly for the three most posterior sectors (including the auditory sector anterior to the splenium).

It thus seems as if an "attention-gating" factor is needed in order to enhance callosal transfer of the left ear score, particularly in a subject population that already has degeneration in the primary sensory callosal pathways. This may suggest a two-channel threshold model of callosal transfer, with a sensory modality-specific channel involving the large diameter myelinated fibers and a diffuse nonspecific sensory channel involving the small diameter nonmyelinated fibers, which are responsible for the transfer of cognitive information.

In closing, I would like to congratulate F&D for their convincing demonstration of the complex, often counterintuitive interactions between structural and functional development. They should be further congratulated for showing how subtle social variables may not only cause hormonal "cascade effects" on the developing nervous system (cf. Geschwind 1984) but that such variables may also alter the structure of the brain tissue "hardware."

Updates on axons in the rat corpus callosum

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Abstract: Developmental counts of axons in the splenium of the rat corpus callosum are compatible with the hypothesis that estrogen may be acting late in development to sculpt the female nervous system.

Our recent data expand the discussion (sect. 6.2) of sex and the axonal composition of the rat corpus callosum. Our findings may also have implications for pubertal effects in female rats that are concordant with the observations on gross size from Denenberg's laboratory and other studies discussed by Fitch and Denenberg (F&D).