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Gender Differences in Cerebral Blood Flow as a Function of Cognitive State with PET

Giuseppe Esposito, John D. Van Horn, Daniel R. Weinberger and Karen Faith Berman
Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, Washington, D.C.

This study explored the role of cognitive states in gender-based differences in brain function. **Methods:** We used the ^{15}O-water bolus method to measure cerebral blood flow (CBF) in 14 young normal volunteers with PET. Each subject was scanned six times, three during different neuropsychological tasks linked to the prefrontal cortex and three others during customized sensorimotor control tasks. The prefrontal tasks were the Wisconsin Card Sorting (WCS) Test, Delayed Alternation task (DA) and Spatial Delayed Response task (DR). **Results:** A significant main influence of sex on global CBF (ml/min/100g) was seen, with higher values in women, as viewed across all six conditions (means: 60.9 versus 53.2, ANOVA F = 9.35, $p < 0.01$). Post-hoc contrasts, however, showed that this finding was not uniform in all conditions. Differences between men and women were seen during performance of the frontal lobe tasks, but not during the sensorimotor control tasks. Even within the three frontal lobe tasks, results tended to vary: the differences between the sexes were most significant during the DA and just reached traditional levels of significance during the WCS. Therefore, if we had utilized a single task condition to determine whether men and women have different global CBFs, disparate conclusions would have been reached depending upon the task chosen. **Conclusion:** Although clear sex differences in global CBF can be demonstrated, the cognitive state of the subjects must be controlled and considered when interpreting the differences. Also, variations in the cognitive state might explain some of the discrepancies in gender studies in the rCBF and cerebral glucose metabolism literature.

Key Words: cerebral blood flow; PET; cognitive stimulation; gender differences; frontal lobe

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The search for sexual dimorphism and for gender-based functional differences in the human brain has produced a large amount of research in the neuroscience literature. Several studies have found structural (*1–3*) and electroencephalographic (*4,5*) differences between male and female brains. A considerable amount of research has also arisen from neuropsychological comparisons between the sexes, including observations that men and women have different verbal and/or spatial skills (*6–8*).

Both regional and global differences between the sexes have been reported with functional brain imaging techniques. As for regional patterns, findings in the frontal lobes have been particularly prevalent. Mathew et al. (*9*) found a more robust difference between men and women in frontal areas than in the parietal, temporal, or occipital regions. Azari et al. (*10*) found gender-related differences in interregional correlational patterns of glucose metabolism particularly involving the left frontal lobe, suggesting tighter functional coupling between this and other brain areas in women. Andreason et al. (*11*) reported higher orbitofrontal cerebral glucose metabolism (CMRGlu) values in women, while Rodriguez et al. (*12*) found frontal asymmetry (right > left) in men that was absent in women.

Nevertheless, these findings have been extremely controversial. A majority of previous studies have demonstrated higher global CBF or CMRGlu metabolism in women (*11–16*), but a number of others found no sex-based differences (*10,17–20*). Despite these inconsistencies, there have been no reports of higher brain activity in men than women. Considerable variation exists among these studies as to how measurements were obtained and what functions were measured. Positive findings, however, have emerged regardless of the technique used: with xenon technology (*9,12,15*), SPECT (*14*) and PET (*16*); with measurements of rCBF as well as glucose metabolism; and in studies performed both with subjects at rest (*9,12,14–16*) and during activation (i.e., when subjects were asked to perform motor, sensory or cognitive activities during the scan) (*11,13*). In contrast, studies that have failed to demonstrate gender differences in global brain activity have mainly been performed while subjects were at rest (*10,17,19,20*), a condition which has been demonstrated by some authors to be more variable than when subjects are active (*21*). There has been only one activation study that has failed to delineate global gender differences in brain activity (*18*).

While the explanation for these striking discrepancies in the literature regarding global flow is not entirely clear, a variety of factors have been suggested. Among the more relevant explanations are the possibility that variable brain size of subject groups could add variability to the results (*22*). Moreover, disparate results could be explained by an interaction between subject's age and sex, as evidenced by the fact that differences between men and women occur in younger cohorts only and converge in later years (*14,15,23*). Another potentially crucial source of variation that has not received sufficient attention is the cognitive state of the subjects (*16,20*). The present study, therefore, sought to explore this factor in healthy young men and women by measuring their rCBFs while performing a variety of cognitive tasks. These tasks include some that are traditionally linked to the region most implicated by previous functional brain imaging studies of gender differences—the frontal lobes.

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For correspondence or reprints contact: Giuseppe Esposito, MD, National Institutes of Health Building 10, Room 4N-317, 9000 Rockville Pike, Bethesda, MD 20892.

MATERIALS AND METHODS

Subjects

Fourteen healthy volunteers (6 women, 8 men; mean ages 28 and 25.3 yr, respectively; range: 22–35 and 20–31 yr) gave informed consent in accordance with National Institutes of Health Institutional Review Board and Radiation Safety Committee guidelines. All participants with neurological, psychiatric or medical disorders were excluded, as were those with a history of alcohol or drug abuse. Subjects were asked to refrain from caffeine and nicotine for 4 hr prior to initiation of the study. The women had received 17.5 yr of education on average, while the men had received 17. Thirteen subjects were right-handed and one woman was left-handed. Analyses performed without the left-handed subject were virtually identical to those for the whole group, except for the expected small loss of statistical power; therefore, the results for the full group are reported.

PET

Data were acquired on a tomograph with a spatial resolution of 6.0–6.5 mm in both the z-axis and in-plane which produced 15 contiguous slices per scan simultaneously. Each patient was scanned six times, each of which followed bolus intravenous injection of 40–46 mCi of $H_2{}^{15}O$. A thermoplastic mask individually molded to each subject was used to immobilize the head. Scans were oriented parallel to the canthomeatal line. Data were acquired for 4 min in 16 frames (12 frames of 10 sec each, followed by four frames of 30 sec each). Transmission scans were used to correct for radiation attenuation through skull and brain tissue. Scan data were reconstructed with corrections for attenuation, scatter, random coincidences and deadtime.

Arterial input functions were measured with automated arterial blood sampling, with blood withdrawn continuously at a rate of 3.8 ml/min, and coincident events were counted by paired sodium iodide detectors and corrected for random coincidences and dispersion (*24*). Arterial time-activity curves were used with a pixel-by-pixel least squares method (*25*) to produce quantitative rCBF images. Arterial blood samples were drawn at the end of each scan to assess levels of partial carbon dioxide pressure (pCO_2), since this is a well-known determinant of global CBF (*26–28*). For review, refer to Purves (*29*).

Cognitive Conditions

Tasks were started 1 min before injection and were continued for the 4 min of data acquisition. Subjects performed a different neuropsychological task during each of the six scans. Tasks were counterbalanced to avoid order effects and were presented on a 19″ computer monitor. Subjects responded using a button-pressing device held in the right hand. Three different cognitive tasks involving the prefrontal cortex—the Wisconsin Card Sort (WCS), Delayed Alternation (DA) and Spatial Delayed Response (DR)—and a specially designed sensorimotor control task matched to each task were administered. The WCS, DA and DR require the ability to hold perceptually absent information in mind, i.e., working memory. These tasks have been shown to activate the frontal cortex in normal patients (*30,35,38*). WCS and DA tasks initially involve the discovery of a simple rule of response through the use of working memory and feedback, and then require application of the rule in response to the stimuli. Like the DA and WCS tasks, the DR task requires working memory to hold the stimulus in mind during the delay by the means of an internal representation, but unlike the DA and the WCS, the DR does not require updating and utilization of cue information during the delay periods. As a consequence, its working memory load is presumably lower. The sensorimotor control tasks are simple, no-delay matching to sample tasks, and identical to the prefrontal tasks in terms of stimulus presentation, visual stimulation and response mode, but they do not require abstract reasoning and problem solving, and no working memory is involved.

WCS. The WCS was first validated by Milner (*31,32*) as a sensitive indicator of the integrity of the frontal cortex in humans. It has been shown to be particularly sensitive to dysfunction of the dorsolateral portion of the prefrontal cortex (*33,34*). In our computerized version, subjects were shown a central "target stimulus" and four surrounding "answer stimuli" arranged in a cross-shaped array. The stimuli consist of designs varying in color, shape and number of elements. Subjects must determine the correct rule (color, number or shape) for matching the target to one of the answers by using feedback about the correctness of their responses, keeping this information in mind with working memory. The category changed after ten consecutive correct answers. Abstract conceptualization, mental flexibility and maintenance of cognitive set are required to perform this task.

WCS Control Task. The sensorimotor control task for the WCS was a simple no-delay, matching-to-sample task in which a central target stimulus and four unchanging surrounding answers consisted of one, two, three or four bars in various orientations. Subjects were required simply to match the target to one of the answers, one of which was identical.

Delayed Alternation (DA). This task is a human adaptation of the classical paradigm used to test the integrity of the prefrontal cortex in monkeys. The subject is initially shown a filled box along side an empty box for 1 sec, the relative positions of which vary randomly over subsequent trials. After a 2.5-sec delay, the subject then sees two empty boxes and is asked to choose one of the two. The correct answer alternates between being on the same side as the filled box and being on the same side as the empty box. Subjects receive feedback after every response to help them discover this rule. The task requires that the subject remember the relative positions of the filled and unfilled boxes during the delay, as well as the current position within the alternation sequence. This dual tracking is heavily dependent on working memory (*35*).

DA Control Task. For this control task, subjects were simply shown a filled box and an empty box in randomly varying relative positions; they were then asked to immediately indicate the position of the filled box by pressing the appropriate button. Stimulus presentation time and delays were the same as in the DA.

Delayed Response. Tasks like the DR developed by Jacobsen (*36*) are standard paradigms for testing frontal lobe function in the adult, nonhuman primate (*37*). In our version the target stimulus consisted of an irregular array of circles, some of which were filled. This array was shown for 3 sec and followed by a 7-sec delay period. A second array is then shown, and the subject must indicate whether the new array is the same or different from the original. The task contains two crucial components: its spatial nature and the delay between stimulus and response (*38*). Impaired performance on DR has been shown in patients with frontal lobe lesions (*39*).

DR Control Task. The stimulus and response were identical to the DR, but the 7-sec delay was imposed between the presentation of the two arrays of circles (i.e., between trials) rather than between members of the trial pair.

Regions of Interest

MRI with the same slice orientation and start position relative to the CM line and the same slice thickness as the PET scans was performed on each subject with a double-echo sequence (TR = 2000; TE = 20/80). The MR images were used as anatomical references to draw individual regions of interest (ROIs) templates for each subject, including the following: inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, parietal lobe, temporal lobe, occipital lobe, caudate nucleus, putamen, thalamus, anterior cingulate cortex and hippocampus. ROIs were drawn in reference to an atlas of the human brain (*40*). Area-weighted mean regional rCBF values were calculated for each cortical and subcortical region as described elsewhere (*30*). This procedure allows reduction of the number of the statistical comparisons.

Statistical Analysis

Statistical analysis of the data was performed using Statistical Analysis System programs (*41*). Regional PET data were analyzed using absolute global and regional CBF values, as well as normalized regional values (absolute rCBF/whole-brain CBF). We subtracted the CBF values of each control task from those obtained from the respective frontal task to derive the activation due to the cognitive components of the tasks. To determine the main effect of gender and the interaction of task × gender on global CBF, separate two-way repeated measures ANOVAs were performed with one independent measure (sex) and one repeated measure (task), having six levels for all tasks or three levels for each of the following comparisons: (a) the three frontal lobe tasks, (b) the three control tasks and (c) activation data. A separate ANOVA was carried out for each region—absolute, normalized, and activation. Post-hoc t-tests were performed separately for each of the six tasks and for the three activations, both for global values and for selected regions. Since the t-test method is the approach used most in PET studies, in which a single scan condition was examined (*11–16*), this allowed us to compare our results to those obtained by other investigators. P values ≤ 0.05 were considered significant for both the ANOVA and t-tests. Task performance data were analyzed for between sex effects using t-tests.

The possibility of gender difference in arterial pCO_2 values was investigated with an ANOVA with one repeated measure and post hoc t-tests to evaluate whether our results were affected by the pCO_2 levels. We made no corrections in CBF values for pCO_2, since the exact magnitude of the correction when pCO_2 values are in the normal range remains controversial (*42*).

RESULTS

Task Performance and Blood Gases

There were no significant performance differences between men and women for the three prefrontal tasks (Table 1). All subjects performed almost perfectly on the control tasks. The analysis of arterial pCO_2 levels (available on 13 of the 14 subjects, Table 1) yielded no significant task × gender interaction, but a significant main effect of gender was seen [ANOVA $F(1,11) = 10.66$, $p = 0.01$], with lower values for women (36.3 ± 2.9 mmHg) than men (41.2 ± 2.9 mmHg). The effect of this difference, if anything, would have been to increase the CBF values of men relative to women.

Global Brain Blood Flow

When all six tasks were considered together, women had a mean absolute global CBF value that was 14.4% higher than men (60.9 ± 6.4 versus 53.2 ± 6.2; ANOVA: $F(1,12) = 9.35$, $p = 0.01$). Figure 1 (top) shows the mean global CBF for the single tasks. Women always showed higher values with respect to men, regardless of the task they performed. The size of the statistical difference between the two sexes, however, depended on the task type. The main effect of sex was highly significant for the three frontal lobe tasks (ANOVA $F(1,12) = 19.4$, $p < 0.0008$), but not for the control tasks ($F(1,12) = 3.12$, $p > 0.1$). No main effect of task or task by sex interaction was found with either the frontal or control task ANOVA, but the effect of gender on global CBF varied across the tasks as assessed with the t statistic (Fig. 1, bottom). The t-statistic reached traditional levels of significance during each of the prefrontal tasks, but not during the sensorimotor control tasks. Even among the three prefrontal tasks the significance of the difference between men and women tended to vary. The significance was greatest during DA ($p = 0.001$) and smallest during the WCS ($p = 0.05$). There was no correlation between the t-statistic values for global CBF differences and the t values for pCO_2 differences.

An ANOVA performed on the global activation data (task minus control) for absolute values of global CBF did not reach significance for either a main effect of gender [$F(1,12) = 2.55$; $p = 0.13$] or a task × gender interaction [$F(2,24) = 1.67$; $p = 0.2$]. T-tests performed on the global activation values for each task separately showed no significant sex effect for the WCS ($p = 0.4$) or the DA ($p = 0.6$). Consistent with this was the fact that both men and women had higher CBF during the WCS than during the WCS control (9.5% increase above control task for both sexes), and that during the DA, compared to the DA control, women showed a CBF increase of 3.3% while men had only a 0.3% increase. A significant gender effect ($p = 0.03$) in whole brain activation was present for the DR; women had higher CBF during this task compared to its control task (increase of 6.5%), whereas men had higher global activation during the sensorimotor control task (with a decrease in CBF of 7.3% during the DR task).

Absolute Regional Values

Consistent with the global results, virtually all regions examined showed higher CBF values in women than men. These differences reached statistical significance (main effect of gender by ANOVA) in all ROIs except for the left anterior cingulate, left hippocampus, left and right occipital lobes, left somatosensory cortex, left putamen and right thalamus. Interestingly, those regions with the greatest statistical gender differences ($F > 10.4$, $p < 0.01$) were all in the frontal lobes: left and right inferior frontal gyri (inferior portions), left middle frontal gyrus (superior portion), left superior frontal gyrus (superior portion). No significant task × gender interactions were found for any of the absolute regional data.

With regard to the absolute regional activation data (task-control), ANOVA revealed a significant gender effect only for the left anterior cingulate (superior portion) ($F(1,12) = 23.35$; $p = 0.0004$), left caudate ($F(1,12) = 10.54$; $p = 0.007$) and for the left hippocampus ($F(1,12) = 5.81$; $p = 0.03$), with women always showing greater activation than men. No significant task × gender interactions were found. Post-hoc t-tests between the sexes on the absolute regional activation data for each task revealed no significant differences during the WCS or the DA paradigms. During DR, significant differences were noted in the following regions: right and left superior frontal gyri, right and left inferior frontal gyri, right middle frontal gyrus, left (superior and inferior) and right (superior) parietals, right occipital, left anterior cingulate and left hippocampus. Women had higher activation values in all the above-mentioned regions.

Normalized Regional Values

Consistent with the notion that the main differences between men and women in the present data were accounted for by global differences, most of the regional sex differences were abolished by the normalization process. Only two regions retained significant gender effects: left anterior cingulate (inferior portion) and left somatosensory cortex ($F(1,12) = 6.43$ and 5.85; $p = 0.02$ and 0.03, respectively). In both of the regions, men had higher normalized values than women. No significant task × gender effects were found for the normalized data.

No gender effect was found for the normalized regional activation data, but a significant task × gender interaction was found for the left inferior frontal gyrus (ANOVA: $F(2,24) = 4.32$; $p = 0.02$; between group t-tests: WCS $p = 0.2$, DA $p =$

TABLE 1
Performance Scores and pCO_2

	Men	Women	t Values*	p*
		Performance†		
WCS				
No. completed	86 (10.7)	84.8 (8.1)	0.22	0.82
% Correct	80.9 (11.7)	82.3 (4.3)	0.27	0.79
No. of categories	5.8 (1.7)	6.3 (1.5)	0.52	0.61
% Perseverative	8.8 (2.6)	9.4 (1.3)	0.53	0.6
DA				
No. completed	46.2 (4.0)	46.3 (1.8)	0.04	0.96
% Correct	68.9 (21.3)	63.8 (23.1)	0.42	0.67
DR				
No. completed	22.6 (0.5)	22.5 (0.5)	0.43	0.67
% Correct	97.2 (4.0)	91.7 (7.3)	1.77	0.1
		pCO_2 (mmHg)		
WCS	42.4 (3.2)	36.0 (2.6)	3.67	0.004
DA	41.9 (4.1)	35.6 (4.3)	2.46	0.03
DR	41.6 (3.6)	36.6 (2.1)	2.72	0.02
WCSc	40.0 (1.7)	36.4 (3.4)	2.11	0.06
DAc	40.9 (2.5)	36.0 (4.0)	2.64	0.02
DRc	40.0 (1.4)	37.1 (2.0)	2.76	0.02

*Unpaired t-tests; two-tailed. .
†Performance data are collected for approximately 5.5 min.
WCS = Wisconsin Card Sort task; DA = Delayed Alternation task; DR = Spatial Delayed Response task; WCSc = Wisconsin Card Sort control task; DAc = Delayed Alternation control task; DRc = Spatial Delayed Response task.
Values are expressed as mean (s.d.)

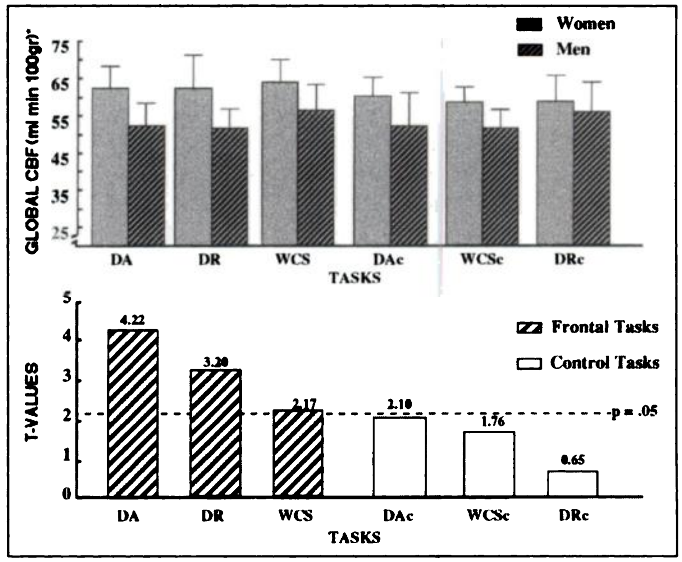

FIGURE 1. Mean absolute global values of CBF for men and women (top) and the respective t-values for between-sex comparison (bottom) represented for each task. Vertical bars indicate standard deviations. DA = Delayed Alternation task; DR = Spatial Delayed Response task; WCS = Wisconsin Card Sort task; DAc = Delayed Alternation control task; DRc = Spatial Delayed Response control task; WCSc = Wisconsin Card Sort control task. The p = 0.05 horizontal dotted line in the bottom corresponds to a t-value of 2.16. The asterisk indicates ANOVA for overall gender effect across tasks: $F(1,12) = 9.35$; $p = 0.009$.

0.007, DR p = 0.4, with men showing higher values than women during the WCS and the DA and lower values during the DR). In view of the large number of comparisons that were made, however, this as well as the other normalized regional findings, could be chance results.

DISCUSSION

The present study investigated gender differences in brain function and, moreover, examined the role of cognitive state by comparing blood flow in men and women during six different cognitive conditions. Despite our relatively small sample size, which is consistent with the results of previous studies of CBF (*12–15*) and CMRGlu (*16*), we found that women had higher levels of global CBF than men (14%) when all scan conditions were considered together, and that a few regional differences existed as well. We also found that the degree to which men and women differed and, indeed, whether differences could be reliably demonstrated at all, depended on the nature of the cognitive activity in which the subjects were involved during the scan.

Cognitive and Behavorial Factors

A number of studies suggest the possibility of a neuropsychological basis for the cognitively-related differences in brain function documented in this and previous functional brain imaging studies. Since it has been shown that men and women differ in a number of cognitive domains (*8,43–47*), it is conceivable that the sex differences we observed in blood flow might be based on differences in how well the men and women performed our tasks during PET imaging. There were no differences, however, in any performance parameter on any of the tasks.

While this suggests that we must look elsewhere for explanations of the sex-related CBF differences that we observed, it does not mean that differences in difficulty and mental effort among the tasks do not play a role in our findings. In fact, the global CBF differences were more striking during the more difficult frontal lobe tasks than during the control tasks on which virtually all subjects performed perfectly. Furthermore, women and men did not differ to the same degree during all three frontal lobe tasks, and the data indicate that how well the subjects performed and the differential degrees to which they found these tasks difficult may have some bearing on the CBF observations. For example, as indicated by the performance scores and as reported by the subjects, delayed alternation was the most challenging of the tasks for both men and women; interestingly, global CBF differences between the sexes were best demonstrated during this task. On the other hand, men and women both scored extremely well during the DR and the WCS (performance of the latter is characterized by a ceiling effect that precludes near perfect scores) tasks, and CBF differences between the sexes tended to be less robust during these two tasks.

Delineation of the exact relationship between mental effort and CBF in this context will require further research. Nonetheless, these observations may also offer a possible explanation for the fact that, while some functional brain imaging studies during the variable condition of "rest" find that women have more active brains than men, almost as many do not. Perhaps undergoing a resting study is a difficult and mentally effortful experience in some laboratories for some individuals but not others. In contrast, cognitive activation paradigms impose a more consistent mental effort burden. Whether or not this speculation is correct, the present results clearly underscore the potential importance of interactions between the cognitive state and the sex of the subject in measurements of brain activity.

That there were no differences in how successfully men and women performed our tasks and yet the fact that both regional and global physiological differences did exist suggests that men and women obtain similar cognitive results by different brain mechanisms. This notion is supported by the fact that men and women show different patterns of hemispheric specialization during certain cognitive behaviors (*6*), and that the consequences of brain lesions may differ in men and women depending on which hemisphere is involved (*48–49*). While the bulk of the data on cognitive differences between men and women has been collected with spatial and verbal tasks, the tasks with which global and regional physiological sex differences were best demonstrated in the present study were neither spatial nor verbal tasks per se, but rather were working memory tasks that are traditionally linked to the prefrontal cortex (*31,32,36,37*).

Gender Differences and Frontal Lobes

While little data have been collected on humans, there is evidence from nonhuman primates that sex-linked differences in neuropsychological abilities may have particular relevance for cognitive processing involving frontal cortical areas, the areas most relevant to the present study. McDowell et al. (*50*) found differences in the ability of monkeys to perform a task similar to our prefrontally linked DR task among males and females. Goldman et al. (*51*) demonstrated that the age at which cognitive deficits emerged following prefrontal lesions depends on the sex of the monkeys, with males being impaired earlier than females. Clark and Goldman-Rakic (*52*) found that male and females monkeys made fewer errors on delayed response when receiving androgens. In light of these data, it is particularly interesting that male-female differences in global flow were best demonstrated during the three tasks that are traditionally considered to reflect frontal lobe function and not in the control tasks. Moreover, regional differences in absolute blood flow were best demonstrated in the frontal lobes. Although the frontal lobe has been the site of sex differences seen at rest and during nonspecific activities (*9–12*), most of the regional sex differences found with absolute values in our study disappeared after normalization to global CBF, indicating that the bulk of the gender differences are related to differences in global flow.

Possible Mechanisms

The mechanism by which the gender differences in brain activity described in our study and in others may occur remains to be fully explained, but several proposals have been put forth in the literature, including differences in neuronal packing (*22*) and brain size (*53*). The latter has been proposed to be of particular importance when calculated rather than measured attenuation corrections are made (*20*). In our study, attenuation corrections were based on actual measurements for every pixel in each individual. Moreover, since our results show that statistically significant gender differences in brain function can be found under some cognitive conditions (the three frontal lobe tasks) and not under others (the sensorimotor control tasks), our findings are likely to be independent of any differences between men and women in brain size, neuronal packing or any other technical features, such as the spatial resolution of the scanner (*20*), since such factors are in effect during both the sensorimotor control tasks and the prefrontal tasks. For the same reason, our findings are likely to be independent of any differences between men and women in peripheral physiological factors such as hematocrit, arterial oxygen carrying capacity and blood viscosity that might relate to differences in progesterone levels and/or blood loss during the menstrual cycle (*15*).

Since the partial pressure of arterial carbon dioxide has been shown to have a powerful direct effect on global CBF levels, pCO_2 is another peripheral physiologic factor that potentially could have explained our findings had we found higher pCO_2 levels in women than men. The blood gas values in the women in our study, however, were actually lower than those of the men. A similar finding, though not statistically significant, was reported by Mathew et al. (*9*). The explanation for the lower values in women is not clear but, regardless, the difference in global flow between the sexes would have been even larger had we corrected CBF values for pCO_2. Since there was no task × sex interaction in the pCO_2 values and no relationship between the magnitude of the pCO_2 differences between the sexes and that of the global CBF differences across the tasks, arterial carbon dioxide cannot explain the differential ability of the tasks to demonstrate sex differences in CBF.

A variety of data suggest that gonadal hormones may play an important role in CBF/CMRGlu differences between men and women. First, several investigators (*14,15,23,54*) have reported a reduction of gender differences in CBF after the fifth or sixth decade, a time when female sex hormones dwindle following menopause. Second, gonadal hormones also appear to affect cognitive function, since how well women perform motor and perceptual-spatial tasks may vary with the menstrual cycles and estrogen levels (*55*). Studies in animals and humans provide evidence that these hormonally driven cognitive changes may be based in hormonally driven changes in brain activity. For example, ^{14}C-deoxyglucose brain uptake in rats was greatest during the period of the estrous cycle, in which estrogen levels are highest (*56*). Baxter et al. (*16*) have suggested that their findings of higher glucose metabolic rates in women than men could be estrogen-related since all of their women subjects were examined between Days 5 and 15 of the menstrual cycle, when estrogen levels are highest. We made no attempt to control the menstrual cycle phase during which women were scanned for the present study, but we still found that they had higher CBF levels. This suggests that if sex hormones do play a role, it may be a chronic one. Further research, however, will be necessary to reach definitive conclusions.

CONCLUSION

Despite a vast number of research articles and a variety of proposed mechanisms, it remains unclear which of those mentioned above may underly the gender differences in brain function that we and others have described. Our finding that women as a whole do have higher CBF than men, but that the difference does not reach statistical significance during all conditions, may suggest that the use of cognitive activation paradigms has a distinct advantage over resting studies for testing various mechanisms. At any rate, the present data suggest that the cognitive state of the subjects in functional brain studies is an important determinant of the outcome and indicate that the cognitive state of the subjects must be carefully controlled and taken into account when interpreting the results from studies comparing cerebral function of men and women.

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