GENDER COMPARISONS OF CEREBRAL GLUCOSE METABOLIC RATE IN HEALTHY ADULTS DURING A COGNITIVE TASK

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Summary—Forty-one healthy volunteer subjects (26 men and 15 women; ages 18-45) underwent positron emission tomography (PET) to measure global and regional cerebral glucose metabolic rate (GMR). Subjects performed a cognitive activation task, the continuous performance test of attention, during uptake of the [18F]deoxyglucose as a metabolic tracer. No gender effect was seen in regional or global GMR: relative GMR (ratio of regional GMR to whole brain GMR) showed seven regions that differed between males and females. This suggests that during an activation task some brain regions may elicit gender differences when compared to the whole brain.

INTRODUCTION

Neuroanatomical and functional gender differences are extensive and have been well documented for whole brain, cortical, midcortical, and subcortical areas (Allen, Richey, Chai & Gorski, 1991a; Allen & Gorski, 1991b; Witelson, 1991; Swaab & Fliers, 1985; De Vries, De Bruin, Uylings & Corner, 1984). Sex differences have been suggested in areas of cognitive functioning, verbal abilities, spatial orientation and visualization abilities, lateralization, and degree of hemispheric specialization (Howard, Fenwick, Brown & Norton, 1992; Janowsky, 1989; McGlone, 1980).

Psychological testing of functions localized to a particular brain region, e.g. verbal and spatial abilities, suggests gender differences in the degree and direction of asymmetries. Females have been reported to have more representation of language and praxis functions in the left cerebral hemisphere, whereas males were reported to show left hemispheric asymmetry in verbal tasks and right hemispheric asymmetry in spatial tasks (Howard et al., 1992; McGlone, 1980). Increased lateralization of brain functions is suggested to be greater in men as compared to women (Janowsky, 1989; McGlone, 1980).

Positron Emission Tomography (PET) studies of gender differences in resting state cerebral glucose metabolism (GMR) have shown mixed results (Table 1). Baxter, Mazziotta, Phelps, Selin,

Table 1. Studies investigating functional gender differences

<table>
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<tr>
<td>Baxter et al. (1987)</td>
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<td>Yoshii et al. (1988)</td>
<td>76 PET</td>
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<td>Whole brain glucose usage female &gt; male 24%</td>
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<td>Miura et al. (1990)</td>
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<td>No significant difference</td>
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<td>76 SPECT</td>
<td>Resting</td>
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<td>Daniel et al. (1980)</td>
<td>95 SPECT</td>
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<td>Melamed et al. (1980)</td>
<td>44 SPECT</td>
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Guze and Fairbanks (1987) observed that whole brain glucose in seven females was 19% higher than whole brain glucose in seven males. Additionally, females displayed higher mean metabolic rates than males in all the neuroanatomical structures examined. Yoshii, Barker, Chang, Lowenstein, Apicella, Smith, Boothe, Ginsberg, Pascal and Duara (1988), in a study of 76 men and women between 21 and 84 years of age, similarly found women to have a significantly higher overall mean resting cerebral glucose metabolic rate than that of men (24.6%). This was due to an overall effect, as all lobes had higher metabolic values. However, when corrected for brain volume and brain atrophy based on extrapolation of one slice by computed tomography, all gender effects were lost and there was no significant difference between men and women. Covarying brain volume resulted in a significant interaction such that individuals with smaller brains displayed higher mean cerebral metabolic rates (see also Haier, Chueh, Touchette, Lott, MacMillan, Buchsbaum, Sandman, LaCasse, Friedman & Sosa, 1995).

Two PET studies found no differences between men and women in resting regional or global cerebral GMR (Miura, Schapiro, Grady, Kumar, Salerno, Kozachuk, Wagner, Rapoport & Horwitz, 1990; Azari, Rapoport, Grady, DeCarli, Haxby, Shapiro & Horwitz, 1992). Miura et al. (1990) did report one relative GMR difference (ratio of regional GMR to whole brain GMR) in the posterior cingulate. This was de-emphasized by the authors as within the possibility of a chance occurrence, given the number of t-tests performed. Azari et al. (1992) noted four relative GMR regions-of-interest that differed significantly between men and women, but these areas were not named. A recent PET study by Gur, Mozley, Mozley, Resnick, Karp, Alavi, Arnold and Gur (1995) reported on 61 healthy adults at rest. Higher GMR was found in temporal-limbic areas and cerebellum for males, although the authors noted that males and females were more similar in regional GMR than they were different.

Only two PET studies and one functional MRI study of gender comparisons during cognitive activation have been reported. Andreason, Zamenkin, Guo, Baldwin and Cohen (1994) studied 18 females and 21 males for global and regional differences in cerebral metabolic rate for glucose. An auditory CPT task was utilized to accentuate frontal lobe functional differences and to lower variance that may occur as a result of variable cognitive activity at rest. A trend for higher global GMR in females was noted (P < 0.06, one-tailed) and significant GMR differences were found for orbital frontal regions (female > male). Haier and Benbow (in press) reported a PET/FDG comparison of 22 males to 22 females while they performed a mathematical reasoning task. Males and females were matched for superior or average mathematical ability. No mean cortical GMR sex differences were found. However, GMR in temporal lobe areas, bilaterally, was correlated significantly to Math task score in the males but not in the females. The functional MRI study (Shaywitz, Shaywitz, Pugh, Constable, Skudlarski, Fulbright, Bronen, Fletcher, Shankweller, Katz & Gore, 1995) reported a gender difference during a language task. Males showed blood flow activations in frontal lobe areas during phonological processing, whereas females showed more diffuse areas of activation.

Studies of cerebral blood flow (CBF) using xenon-133 inhalation and SPECT also show mixed results, but suggest the presence of a gender effect. Cerebral blood flow has been linked to resting cerebral metabolic rate (Baron, Rongemont, Collard, Bastany, Bousser & Comar, 1985; Raichle, Grubb, Gado, Eichling & Ter-Pogossian, 1976). Differences in resting CBF between 38 men and 38 women were found to be 11% by Rodriguez, Warkent, Risberg and Rosadini (1988), while Gur, Gur, Obrist, Hungerhubler, Younkin, Rosen, Skolnick and Reivich (1982) reported a 15% difference between 30 men and 32 women. Both studies noted blood flows that were higher in the females than with age matched males. This female greater than male blood flow difference persisted when subjects performed a spatial or verbal cognitive task (Gur et al., 1982). Daniel, Mathew and Wilson (1989), in a study of resting CBF, investigated the effects of sex roles as quantified by Bem’s Sex Role Inventory. Their results show females with a higher CBF than males, especially evident in the frontal regions. When sex was covaried, males and females with high femininity had higher CBF than their counterparts with low femininity. Contrary to these studies, other investigators found no gender difference in CBF (Melamed, Lavy, Bentin, Cooper & Rinot, 1980; Hannay, Leli, Falgout, Katholi & Halsey, 1983). Hannay et al. (1983) studied 20 volunteers (mean age 44.2 yr) during a cognitive task and found no sex effect in either the pattern or the amount of regional CBF. Additionally, Melamed et al. (1980) reported no sex effect in 44 subjects (mean age 42 yr) while at rest.
Neuroanatomical, functional and neuropsychological studies have suggested evidence for possible gender differences. As summarized in Table 1, some PET studies have suggested a gender difference in resting regional and global GMR, other studies suggest no difference in GMR between the sexes during resting conditions. Information on cerebral blood flow seems to indicate a female greater than male sex difference in both resting and during cognitive tasks. In this study, we have used PET to quantify the difference in regional and global cerebral GMR between men and women while performing a cognitive activation task, the continuous performance test of attention.

METHODS

Subjects

Twenty-six males (18–42 years old) and 15 age matched females (18–45 years old) volunteered to undergo PET scans. None of the 41 normal Ss had a history of psychiatric problems, head injury, or major medical illness. All were right-handed and not taking any medications.

PET tracer

After screening, each S completed a PET scan. The PET procedure used \( ^{18}F \)deoxyglucose (FDG) as the metabolic tracing agent. FDG has a time resolution of about 32 min and has advantages over shorter isotopes like \( O^{15} \) used for PET blood flow studies. The principal advantages of FDG are the added reliability of many stimuli presentations and the stronger signal-to-noise ratio. FDG is quantified in \( \mu \)moles of glucose per 100 g of brain tissue per min. It is important to note that the FDG tracer is injected into the S in a sound and light controlled test room and is taken up by the brain for a 32-min period during which the S performed the CPT, described below. At the end of this period, 80–90% of the FDG has been taken up by the brain and converted to FDG-6-phosphate. This compound serves as the marker of metabolic rate and remains in place after the uptake period and cognitive task arc over. The actual scanning begins only after the 32 min of uptake and is done in an adjoining room. Thus, the PET image reflects GMR during the cognitive task and not during the scanning.

Cognitive task

We have used the degraded Continuous Performance Test (CPT; Nuechterlein, Parasuraman & Jiang, 1983) in several PET studies of attention. For the CPT, Ss are seated 1 m from a rear projection screen on which single digits (0–9) are presented for 40 msec at the rate of 1.5 per sec. Ss are asked to respond by pressing a button each time that they detect the digit 0. Targets are presented irregularly with a probability of 0.25 through the use of a Kodak Carousel slide projector fitted with an Ilex No. 4 Synchro-Electric Shutter and controlled by computer. Stimuli are degraded to 2.8 diopters by adjusting the lens. The spatial frequency of the stimuli is about 0.5 cycles/cm.

The CPT is presented over the 32 min FDG uptake period. Target and non-target digits are presented in pseudorandom order. Accuracy and reaction time are recorded by the computer. The S is instructed to press the button to respond to the zero and not to respond to the other digits. Performance is reported as \( d' \) calculated across the 32 min.

PET scanning

The Ss were seated in an acoustically attenuated, darkened psychophysiological testing room. An intravenous line with a 0.9% saline drip was inserted into the S's right arm for radiotracer injection and a second line into the S's left arm with a plastic cannula for blood sampling. The left arm was wrapped in a hot pack for arterialization of venous blood (which gives adequate glucose values; see Phelps, Huang, Hoffman, Selin, Sokoloff & Kuhl, 1979). Intravenous lines were started about 60 min before FDG injection. Ten minutes before FDG injection, subjects had a warm-up trial; 2–3 min before injection, the CPT was started so that the initial novelty of the task was not FDG labeled.

After 32 min of FDG uptake, the right arm IV was removed, the S allowed to void, and then transferred to the adjacent PET scanner room. An individually molded, thermosetting plastic head holder was used to maintain head position during the scan.
Fig. 1. Surface cortical regions subdivided by gyri. Pictured is the position of the cortical gyri, with individual gyri shaded to show anatomy.

Nine or ten slices at 10-mm intervals were obtained parallel to the canthomeatal (CM) line on a NeuroEcat scanner. Scans started at about the level of 85% of head height (vertex to CM line, usually 12–14 cm) and progressed downward in steps of 10 mm. The PET scanner has a single ring with shadow shields and septae to achieve 7.6-mm resolution (FWHM, full width half maximum) in plane and 9.9-mm resolution in the Z-dimension. This is adequate for all the areas in our standard template. The risk of partial voluming is diminished because many structures of particular interest in this study, including the medial areas of the frontal lobe, cingulate and thalamus extend vertically more than one slice thickness.

**PET quantification**

Scans were reconstructed with a calculated attenuation correction and high resolution filter. The rate of glucose metabolism was calculated according to Sokoloff, Reivich, Kennedy, Bes Rosiers, Patlak, Pettigrew, Sakurada and Shinohar (1977), using our adaptation of Sokoloff’s original autoradiographic program. The lumped constant from Phelps et al. (1979) was used.

**Brain region identification**

PET quantification avoids bias in region-of-interest selection by identifying all brain areas based on computer algorithms. Cortical brain regions and cortical, midcortical and subcortical regions of interest were identified and quantified using a standard template (see Buchbaum, Haier, Potkin, Nuechterlein, Bracha, Katz, Lohr, Wu, Lottenberg & Jerabek, 1992) based on stereotaxic coordinates and the Matsui and Hirano (1978) brain atlas. Neuroanatomical locations depicting the positions of the cortical peel regions and cortical, midcortical and subcortical boxes are shown in Figs 1 and 2, respectively.

**RESULTS**

The men \((N = 26)\) and women \((N = 15)\) did not differ on age (men: mean ± SD = 26.2 ± 7.2 yr; women: mean ± SD = 27.0 ± 9.2 yr; \(t = -0.35, P = 0.726\)). Similarly, there was no difference between men and women for performance on the CPT (men: mean ± SD = 3.89 ± 0.32; women: mean ± SD = 3.88 ± 0.38; \(t = 0.11, P = 0.913\)). GMR did not differ in the overall cortex between the groups (men: mean ± SD = 27.1 ± 10.4; women: mean ± SD = 26.5 ± 9.3; \(P > 0.05\)).

Cortical GMR compared by four-way ANOVA with repeated measures, sex (male, female) \(\times\) lobe (frontal, parietal, temporal, occipital) \(\times\) segment (1–4) \(\times\) hemisphere (left, right), showed no significant sex effect or interactions (Table 2). Normalization of regional GMR to whole brain GMR was done to offset the wide variability in GMR among people. When the four-way ANOVA was
repeated using this relative GMR data (ratio of regional GMR to whole brain GMR), no significant gender effect or interactions were apparent (Table 3).

$t$-Tests were performed on GMR for 28 areas identified a priori from previous neuroanatomical and neurofunctional work as possibly having a gender difference. These 28 areas were investigated bilaterally and include boxes sampled across several slice levels for the superior, middle, rectal and orbital gyri of the frontal lobe, the paracentral and precuneus lobules of the parietal lobe, the visual association cortex (area 18 and 19), the anterior, middle and posterior portions of the corpus callosum.
callosum, the caudate nucleus, and the amygdala. Exploratory \(t\)-tests were performed on the remaining 37 bilateral areas of our standard template (Fig. 2).

No gender effects were apparent anywhere for GMR. For relative GMR data, however, seven regions showed higher rates for women (Table 4): right and left posterior middle frontal (slice 68% of head height measured from the canthomental line), left paracentral lobule (68% slice), right optic radiation (41% slice), right caudate (34% slice), right middle temporal (34% slice) and right amygdala (21% slice).

\(t\)-Tests were computed on GMR and relative GMR to look for any left hemisphere minus right hemisphere asymmetry for each of the regions-of-interest. Three regions showed gender differences:
the caudate nucleus (slice level 34%), the amygdala (21% slice) and the precuneus (68% slice). The caudate nucleus and amygdala showed significant left minus right asymmetry for both GMR and for relative GMR, whereas the precuneus was significant only for relative GMR. The right caudate nucleus had a higher GMR and relative GMR than the left caudate nucleus in both females and males. However, the amygdala showed a right greater than left GMR and relative GMR in females, but an opposite left greater than right GMR and relative GMR in males. The precuneus showed a right greater than left relative GMR for the males, but a left greater than right relative GMR for the females.

**DISCUSSION**

We found no sex differences in global or regional GMR during the CPT. This is consistent with most other previous investigations (Miura et al., 1990; Azari et al., 1992; Gur et al., 1995; Haier & Benbow, in press).

When relative GMR (regional GMR to whole brain GMR) was compared between men and women, seven regions-of-interest were significantly higher in females (Table 4). One of the regions, posterior medial frontal, showed bilateral significance. This is similar to the CBF finding of Daniel et al. (1989) using Xe-133 and SPECT which also revealed a frontal region effect of females higher than males. Andreason et al. (1994) also showed other frontal regions GMR higher in females during an attention task.

We also found GMR higher in the right caudate nucleus in females, whereas, Andreason et al. (1994) reported a difference in the left caudate. The caudate has not shown sex differences in other studies (Petersen, Riddle, Cohen, Katz, Smith & Leckman, 1993; Small, Kuhl, Riege, Fujikawa, Ashford, Metter & Mazzotti, 1989).

Buchsbaum, Nuechterlein, Haier, Wu, Sicotte, Hazlett, Asarnow, Potkin and Guich (1990) in a previous PET study of normal controls, females and males combined, performing the CPT task showed an activation of the frontal, temporo-parietal, and overall right cortical hemisphere. Haier, Siegel, Nuechterlein, Hazlett, Wu, Paek, Browning and Buchsbaum (1988) reported CPT GMR data only in males from the same sample. They found an overall right cortical hemisphere activation, but failed to find any frontal activation, suggesting a possible gender effect. Our findings show that the posterior medial frontal (bilaterally), the medial temporal, and the left paracentral boxes were significantly different between men and women, with women having higher relative GMR than men.

Some other regions identified a priori from previous work on structural and functional sex differences showed relative GMR differences. Our GMR data in the temporo-parietal region showed a significant sex effect in relative GMR for both the left paracentral lobule and the right medial temporal gyrus box. Evidence of functional sex difference exists for the left paracentral lobule (for review see Witelson, 1991). Also, the left sylvian fissure, the left Wernicke’s area and the left planum temporale (superior surface of the superior temporal gyrus) have been indicated as having gender differences (for review see Witelson, 1991). However, in our data the right medial temporal gyrus GMR, inferior and opposite to the left superior temporal findings, is significant.

Neuropsychological functional asymmetries and lateralization of the male brain as compared to female brains has been proposed previously (Janowsky, 1989; McGlone, 1980). Our results using a cognitive test of attention failed to yield any hemispheric asymmetries. The caudate, precuneus and
amygdala regions-of-interest, however, did show evidence of asymmetry. The significance of these findings is most likely negligible. Areas suggested as having functional gender differences, such as those involved in visual–spatial and verbal abilities, are at too gross a level to accurately correlate with the specific neuroanatomical locations of the precuneus, caudate and amygdala.

The isthmus of the corpus callosum, a white matter bundle which structurally may be much larger in women than in men (Holloway & de Lacoste, 1986; Witelson, 1989; Elster, DiPersio & Moody, 1990), showed no sex difference in GMR in our study. Witelson (1991) has suggested that the sex difference in the isthmus of the corpus callosum is related to a functional difference between the sexes in the temporoparietal cortex.

Hines, Allen and Gorski’s (1992) volume analysis of rats revealed that the medial nucleus of the amygdala of male rats was 85% larger than that of females. Our results indicate that males have an amygdala relative GMR only 86.6% of that of females during the CPT.

Relationships between brain volume, neuronal packing density and GMR are complex and not well understood. Recent studies indicate that the smaller the normal functioning brain size, the higher the metabolic rate (Hatazawa, Brooks, DiChiro & Bacharach, 1987; Yoshii et al., 1988; Haier et al., 1995). This may be the result of increased neuronal packing density in anatomically smaller structures. Male brain volume is reported to be only slightly greater than female brain volume. If this global brain sex difference is representative of individual structures in the brain, a small difference in mass may account for a small but significant difference in relative GMR, demonstrable only in sample sizes of sufficient statistical power. This could account for some neuroanatomically smaller structures having higher relative GMR.

In summary, no gender differences were found in either regional or global GMR while performing the CPT. Analysis of relative GMR, however, showed seven specific regions where females had significantly higher glucose rates than males. These differences may be a result of Type II error or a function of neuroanatomical size difference between men and women. Different scanning parameters (especially spatial resolution, anatomical localization techniques, task selection, and statistical power) among imaging studies contribute to the lack of consistent findings to date. Areas of the frontal lobe may show the most potential for consistent female greater than male functional differences.

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