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Gender Differences in Cortical Glucose Metabolism in Alzheimer's Disease and Normal Aging

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Male Alzheimer's disease patients, studied with 18-fluoro-2-deoxyglucose positron emission tomography while performing a verbal memory test, showed a right-greater-than-left asymmetry of cortical metabolism that tended to be greater than that in healthy, age-matched control subjects. This asymmetry was absent in female patients, preliminarily suggesting a propensity for left hemispheric involvement in the Alzheimer's disease process in males.

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In most,¹⁻⁴ but not all,^{5,6} cerebral blood flow (CBF) and positron emission tomographic (PET) studies of gender differences, women have higher cortical CBF and glucose metabolic rate (GMR) than men early in adulthood; the rates become similar after age 50. The reason for the higher CBF and GMR in young females in these studies is unclear.

PET and CBF studies of Alzheimer's disease (AD) have demonstrated reduced whole-brain activity, most prominently in parietal and temporal lobes, and greater than normal variance of cortical asymmetry.⁷ Small et al.⁸ found statistically nonsignificant higher GMR in female than in male AD patients.

No PET study of AD and normal aging has explored gender differences in regional brain metabolism during a task sensitive to AD pathology. In this study we sought to explore gender differences in regional cerebral glucose metabolism in normal elderly persons and AD patients while they were performing a task on which performance is impaired early in the course of AD: a delayed verbal memory test.

METHODS

Subjects

We recruited the patients, all of whom had a clinical diagnosis of probable AD, by referral and through advertisements. Diagnosis was confirmed by NINCDS-ADRDA criteria by a neurologist (A.S.). The patient group consisted of 38 elderly adults (19 men, mean age $\pm$ SD = 72 ± 8 years, range 56-91, Mini-Mental State Examination [MMSE] score = 19 ± 4 ; 19 women, mean age = 75 ± 9 , range 52-84, MMSE = 20 ± 5). Nineteen healthy control subjects were primarily spouses and siblings of patients. The control subjects were 9 men (mean age = 70 ± 8 , range 58-82, MMSE = 27 ± 2) and 10 women (mean age = 71 ± 5 , range 62-80, MMSE = 27 ± 2). Data on neuropsychological⁹ and EEG topographic¹⁰ correlations with GMR in this sample have been reported elsewhere. All patients and control subjects were judged to be in good health on the basis of medical and psychiatric history, physical examination, and laboratory analyses. Patients and control subjects had not been taking any centrally acting medication for a minimum of 2 weeks prior to scanning. All patients and control subjects had MRI scans, which were negative except for atrophy in some patients. The Hachinski score,¹¹ a rating of the likelihood of ischemic dementia based on the history of illness progression, was less than 4 in all patients. Patients gave informed consent for participation in the study after we fully explained the procedures.

Neuropsychological Testing

A research assistant who had been trained by a neuropsychologist tested each patient. The test battery included the Wechsler Adult Intelligence Scale Digit Symbol subtest, the Wechsler Figure and Story Recall, the MMSE, the Bender-Gestalt, and Word Fluency. Testing was done within 2 weeks of the PET scan.

Activation Task and Scan Procedure

Words from a 150-item word list were presented on a monitor for 300 ms at 3-second intervals. Each word was presented a first time and later repeated after a 6- to 18-second delay. All words were thus presented as novel (initial presentation) and familiar (second presentation) items. The subject's task was to press one key with the index finger when a novel stimulus was pre-

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sented and another key with the ring finger for a familiar stimulus.

Patients and healthy control subjects, who had all fasted for at least 4 hours, performed the memory task in a darkened isolation room during the 30-minute uptake of 4.0–5.2 mCi of [^{18}F]deoxyglucose (FDG). The procedure of infusion and blood sampling for glucose quantification is described elsewhere.¹² After the task, subjects moved to the scanner (CTI NeuroECAT IV). We obtained nine planes parallel to the canthomeatal (CM) line, starting at 95 mm above the CM line and at 10-mm increments, over a period of 45 to 100 minutes. We transformed scans to GMR according to the model of Sokoloff,¹³ using an adaptation of Sokoloff's program, kinetic constants, and the lumped constant.¹²

Region of Interest Localization

Because of differences in both head height and brain proportion, a rater chose slices for analysis on the basis of their resemblance to the Matsui and Hirano¹⁴ atlas levels. For each slice, the outer brain contour was outlined with a boundary-finding technique, and a strip of pixels 2 cm thick was then identified.¹² As in our previous study,¹⁵ cortical peel regions were divided anatomically into frontal, parietal, temporal, and occipital lobes based on the percentage of the brain perimeter accounted for by each lobe at each level in the Matsui and Hirano atlas. Each lobe was divided into four regions based on the same stereotactic principle.

Medial temporal structures were located in the Matsui and Hirano atlas; proportional locations, defined on the anteroposterior and lateral axes, were transferred automatically without operator intervention to the PET slices; and mean GMR was calculated.¹⁵ The medial temporal areas examined in this study were the region of the hippocampus at atlas levels 9, 10, and 11 and the region of the uncus at the 11 level. Analysis was carried out on absolute GMR expressed in $\mu\text{mol} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, and as relative GMR, expressed as ratio of regional GMR to whole-brain GMR for cortical areas and expressed as ratio of regional GMR to whole-slice GMR for medial temporal areas.⁹

Statistical Analysis

Absolute and relative GMR data were analyzed by using repeated-measures analysis of variance (ANOVA). The five-way ANOVAs for the lateral cortex were group (control subjects, AD) $\times$ gender $\times$ cortical lobe (frontal, parietal, temporal, and occipital cortices) $\times$ cortical region $\times$ hemisphere. For medial temporal regions, four-way ANOVAs were calculated: group $\times$ gender $\times$ medial cortical region $\times$ hemisphere. Only group and/or gender main effects and interactions with region

and/or hemisphere were evaluated. Simple interactions were evaluated where indicated by significant interactions in an ANOVA.

RESULTS

Gender Effects

Male patients showed a right-greater-than-left asymmetry of cortical GMR (left hemispheric relative GMR 1.07, right 1.13) that was absent in the females (left and right both 1.11), as confirmed by a trend-level hemisphere $\times$ gender effect ($F = 4.06$, $df = 1,36$, $P = 0.051$) for relative GMR in the gender $\times$ cortical lobe $\times$ cortical region $\times$ hemisphere ANOVA for patients (Table 1). Gender $\times$ cortical region $\times$ hemisphere simple interactions demonstrated this gender $\times$ hemisphere effect in parietal cortex and in temporal cortex at a trend level, but not in frontal or occipital cortices in the patients (Table 1). On the other hand, male and female control subjects (both left 1.09, right 1.11) showed a degree of right-greater-than-left asymmetry of cortical GMR somewhat less than that of male AD patients and slightly greater than that of AD females. However, control subjects did not differ significantly in gender differences in cortical asymmetry from patients (group $\times$ gender $\times$ hemisphere interaction from the 5-way ANOVA for relative GMR, $P = 0.15$).

There were no significant gender main effects in the gender $\times$ lobe $\times$ cortical region $\times$ hemisphere ANOVAs for absolute GMR in either diagnostic group. Control females had a cortical GMR of $29.4 \mu\text{mol} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, whereas for males it was 27.4 (gender main effect: $F = 0.97$, $df = 1,17$, $P = 0.30$). Female patients had a cortical GMR of $21.5 \mu\text{mol} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, and in males it was 19.9 (gender main effect: $F = 0.39$, $df = 1,33$, $P > 0.50$). Female control subjects showed higher temporal relative GMR than males, as demonstrated by a significant gender effect in the gender $\times$ cortical region $\times$ hemisphere simple interaction ANOVA for the temporal lobe, but no significant gender $\times$ cortical lobe effects were demonstrated in the patients (Table 1).

Group Effects

AD patients had significantly reduced absolute GMR (mean $\pm$ SD = $20.7 \pm 4.0 \mu\text{mol} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$) for the whole cortex (group main effect in the 5-way ANOVA: $F = 17.62$, $df = 1,50$, $P = 0.0001$) compared with control subjects (28.4 ± 15.5). There were no significant lobe or hemisphere interactions with diagnostic group in the ANOVAs for either absolute or relative GMR, nor were there significant group $\times$ gender effects for absolute or relative GMR of cortical or medial temporal regions.

TABLE 1. Cortical relative glucose metabolic rate by lobe and gender for Alzheimer's disease (AD) patients, healthy elderly control subjects, and the two groups combined

Region	AD Patients ^a		Control Subjects ^b		AD + Control ^c	
	Male	Female	Male	Female	Male	Female
Frontal lobe						
Left	1.07	1.07	1.12	1.09	1.09	1.08
Right	1.12	1.08	1.15	1.12	1.14	1.10
Total	1.10	1.07	1.13	1.10	1.11	1.09
Parietal lobe						
Left	1.13	1.17	1.18	1.10	1.15	1.14
Right	1.19	1.12	1.19	1.11	1.19	1.11
Total	1.16	1.14	1.18	1.10 ^d	1.17	1.13
Temporal lobe						
Left	0.91	0.99	0.92	0.98	0.91	0.99
Right	0.98	0.99	0.95	1.01	0.97	1.00
Total	0.95	0.99	0.93	1.00 ^e	0.94	0.99 ^f
Occipital lobe						
Left	1.15	1.22	1.15	1.17	1.15	1.20
Right	1.12	1.26	1.17	1.20	1.19	1.23
Total	1.18	1.24	1.16	1.19	1.17	1.22 ^g

^aTrend hemisphere $\times$ gender effect for entire cortex: $F = 4.06$, $df = 1,36$, $P = 0.051$; for parietal cortex, $F = 6.53$, $df = 1,36$, $P = 0.015$; for temporal cortex, $F = 3.46$, $df = 1,36$, $P = 0.071$. Lobe $\times$ gender effect not significant ($F = 1.27$, Huynh-Feldt adjusted $df = 2.97, 107.01$, $P = 0.29$).

^bLobe $\times$ gender effect: $F = 4.95$, Huynh-Feldt adjusted $df = 2.88$, 49.02 , $P = 0.0049$.

^cLobe $\times$ gender effect: $F = 3.24$, Huynh-Feldt adjusted $df = 2.98$, 168.09 , $P = 0.024$.

^dDiffer from male control subjects, gender main effect for parietal lobe: $F = 4.77$, $df = 1,17$, $P = 0.043$.

^eDiffer from male control subjects, gender main effect for temporal lobe: $F = 5.30$, $df = 1,17$, $P = 0.034$.

^fTrend difference from males, gender main effect for temporal lobe: $F = 3.84$, $df = 1,55$, $P = 0.055$.

^gDiffer from males, gender main effect for occipital lobe: $F = 4.82$, $df = 1,55$, $P = 0.032$.

Neuropsychological Test Performance

There were no gender differences in either diagnostic group in performance of any of the neuropsychological tests that were administered. Control subjects scored significantly better than patients on all of the tests ($P < 0.005$ by two-tailed t -tests), with the exception of the Bender-Gestalt, where there was no group difference.

DISCUSSION

This PET study of gender differences in cortical glucose metabolism in healthy elderly persons and patients with early to moderate-severity Alzheimer's disease suggests gender differences in hemispheric asymmetry of cortical GMR in AD patients but not in healthy elderly adults. Male AD patients had a right-greater-than-left asymmetry that was absent in females, the difference

almost reaching statistical significance, whereas male and female healthy elderly control subjects both had similar degrees of right-greater-than-left asymmetry, intermediate between AD males and females. This finding suggests that males are particularly susceptible to left-sided involvement by the pathological process in AD, which may have important implications for the nature of Alzheimer's disease. Small et al.⁸ did not report gender or gender by group differences in cortical metabolic asymmetry; however, the number of patients in their study was somewhat smaller, and because they did not publish a table with GMR data for males and females separately, it is unclear whether there was a similar trend. At this point, given the small number of subjects studied and the number of statistical comparisons calculated, we consider our findings to be preliminary. Future studies should examine larger groups of patients and control subjects of both genders and should investigate interactions of gender and neuropsychological deficits with regional metabolism.

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