Gender Differences in Cerebellar Metabolism: Test-Retest Reproducibility

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Objective: *The purpose of this study was to evaluate gender differences in baseline measures of regional brain metabolism and to assess their reproducibility.* *Method:* *Fifteen male and 13 female healthy subjects, whose mean age was 44 years, were tested with positron emission tomography and [^{18}F]fluorodeoxyglucose (FDG) under resting conditions; eight of the men and 11 of the women underwent a second FDG scan under the same conditions 4–6 weeks later to assess the reproducibility of the previous results.* *Results:* *There were no differences in whole brain metabolism between the women and the men. In the first evaluation the female subjects showed significantly higher metabolism in the temporal poles and cerebellum than the male subjects. During the second evaluation the female subjects had significantly higher metabolism only in the cerebellum.* *Conclusions:* *This study documents significant and reproducible gender differences in cerebellar metabolism; their functional significance merits further evaluation.*

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The use of [^{18}F]fluorodeoxyglucose (FDG) in conjunction with positron emission tomography (PET) has enabled researchers to investigate regional brain glucose metabolism in human subjects at baseline and during activation. Studies conducted under baseline conditions have shown substantial intersubject variability in regional brain metabolism. Variables accounting for this variability have been described and include, among others, age and gender (1). Gender effects on metabolism have not been consistent, with some studies reporting higher brain metabolism in women than men (2, 3), others reporting no differences (4), and others reporting differences in regional measures only (5). These discrepancies probably reflect multiple factors, including study conditions, subjects' characteristics, analysis strategies, and measurement variability.

In this study we investigated gender effects on baseline metabolism in two evaluations to determine the reproducibility of group differences in regional metabolic measures.

METHOD

We studied 15 men (mean age=44 years, SD=8; mean level of education=14 years, SD=3) and 13 women (mean age=44 years, SD=6; mean level of education=14 years, SD=2). They were right-handed, healthy subjects who had been screened for absence of medical, neurological, and psychiatric disease. Persons in need of medication and those with past or present alcohol or drug use (except for caffeine and nicotine) were excluded. Pre-scan tests ensured the absence of psychoactive drug use. Details have been published elsewhere (1). Written informed consent was obtained from the subjects according to the guidelines of the institutional review board at Brookhaven National Laboratory.

All subjects underwent PET scans with FDG under baseline conditions (lying supine, eyes open, and ears unplugged); 19 of the subjects (eight male and 11 female) underwent a second baseline scan 4–6 weeks later. Twenty-minute scans were done with a CTI-931 scanner 35 minutes after injection of 4–6 mCi of FDG. Details on the procedure have been described (1). For the female subjects, scans were done within the first 10 days of their menstrual cycle.

The template used to locate the regions of interest in the PET scans has been published (6). Absolute as well as "relative" (region of interest divided by the whole [average metabolic rate in the 15 brain slices]) metabolic measures were obtained in 14 "composite" brain regions (6).

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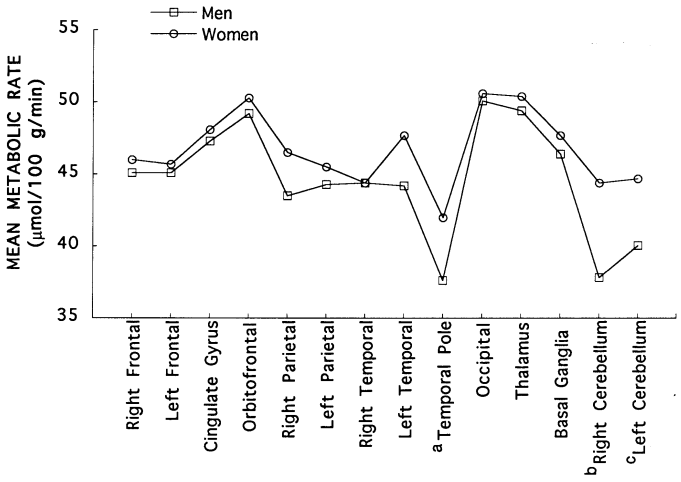
FIGURE 1. Absolute Measures of Regional Brain Glucose Metabolism in 15 Healthy Men and 13 Healthy Women



[a]Significant difference between men and women (F=4.7, df=1, 27, p<0.04).
[b]Significant difference between men and women (F=9.7, df=1, 27, p<0.005).
[c]Significant difference between men and women (F=7.1, df=1, 27, p<0.02).

Differences in regional metabolism were tested with analysis of variance (ANOVA) for a gender-by-region interaction. Follow-up factorial ANOVAs were then performed to evaluate the regions that differed between genders.

RESULTS

The results from the ANOVA showed no main group effect (male versus female subjects: F=1.3, df=1, 338, p=0.27) but showed a significant region-by-group interaction (F=4.5, df=13, 338, p<0.0001), indicating differences in metabolic activity between the genders across brain regions. Follow-up ANOVAs on the regional measures revealed significantly higher metabolism in the right and left cerebellum and in temporal poles in the women (figure 1). In the second evaluation, the women had significantly higher metabolism in the right cerebellum (women: mean=44.4 µmol/100 g per minute, SD=3; men: mean=37.8 µmol/100 g per minute, SD=4; F=16.0, df=1, 18, p<0.001) and in the left cerebellum (women: mean=44.7 µmol/100 g per minute, SD=3; men: mean=40.0 µmol/100 g per minute, SD=5; F=6.1, df=1, 18, p<0.03).

The results from the ANOVA on the relative metabolic measures were the same as those for the absolute measures (data not shown).

DISCUSSION

Gender differences in cognitive, motor, and emotional behaviors have been documented (7). Imaging technologies now enable us to investigate gender differences in cerebral activity at baseline and during activation that may underlie some of these differences (5). In this study, we documented significantly higher cerebellar metabolism in female subjects than in male subjects, and this was reproducible with repeated evaluation. There is increasing evidence that in addition to participating in motor coordination, the cerebellum participates in emotional (8, 9) and cognitive (10, 11) behaviors, including language (12). Hence, one could speculate that gender differences in language and motor coordination (7) may be accounted for in part by gender differences in cerebellar activity. However, further studies are required to establish this association.

The regional pattern of differences detected during the first evaluation is quite similar to that reported by Gur et al. (5), except that in their study the direction of differences is reversed: the male subjects had higher metabolism in the cerebellum and temporal poles. This difference in results could result from the substantial age differences between the two study groups: the subjects in the Gur et al. study were considerably younger than those in the current investigation (mean age=27.5 years, SD=7, versus mean=44.0 years, SD=7). This may be particularly relevant for our group, since it included both premenopausal and postmenopausal women, and estrogen is known to affect brain function (13). It is also possible that what both studies detected is those regions which are most likely to differ between men and women and that the direction of the differences may be a result of the conditions of the studies. This discrepancy highlights the difficulties that arise in linking functional significance to the direction of metabolic changes in normal populations (i.e., more activity linked with better function and vice versa).

This study documents reproducible differences in cerebellar metabolism between male and female subjects; the functional significance and relationship to experimental conditions of these differences require further evaluation.

REFERENCES

1. Wang G-J, Volkow ND, Wolf AP, Brodie JD, Hitzemann RJ: Intersubject variability of brain glucose metabolism in young normal males. J Nucl Med 1994; 35:1457–1466
2. Baxter LR, Mazziotta JC, Phelps ME, Selin CE, Guze BH, Fairbanks L: Cerebral glucose metabolic rates in normal human females versus normal males. Psychiatry Res 1987; 21:237–245
3. Yoshii F, Barker WW, Chang JY: Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy and cerebrovascular risk factors. J Cereb Blood Flow Metab 1988; 8:654–661
4. Miura SA, Schapiro MB, Grady CL: Effects of gender on glucose utilization rates in healthy humans: a positron emission tomography study. J Neurosci Res 1990; 27:500–504
5. Gur CR, Harper-Mozley L, Mozley DP, Resnick SM, Karp JS, Alavi A, Arnold SA, Gur RE: Sex differences in regional cerebral glucose metabolism during a resting state. Science 1995; 267: 528–531

6. Wang G-J, Volkow ND, Roque C, Cestaro V, Hitzemann R, Cantos E, Levy AV, Wolf AP: Functional significance of ventricular enlargement and cortical atrophy in normals and alcoholics as assessed by PET, MRI and neuropsychological testing. Radiology 1992; 186:59–65
7. Lezak MD: Neuropsychological Assessment, 3rd ed. New York, Oxford University Press, 1995
8. Berman AJ, Berman D, Prescott JW: The effect of cerebellar lesions on emotional behavior in the rhesus monkey, in The Cerebellum, Epilepsy, and Behavior. Edited by Cooper IS, Riklan M, Snider RS. New York, Plenum, 1974, pp 277–284
9. Snider RS, Maiti A: Cerebellar contributions to the Papez circuit. J Neurosci Res 1976; 2:133–146
10. Kim S-G, Ugurbil K, Strick PL: Activation of a cerebellar output nucleus during cognitive processing. Science 1994; 265:949–951
11. Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Rezai K, Watkins GL, Ponto LL, Hichwa RD: Short-term and long-term verbal memory: a positron emission tomography study. Proc Natl Acad Sci USA 1995; 92:5111–5115
12. Leiner HC, Leiner AL, Dow RS: Cognitive and language skills of the human cerebellum. Trends Neurosci 1993; 16:444–447
13. Joseph JA, Kochman K, Roth GS: Reduction of motor behavioral deficits in senescence via chronic prolactin or estrogen administration: time course and putative mechanisms of action. Brain Res 1989; 505:195–202