# Cerebellar Glucose Consumption in Normal and Pathologic States Using Fluorine-FDG and PET

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We studied cerebellar metabolism in 118 subjects including young and elderly controls and patients suffering from stroke, supratentorial brain tumor and Alzheimer's disease using fluorine-18 fluorodeoxyglucose ([$^{18}$F]FDG) and position emission tomography (PET). Alzheimer's disease and normal aging did not alter mean cerebellar metabolism. In stroke and tumor mean cerebellar metabolism was lower in the hemisphere contralateral to the supratentorial lesion. In tumor bilaterally significant reductions in absolute cerebellar metabolism also were noted, unlike stroke. Primary sensory stimulation did not alter absolute or relative cerebellar metabolism. These results show that absolute and relative values for cerebellar metabolism vary depending on the process under study. Thus analysis schemes employing normalization of regional metabolic data to cerebellar values may be subject to error.

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Functional imaging of cerebral metabolism using positron emission tomography (PET) has demonstrated that cerebral metabolic alterations in pathologic states need not be confined by conventional anatomic localization (*1,2*). Previous reports have described crossed cerebellar dysmetabolism accompanying focal supratentorial lesions (*3,4*). The exact mechanism underlying this phenomenon is uncertain but much older reports also have linked cerebellar symptoms and chronic cerebellar pathologic change to contralateral supratentorial lesions (*5,6*). These recent descriptions of crossed cerebellar dysmetabolism were made possible by studies of cerebral metabolism employing PET and this effect could not be anticipated from anatomic data derived from computed tomography or magnetic resonance imaging (*4*).

In order to probe further possible functional alterations in the metabolism of the cerebellum we studied cerebral and cerebellar metabolism in various normal states, degenerative disorders, and focal cerebral pathology.

## METHODS

The study group included: unilateral cerebral infarction—23 (mean age 65 yr, range 47–80 yr), unilateral cerebral tumor—23 (mean age 52 yr, range 37–71 yr), Alzheimer's disease (SDAT)—24 yr (mean age 67, range 54–77 yr), healthy elderly volunteers—17 (mean age 62 yr, range 47–73 yr), young volunteers studied under varying conditions of sensory stimulation—28 (mean age 23 yr, range 18–34 yr). All elderly controls, stroke, tumor and Alzheimer's patients had normal CT of the cerebellum. All Alzheimer patients had nonischemic dementia scores by Rosen's modification of the Hachinski scale (*7*). Chawluk (*8*) et al. has described previously the severity of cognitive decline in the Alzheimer's patients based upon the results of the 30-point Mini-Mental State Examination (MMSE) described by Folstein et al. (*9*). Eleven patients had mild dementia (MMSE score 20–30), six had moderate dementia (MMSE score 10–20) and seven had severe dementia (MMSE score < 10). Seven young normals were scanned under conditions of maximal sensory deprivation (blindfolded with ears plugged). Eight young normals were scanned during the performance of a visual fixation task where stimulation consisted of a central light emitting diode. Thirteen normals were exposed to ambient light and sound conditions in the PET laboratory. All other subjects were studied under these ambient laboratory conditions.

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TABLE 1
Effect of Aging and Dementia on Cerebellar Glucose Metabolism

| Group | N | GMRglu | CerMRglu | CerMRglu/GMRglu |
|---|---|---|---|---|
| Young controls | 13 | 5.48 ± 0.74 | 4.12 ± 0.59 | 73.7% |
| Elderly controls | 17 | 6.00 ± 1.10 | 3.88 ± 0.57 | 66.7% |
| SDAT | 24 | 5.26 ± 1.50 | 3.66 ± 1.01 | 69.1% |

Values given have units of mg/100 g/min ± s.d.
No significant differences were found.

### Metabolic Imaging

All patients underwent imaging of local cerebral glucose metabolism using fluorine-18 fluorodeoxyglucose (FDG) and PET. This technique has been fully described previously (*4,10–12*).

In each subject the absolute value for global cerebral glucose consumption (GMRglu) was calculated as was the rate for glucose consumption within the cerebellum (CerMRglu) (*4*). The effect of cerebral atrophy upon the calculation of GMRglu was compensated for by applying the technique described previously by Chawluk et al. (*8*). The resultant adjusted values for GMRglu were 9% and 17% higher than uncorrected values for the elderly controls and dementia patients, respectively. These findings are similar to those results described previously by Herscovitch et al. (*13*). In all groups review of the anatomic images (CT or MR) showed no abnormalities of the posterior fossa contents, including the cerebellum (*4,14*). Between group differences in global and cerebellar glucose consumption were sought by analyzing absolute values and the normalized expression [CerMRglu/GMRglu]. In the normal volunteers values for right and left CerMRglu were averaged while in the cases of focal cerebral pathology such as tumor and infarction the expression CerMRglu/GMRglu for each cerebellar hemisphere was analyzed according to the laterality of the cerebral lesion. Effects of aging, diffusion and focal cerebral pathology, and sensory stimulation (or deprivation) were sought using the t-test as a parametric statistic. Differences are cited as being significant for p values $< 0.05$.

## RESULTS

### Normal Aging and Senile Dementia

Values for global cerebral glucose consumption and cerebellar glucose consumption are summarized in Table 1. The GMRglu values were not significantly affected by the process of normal aging. These values compare favorably with other reports using PET and the Kety-Schmidt technique (*11*). In SDAT patients the mean GMRglu was significantly lower when compared to both the young and elderly control groups. In contrast to the significant decline in global cerebral glucose consumption noted in SDAT, no significant change in cerebellar glucose consumption was noted although the lowest CerMRglu value occurred in the SDAT group. The normalized expression for cerebellar metabolism (CerMRglu/GMRglu) was similar for the young and elderly controls. This ratio was highest in the SDAT group but this difference was not significant. In four of the 24 DSAT subjects asymmetries were found in CerMRglu between the two cerebellar hemispheres (Fig. 1).

### Focal Cerebral Disorders

Compared to elderly controls, GMRglu was significantly lower in both the stroke and tumor groups (Table 2). In stroke CerMRglu in either cerebellar hemisphere did not differ significantly from elderly control values. Mean CerMRglu was lower in the contralateral hemisphere but no significant difference in mean CerMRglu was noted between the ipsilateral and contralateral cerebellar hemispheres. Notable was the significant increase in CerMRglu/GMRglu in the ipsilateral cerebellar hemisphere. In tumor CerMRglu was significantly lower relative to elderly controls in both cerebellar hemispheres. The lower value of CerMRglu occurred in the contralateral cerebellar hemisphere while a significant depression of CerMRglu/GMRglu also oc-

TABLE 2
Effect of Focal Cerebral Disease on Cerebellar Metabolism

| | | | CerMRglu | | CerMRglu/GMRglu | |
|---|---|---|---|---|---|---|
| | | | 3.88 ± 0.57 | | 76.1 ± 10.7 | |
| Group | N | GMRglu | IPSI | CONTRA | IPSI | CONTRA |
| Elderly controls | 20 | 6.00 ± 1.1 | | | | |
| Stroke | 23 | 4.36 ± 1.41* | 3.5 ± 0.9 | 3.2 ± 0.8 | 81.7 ± 13.5* | 74.8 ± 15.9 |
| Tumor | 23 | 3.99 ± 1.59* | 3.24 ± 1.47* | 2.83 ± 1.12* | 78.3 ± 17.7 | 71.1 ± 12.7* |

Values given have units of mg/100 g/min ± s.d.
IPSI = cerebellar hemisphere ipsilateral to the cerebral lesion, CONTRA = cerebellar hemisphere contralateral to the cerebral lesion.
* $p < 0.05$

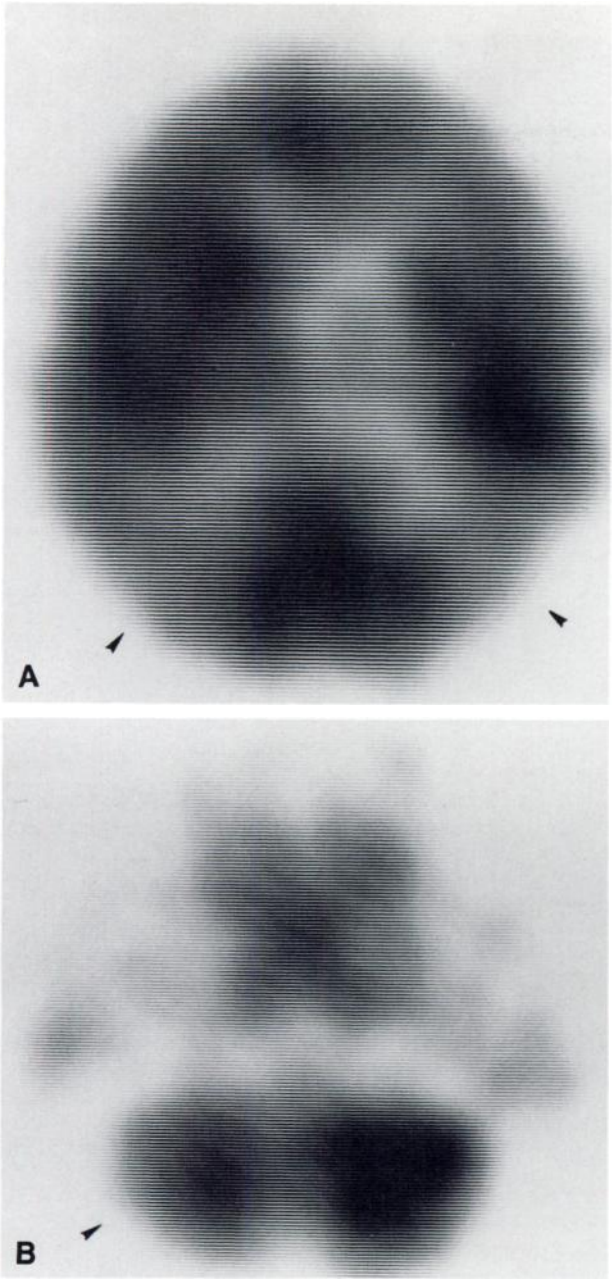


**FIGURE 1**
Metabolic images from an Alzheimer's disease patient showing cerebellar metabolic asymmetry. The right side of the brain is to the viewer's right. Cerebral (A) and cerebellar (B) FDG-PET images obtained from a 63-yr-old man with mild dementia. The neurologic examination was nonlateralizing and the CT showed mild atrophy. There is biparietal hypometabolism (arrowheads) without gross cerebral metabolic asymmetry. A 20% depression in metabolism is noted in the left cerebellar hemisphere (arrowhead).

curred in the contralateral cerebellar hemisphere. The value for CerMRglu/CMRglu in the ipsilateral hemisphere was similar to that for the elderly controls.

### Effect of Sensory Stimulation

Overall, varying the conditions of sensory stimulation did not have any significant impact on cerebellar metabolism. Values for CerMRglu/GMRglu were similar over all three stimulus conditions (Table 3). Mean GMRglu was lowest in subjects exposed to ambient conditions but this difference was not statistically significant. CerMRglu also was not significantly affected by the state of sensory stimulation or visual fixation the performance of the visual fixation task.

## DISCUSSION

These findings demonstrate that cerebellar metabolism may differ depending upon the state or process under study. In Alzheimer's disease absolute cerebellar metabolism is spared the diffuse decline felt by the cerebral hemispheres. Our results show also for the first time that asymmetries in cerebellar metabolism may be encountered in Alzheimer's disease which are similar to the crossed cerebellar dysmetabolism found more often with focal supratentorial lesions.

In both glioma and stroke, significant alterations in global cerebral glucose consumption occurred but their effect on absolute and relative cerebellar metabolism differed. In stroke no significant difference from normal controls was found for absolute values of cerebellar glucose metabolism while in tumor these values were significantly lower than control in both cerebellar hemispheres. Relative cerebellar metabolism was unchanged or greater than control in stroke depending upon the laterality of the cerebellar hemisphere. In tumor, relative cerebellar metabolism was significantly lower than that found for the controls in the cerebellar hemisphere lying contralateral to the tumor. Unlike stroke, relative cerebellar metabolism in the hemisphere ipsilateral to a glioma was similar to control values. Previously we had reported a decline in CerMRglu in a mixed group of stroke and tumor patients (*4*). In this larger series a significant decline in CerMRglu is detected only for tumor patients. For stroke these findings are similar to those reported by Pantano et al. (*15*) in studies of acute and chronic stroke.

The presence of persistent cross cerebellar dysmetabolism and a depression of relative cerebellar metabolism may indicate a state of continuous disruption of cerebral-cerebellar interconnections (*15–18*). The explanation for this depression of metabolism in the ipsilateral cerebellar hemisphere is unclear.

Normalization of local cerebral metabolic data to cerebellar metabolic values had been advocated for the analysis of emission computed tomographic data from dementia patients (*19*). Problems could arise with such analysis schemes if cerebellar metabolism is affected by the primary disease process or if bilaterally symmetric cerebellar metabolism is erroneously interpreted as implying bilateral normality. While this approach may be more valid for cases of normal aging or a diffuse degenerative disorder such as Alzheimer's disease, problems

**TABLE 3**
Effect of Sensory Stimulation on Cerebellar Glucose Metabolism in Young Normals

| Group | N | GMRglu | CerMRglu | CerMRglu/GMRglu |
|---|---|---|---|---|
| Sensory deprived | 7 | 6.49 ± 1.57 | 4.63 ± 0.50 | 0.71 ± 0.14 |
| Visual fixation | 8 | 5.70 ± 1.0 | 4.32 ± 0.9 | 0.76 ± 0.11 |
| Ambient conditions | 13 | 5.48 ± 0.84 | 4.12 ± 0.57 | 0.75 ± 0.04 |

Values given have units of mg/100 g/min ± s.d.
No significant differences were found.

clearly exist when focal cerebral pathology is present. In focal cerebral disorders a normalized ratio for cerebellar metabolic activity may be normal in the absence of cerebellar pathology. Conversely, in disease states the use of metabolic region of interest ratios indexed to cerebellar values could lead to falsely abnormal results when quantitation is unavailable.

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## REFERENCES

1. Reivich M, Kushner M, Alavi A, et al. Measurement of local cerebral glucose metabolism: effect of pathology and functional stimulation. In: Hoyer S, Hartmann A, eds. Cerebral blood flow and metabolism measurement. Berlin Heidelberg, Springer-Verlag, 1985, 410–418.
2. Kushner M, Reivich M, Fieschi C, et al. Focal and remote effects on local cerebral glucose metabolism of acute ischemic infarction in man. In: Fieschi C, Battistini N, eds. Acute brain ischemia. New York: Raven Press, 1986:89–95.
3. Baron JC, Bousser MG, Comar D, et al. "Crossed cerebellar diaschisis": a remote functional depression secondary to supratentorial infarction in man. *J Cerebral Blood Flow Metab* 1981; 1(suppl):S500–S501.
4. Kushner M, Alavi A, Reivich M, et al. Contralateral cerebellar hypometabolism following cerebral insult: a positron emission tomographic study. *Ann Neurol* 1984; 15:425–434.
5. Grant FC. Cerebellar symptoms produced by a supratentorial tumors. *Arch Neurol Psychiatr* 1928; 20:292–317.
6. Hassin GB. Crossed atrophy of the cerebellum: pathologic study of a case. *Arch Neurol Psychiatr* 1935; 33:917–928.
7. Rosen WG, Terry RD, Fuld P, et al. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol* 1980; 7:486–488.
8. Chawluk JB, Alavi A, Dann R, et al. Positron emission tomography in aging and dementia: effect of cerebral atrophy. *J Nucl Med* 1987; 28:431–437.
9. Folstein M, Folstein S, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189–198.
10. Reivich M, Kuhl D, Wolf A, et al. The ($^{18}$F) fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 1979; 44:127–137.
11. Reivich M, Alavi A, Wolf A, et al. Glucose metabolic rate kinetic model parameter determination in man: the lumped constants and rate constants for 18F-fluorodeoxyglucose and 11C-deoxyglucose. *J Cereb Blood Flow and Metab* 1985; 5:179–182.
12. Jones SJ, Robinson GD, McIntyre E. Tandem Van de Graaff accelerator production of positron labeled radiopharmaceuticals for routine clinical use. *Int J Appl Radiat Isot* 1984; 35:721–729.
13. Herscovitch P, Alexander PA, Gado M, et al. Correction of positron emission tomography data for cerebral atrophy. *J Cereb Blood Flow Metab* 1986; 6:120–124
14. Kushner M, Reivich M, Fieschi C, et al. Metabolic and clinical correlates of acute ischemic infarction. *Neurology*: in press.
15. Pantano P, Baron JC, Samson Y, et al. Crossed cerebellar diaschisis. *Brain* 1986; 109:677–694.
16. Evarts EV, Thach WT. Motor mechanisms of the CNS: cerebrocerebellar interrelations. *Ann Rev Physiol* 1969; 31:451–498.
17. Brodal A. Cerebrocerebellar pathways: anatomical data and some functional implications. *Acta Neurol Scand* 1972; 51(suppl):153–195.
18. Allen GI, Tuskahara N. Cerebrocerebellar communication systems. *Physiol Rev* 1974; 54:957–1006.
19. Johnson KA, Muelle ST, Walihe TM, et al. Cerebral perfusion imaging in Alzheimer's disease with SPECT and I-123 IMP. *Neurology* 1985; 35(suppl 1):235.