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Alzheimer's Disease, Dementia and Down Syndrome: An Evaluation Using Positron Emission Tomography (PET)

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The assessment of brain metabolism using positron emission tomography (PET) and radioactive tracers holds promise in the differential diagnosis and early detection of various dementing disorders. Such research may also further our understanding of normal aging and of underlying disease mechanisms in pathologic conditions. For example, PET measurement of cerebral metabolic rates for glucose (CMRglc) appears to be a more sensitive indicator of brain changes in Alzheimer's disease than cognitive and sensory tests. In Down's syndrome patients, age-related decrements in CMRglc are seen that are consistent with the neuropathologic changes associated with the disease; by contrast, CMRglc appears to be age-invariant in normal subjects. Such assessments have also revealed differences from normal controls among individuals at genetic risk for Huntington's disease. These findings and other data on brain metabolism rates in the dementing disorders are critically reviewed, and avenues for future research are suggested.

Functional deficits in dementing disorders could be measured only indirectly (neuropsychological tests) until the development of techniques permitting in vivo assessment of the dementias associated with Alzheimer's disease (AD), Cruetzfeldt-Jakob disease (CJD), Huntington's disease (HD), normal pressure hydrocephalus NPH), and Down's syndrome (DS).

Neurological test performance has traditionally been used to measure brain function in these populations. Examination of brain oxidative metabolism provides an alternate method of assessing the functional implications of age and disease-related neurochemical, morphometric, and anatomic decrements. The brain accounts for approximately 25% of total body oxygen consumption at rest. As glucose is the major substrate for brain oxidative metabolism,

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cerebral metabolic rates of oxygen and glucose (as well as cerebral blood flow [CBF], which is related to these measures) can be used to examine brain function.

The development of positron emission tomography (PET) has increased our ability to assess regional cerebral metabolic rates (rCMR) and CBF. The forerunner of PET was a deoxyglucose model developed for determining cerebral metabolic rates of glucose (CMRglc) in animals using autoradiography and [^{14}C] deoxy-2-D-glucose as the tracer. This technique was then applied to humans using [^{18}F]-fluoro-2-deoxy-D-glucose (^{18}FDG) as tracer and PET as an *in vivo* autoradiography technique (Sokoloff et al., 1977).

Up to seven serial PET slices can be obtained parallel to and 5–100 mm above the external inferior orbitomeatal (IOM) line. Because of individual variations in head size and shape, the height above the IOM line of the slice was aligned. Comparison of PET, computerized tomography (CT) and magnetic resonance image (MRI) scans at identical heights above the IOM line, using an atlas, permits identification of anatomical regions of interest (ROIs) in the PET scans (Alavi et al., 1986; Duara et al., 1984). The results obtained for CMRglc by this method under various conditions were similar to those found by previous investigators using a direct invasive approach, the Kety-Schmidt technique, without the need for invasive methods.

Important variables in studying cerebral metabolism include (a) mental status of the subjects; (b) health status of the subjects; and (c) influence of visual, auditory and somatosensory stimuli. Another important factor in calculating brain metabolic values is brain atrophy. This factor could account for the differences found in both normal aging and dementia (Herscovitch, Auchus, Gado, Chi, and Raichle, 1986; Herscovitch, Gado, Minton, and Raichle, 1984). All of these factors may affect cerebral metabolism.

Brain metabolism in normal aging has been investigated in cross-sectional studies in healthy individuals to assess the changes, if any, associated with the normal aging process. We initially evaluated 40 healthy males between the ages of 21 and 83 (Duara et al., 1984). No statistically significant correlation was found between CMRglc and age ($p > 0.05$) (see Figures 1 and 2). This finding has now been extended to a total of 49 healthy men in this age range (Schlageter et al., 1987).

Our observation that brain glucose utilization is not correlated significantly with age is consistent with the findings of Dastur et al. (1963), who examined CBF and $CMRO_2$ and Ferris et al. (1983), who used PET with ^{18}FDG. By contrast, Gottstein et al. (1979) reported reduced $CMRO_2$ in the elderly. Two other studies using PET and brain metabolism reports (Frackowiak, Lenzi, Jones, and Heather 1980; Kuhl, Metter, Riege, and Phelps, 1982) have produced data that differ from our findings. However, it is not clear whether these investigators screened their subjects rigorously for vascular artherosclerotic changes or hypertension, which might explain their findings of reduced cerebral metabolism.

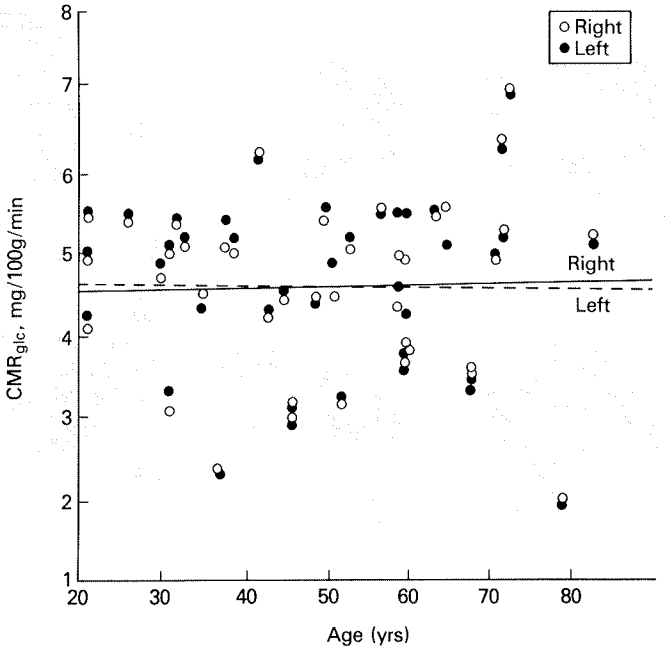

Figure 1: Cerebral metabolic rates for glucose (CMRglc) for each hemisphere, 30–80 mm above the inferior orbitomeatal (IOM) line, in 40 healthy subjects aged 21–83 years. No correlation coefficient was statistically significant ($p > 0.05$) [From Duara et al., 1984]. Reprinted with permission from *Annals of Neurology, 16,* 702–713. ©1984, Little, Brown and Company: Boston.

The apparent age invariance in brain metabolism found in both animals (London, Nespor, Ohata, and Rapoport, 1981) and humans (Duara et al., 1984) exists in spite of morphologic changes (e.g., neuronal dropout) and neurochemical alterations in enzyme production with age. This may be explained by compensatory mechanisms such as neuronal plasticity and increased dendritic arborization (Buell and Coleman, 1981).

Brain Metabolism in Alzheimer's Disease

Alzheimer's disease is a slowly progressive disorder characterized clinically by intellectual decline and personality deterioration. Postmortem studies of AD patients have documented several morphologic and neurochemical alterations: (a) neurofibrillary tangles in cerebral cortex; (b) preferential loss of large cortical neurons in midfrontal and temporal regions; (c) neuritic plaques in cerebral cortex and amygdala; (d) reduced choline acetyltransferase activity; (e) decreased brain concentrations of dopamine and norepinephrine; and (f) reductions in muscarinic, cholinergic, and dopaminergic receptors (Terry and

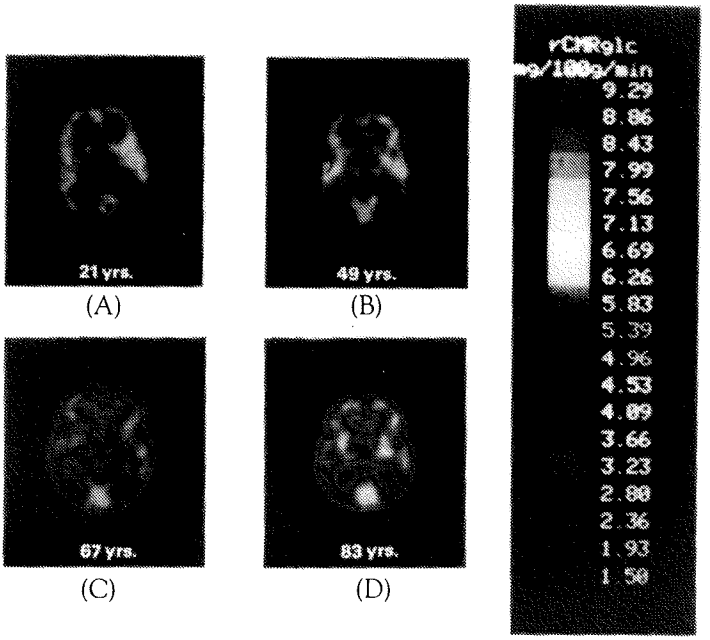

Figure 2: PET scans at 50 mm level above inferior orbitomeatal (IOM) line. (A) Normal 21-year-old subject; (B) normal 49-year-old subject; (C) normal 67-year-old subject; (D) normal 83-year-old subject. Representative PET scans from four different age groups qualitatively show no overall change in brain metabolism with age.

Davies, 1983). Further autopsy studies of AD compared with age-matched controls have found that the greatest cell loss and most extensive neuropathologic changes tend to be in the temporal and parietal lobes. Changes also have been shown in the hippocampus, amygdala, and uncal regions (Tomlinson, Blessed, and Roth, 1970).

With the development of PET scanning with ^{18}FDG, there have been numerous attempts to accurately assess variabilities in regional metabolism (glucose utilization) changes in AD. Early studies of AD using PET scanning with ^{15}O (e.g., Frackowiak et al., 1981) found that patients with mild AD had reduced rCMRglc in the parietal lobe compared to the temporal lobe and other regions, whereas in more severe cases the greatest decrements were in the frontal lobes, with sparing of the occipital lobes. Other investigators (Ferris et al., 1983) have reported generalized reductions in rCMRglc in the frontal, temporal and parietal lobes, with sparing of the occipital lobe in patients with AD of varying degrees of severity. Attempts to relate severity scale measures to reductions in metabolism have been conducted. We have reexamined the

ability of PET scanning to measure CMRglc in patients with mild-to-moderate and severe forms of AD, and have compared our findings with the results of neuropsychological performance measures (Cutler, 1985; Cutler et al., 1984; Cutler and Schapiro, 1984; Duara et al., 1986).

Table 1

Metabolic Rates In Normal Healthy Subjects for Different Lobes of Brain

Brain Region	Hemisphere	rCMR Frontal	Parietal	Temporal	Occipital
Frackowiak et al. (1981)		3.55 ± 0.53[a]	3.50 ± 0.51	3.76 ± 0.35	4.06 ± 0.69
Kuhl et al. (1982)[b]		5.88 ± 0.92	5.93 ± 0.78	6.16 ± 0.75	5.16 ± 0.69
Duara et al. (1984)	4.60 ± 1.08[c]	5.41 ± 1.35	5.45 ± 1.32	4.48 ± 1.25	5.39 ± 1.23
Schlageter et al. (1987)[c,d]		5.78 ± 1.38	5.38 ± 1.26	5.13 ± 1.06	5.94 ± 1.20

[a]All rCMR rates are expressed as means ± SD (right side) in ml O_2.100g^{-1}.min^{-1} for 14 subjects (age range, 53–69).
[b]All rates were expressed as means (right side) in mg.100g^{-1}.min^{-1} for 40 subjects (17 males) (averaged over the entire age groups, range, 18–78 years).
[c]All rCMR rates are expressed as means ± SD (right side) in mg.100g^{-1}.min^{-1} for 49 subjects (age range, 21–83 years).
[d]49 healthy men (age range, 21–83 years).

We have extended our initial study (Cutler, 1984; Cutler, Haxby, Duara, Grady, Kay et al., 1985) and examined 21 patients with a diagnosis of AD (as determined by the *Diagnostic and Statistical Manual for Mental Disorders, third edition*, 1980; and NINCDS-ADRDA criteria, McKhann et al., 1984; and by the agreement of two neurologists). All patients had normal findings on physical, neurological and laboratory examinations, except for those related to their illness. The patients were classified as mildly (N=10, 8M), moderately (N=7, 2M) and severely (N=4, 2M) demented by their mean score on the Mini-Mental State Exam (MMSE) (Folstein, Folstein, and McHugh, 1975). A second measure, the *Mattis Dementia Scale* (Mattis, 1976) was also administered to confirm the severity class. The higher the score, the less demented. The mildly demented group had a Mattis score of 131 ± 6, out of a possible 140; the moderate group's score was 103 ± 23 and the severely demented group's score was 40 ± 10. The control subjects, described in detail elsewhere (Duara et al., 1984), were rigorously screened males free of primary and secondary brain disease and medical illness. The 29 controls had a mean age of 63 years (SD=10). Assessment of intellect and memory functions was based on results of the *Wechsler Adult Intelligence Scale* (WAIS) (Wechsler, 1958) and the Wechsler Memory Scale (Wechsler, 1945).

Compared to controls, the mild-to-moderate AD group showed significant intellectual deficits on WAIS testing. The severe AD group was incapable of

undergoing the formal testing. The 29 control subjects had mean full-scale WAIS scores in the normal range (128 ± 11). Moreover, scores on the *Wechsler Memory Scale* revealed that the mildly to moderately affected AD patients on all subtests significantly decreased performance compared with controls ($p < 0.05$). Thus, the patients with presumptive AD classified as mild to moderate and as severe had marked intellectual and memory dysfunction.

Table 2

Metabolic Rates For Alzheimer's Disease for Different Lobes of Brain

Brain Region	rCMR Frontal	Parietal	Temporal	Occipital
Frackowiak et al. (1981)				
Mild–moderate (N=4)	3.02 ± 0.28[a]	2.64 ± 0.33*	2.88 ± 0.27*	3.61 ± 0.65
Severe (N=5)	2.14 ± 0.42	2.09 ± 0.34*	2.77 ± 0.35*	3.07 ± 0.56*
Foster et al. (1984)				
Mild (N=7)	6.00 ± 0.4[b]	4.60 ± 0.2*	4.90 ± 0.4*	4.80 ± 0.3*
Severe (N=8)	5.50 ± 0.4	4.40 ± 0.4*	4.50 ± 0.3*	4.50 ± 0.4*
Duara et al. (1986)				
Mild (N=10)	4.61 ± 0.83[c]	4.28 ± 1.27	3.44 ± 0.78	4.45 ± 1.14
Moderate (N=7)	5.03 ± 1.18	4.62 ± 1.10	3.95 ± 1.10	5.66 ± 0.97
Severe (N=7)	3.70 ± 0.79	2.89 ± 0.95	2.90 ± 0.62*	4.50 ± 0.96

[a]All rCMR rates are expressed as means ± SD (right side) in ml $0_2.100g^{-1}.min^{-1}$.
[b]All rCMRglc rates are expressed as means ± SEM in $mg.100g^{-1}.min^{-1}$.
[c]All rCMRglc rates are expressed as means ± SD (right side) in $mg.100g^{-1}.min^{-1}$.
*Significantly different from controls ($p < 0.05$).

An examination of CMRglc in parietal, frontal, temporal, and occipital lobes with PET scanning using methods previously described (Duara et al., 1984), showed no significant reductions in lobar metabolism in the mild, moderate AD patients compared to controls ($p > 0.05$). The severe AD group showed statistically significant reductions ($p < 0.05$) in three of the four lobes evaluated (see Table 2 and Figure 3). The relative lack of difference between the mild to moderate subjects and controls may reflect the intersubject variation (approximately 20–25%) in the cerebral metabolic rates. In view of the large coefficient variation we analyzed regional rates normalized to the mean cerebral metabolic rate (rCMRglc/sensorimotor). CMRglc at each of the four lobes was performed to reduce the coefficient of variation by approximately 50% and thus increase the sensitivity of PET to smaller differences. This analysis revealed statistically significant coefficient variant deficits in the parietal lobes (Duara et al., 1986) in the mild-to-moderate group. The severe group had deficits in both the parietal and temporal lobes. Thus, the intellectual deficits in AD, even in mild to moderate cases, is accompanied by selected changes in cortical cerebral metabolism, as assessed by ratio analysis.

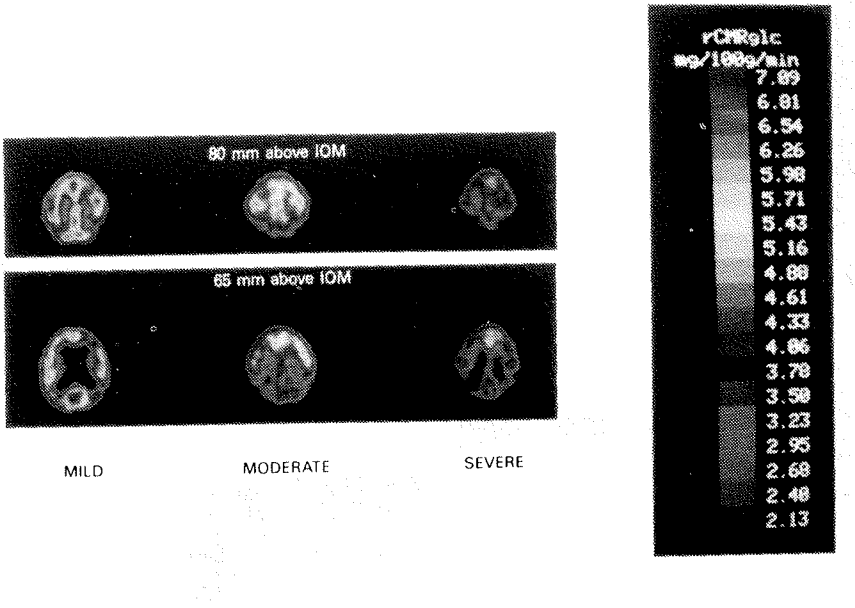

Figure 3: PET scans at the 80 and 65 mm level above the inferior orbitomeatal (IOM) line in Alzheimer's patients with mild, moderate and severe forms of the disease.

Other studies that have carefully distinguished severity of disease indicate change or reduction in either the temporal lobe (Foster et al., 1984; Frackowiak et al., 1980; Frackowiak et al., 1981) or parietal lobe (Cutler, Haxby, Duara, Grady, Kay et al., 1985) in mild AD. The greatest reduction in metabolism in the frontal lobes has been observed in the severe or late forms of the disease (Frackowiak et al., 1981). In severe AD, the present authors and others have generally found metabolic reductions throughout the brain (Ferris et al., 1983; Frackowiak et al., 1981; McGeer et al., 1986).

There are several methodological limitations that must be addressed in discussing research on AD. For example, definitive diagnosis can only be made by cerebral biopsy or at autopsy, and we are awaiting the results of such investigations. On clinical grounds, our diagnosis has a probability of about 70 to 80% of being accurate. Parameters relating to the PET technique include spatial resolution and partial voluming (Cutler, Haxby, Duara, Grady, Kay et al., 1985; Duara et al., 1984).

Ultimately the findings that are consistent with a diagnosis of AD include: (a) marked memory and cognitive deficits, as represented by low Wechsler memory and full-scale intelligence scores; (b) but, no differences in mean rCMRglc lobar values as derived by PET in mild to moderate AD compared to controls; (c) reduced parietal lobe regional-to-regional sensorimotor metabolic ratios; and (d) cerebral metabolic rates and ratios consistently reduced in the

parietal and temporal lobes in late or severe AD. The study of more patients with presumptive AD, and confirmation of these cases with neuropathological evidence obtained with PET, should explain many cerebral metabolic patterns which will help better characterize the heterogeneous disease process.

In addition, initial studies with radiotracers may have utility in determining the involvement or lack of involvement of various neurotransmitter systems. Recent studies with 3-N[^{11}C]-methylspiperone examining dopamine receptors reveal normal caudate/putamen uptake in AD patients (Inoue et al., 1985), suggesting the lack of dopaminergic involvement in AD. We await the development of alternative radiotracers to carefully evaluate other neurotransmitter systems—noradrenergic, cholinergic and serotoninergic—in AD.

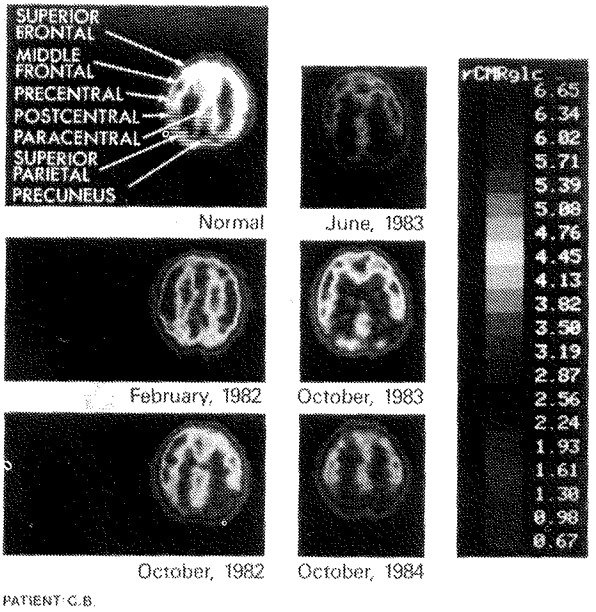

Figure 4: PET scans at 80 mm above the inferior orbitomeatal (IOM) line. A normal 58 years old subject; and the patient (age = 57 years) for each of the scans dated accordingly.

We have also performed serial assessments of CMRglc and of cognitive function in a patient in the very early stages of familial AD (Cutler, 1985; Cutler, Haxby, Duara, Grady, Moore et al., 1985). Two of the patient's first-degree relatives had neuropathological evidence of AD on autopsy. Our patient experienced the first signs of dementia 5 years ago and has been studied for the past 2½ years. In the early stages, the patient scored 30 on the *Blessed*

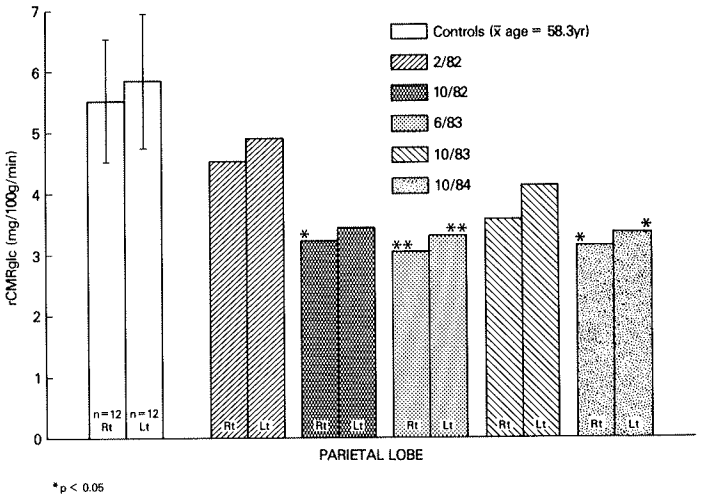

Figure 5: Serial regional cerebral metabolic rates for glucose (rCMRglc) of the parietal lobe (65–100 mm above the inferior orbitomeatal line) in a familial Alzheimer's disease (AD) patient showing progressive reduction over 2½ years.

Memory Information Concentration Test (Blessed, Tomlinson, and Roth, 1968) and 29 on the MMSE (Folstein, Folstein, and McHugh, 1975). The severity scales and cognitive tests of parietal lobe function showed essentially no change over the first 1½ years of assessment, although an increase in severity was demonstrated by reduced rCMRglc over the same period, particularly in the parietal lobe rCMRglc was reduced with time (see Figures 4 and 5). Neuropsychological tests of memory function revealed significantly reduced immediate and delayed memory but no changes in parietal lobe functions such as naming, arithmetic, or visuospatial construction. Our findings suggest that PET measurements of brain glucose utilization at the parietal lobe result in more sensitive measures of brain changes in AD than tests of cognitive and sensory function in this brain region (Cutler, Haxby, Duara, Grady, Kay et al., 1985).

The apparent temporal precedence of metabolic reductions in the parietal lobe compared to neuropsychological testing deficits suggests that a "threshold" of metabolic reduction or brain damage (Roth, Tomlinson, and Blessed, 1966) must possibly be exceeded before neuropsychological testing can distinguish between normal and diseased subjects.

The failure of PET to show any metabolic changes in brain regions associated with memory may be due to methodological limitations of the technique, such as limited spatial resolution, a partial voluming effect, or errors in reconstruction. Also, it is possible that hippocampal degeneration is not accompanied by brain metabolic changes in the resting state. These issues await resolution.

Brain Metabolism in Other Dementias

Cruetzfeldt-Jakob Disease

Cruetzfeldt-Jakob disease (CJD), caused by a slow virus, is characterized by mental deterioration, gait disturbance, and a rapid course (6 to 24 months until death). The only reported study of PET in CJD (Friedland, Prusiner, Jagust, Budinger, and Davis, 1984) was conducted in a 54-year-old man with a 4-month history of clinically diagnosed CJD (the diagnosis was later confirmed on autopsy). His PET findings were compared to those for 17 AD patients and 7 healthy controls. The CJD patient had asymmetric temporal focality, which differed from controls and from the temporoparietal reductions seen in AD patients.

Huntington's Disease

An autosomal dominant disorder, Huntington's Disease (HD) usually manifests in midlife with chorea and personality change. A progressive and fatal dementing course (usually 12–17 years) ensues. Several laboratories have examined the utility of PET scanning in HD. The initial report (Kuhl, Metter, Riege, and Phelps, 1982) described reductions in brain metabolic rates in the caudate and putamen in 13 HD patients; these changes were not associated with disease duration or the presence of caudate atrophy. In subjects at genetic risk for HD who were asymptomatic and had normal CT scans, the CMRglc and rCMRglc were within normal limits except for hypometabolic values in the caudate (Kuhl et al., 1985; Mazziotta et al., 1986). Recently, Hayden and associates (1986) confirmed the earlier reports of Kuhl, Metter, Riege and Phelps (1982) of caudate hypometabolism in 10 HD patients; in addition, 6 of 17 patients at risk for HD had striatal metabolic rates below control values. These reports of decreased metabolic rates in the caudate/putamen regions have been supported by findings of reduced dopamine receptor binding, using 3–N[^{11}C]–methylspiperone as a tracer in one HD patient (Inoue et al., 1985). Thus, PET scanning appears to have utility in Huntington's disease both in early diagnosis and in assessments of individuals at genetic risk for the disease.

Normal Pressure Hydrocephalus

A treatable dementia, normal pressure hydrocephalus (NPH) is characterized by a gradual decline in cognitive function, gait difficulty, and urinary incontinence.

To date, only one group has examined NPH patients with PET scanning and ^{18}FDG (Jagust, Friedland, and Budinger, 1985). Patients with clinically diagnosed NPH were compared to 7 healthy age matched controls and 10 AD

patients. The rCMRglc values for the NPH patients were uniformly lower than those for controls and AD patients. The NPH group showed an even distribution of the rCMRglc with no focality, while the AD group exhibited the characteristic temporoparietal reductions in rCMRglc. The authors' suggestion that PET is a useful tool in the differential diagnosis of NPH requires confirmation in larger patient populations.

Brain Metabolism in Down Syndrome

The relationship between dementia and Down syndrome (DS) has been recognized since the early 1800's (Fraser and Mitchell, 1976). The incidence of dementia in DS is about 30%. Observed mental status changes have been related to postmortem findings from DS patients over the age of 35, which included the presence of senile plaques, neurofibrillary tangles, neuronal degeneration, and reduced neurotransmitter concentrations (Nyberg, Carlsson, and Winblad, 1982; Wisniewski, Wisniewski, and Wem, 1983). These neuropathological changes are similar to those in postmortem studies of AD patients. To determine further the functional alternations in DS, brain metabolism was measured with PET scanning and ^{18}FDG in carefully screened healthy subjects with DS versus age-matched controls (Duara et al., 1984).

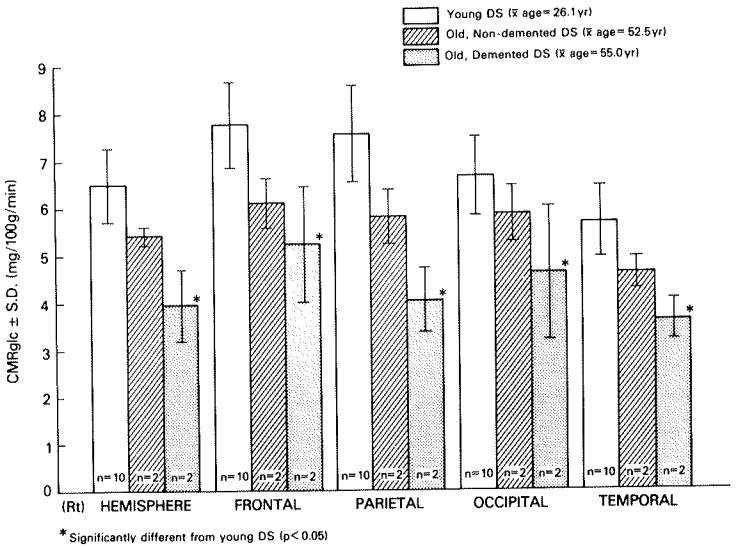

Figure 6: Regional cerebral metabolic rates for glucose (rCMRglc) in the right hemisphere and the four lobes (frontal, parietal, temporal and occipital) of young adult, middle-aged and demented Down syndrome (DS) individuals. Significant elevations in metabolism are found in young adult DS (CMRglc = 5.07 + 0.63 mg/100g/min) compared to young controls, $p < 0.05$ and significant reductions in the demented DS individuals as compared to the young adult DS ($p < 0.05$), but not as compared to healthy controls ($p > 0.05$).

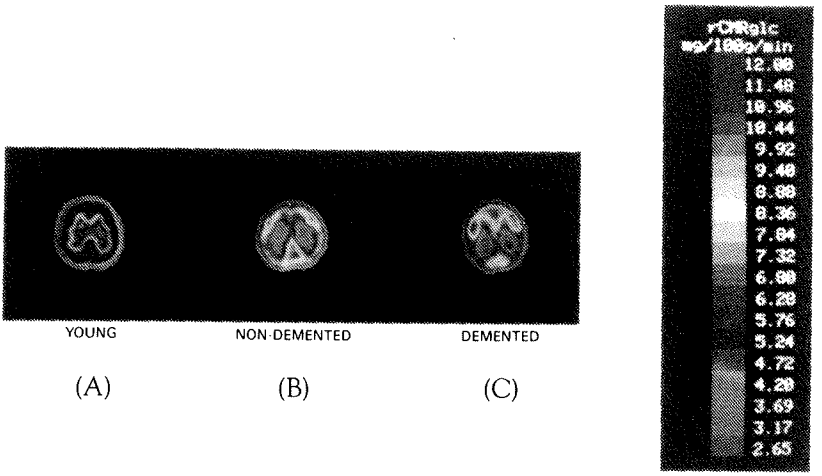

Figure 7: PET scans at 45 mm level above inferior orbitomeatal (IOM) line. (A) 22-year-old subject with Down syndrome (DS); (B) 50-year-old subject with DS; (C) 63-year-old demented subject with DS.

The CMRglc was assessed in 14 young adult subjects with DS (age range, 19–33 years), and in 6 older DS subjects (47–63 years), 4 of whom were diagnosed as demented (based on a history of mental deterioration, disorientation, and hallucinations). Controls were 15 healthy males aged 20–35 years and 20 aged 45–64 years. rCMRglc was also determined for both cerebral hemispheres and individual brain regions; CMRglc did not differ significantly between young and older control groups ($p > 0.05$). However, significant ($p < 0.05$) elevations of 20–30% in glucose utilization were evident in young DS subjects as compared to young controls (see Figures 6 and 7) [Schapiro et al., 1987]. This is in agreement with our earlier findings (Schwartz et al., 1983; Cutler and Schapiro, 1984; Cutler and Schapiro, 1985). For the six older DS subjects—four nondemented (age 49–55 years) and two with dementia (47 and 63 years)—CMRglc was significantly lower than the mean values for young DS subjects but did not differ significantly from the mean of the older control group (see Figures 6 and 7). Ratios of lobar brain regions have demonstrated rCMR decrements in the temporo-parietal regions of the older DS group. These results indicate that (a) CMRglc is elevated in young DS subjects; (b) CMRglc declines significantly with age in DS but not in healthy controls; (c) reductions in temporal and parietal lobar regions in elderly DS subjects; (d) decreases in CMRglc in elderly DS subjects, with or without dementia, are not as marked as those seen in severe AD (Schapiro et al., 1987).

There are several possible explanations for the significant elevations of brain metabolism in young adult DS subjects who lack obvious neuropathology including: (a) reduced coupling between adenosine triphosphate consumption

and active Na transport; (b) increased neuronal activity in redundant circuitry; (c) neurochemical imbalance; and (d) inefficient glucose utilization. The age-related declines in brain metabolism are consistent with the neuropathological changes associated with DS (Wisniewski et al., 1983). The relationship between brain metabolic function, neuropathological changes, and dementia in DS remains to be examined.

Conclusions

The use of PET scanning to distinguish brain metabolic patterns in the various dementias holds much promise for differential diagnosis, particularly in Alzheimer's disease. Estimation of local metabolism is the main advantage of FDG tomography, but because of its limitations, the most accurate estimates may be those averaged over whole brain hemispheres. Our findings that brain glucose utilization, as measured by PET and the 2-deoxyglucose technique, is not correlated with age in healthy subjects suggest that oxidative metabolism is age-invariant in the absence of pathologic processes, due to compensatory processes in the healthy brain. In pathologic conditions such as AD, significant metabolic reductions occur throughout the brains of late-stage Alzheimer's disease (severely demented) patients but not in mildly or moderately demented patients. These reductions may reflect a "threshold principle" of brain damage, as postulated by Roth, Tomlinson, and Blessed (1966) for clinical dementia. In other dementias, such as NPH, there is a general reduction of brain metabolism, with cortical hypometabolism and focality similar to findings in Alzheimer's disease and Cruetzfeldt-Jakob disease—as well as subcortical metabolic reductions, as found in Huntington's disease. PET appears to have utility for both the early detection of Huntington's disease and in the "at risk" group with characteristic reduced caudate/putamen metabolic rates. In Down syndrome, which is associated with neuropathological changes similar to those in Alzheimer's disease, young adult subjects showed marked elevations in brain metabolism while middle-aged subjects had age-related declines that were more pronounced in those with dementia. Further study of demented individuals with Down syndrome using PET may provide a model for understanding underlying disease mechanisms.

As the resolution of scans improves and more radioactive tracers and activation studies (Ginsberg et al., 1986) are developed, in vivo exploration of the human brain in normal subjects and in pathological conditions may provide more accurate diagnoses of the dementing diseases and a better understanding of the various mechanisms responsible for them.

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