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Brain Size and Cerebral Glucose Metabolic Rate in Nonspecific Mental Retardation and Down Syndrome

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Brain size and cerebral glucose metabolic rate (GMR) were determined with magnetic resonance imaging (MRI) and positron emission tomography (PET) in individuals with mild mental retardation (MR), individuals with Down syndrome (DS) without dementia and in matched controls. The MRI data showed that the MR and the DS groups both had brain volumes of about 80% of controls; variance was greatest within the MR group. PET was obtained with [18F]-fluorodeoxyglucose (FDG) as the tracer during a test of attention (Continuous Performance Test; CPT). Whole brain cortex GMR was higher than the controls in both the MR and the DS groups. For all subjects combined, the correlation between brain size and IQ was .65 ($p < .005$).

Brain imaging with magnetic resonance imaging (MRI) and positron emission tomography (PET) provides an opportunity to characterize brain abnormalities *in vivo*. Structural analyses in severe mental retardation (MR) often reveal brain damage of varying degrees (Gabrielle et al., 1990; Huttenlocher, 1991; Shaw,

1987). In mild MR (IQ = 50–75), up to 62% of cases have no identifiable etiology (McLaren & Bryson, 1987).

MRI studies of individuals with Down syndrome (DS) indicate smaller whole brain volumes compared to individuals of average intelligence (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993). As measured by volumetric MRI, decreases in size of frontal cortex and hippocampus have been reported for DS. Conversely, an increased size in the medial temporal and parahippocampal areas in DS was reported when compared to non-Down-syndrome persons (Kesslak, Nagata, Nalcioglu, & Lott, 1994). On MRI, some cases of MR show a thickened or "double" cortex (Livingston & Aicardi, 1990; Marchal et al., 1989; Palmini et al., 1991) that might suggest a developmental problem of neural migration. We found no MRI studies of brain size in people with mild MR. In individuals with average to high intelligence, Willerman, Schultz, Rutledge, and Bigler (1991) reported a positive correlation between MRI measures of brain size and IQ (r = .51; males and females combined; r = .35 corrected for extreme groups).

Functional brain imaging with PET has been used to study severe MR and DS. Most children with severe MR studied with PET at rest show decreased glucose metabolic rate (GMR; Chugani, Phelps, Light, & Mazziotta, 1987). We are not aware of any PET studies of mild MR of unknown etiology. Schwartz et al. (1983) and Cutler (1986) reported higher than normal cerebral GMR in a small number of young DS individuals, but Schapiro et al. (1990) failed to find any GMR differences between DS and a control sample. Melamed, Mildworf, Sharav, Belenky, and Wertman (1987) reported a decrease in cerebral blood flow in DS. Both the Schapiro et al. and the Melamed et al. studies, however, were conducted with subjects at rest, a condition not likely to accentuate any functional differences. It remains to be determined if brain GMR differences relevant to cognitive stimulation characterize DS.

PET findings of higher than normal cerebral GMR in DS would be consistent with the inverse correlations between cerebral GMR and intelligence of individuals in the normal range of intelligence as reported by Haier et al. (1988) and Haier (1993). In their studies, the subjects completed the Raven's Advanced Progressive Matrices (RAPM) during the PET tracer uptake. Scores on the RAPM were correlated with cortical GMR; significant correlations ranged between −.72 and −.84 for different cortical areas. Other PET studies of individuals with normal range intelligence by Parks et al. (1988), Berent et al. (1988), and Boivin et al. (1992) also reported inverse correlations between cerebral GMR and measures related to intelligence. Diamond (1988) reported similar audioradiographic findings in a small sample of rats; rats raised in an enriched environment used less brain glucose than control rats raised in a restricted environment. Haier, Siegel, McLachlan, et al. (1992) reported that GMR decreased in subjects after learning a complex visuospatial task and that high IQ subjects showed the greatest GMR decreases after learning (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992.

Haier (1993) reviewed the literature relating high IQ to low GMR and the concept of brain efficiency. Following Huttenlocher (1979), Haier proposed that a failure of neural pruning may lead to an overabundance of synaptic connections, or redundant brain circuitry that could result in the poor problem-solving characteristic of mild MR. The hyper connectivity postulated by the brain efficiency model predicts more brain activity and higher than normal cerebral GMR in cases of mild MR of unknown etiology. Huttenlocher (1974) and Cragg (1975) reported a small number of MR cases in which higher than normal synaptic density was found at autopsy.

If individuals with mild MR are characterized by neural inefficiency, a pattern of widespread cortical GMR elevations might be expected, based on the PET/intelligence data in individuals in the normal range of intelligence. Alternatively, mild MR may result from specific brain damage in a relatively few areas. If so, localized GMR for impaired regions would be lower than normal in cortical and subcortical regions of interest that might be most sensitive to early damage.

This preliminary study investigated the functional and structural basis of mild MR in individuals with nonspecific cognitive deficits and others with DS. Following the previous findings of inverse correlations between psychometric scores and cerebral GMR, low-IQ participants were hypothesized to have higher cerebral GMR than normal controls.

METHOD

Participants

Ten young adults with mild MR (3 males, 7 females; *M* age = 28.4, *SD* = 8.4) were recruited through community programs. Each completed a Wechsler Adult Intelligence Scale–Revised (WAIS–R) and scored a full-scale IQ between 52 and 78 (*M* = 63.1, *SD* = 7.9; all cases were between 52–70 except one case of 78, and excluding this case from analyses had no effect on results); most had no WAIS–R subtest scores greater than 6. None had a known genetic or metabolic abnormality, traumatic head injury, or a concurrent psychiatric *Diagnostic and Statistical Manual of Mental Disorders* (DSM–III–R) Axis I diagnosis. None were taking psychoactive medication. All were right-handed.

Seven individuals with DS were recruited (2 males, 5 females; *M* age = 28.1, *SD* = 6.6) and screened on the WAIS–R. All had full-scale IQs between 51 and 61 (*M* IQ = 54.2, *SD* = 3.9), all were right-handed, and none were taking psychoactive medication. None had dementia.

Ten control individuals in the normal range of intelligence (all college students or graduates) were age (*M* = 26.4, *SD* = 10.7) and gender-matched (3 males, 7 females) to the MR and DS groups and completed PET scanning. These 10 controls did not have MRI evaluations. For the MRI comparisons, a different set of 11 normal individuals (*M* IQ = 125.6, *SD* = 11.9, range = 106–144) had been tested for another project, and they were used for comparison to the MR and

DS groups (10 males, 1 female; M age = 23.8, SD = 5.3). These 11 controls, however, did not perform the same task during their PET scans as did the MR and DS subjects. Thus, there was one control group for the PET comparisons (n = 10) and a second control group for the MRI comparisons (n = 11). None of the 21 controls had a history of psychiatric problems, head injury, or major medical illness. All were right-handed and not taking any medications.

Procedure

PET Tracer
After screening, each participant completed PET and MRI scanning on separate days. The PET procedure used [18F]-fluorodeoxyglucose (FDG) as the metabolic tracing agent. FDG has a time resolution of about 32 min. The FDG tracer was injected into the participant in a sound- and light-controlled test room and was taken up by the brain for 32-min period during which the participant performed the cognitive task described later. At the end of this period, 80% to 90% of the FDG has been taken up by the brain and converted to FDG-6-phosphate. This compound served as the marker of metabolic rate and remained in place for the scanning after the uptake period and cognitive task were over.

PET Cognitive Task
We have used the degraded Continuous Performance Test (CPT; Nuechterlein, Parasuraman, & Jiang, 1983) in a number of PET studies of attention (Buchsbaum et al., 1990; Haier et al., 1988). Tomporowski and Simpson (1990) and Tomporowski and Allison (1988) found that participants with mild MR could perform vigilance and target selection tasks such as the CPT for periods greater than the 32 min required for the FDG uptake. For the CPT, participants are seated 1 m from a rear projection screen on which single digits (0–9) are presented for 40 ms at the rate of 1.5/s. Participants are asked to respond with a button press 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 Number 4 Synchro-Electric Shutter and controlled by computer. Stimuli can be degraded or sharpened by adjusting the lens. The spatial frequency of the stimuli is about 0.5 cycles/cm.

The CPT was presented over the 32-min FDG uptake period. Target and non-target digits were presented in pseudorandom order. Accuracy and reaction time were recorded by the computer. Performance was reported as d' calculated across the 32 min. To make the task easier for the participants with MR and DS, the stimuli were presented without any blurring; for control participants, stimuli were 2.8 diopters out of focus. Each individual in the MR and DS groups received instruction and practice to assure best performance. Fewer than 10 trials were necessary before the individuals with MR understood the task, whereas some individuals with DS required 80 trials of practice. For 40 normal control

participants, mean d' is 2.5 (SD = .8). All participants with MR and DS scored within two standard deviations of 2.5 (0.9–4.1) with two exceptions (an MR case [d' = 0] and a DS case [d' = 0.6]).

PET Scanning

The participants were seated in an acoustically attenuated psychophysiological testing room. An intravenous line with a 0.9% saline drip was inserted into the participant's right arm for radiotracer injection and a second line into the participant'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 et al., 1979). Intravenous lines were started about 60 min before FDG injection. Participants had a warm-up trial 10 min before FDG injection; the CPT was started 2 to 3 min before injection so that the initial novelty of the task was not FDG labeled. The participant's left arm protruded through slits in a black screen so that the blood sampling was not seen by the participant.

After 32 min of FDG uptake, the right-arm IV was removed, the participant allowed to void, and was then transferred to the adjacent PET scanner room. An individually molded, thermosetting plastic head holder was used to maintain head position during the scan; the same individualized head holder for each participant was also used for positioning in the MRI.

Eight to 10 slices at 10 mm intervals were obtained parallel to the line obtained from the MRI sagittal plane brain landmarks on a NeuroEcat scanner. Scans started about at the level of 85% of head height (vertex to CM line, usually 12–14 cm) and step downward in 10 mm increments. The PET scanner has a single ring with shadow shields and septae to achieve 7.6 mm resolution (full width half maximum) in plane and 9.9 mm resolution in the z-dimension. This is adequate for the areas in our standard templates. The risk of partial voluming is diminished because most 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 and Regions of Interest

The PET scanner was calibrated using a cylindrical phantom uniformly filled with F-18, an aliquot of which is counted in the gamma counter in which the blood samples are counted. Scans were reconstructed with a calculated attenuation correction and high-resolution filter. This method is reliable and not overly sensitive to brain size differences (Huang, Hoffman, Phelps, & Kuhl, 1979). The GMR was calculated according to Sokoloff et al. (1977) using a PASCAL adaptation of Sokoloff's original autoradiographic program written in BASIC. The lumped constant from Phelps et al. (1979) was used. GMR is reported as micromoles glucose per 100 g brain tissue per minute.

Brain Region Identification. PET quantification avoids bias in region-of-interest selection by identifying all brain areas based on computer algorithms or MRI image. Cortical regions of interest were measured using a modification of our cortical peel technique (Buchsbaum et al., 1984). Briefly, a computer algorithm for boundary finding was used to outline the PET slice. A line segment joining the center and the outline was calculated and this line was moved radially, connecting each pixel in the outline sequentially with the center. The area swept by the outer 2 cm of this radius corresponds to the lateral cortex. The cortical strip from each hemisphere consists of 70 to 98 pixel values for mean metabolic rate. A similar strip of pixels was obtained by applying the peel method to a digitized photograph of the brain from the atlas of Matsui and Hirano (1978). The margins of regions of interest were marked on these strips of pixels and the locations expressed as a percentage of the circumference of the hemisphere. For example, the Number 3 slice shows 34 pixels in the atlas from frontal midline to the posterior margin of the frontal lobe, 36 pixels in the parietal lobe, and 19 in the occipital lobe, for a total of 89 pixels. The frontal lobe extends from 1% to 38% of the perimeter (34 out of 89).

The PET slice images were then sorted to match the levels in the atlas by one of the investigators blind to the experimental condition. The percentages were then applied to each PET image similarly outlined, and the mean GMR across each sector calculated (average over the pixels falling within these limits). Metabolic rates for cortical areas falling across more than one slice were calculated as the weighted average of the number of pixels contributing from each slice. Each cortical region is shown in Figure 1.
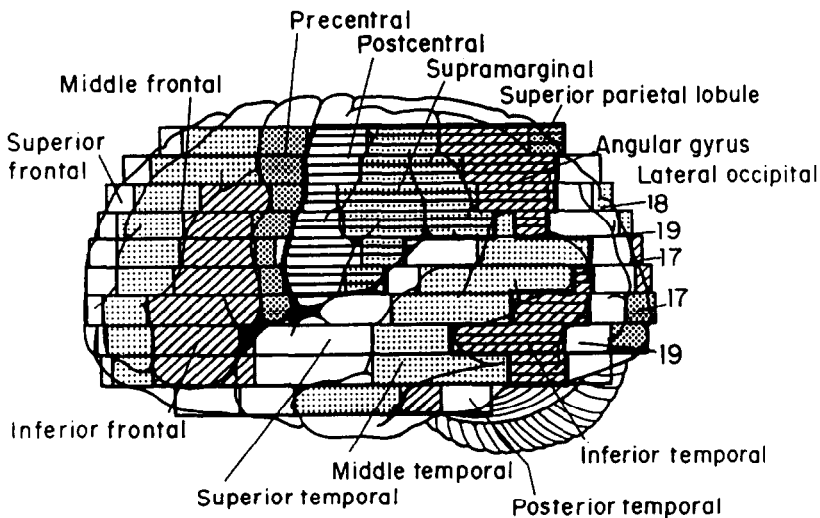

Figure 1. This lateral cortex view shows each of the four segments in each lobe defined stereotactically.

In addition to the cortical peel analysis, 3 × 3 pixel region-of-interest boxes were placed on PET slices in cortical, medial cortical, and subcortical structures at each level according to a standard list. Stereotactic coordinates for each box were determined from Matsui and Hirano (1978), and the proportional coordinates for each box were then located on corresponding PET slices. Mean GMR values for each box (right and left hemisphere separately) and for whole slices were calculated and entered into summary files for statistical analysis. The location of each box is shown in Figure 2.

MRI Scanning and Measurements

All participants had transverse MRI images taken with a GE 1.5T scanner using spin echo pulse sequences (TR = 2800 ms and TE = 30; 120 ms at 5 mm intervals of the entire brain). Approximately 18 images were obtained for each participant. We used echo 1st of 4 for gray/white structure identification.

Each participant had the same individualized head holder used for the PET scan. We have studied the accuracy of repositioning the head in the PET scanner to match the MRI slices. Errors are within about 2 mm, well within the spatial resolution of PET.

Area identification and analyses were performed on IBM 386 computers and done blindly with respect to group membership. Images were scaled using the field-of-view information into a 256 × 256 pixel matrix with each pixel representing an area of 5 mm^3. The axial slices were first edged to remove the skull and the scalp. The edging algorithm was determined by a radial scan of the image from the geometric center. Each radial profile was analyzed and the first point that dropped 50% of the average intensity was taken to be a point on the edge. The resulting set of points were then visually inspected for consistency. Occasional errors were caused by a strong signal between the scalp and the cortex, particularly on the slices closer to the apex. These errors were edited manually. The points were then connected and an edged outline of the brain slice was obtained. Seven points were chosen visually to determine the midline of the brain. On lower slices, these points were taken from clearly visible landmarks such as the anterior commissure and the posterior commissure, points around the septum pellucidum, and the point separating the right and left thalami. On higher slices, the midline could be identified as the longitudinal fissure. The points were linearly interpolated to form the midline. Once the brain slice was divided into right and left hemispheres, an area measurement of each half was made. Total hemisphere volume was obtained by integrating or adding together the individual slice volumes.

The extreme top and bottom slices of the brain were excluded due to extreme distortion of shape typical at these levels. Skull and scalp interference were also high at these levels making precise measurements difficult. As a result, only approximately 80% of whole brain volume was measured.
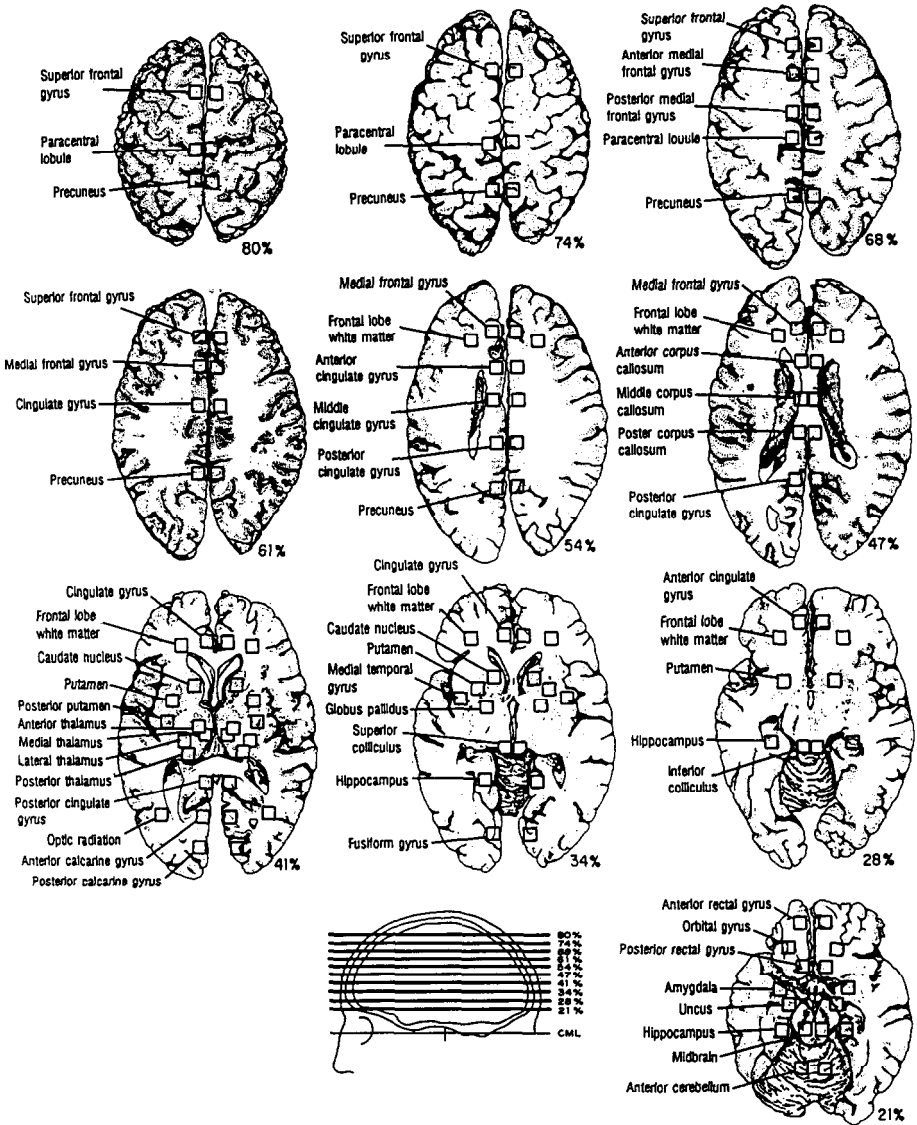
Figure 2. Each axial slice is labeled as a percentage of head height measured from the CM line. Regions of interest are located stereotactically.

Statistics

PET and MRI measure the whole brain simultaneously, generating many thousands of data points. Cost of imaging routinely limits sample sizes to well below that typically required for the usual multivariate statistical approaches to large data sets. We and others have used repeated-measures analysis of variance (ANOVA) on cortical GMR data to identify main effects and interactions for group, lobe, and hemisphere variables. In this study, we test a priori hypotheses about GMR and brain size based on earlier work. We also apply the Bonferroni correction to the exploratory multiple comparisons of GMR in medial and subcortical regions of interest, although the very large number of nonindependent comparisons may make this correction overly strict. These exploratory analyses are useful for generating new hypotheses and for providing a full description of the data for potential replication by other investigators. The risk of Type I and Type II errors in such small samples requires caution in interpreting all findings.

RESULTS

GMR

Cortical GMR was compared among the MR ($n = 9$; one case was deleted because of blood sampling difficulties, but this case will be included in the relative GMR analyses later), DS ($n = 7$), and control ($n = 10$) groups with a four-way ANOVA (Group × Hemisphere × Lobe × Segment; BMDP4V). There were two hemispheres (left and right), four lobes (frontal, parietal, temporal, occipital), and four segments in each lobe (shown in Figure 1). Using the BMDP 4V "structure" option, the lobes were nested in hemispheres and segments were nested in lobes. The ANOVA revealed a nearly significant main effect for group, $F(2, 23) = 3.27$, $p = .056$; no interactions were significant. Mean GMRs and standard deviations for each lobe and for whole cortex are shown in Table 1; lobe boundaries are shown in Figure 1 (whole cortex: controls = 36.3 micromoles glu-

TABLE 1
Mean GMR in Cortical Lobes for MS, DS, and Control Groups

	MR[a]		DS[b]		Control[c]	
	M	SD	M	SD	M	SD
Frontal	48.4	13.9	48.3	9.7	38.6	8.0
Parietal	51.5	16.0	48.4	11.1	39.1	8.7
Temporal	40.1	10.7	38.3	11.4	30.2	7.2
Occipital	49.5	14.6	49.6	12.4	37.3	7.9
Whole cortex	47.4	14.5	46.1	12.0	36.3	8.7

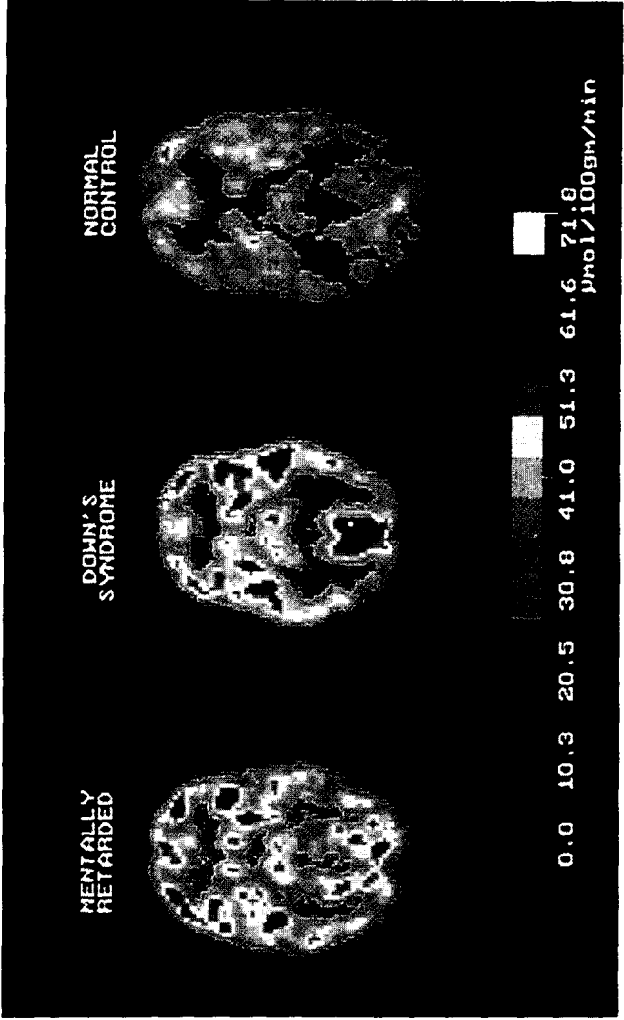[a]$n = 9$.   [b]$n = 7$.   [c]$n = 10$.

200

Figure 3. One case from each group (MR, DS, control) is shown on a common metabolic scale. This illustrates the higher GMR in the MR and DS groups compared to controls.

cose/100 g brain tissue/min, $SD = 8.7$); MR $= 47.3$, $SD = 14.5$; DS $= 46.1$, $SD = 12.0$). Both the MR and DS GMR means are significantly higher, as predicted, than the controls by independent t tests, $p < .05$, one-tailed. The effect sizes for MR and DS, respectively, are .86 and .76. According to Cohen (1988), these are moderate to large in size. Figure 3 illustrates the GMR differences among groups.

Although there was no significant lobe by group effect, we calculated an exploratory follow-up ANOVA for the temporal lobe since the original RAPM study (Haier et al., 1988) showed the largest effects in the temporal lobe (Haier, 1993). This analysis revealed a significant Group $\times$ Segment interaction in the temporal lobe ($T^2 = 18.1$, $p = .028$). The greatest difference was between the control and the MR groups in the posterior temporal lobe (right and left hemisphere; two-tailed t tests, $p < .01$; see Table 2). For comparison, there were no significant interactions in the other three lobes. We also examined GMR in the cerebellum as a nonneocortical control area. Anterior and posterior cerebellar regions of interest were increased above controls both in MR and DS groups (Table 3).

Any specific areas of abnormal GMR might be masked by the wide individual differences in GMR among people. Therefore, we computed the relative GMR for each cortical segment and for each sub- and medial-cortical region of interest (Figure 2) by dividing GMR in each specific area by whole slice GMR. None of the significant differences met the Bonferroni correction; however, the very large number of comparisons may make this correction overly strict. Therefore, we report the uncorrected significant values in the Appendix as exploratory with the required caution.

Compared to the control group ($n = 10$), the MR group ($n = 10$) showed significantly lower relative GMR in superior frontal, medial frontal, cingulate (Slices 8 and 9), caudate, putamen, posterior rectal gyrus, and uncus areas. Higher than normal relative GMR in the MR group was found in cingulate (Slice 5), frontal white matter, globus pallidus, and posterior cerebellum.

Compared to the control group, the DS group ($n = 7$) showed significantly

TABLE 2
Mean GMR in Areas of the Temporal Lobe for MR, DS, and Control Groups

	MR[a]		DS[b]		Control[c]	
	M	SD	M	SD	M	SD
Superior	42.3	10.7	43.1	11.2	34.1	7.1
Middle	43.2	11.3	42.1	10.9	33.2	6.4
Inferior	39.3	10.1	37.3	9.6	29.9	5.9
Posterior	35.6	9.9	30.7	10.5	23.6	4.1

[a]$n = 9$.   [b]$n = 7$.   [c]$n = 10$.

TABLE 3
Mean GMR in Cerebellum Areas in MR, DS, and Control Groups

	Left Anterior		Left Posterior		Right Anterior		Right Posterior	
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
MR ($n = 9$)	30.5[a]	9.7	35.5[a]	10.4	31.2[a]	10.8	35.5[a]	11.1
DS ($n = 7$)	29.6	13.2	31.9	12.0	28.9[b]	9.2	34.7[a]	11.3
Control ($n = 10$)	20.7	4.8	22.9	4.5	20.7	4.5	24.1	3.5

[a]Control versus impaired group, $p < .01$.　[b]Control versus impaired group, $p < .05$.

lower relative GMR in medial frontal, cingulate (Slice 8), caudate, medial thalamus, anterior cingulate, putamen, uncus, and medial temporal areas. Higher relative GMR in the DS group was found in areas of frontal white matter and the anterior cerebellum.

The MR and the DS groups significantly differed in four regions of interest. The DS group had lower relative GMR than the MR group in areas of the precuneus, medial frontal gyrus, and cingulate. The orbital gyrus, bilaterally, had higher relative GMR in the DS compared to the MR group.

MRI Size

The mean brain volumes (including about 80% of whole brain as explained in the MRI method section) for the groups were controls ($n = 11$): $M = 1,115$ cm³ ($SD = 98$); MR ($n = 9$; one case declined MRI); $M = 920$ cm³ ($SD = 182$); and DS ($n = 6$; one case declined MRI): $M = 892$ cm³ ($SD = 85$). The MR group mean is 82.5% of the control mean and the DS mean is 80% of the controls (Group × Hemisphere ANOVA); main effect for group, $F(2, 23) = 7.92$, $p = .0024$. Although not statistically different from each other, both the MR and the DS groups are significantly smaller than the controls by post hoc t tests. The greater variance in the MR group does not differ significantly from controls, $F(2, 23) = 3.45$, $p < .10$, two-tailed.

GMR/Size/IQ Correlations

All participants in the three groups (MR, DS, and MRI controls) were combined and correlations computed among whole brain GMR, MRI-measured brain size, and full-scale IQ. As reported by others measuring brain size (Andreasen et al., 1993; Willerman et al., 1991), or head size (Jensen & Johnson, 1994), there is a positive correlation of .65 ($p < .005$, one-tailed) between brain size and full-scale IQ (this is reduced to .36 when corrected for extreme groups, following Willerman et al., 1991, and matches their corrected value of .35). Consistent

with the earlier reports of inverse correlations between IQ and GMR, there is a negative correlation in this combined sample of −.58 (p < .005, one-tailed). We also found a negative correlation between brain size and GMR of −.69 (p < .005, one-tailed), similar to that reported by Hatazawa et al. (1987). Rank order correlations (Spearman and Kendall) showed the same pattern of results. However, our correlations of whole brain GMR with brain size, and IQ must be viewed cautiously because the controls did not perform the same CPT task as the MR and DS groups.

DISCUSSION

Cortical GMR is higher than normal in both the MR and the DS groups during performance of an attention task. This finding is consistent with a general inefficiency hypothesis and extends the inverse correlations reported between GMR and intelligence in individuals of normal range intelligence. The finding also is consistent with earlier reports of high GMR in DS (Cutler 1986; Schwartz et al., 1983) and with high synaptic densities in some DS brain regions (Cragg 1975; Huttenlocher 1974).

Reports of fewer than normal cell densities in some brain areas of DS at various ages (Becker, Takashi, Sachio, & Onodera, 1991; Coyle, Oster-Granite, & Gearhart 1986; Ross, Galaburda, & Kemper, 1984; Wisniewski, Laure-Kamionowska, Connell, & Wen, 1986) suggest that it is more moles of glucose per minute per cell than closer packing of neurons responsible for our observation of increased metabolic rate per unit area. However, there is difficulty in relating cell density data to GMR. For example, a localized decrease in density of inhibitory cells may lead to increased activation and higher GMR in several "downstream" regions of the circuit. Often, cell density differences involve a relatively small number of cells, and the resulting effect on GMR may be too small to measure with PET altogether. The fairly large increase in cortical GMR in both the MR and DS groups, however, appears robust.

Both the MR and DS groups in this study show about a 30% GMR increase over control individuals of normal range intelligence and about a 20% decrease in whole brain size. This is consistent with findings that smaller mammal brains have higher cell densities (Reichenbach, 1989; Stolzenburg, Reichenbach, & Neumann, 1989) and that, in humans, smaller brains have higher metabolic rates (Hatazawa, Brooks, DiChiro, & Bacharach 1987; Yoshii et al., 1988). Jernigan and Bellugi (1990) reported a similar decrease in cerebral volume in DS and in Williams syndrome compared to controls. Wisniewski et al. (1986) reported a 30% reduction in brain weight in DS compared to individuals of average intelligence. The smaller brain sizes we report for the MR and DS groups, although consistent with earlier literature, are interpreted cautiously because the controls for this comparison were not well gender matched.

Because DS and MR have about 20% smaller brains and 30% higher metabol-

ic rates per unit area, total brain micromoles glucose/100 g brain tissue/min are not entirely dissimilar between the impaired groups and controls (although GMR increases more than compensate for size). It should be noted that if the MR, DS, and control groups have similar brain GMR per unit area after correcting for brain size, one interpretation is that the impaired groups show poorer task performance per micromoles of glucose. This would be consistent with the hypothesis of brain inefficiency. Also, in DS, the lobe reported to have the greatest shrinkage, the temporal lobe (Wisniewski et al., 1986), had the smallest increase in GMR (8.1 micromoles), whereas the occipital lobe, in which prominent shrinkage has not been reported, had the largest increase (12.3 micromoles).

In the MR group, relative GMR was lower than normal in areas that included the superior frontal lobe, cingulate, and caudate. Specific difficulties of emotional control or learning that characterize mild MR might be related to function in or among these areas. Similarly, learning problems in DS may arise from abnormalities in medial frontal and medial temporal areas, both showing low GMR in the DS group compared to the controls. De La Monte and Hedley-Whyte (1990) found evidence of arrested neurodevelopment in the anterior frontal and temporal region in DS. Other data suggest that the medial temporal lobe in DS is larger than normal (Kesslak, Nagata, Nacioglu, & Lott, 1994); our finding of lower relative GMR in this area may be an example of efficient GMR in a large, salient area.

PET studies of Alzheimer's disease reveal decreased GMR in temporal areas (e.g., Buchsbaum et al., 1991; Grady et al., 1990; Miller et al., 1987). The medial temporal relative GMR decrease in these young individuals with DS may be an early sign of developing Alzheimer's disease but longitudinal follow-up is required to test this.

The MR group showed lower mean GMR in caudate areas; four cases had caudate GMR lower than two standard deviations below normal. These cases might be more responsive to neuroleptic treatment although there are no data on this point.

Zigler and Hodapp (1986) viewed some mild MR as the low-end manifestation of normal brain functioning rather than the result of abnormal function or damage. Our data suggest some brain function differences exist in the mild MR group. Not all individuals in the group, however, show hypercortical GMR or subcortical deficits. One way to potentially differentiate the organic kinds of mild MR from nonorganic kinds may be based on PET determinations (see Haier et al. in press). Brain size also may help distinguish subgroups within mild MR. The larger variance of brain size within the MR group compared to normals was not significant, $p < .10$, two-tailed. However, examination of the distribution shows three MR individuals have brain sizes in the normal range (all above 1000 ccm). These three people may differ from the six other MR people with smaller brains on WAIS–R profiles or other variables, although we lack the statistical power for such analyses here.

The CPT might be more stressful for participants who do poorly. Could the higher GMR seen in the MR and DS groups be due to increased anxiety? PET studies of state anxiety do not show a global increase in cortical GMR and no specific regions of interest have been implicated as anxiety sensitive (Giordani et al., 1990). Buchsbaum et al. (1987) studied patients with Generalized Anxiety Disorder and found GMR increases mostly in occipital areas, consistent with the distribution of benzodiazapine receptors.

Our original observation of cerebral efficiency was made within a single group of normal participants who performed the same task with varying success; more successful participants showed lower GMR. This is also found in this study. It might be argued that a comparison of a task condition to a resting condition is necessary to establish whether low GMR is a state or trait feature of better performance. The resting condition, however, presents difficulties. Resting PET scans have produced contrary results in DS (Schapiro et al., 1990; Schwartz et al., 1983). Resting with no task is actually an uncontrolled task subject to possibly great differences in cognitive demand among groups. The strong and stable individual differences in cerebral blood flow patterns during rest is consistent with the problem of heterogeneity of rest. It may be more desirable to contrast GMR in subjects performing exactly the same workload. That was our goal with the CPT. Slow paced and simple tasks might yield more equal performance between controls and impaired groups but there is the possibility that each group might approach the task differently and use different brain areas. Tasks differing systematically in workload per unit time or in strategy may be the most useful. Larson, Haier, LaCasse, and Hazen (in press), for example, reported PET data in high- and average-IQ subjects performing easy and hard versions of digit span backwards. GMR is highest in high-IQ subjects while performing the hard task. As noted in our original efficiency discussion (Haier et al., 1988) and subsequent learning results (Haier, Siegal, McLachlan, et al., 1992), task strategy may be the most important factor. Knowing which brain areas not to use may be the basis of lower GMR associated with better performance.

Our current results derive from a small number of participants studied both with PET and MRI. Many brain areas can be compared because both PET and MRI measure the whole brain simultaneously. Statistical power is not strong and Type I and Type II errors are a concern. The DS results replicate and elucidate some earlier findings of other investigators. To our knowledge, the indications of higher than normal cortical GMR in mild MR are new, as is the finding of smaller brain size in the MR group with somewhat larger variance (a finding also noted by R.T. Schultz, personal communication, December, 1994). Correcting for brain size may suggest similar GMR per unit of brain area among all three groups, but given the poorer task performance of the MR and DS groups, normals produce a higher rate of performance per micromole glucose, consistent with a simple efficiency hypothesis. Undoubtedly, the reality will prove more complex as new data are generated. Additional study is warranted to examine GMR changes with task

effort using a variety of cognitive tasks and new tracers of brain function (e.g., fluorinated dopa) to help identify the functional basis for different kinds of mental retardation and the relation of functional measures to structural abnormalities.

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APPENDIX
Relative GMR Mean Differences in Regions of Interest Among MR, DS, and Control Groups

	MR		DS		Control	
	m	**sd**	**m**	**sd**	**m**	**sd**
Right superior frontal (74%)[a]	1.14	0.10*	1.17	0.19	1.26	0.09
Left precuneus (68%)	1.36	0.10***	1.25	0.08	1.30	0.12
Right superior frontal (61%)	1.13	0.13*	1.24	0.14	1.29	0.13
Left medial frontal (61%)	1.10	0.07***	0.98	0.14	1.10	0.12
Right cingulate (61%)	1.10	0.12* ***	0.86	0.19	0.92	0.14
Left medial frontal (54%)	1.18	0.17	1.06	0.16*	1.31	0.12
Left medial frontal (47%)	1.16	0.14*	1.06	0.21*	1.33	0.13
Right medial frontal (47%)	1.28	0.26	1.10	0.17*	1.38	0.17
Left cingulate (41%)	1.08	0.19**	0.98	0.32**	1.24	0.11
Right cingulate (41%)	1.14	0.22**	1.05	0.06*	1.33	0.08
Left frontal white (41%)	0.96	0.15**	0.97	0.21	0.77	0.19
Left caudate (41%)	1.07	0.13**	1.01	0.22**	1.20	0.09
Left medial thalamus (41%)	1.31	0.20	1.12	0.21**	1.31	0.12
Right anterior cingulate (34%)	1.20	0.16	1.11	0.08*	1.29	0.09
Left frontal white (34%)	0.73	0.26**	0.67	0.15**	0.51	0.07
Left caudate (34%)	1.19	0.17	1.15	0.15**	1.27	0.08
Right caudate (34%)	1.24	0.15**	1.23	0.17**	1.39	0.11
Left medial temporal (34%)	1.09	0.14	1.05	0.11**	1.17	0.11

(continued)

APPENDIX *(Continued)*

	MR		DS		Control	
	m	**sd**	**m**	**sd**	**m**	**sd**
Right medial temporal (34%)	1.16	0.16	1.04	0.14*	1.29	0.16
Left putamen (34%)	1.31	0.20**	1.27	0.15*	1.46	0.12
Left globus pallidus (34%)	1.07	0.15**	1.01	0.09	0.94	0.10
Left orbital gyrus (28%)	1.17	0.14***	1.32	0.14	1.24	0.20
Right orbital gyrus (28%)	1.13	0.22***	1.40	0.16	1.25	0.20
Left postrectal gyrus (28%)	1.13	0.18*	1.20	0.16	1.31	0.11
Left uncus (21%)	0.84	0.10*	0.85	0.12**	0.99	0.14
Left anterior cerebellum (21%)	0.90	0.13	0.93	0.07**	0.84	0.11
Left posterior cerebellum (21%)	1.06	0.11**	1.02	0.10	0.93	0.13
Left posterior temporal (21%)	0.84	0.14*	0.68	0.18	0.69	0.07
Right posterior temporal (21%)	0.87	0.15*	0.74	0.16	0.72	0.06
Left occipital area #17 (21%)	1.17	0.12	1.29	0.17**	1.14	0.10
Right occipital area #17 (21%)	1.25	0.09*	1.27	0.20	1.14	0.10

Note. None of the differences were significant following Bonferroni correction.

[a] Percentage indicates slice level measured as percentage of head height above CM line; only regions with significant comparisons are listed.

*Compared to normal $p < .02$. **Compared to normal $p < .05$. ***MR/DS difference $p < .05$.