Regional Cerebral Function Determined by FDG-PET in Healthy Volunteers: Normal Patterns and Changes with Age

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The main objective of this study was to determine patterns of regional brain metabolic activity utilizing high-resolution PET in normal healthy volunteers and variations in different age groups. **Methods:** High-resolution [^{18}F]FDG PET images of the entire brain were obtained in 120 healthy normal volunteers (64 men, 56 women), age range from 19 to 79 yr. Each anatomic region was assessed using a qualitative rating scale with a score ranging from 1 to 6 (1 = definitely normal and 6 = definitely abnormal). Local metabolic activity was also estimated as showing increased (+) or decreased (−) compared to normal (0) states. **Results:** The most consistent finding in normal aging was decreased cortical metabolism, particularly in the frontal lobes. Temporal, parietal and occipital lobe metabolism varied considerably among subjects within the same age group as well as over decades. Basal ganglia, hippocampal area, thalami, cerebellum, posterior cingulate gyrus and visual cortex remained metabolically unchanged with advancing age. **Conclusion:** These data indicate that qualitative interpretation of FDG-PET images allows accurate assessment of regional metabolic activity of the brain in normal subjects similar to those described with quantitative techniques. Adequate knowledge of normal variations and changes related to normal aging is necessary for optimal assessment of pathologic states.

Key Words: positron emission tomography; fluorine-18-fluorodeoxyglucose; cerebral function

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Normal aging results in detectable changes in brain structure and function. Modern in vivo imaging techniques provide a powerful means to examine these alterations and to separate age-related changes from pathological states. While CT and MRI allow detailed assessment of brain structure, the functional state of the brain can be best detected by either PET or SPECT.

Postmortem studies have shown an overall stable neuronal count accompanied by a definite loss in neuronal size and decreased total number of glial cells with advancing age (*1,2*). The greatest decrement is found in the frontal and parasagittal parietal regions with subsequent cortical atrophy in these structures (*3*). This results in gross structural changes such as loss in weight and volume of the brain with an expansion of the cerebrospinal (CSF) spaces. Significant variability of these changes, however, has been reported (*2,4–7*).

In vivo morphological imaging of the aging brain has shown enlargement of cerebrospinal (CSF) spaces with advancing age (*8–13*), as evidenced by the increased ventricular and the cortical sulcal volumes that are more noticeable beyond the fifth decade of life (*14–17*) and changes of the white matter and to a lesser extent the gray matter (*18–26*).

Since functional disturbances precede structural changes, in vivo imaging with PET or SPECT may be abnormal while the brain anatomy appears normal. Fluorine-18-fluorodeoxyglucose (FDG) has been used to reveal alterations in regional metabolic rates in the aging brain as well as in various neuropsychiatric disorders (*27*). Results from previous reports describing age-related changes appear inconsistent. Some indicate no noticeable changes with age (*28,29*), while others report significantly decreased metabolic rates in certain brain regions such as the frontal lobe (*30–35*). In particular, previous reports fail to describe normal variation within and among different age groups which is critical for detecting changes associated with pathological states, especially in elderly patients.

This study was undertaken to determine the regional metabolic changes that take place with advancing age with high-resolution PET instruments. Qualitative assessment of regional cerebral metabolism using a practical rating scale can detect alterations in brain function comparable to quantitative techniques. We also determined normal variation in regional metabolic activity within similar and different age groups. In addition, findings in specific areas of the brain are described. Characterization of these specific signs may assist in developing criteria for interpreting PET and SPECT brain images.

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TABLE 1
Distribution of Subjects by Age

Group no.	Age range	No. of objects
1	19–25 yr	43
2	26–30 yr	23
3	31–35 yr	18
4	36–40 yr	7
5	41–60 yr	15
6	61–79 yr	14

METHODS

Subjects

One hundred and twenty normal, healthy right-handed volunteers were enrolled in this study. The subject population included 64 men and 56 women (aged 19 to 79 yr). The subjects for this study were recruited in response to advertisements in community newspapers. After a telephone interview, suitable candidates were chosen for further evaluation and enrollment in the study.

All subjects underwent thorough medical screening, including a complete history and physical examination, a battery of blood tests, a chest x-ray (only in the older subjects), neurobehavorial testing, including a Mini Mental Status Exam (MMSE), neuroanatomical imaging (MRI in all and CT in the older subjects only) and neurophysiological studies which included a FDG-PET scan.

Young subjects (40 yr) were completely healthy. Individuals older than 41 yr with mild medical conditions such as controlled hypertension, osteoporosis, arthritis, asthma or other minor problems were included in the study. Subjects with diabetes mellitus were excluded from the study.

Subjects with a history of significant head trauma, psychiatric or neurologic disorders, major medical disease and recent use of any medication except for antihypertensive drugs were excluded. Also, those with a MMSE score of less than 28 or any meaningful abnormality in the blood tests, neurocognitive, neuroanatomical or neurophysiological studies were considered unsuitable for enrollment in this study. The population was divided into six age groups as shown in Table 1.

Groups 1–4 (aged 19–40 yr) were recruited as healthy controls for a study of brain structure and function in schizophrenia, and Groups 5 and 6 (aged 41–79 yr) served as control subjects for another study that examined central nervous system changes in several dementing disorders. Subjects in Groups 1–4 were considered to represent the "relatively young" population and subjects in Groups 5 and 6 were designated to represent the "relatively old" population.

Image Acquisition

A PENN-PET scanner (*36,37*) with a resolution of 5.5 mm in all three planes and a previously described routine FDG technique (*38*) were used to image the entire brain. Intravenous and intra-arterial catheters were inserted while subjects were under local anesthesia. All subjects were examined with eyes open, ears unoccluded and the background noise was kept to a minimal level. For each examination, 114 μCi/kg ^{18}F-2-FDG were injected intravenously. Blood samples from the arterial line were drawn initially at short intervals and then followed by longer intervals after 15 min. Although arterial blood samples were obtained as part of this research study, no attempt was made to include quantitative data (absolute metabolic rates for glucose) in this report.

PET imaging was started 40 min after the administration of FDG. Images were acquired in planes parallel to the orbito-meatal (OM) line by using a laser system positioned in the gantry of the imaging instrument. A second laser light was used to ensure that the head was not tilted in the axial direction. The head was fixed in place throughout the study and its correct position was monitored by an investigator or technologist involved in the study. At the completion of the data acquisition, the images were reconstructed in the transaxial planes using an optimized Hanning filter. Also, attenuation correction was performed by applying Chang's method (*39*).

Image Analysis

The FDG-PET images reconstructed in 6–8-mm thick slices in the transaxial plane were interpreted by an experienced nuclear medicine physician blinded to age or other pertinent information. The quality was judged excellent and good in 84% of the images interpreted, whereas the scans were rated of poor but interpretable quality in 16%. In general, poor image quality was attributed to a relatively low number of counts in the images. The availability of multiple sections and the sizable regions chosen for analysis permitted optimal assessment of the patterns visualized in the latter group.

A qualitative rating scale was used to evaluate cerebral metabolic activity of various cranial regions. The rating scale ranged from 1 to 6, with 1 indicating definitely normal; 2 probably normal; 3 possibly normal; 4 possibly abnormal; 5 probably abnormal; and 6 definitely abnormal brain metabolism.

In addition to the latter rating scheme, areas of relatively *increased* and *decreased* metabolic activity compared to supposed *normal* baseline levels were assessed and assigned positive or negative values.

Regional cerebral function was used to describe changes that are noted in regional metabolic activity of the brain. The qualitative findings were determined in the following brain structures bilaterally: frontal, parietal, occipital and temporal lobes, basal ganglia, thalami and the cerebellum. These areas were defined based on known anatomical landmarks. Regions adopted for this analysis were taken from a brain atlas used in our laboratory which is sectioned in a plane parallel to the OM line. This allowed a reasonable estimate of approximate boundaries among different structures chosen for this study. These regions are somewhat large and therefore errors related to approximating these anatomic sites are small and acceptable for this type of qualitative analysis. Also, the basal ganglia-to-cortex ratio, the cerebellum-to-cortex ratio and the anterior-posterior gradient were assessed by the reader.

In addition to these standard regions, several specific findings delineated with high-resolution images are described as part of this analysis. These include a small clear-cut defect in the anterior pole of the frontal lobes (FPD) adjacent to the midline, frontal eye field (FEF), Wernicke's region, hippocampal area (HIP), visual cortex, posterior cingulate gyrus region, an area of intense uptake in the posterior parietal lobe, and the brainstem.

An anterior frontal lobe defect is noted in several sections of the brain close to the midline (Fig. 1). This area appears to have significantly reduced metabolism compared to the adjacent cortex. This defect measures approximately 1–1.5 in. in the x and y axes, is observed in multiple slices, is usually seen in both sides of the midline symmetrically and is of the same size on both sides. No corresponding anatomic abnormality is seen in the cortex on MR images.

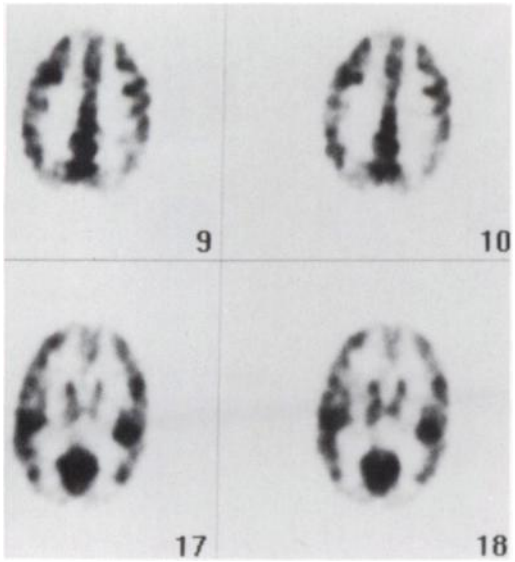

FIGURE 1. Bilateral frontal pole defects, asymmetric FEF, prominent Wernicke-regions and bilateral parietal lobe hypometabolism were considered within normal limits.

The frontal eye field region consists of an area with relatively increased metabolism of approximately 1 cm in size in the x and y axes. This area is also seen in several planes and is located a few centimeters anterior and parallel to the sensorimotor cortex (Fig. 2).

Wernicke's region is defined as an area of moderately intense metabolic activity which measures a few centimeters in x, y and z axes. This functional structure is situated in the posterior-superior temporal lobe region and corresponds to the approximate location of the primary auditory cortex (Fig. 1).

The medial temporal lobe area noted in two to three planes was considered to contain to a great extent the hippocampus. This area is usually well visualized and has a mild-to-moderate degree of metabolic activity.

The visual cortex is defined as the area corresponding to the medial occipital lobe region immediately above the cerebellum as noted in two to three slices. This area is visualized with moderately intense metabolic activity which is usually uniformly distributed throughout the structure (Fig. 3, images 20–24).

The posterior cingulate gyrus represents the continuation of the medial occipital lobe activity immediately above the visual cortex and is seen in multiple planes. This area is noted to have very intense FDG uptake which is uniformly distributed throughout this structure (Fig. 3, images 13–19).

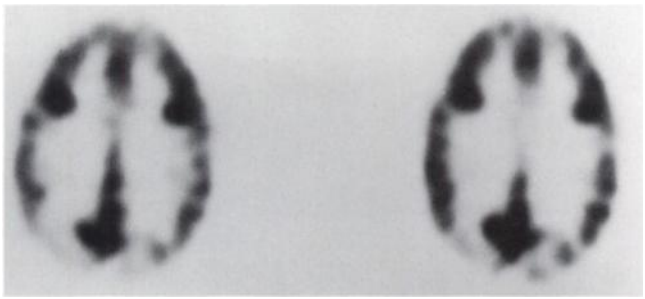

FIGURE 2. Upper frontal-parietal region images reveal intense hypermetabolism in the posterior frontal lobes which are considered to present FEF. This is usually symmetric and seen with more intensity in younger subjects than in the older population. Of interest is the mildly decreased activity in the parietal and occipital lobes bilaterally.

An area of distinctly increased activity was noted with high frequency at the junction of the parietal and occipital lobes just posterior to the Wernicke region. This area measures approximately 1–2 cm in the transaxial planes and is seen in a few sections of the brain (Fig. 4). Brainstem activity was also rated as intense, subtle or absent as demonstrated in several transaxial slices (Fig. 5).

Statistical Analysis

The data from this study were entered into a database and analyzed with a statistical program. Mean values, standard deviation, minimal and maximal values and 95% confidence intervals were calculated for each variable and age group. All variables were tested for consistency with normal distribution to justify the use of parametric procedures in further statistical evaluation. An analysis of variance (ANOVA) of metabolic activity in the defined regions was performed to determine differences among the age groups. Differences were considered to be significant with a probability value of less than 0.05. The data were also analyzed for a linear relationship of changes in metabolic activity in certain areas of interest with advancing age by calculating the Spearman and Pearson correlation coefficients.

RESULTS

The most consistent finding seen in subjects with advanced normal age was significantly decreased metabolic function in the frontal lobes bilaterally ($p < 0.00001$) (Fig. 6). Although only a trend toward this finding was noted in the third and fourth decades, a more dramatic decline was seen after the sixth decade.

The parietal, temporal and occipital lobe activities varied considerably among subjects within the same age group as well as over decades (Fig. 7). Overall, frontal, parietal, left temporal and occipital metabolic activity was relatively low when compared to that in the basal ganglia, the cerebellum and the right temporal lobe.

Some relative metabolic asymmetry was noted in the parietal lobes in Groups 1 and 3, which disappeared in the later years of life. Occipital lobe function remained relatively symmetric throughout the decades. Significant age-related changes were not seen in either the parietal or the occipital lobes.

Temporal lobe activity remained consistently asymmetric for all subjects. The left temporal lobe was hypometabolic compared to the right lobe and the rest of the brain. A tendency towards decreasing metabolic activity was noted in both temporal lobes in subjects 60 yr or older but did not reach a level of significance. Metabolic activity of the basal ganglia, thalami, visual cortices, hippocampi and posterior cingulate gyri remained basically unchanged with advancing age. In a small number of subjects, a mild-to-moderate degree of asymmetry was noted in the calcarine cortex without clinical evidence of any visual defects (Fig. 8).

The cerebellum was found to have variable metabolic function but showed a tendency toward relatively in-

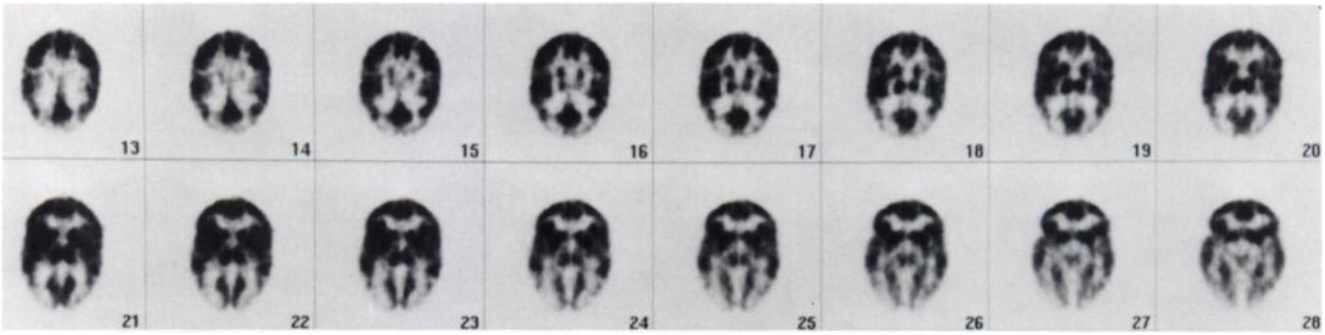

FIGURE 3. Multiple transaxial images extending from the frontal-parietal region to the temporal lobes. A gradient of decreasing activity from frontal to parietal lobes is noted in all visualized planes. Of interest is clear visualization of the calcarine cortex (visual cortex) which is symmetric. Also, intense activity is seen in the posterior cingulate gyrus, which is located in slices above the level of the visual cortex.

creased metabolic activity compared to the cortex after age 40 (Fig. 9A). Substantially reduced metabolic activity, however, was noted in the cerebellum of a few patients (Fig. 9B).

Basal ganglia-to-cortex ratios remained relatively constant among the various age groups. The scores for this ratio, however, were slightly elevated in all groups, indicating a relatively higher metabolic activity in the basal ganglia compared to the cortical areas. No asymmetry was noted in these ratios.

The cerebellum-to-cortex ratio tended to increase with age, which was thought to be consistent with a decline in cortical metabolic activity with advancing age. This is especially apparent after age 40.

The anterior-posterior-gradient appeared to change with advancing age due to a significant decrease in frontal metabolic activity in the later years, which became more apparent after age 30. In young subjects, only a minimum gradient or the frontal lobe appeared more active than the occipital lobe.

Gender differences did not appear to have an effect on the pattern of regional cerebral function in the population examined. The frequency and the incidence of bilaterality of various metabolic signs, especially defined and examined in the population enrolled in this study, are shown in Table 2.

Frontal pole defect (FPD) and the frontal eye field (FEF) activity were noted to have equal intensity in both sides in more than half of the subjects. In the remaining subjects, who had positive FPD or FEF signs on one side, the metabolic findings were more often noted on the right than on the left side ($p < 0.05$). The FEF appeared to be less active in the elderly than in the younger subjects, but this difference was not statistically significant. Wernicke's region tended to show relatively increased uptake with advancing age which was also not statistically significant. Posterior parietal lobe activity was seen bilaterally in approximately 50% of the subjects. It was more often noted on the right than on the left side. No correlation was seen among various metabolic signs with regard to their frequency and their intensity of radiotracer uptake. Also, no significant difference was noted in the frequency or laterality of these signs with advancing age. Brainstem activity was noted in 43.7% of the subjects. The intensity of uptake increased significantly with advancing age (Fig. 10). The correlation coefficient for the entire group was 0.62, which increased to 0.97 when Group 4 was excluded from the analysis.

DISCUSSION

Findings from our laboratory and elsewhere have demonstrated that significant changes in cerebral metabolic rates (measured quantitatively) occur with normal aging

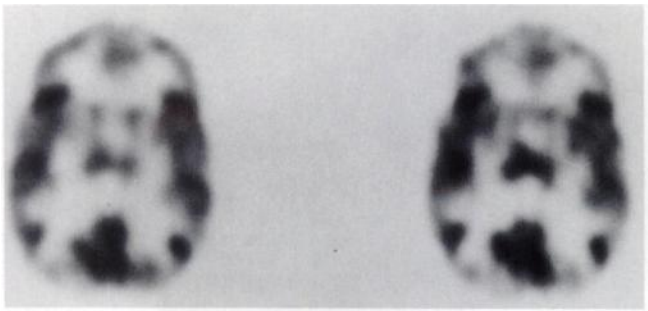

FIGURE 4. Images at the basal ganglia/thalamic level reveal an area of focal intense activity in the posterior parietal region. This is seen in about 50% of the normal population and appears mostly to be symmetric.

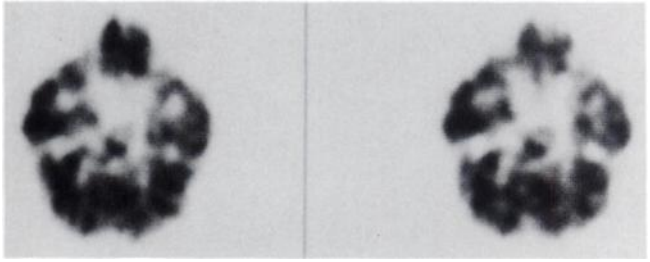

FIGURE 5. Moderate uptake is seen in the brainstem region located in the midline anterior to the cerebellum. Also, the cerebellum and the temporal lobes are visualized with the same intensity. Evidence of clear-cut, metabolic activity of both medical temporal lobes is present.

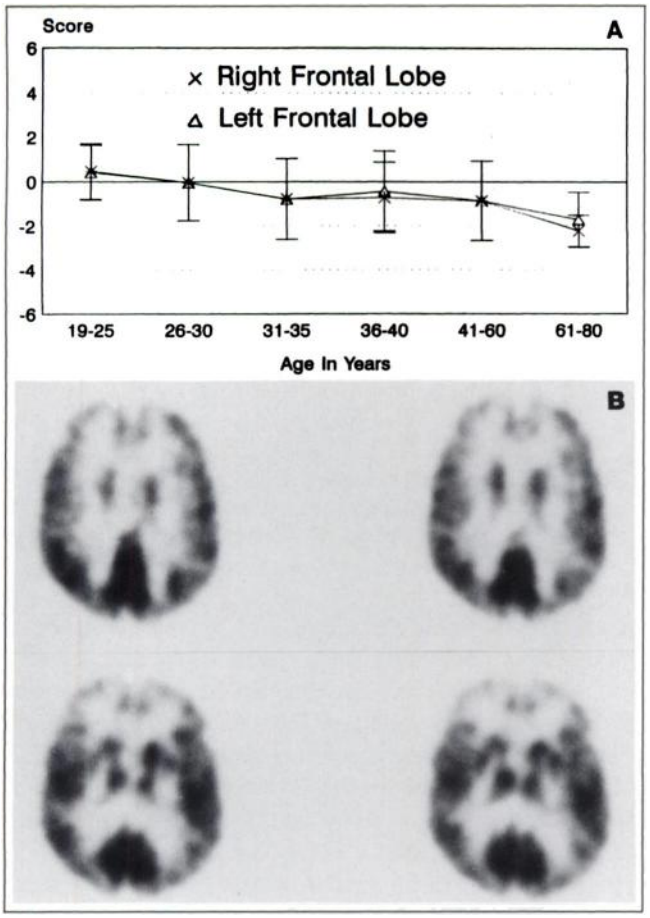

FIGURE 6. (A) Decreasing frontal lobe activity over several decades. Decline of the metabolic rate, however, is more dramatic beyond the age of 60. (B) Transaxial images at the level of basal ganglia and thalami reveal significantly reduced frontal lobe function compared to parietal and temporal lobes. Although this pattern could be seen in young subjects, it is more frequently noted in the older population.

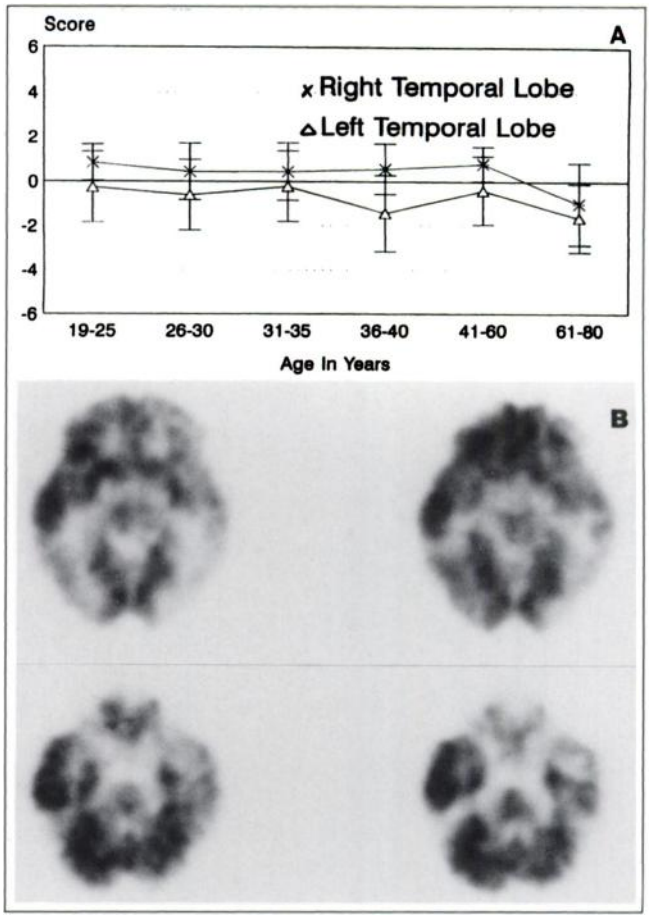

FIGURE 7. (A) Consistent metabolic asymmetry of the temporal lobes throughout the decades shows the left temporal lobe appears less active than the right. No trend toward decreased metabolism is seen with advancing age. (B) Images at the level of upper and middle temporal lobes reveal mild asymmetry in the metabolic activities of the two hemispheres. This is particularly apparent in the left temporal lobe, especially in the lateral aspects.

(*30–35*). These metabolic alterations are primarily seen in the frontal lobes, although other structures such as the parietal and temporal lobes and the sensorimotor cortex appear to be affected. The qualitative data presented in this study clearly demonstrate decreased metabolic activity in the frontal lobes bilaterally with increasing age. The most dramatic decline in frontal lobe function appears to occur after age 60 yr.

Kuhl et al. (*30*) reported a gradual decline in mean CMRglc with age using FDG-PET in 40 normal volunteers. The subjects ranged in age from 18 to 78 yr and were examined with ears unplugged and eyes open. At age 78, the mean CMRglc was, on average, 26% less than at age 18. The decline of metabolic rates with advancing age was similar for the cerebral cortex, centrum semiovale, caudate and putamen. Superior and posterior-inferior frontal regions, however, showed the most rapid decline with age.

Alavi et al. (*32,33*) studied 23 normal elderly subjects with a mean age of 65 ± 10 yr and 21 young controls with a mean age of 27 ± 6 yr using FDG-PET. While no significant differences in regional metabolic rates were found in many areas between the two age groups, a general decrease in metabolic activity was shown in the frontal and the somatosensory cortices.

Chawluk et al. (*34*) measured local CMRglc in 44 healthy volunteers (age 18 to 83 yr) again with eyes open and ears unoccluded. The elderly subjects were noted to have a 17% reduction in absolute frontal lobe metabolism compared to

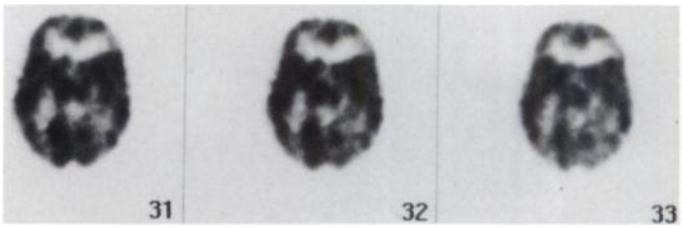

FIGURE 8. Images acquired at the level of the calcarine cortex show significant asymmetry of the visual cortex with decreased metabolic activity on the left compared to the right side. This finding is rare and probably positional in origin. It is crucial that other planes such as coronal and sagittal sections are considered when interpreting this physiologically important region.

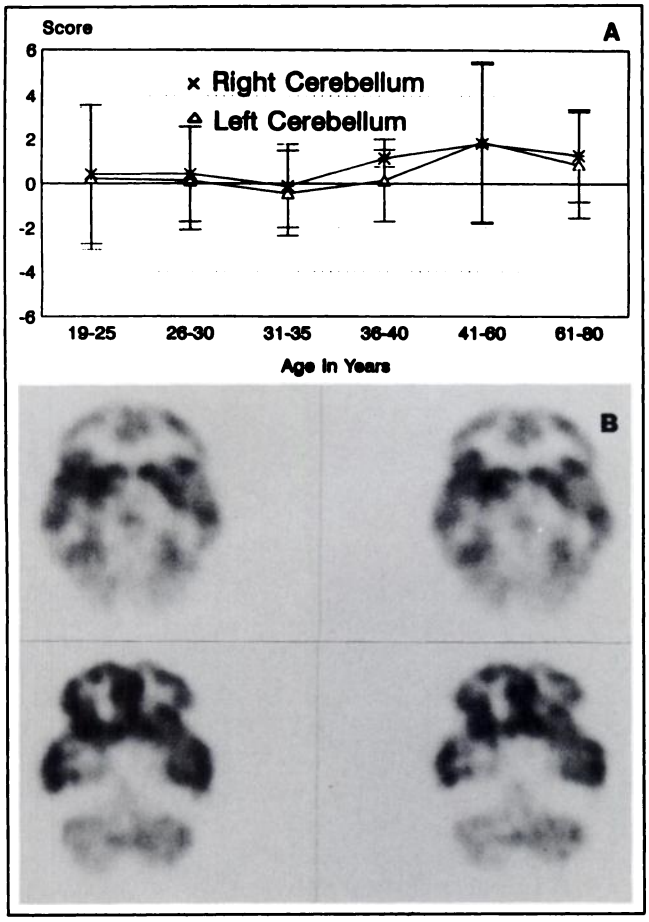

FIGURE 9. (A) The graph above represents the metabolic activity of the cerebellum for all subjects. Cerebellar metabolic rates appeared relatively increased compared to the rest of the brain in the older groups. (B) Images obtained at the level of the temporal lobes and the cerebellum reveal significantly reduced cerebellar activity, which is infrequently seen in normal subjects. The reason for this finding is currently unknown.

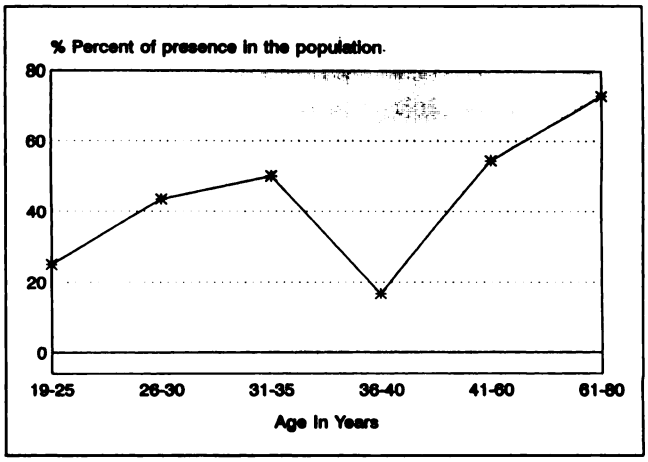

FIGURE 10. Relatively increasing metabolic activity of the brainstem over several decades, as shown above, is an important and interesting finding with statistical significance.

the younger controls. Other significant metabolic decrements were found in inferior parietal, left superior temporal and primary sensorimotor cortices.

Yoshii et al. (*35*) performed FDG-PET imaging on 76 normal subjects aged from 21 to 84 yr and measured local CMRglc. Metabolic rates were reported to be decreased in the frontal, temporal and parietal lobes in the elderly population.

Weiss et al. (*31*) reported a quantitative study in which CMRglc was measured in 85 healthy normal subjects from the third to the ninth decade of life. Decreased absolute brain metabolic activity was seen in the whole brain as well as in the frontal lobe, parietal lobe and sensorimotor strips bilaterally with advancing age. This decline appeared more steep in the frontal lobe than other structures in the brain.

TABLE 2
Frequency of Various Metabolic Signs in the Entire Population

Metabolic sign	% Frequency		% Bilaterality
	Right	Left	(with equal intensity)
Frontal pole defect	84.2	61.7	55.8
Frontal eye field	84.2	76.7	52.5
Wernicke's region	80.0	85.0	55.0
Posterior parietal lobe	58.3	46.0	51.0

In the past decade, several investigators demonstrated that underlying brain atrophy, as seen on anatomical images such as CT and MRI, can supposedly result in areas of hypometabolism on functional images such as PET and SPECT (*40–42*). Therefore, consideration for atrophy is essential in both qualitative as well as quantitative analysis of the data generated from PET or SPECT images. In patients with Alzheimer's disease, correction for atrophy results in significant changes in estimated values for metabolic activities of various lobes, including the frontal and parietal areas (*40*). Similar data demonstrate that correction for atrophy in the frontal lobes of normally aging subjects does not alter metabolic rates (*42*). This indicates that decreased metabolism in the frontal lobes of normal elderly subjects as noted on FDG-PET studies is not related to brain atrophy. One may speculate that these findings truly reflect functional alterations related to normal aging.

The qualitative data presented in this report demonstrate that visual interpretation can be as effective in detecting subtle changes in regional brain function as in those reported with quantitative techniques. Ideally, qualitative data should be correlated with quantitative data in the same subject to determine the validity of the findings described in this report. We have undertaken such analysis, which will be the subject of another article.

Results from this study indicate that no significant decrease in metabolic activity is seen in the temporal, parietal or occipital lobes over many decades. The temporal lobes show a tendency toward decline in metabolic activity beyond 60 yr of age. Therefore, the loss of frontal lobe activity results in a significantly decreased anterior-posterior gradient with advancing age. As indicated above, a decline

in regional metabolic rates has been reported with advancing age in the parietal and temporal lobes (*30,31,34,35*). These changes are quite subtle in extent compared to changes in the frontal lobe and therefore may not be identified with the visual interpretation technique.

Metabolic activity of the frontal, parietal and occipital lobes appears symmetric over decades. An asymmetry of the temporal lobe activity with relative hypometabolism in the left side was found in all age groups. The asymmetry noted on transaxial images in this report is not thought to be related to patient positioning and truly reflects changes in real metabolic activities of the structures described. These findings were seen in multiple planes and did not shift from side to side in the sections analyzed. To avoid such a potential source of error, examination of coronal sections would appear more suitable than transaxial planes. The significance of decreased metabolic activity of the left temporal lobe is uncertain at this time and a similar finding has not been reported by other investigators. Our data indicate that this is probably a normal variant and not an age-related phenomenon. Asymmetric temporal lobe metabolic function was noted among the subjects within the same age group as well as throughout the decades.

Cerebellar metabolic activity was similar to that noted in the temporal and parietal lobes and appeared to be stable up to the fourth decade. A slight relative increase in metabolic activity, however, was noted beyond the fourth decade but did not reach statistical significance. This in turn resulted in an increase in the cerebellar-to-cortex ratio over time. Alavi et al. used a semiquantitative technique and found (*43–45*) an increase in the cerebellar-to-whole brain metabolic rate from 102 bilaterally to 109 on the left and 111 on the right with advancing age. In some subjects, cerebellar metabolism was noted to be significantly reduced compared to the rest of the brain. Although this finding has been described in patients with seizure disorders who have been treated with phenytoin for an extended period of time (*46*), no history of such therapies was elucidated in these subjects and the significance of this finding remains uncertain.

Structural Differences

Metabolic activity of other structures such as the basal ganglia, thalami, hippocampus, the visual cortex and posterior cingulate gyrus appeared stable and relatively symmetric throughout the decades of life. The visual cortices were shown to be relatively more active compared to the rest of the brain in spite of minimal visual input during radiopharmaceutical administration. This relative increased metabolic activity did not change significantly with age. Alavi et al. (*43–45*) studied 11 young and 11 elderly normal healthy subjects with [^{18}F]FDG and determined the visual cortex-to-whole brain metabolic rate ratio. They reported a higher ratio in the anterior calcarine cortex (123 on the left/121 on the right) than the posterior calcarine cortex which was found to have a metabolic rate similar to that in the whole brain (107 on the left/105 on the right). Also, significantly elevated ratios were reported in the elderly compared to the young subjects in their study. We were unable to demonstrate such differences in our study. Although, the calcarine cortices appear symmetric in the majority of the subjects examined, in a small fraction a slight asymmetry was noted without any demonstrable clinical evidence of visual defects.

The significance of the defects seen in the anterior pole of the frontal lobe described in this article remains uncertain at this point. This finding has no anatomic correlation on structural images such as MRI. This area is clearly visualized bilaterally in young subjects and appears poorly defined in the aged population.

Although the oculomotor system is controlled by several strategically placed sites in the cerebral cortex, cerebellum and brainstem, two sites related to this system were identified on a resting functional imaging study (*47*), including the FEF and the posterior parietal cortex. In monkeys, the neurons in the FEF respond to visual stimuli and take part in saccadic eye movement. Unlike the parietal cortex, the FEF neurons do not have enhanced response when the monkey attends to the stimuli without making a saccade to it. The superior colliculus is controlled by the FEF in two ways: (a) by projecting the movement neurons to the intermediate layers of the superior colliculus and (b) by projecting to the caudate nucleus and exciting those neurons that inhibit the substantia nigra. Activity of the FEF sends a saccadic signal which excites the superior colliculus and releases it from inhibition from the substantia nigra by the caudate nucleus. In contrast to the FEF, signals from the parietal cortex are undifferentiated attention rather than carefully crafted movement commands generated by the former site (*48*).

The FEF and the posterior parietal cortex were visualized with variable frequency and different intensities among subjects. In particular, the incidence of distinct activity in the posterior parietal cortex was significantly lower than that seen in the FEF region. Our data present a retrospective analysis of PET-FDG images obtained in the resting state. No attention was paid to the ocular movement during radiopharmaceutical uptake. Prospective studies specifically designed to answer certain questions related to ocular motor function are required to further examine this finding. Alpert et al. (*49*) reported a study examining the neuronal control of eye movements in humans with PET and [^{15}O]CO_2 to measure cerebral blood flow. They found significant activity in the cerebellar flocculus, primary visual cortex and inferior parietal lobule. The angular gyrus, FEF and vestibular cortex at the junction of areas 41 and 42 showed increased flow during activation. These areas were found to be more active during smooth pursuit than saccadic eye movement, which were consistent with the theories of the pathways involved in horizontal smooth pursuit. Earlier quantitative studies have demonstrated that regional cerebral activity in the posterior parietal lobe remained relatively stable throughout different age groups (*43–45*).

The Wernicke region appeared quite active bilaterally despite the fact that the subjects were studied in a quiet environment. This may represent elevated baseline metabolic activity of this region which is enhanced with auditory stimulation.

The metabolic activity of the brainstem increases significantly with advancing age in the population examined. The importance of this finding remains uncertain. It is conceivable, however, that changes in neurotransmitter activities such as the dopamine system may have an effect on the metabolic activities of the brainstem, where the substantia nigra is located. Further studies are underway in our laboratory to investigate this finding quantitatively.

Gender differences in brain structures have been described with MR images in normal subjects (*50*). We were unable to detect any differences in regional cerebral metabolic patterns in any age group. Gur et al. (*50*) reported results of an MRI study of the entire brain in 69 healthy adults (age range 18–80 yr). They found significantly increased CSF space in older men compared to women. Elderly men had disproportionately higher indices for atrophy than equally aged women. Miura et al. (*51*) performed a PET study using FDG-PET in 32 healthy normal subjects (15 women, 17 men) and determined CMRglc in 65 ROIs. No differences in resting CMRglc were noted between young men and women in this study.

CONCLUSION

This article describes significant variations in regional cerebral functions in normal subjects using a high-resolution PET instrument. In addition, age-related metabolic changes in various structures of the brain are presented that resemble those described previously for quantitative techniques.

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REFERENCES

1. Brady H. Organization of the cerebral cortex. III. A study of aging in the human cerebral cortex. *J Comp Neurol* 102:51–56.
2. Terry RD, DeTeresa R, Hansen LA. Neocortical cell counts in normal human adult aging. *Ann Neurol* 1987;21:530–539.
3. Tomlinson BE, Blessed G, Roth M. Observations on the brains of nondemented old people. *J Neurol Sci* 1968;7:331–356.
4. Blinkov SM, Glezer II. *The human brain in figures and tables: a quantitative handbook*. New York; Plenum Press; 1968.
5. Dekaban AS, Sadowsky D. Changes in human brain weights during the span of human life: relation of brain weight to body heights and body weights. *Ann Neurol* 1978;4:345–356.
6. Creasey H, Rappoport SI. The aging human brain. *Ann Neurol* 1985;17:2–10.
7. Riederer P, Jellinger K. Morphological and biochemical changes in the aging brain: pathophysiological and possible therapeutic consequences. In: Hoyer, S., ed. *The aging brain*. Berlin: Springer-Verlag; 1982;158.
8. Baron SA, Jacobs L, Kinkel W. Changes in size of normal lateral ventricles during aging determined by computerized tomography. *Neurology* 1976;26: 1011–1013.
9. Glydensted C, Kosteljanetz M. Measurements of the normal ventricular system with computer tomography. *Neuroradiology* 1976;10:205–215.
10. Hahn FJY, Rim K. Frontal ventricular dimensions on normal computed tomography. *Am J Roentgenol* 1976;126:593–596.
11. Haug G. Age and sex dependence of the size of normal ventricles on computed tomography. *Neuroradiology* 1977;14:201–204.
12. Zatz LM, Jernigan TL, Ahumada, AJ Jr. Changes on computed cranial tomography with aging: intracranial fluid volume. *Am J Neuroradiol* 1982; 3:1–4.
13. De Leon MJ, George AE, Ferris SH, et al. Positron emission tomography and computed tomography assessment of the aging human brain. *J Comput Assist Tomogr* 1984;8:88–94.
14. Nagata K, Basugi N, Fukushima T, et al. A quantitative study of physiological cerebral atrophy with aging: a statistical analysis of normal range. *Neuroradiology* 1987;29:327–332.
15. Yamamura H, Ho M, Kubota H, et al. Brain atrophy during aging: a quantitative study with computed tomography. *J Gerontol Aging* 1980;35: 492–498.
16. Schwartz J, Creasey M, Grady CL. Computed tomographic analysis of brain morphometrics in 30 healthy men, aged 21 to 81 years. *Ann Neurol* 1985;17:146–157.
17. Hubbard BM, Anderson JM. Age, senile dementia and ventricular enlargement. *J Neurol Neurosurg Psychiatry* 1985;44:631–635.
18. Brant-Zawadski M, Fein G, Van Dyke D, et al. MR imaging of the aging brain: patchy white-matter lesions and dementia. *Am J Neuroradiol* 1985; 6:675.
19. George AE, DeLeon MJ, Gentes CI, et al. Leucencephalopathy in normal and pathologic aging. I. CT of brain luencies. *Am J Neuroradiol* 1986;7:561.
20. George AE, DeLeon MJ, Kalmin A, et al. Leucencephalopathy in normal and pathologic aging. II. MRI of brain luencies. *Am J Neuroradiol* 1986;7: 567–570.
21. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Neuroradiol* 1987;8:421–426.
22. Zatz LM, Jernigan TL, Ahumada AJ Jr. White matter changes in cerebral computed tomography related to aging. *J Comput Assist Tomogr* 1982;6: 19–23.
23. Goto K, Ishii N, Fukasawa H. Diffuse white-matter disease in the geriatric population. *Radiology* 1981;141:687–695.
24. Gerard G, Weisberg L. MRI periventricular lesions in adults. *Neurology* 1986;36:998–1001.
25. Zimmerman RD, Fleming CA, Lee BCP, et al. Periventricular hyperintensity as seen by magnetic resonance: prevalence and significance. *Am J Roentgenol* 1986;146:443–450.
26. Kirkpatrick J, Hayman L. White-matter lesions in MR imaging of clinically healthy brains of elderly subjects: possible pathologic basis. *Radiology* 1987;162:509.
27. Alavi A, Hirsch LJ. Studies of central nervous system disorders with single photon emission computed tomography and positron emission tomography: evolution over the past 2 decades. *Semin Nucl Med* 1991;6:775–777.
28. Duara R, Margolin RA, Robertson-Tchabo EA, et al. Cerebral glucose utilisation, as measured with positron tomography in 21 resting healthy men between the ages of 21 and 83 years. *Brain* 1983;106:761–775.
29. DeLeon M, George AE, Tomanelli J, et al. Positron emission tomography studies of normal aging, a replication of PET III and 18-FDG using PET IV and 11-CDG. *Neurobiol Aging* 1987;8:319–323.
30. Kuhl DE, Metter EJ, Riege W II. et al. Effect of human aging on patterns of local cerebral glucose utilisation determined by the (^{18}F) fluorodesoxyglucose method. *J Cerebr Blood Flow Metab* 1982;2:163–171.
31. Weiss DW, Souder E, Alavi A, et al. Effects of aging on whole brain and regional glucose metabolism as assassed by F-18 positron emission tomography [Abstract]. *J Nucl Med* 1995;31:771P.
32. Alavi A. The aging brain. *J Neuropsychiatry* 1989:1(suppl):S51–S56.
33. Alavi A, Jolles PR, Jamison DG, et al. Anatomical and functional changes of the brain in normal aging an dementia as demonstrated by MRI, CT and PET. In: Freeman LM, Weissman HS, eds. *Nuclear medicine annual*. New York: Raven Press; 1989:49–79.
34. Chawluk JB, Alavi A, Dann R, et al. Positron emission tomography in aging and dementia: the effect of cerebral atrophy. *J Nucl Med* 1987;28:431–437.
35. Yoshii F, Barbar WW, Aracy JY, et al. Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy and cerebrovascular risk factors. *J Cerebr Blood Flow Metab* 1988;8:654–661.
36. Reivich M, Kuhl D, Wolf A et al. The (^{18}F) fluoroglucosedeoxyglucose method for the measurement of local cerebral glucose utilisation in man. *Circ Res* 1979;44:127–137.
37. Karp JS, Muehllehner G, Mankoff DA, et al. Continuous slice PENN-PET:

a positron tomography with volume imaging capability. *J Nucl Med* 1990; 31:617–627.
38. Alavi A, Dann R, Chawluk J, et al. Positron emission tomography imaging of regional cerebral glucose metabolism. *Semin Nucl Med* 1986;16:2–34.
39. Chang LT. A method for attenuation correction in radionuclide computed tomography. *IEEE Trans Nucl Sci* 1978;25:638–643.
40. Alavi A, Newberg AB, Souder E, et al. Quantitative analysis of PET and MRI data in normal aging and Alzheimer's disease: atrophy weighted total brain metabolism and absolute brain metabolism as reliable discriminators. *J Nucl Med* 1993;34:1681–1687.
41. Tanna NK, Kohn MI, Horwich DN, et al. Analysis of brain and cerebrospinal fluid volumes with MR imaging: impact on PET data correction for atrophy. Part II. Aging and Alzheimer's dementia. *Radiology* 1991;178:123–130.
42. Chawluk JB, Dann R, Alavi A, et al. The effect of focal cerebral atrophy in positron emission tomographic studies of aging and dementia. *Nucl Med Biol* 1990;17;8:797–804.
43. Alavi A, Chawluk JB, Leonard T, et al. Correlative imaging of the brain in aging and dementia with positron emission tomography, x-ray computed tomography and magnetic resonance imaging. *Proceedings of the WHO Symposium on Mental Health Research in the elderly—Present and future prospects*, Sept. 10–14, 1984; Hafner H, Moschel G and Sartorius N; eds. Heidelberg-New York: Springer-Verlag, 1985.
44. Alavi A, Chawluk JB, Hurtig H, et al. Determinations of patterns of regional cerebral glucose metabolism in normal aging and dementia [Abstract]. *J Nucl Med* 1985;26:P69.
45. Chawluk JB, Alavi A, Hurtig H, et al. Altered patterns of regional cerebral glucose metabolism in aging and dementia [Abstract]. *J Cereb Flow Metab* 1985;5:5121–5122.
46. Theodore WH, Fishbein D, Deitz M, et al. Complex partial seizures: cerebellar metabolism. *Epilepsia* 1987;28:319–323.
47. Goldberg ME, Eggers HM, Gouras P, et al. The ocular motor system. In: *Principles of neural science*, third edition. Kandel ER, Schwartz JH, Jessell TM, eds. New York: Elsevier; 671–677.
48. Guitton D, Buchtel, HA, Douglas RM, et al. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res* 1985;58;455–472.
49. Alpert NM, Rauch JL, Elliott D, et al. Examination of the neural control eye movements with PET [Abstract]. *J Nucl Med* 1993;34:196P.
50. Gur RC, Mozley PD, Resnick SM, et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. *Proc Natl Acad Sci USA, Neurobiology* 1991;88:2845–2849.
51. Miura SA, Schapiro MB, Grady CL, et al. Effect of gender on glucose utilization rates in healthy humans: a positron emission tomography study. *J Neuroscience Res* 1990;27:500–504.