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Sex Differences in Human Brain Morphometry and Metabolism: An In Vivo Quantitative Magnetic Resonance Imaging and Positron Emission Tomography Study on the Effect of Aging

[Original Article]

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Outline

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Abstract^

Background: There are significant age and sex effects in cognitive ability and brain disease. However, sex differences in aging of human brain areas associated with nonreproductive behavior have not been extensively studied. We hypothesized that there would be significant sex differences in aging of brain areas that subserve speech, visuospatial, and memory function.

Methods: We investigated sex differences in the effect of aging on human brain morphometry by means of volumetric magnetic resonance imaging and on regional cerebral metabolism for glucose by positron emission tomography. In the magnetic resonance imaging study, we examined 69 healthy right-handed subjects (34 women and 35 men), divided into young (age range, 20 to 35 years) and old (60 to 85 years) groups. In the positron emission tomography study, we investigated 120 healthy right-handed subjects (65 women and 55 men) aged 21 to 91 years.

Results: In the magnetic resonance imaging study, age-related volume loss was significantly greater in men than women in whole brain and frontal and temporal lobes, whereas it was greater in women than men in hippocampus and parietal lobes. In the positron emission tomography study, significant sex differences existed in the effect of age on regional brain metabolism, and asymmetry of metabolism, in the temporal and parietal lobes, Broca's area, thalamus, and hippocampus.

Conclusions: We found significant sex differences in aging of brain areas that are essential to higher cognitive functioning. Thus, our findings may explain some of the age-sex differences in human cognition and response to brain injury and disease.

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There has been a substantial increase in the number of humans who reach old age, and by the year 2010 the proportion of the population aged more than 65 years will grow by 30%. [1] This has led to an increasing number of people who experience age-related cognitive decline, late-life diseases, such as Alzheimer's disease (AD), late-onset forms of anxiety and affective disorders, and psychotic disorders. [2,3] Furthermore, this same change in population demography has been accompanied by the realization that there may be significant sex differences in age-related cognitive decline [4-6] and in various age-related neuropsychiatric conditions, including AD [7] and late-onset schizophrenia. [8,9] However, research has focused mainly on mechanisms underlying sex differences in reproductive

behavior, and not on sex differences in aging of human brain areas associated with higher cognition.

Postmortem studies reported sex differences in human regional brain weight, area, volume, and asymmetry. [10-15] In general, females have a smaller brain volume with less striking anatomic asymmetries in temporal lobe regions. Postmortem studies that examined sex differences in brain aging found that brain weight decreases in the fifth and sixth decades of life in women compared with the sixth and seventh decades of life in men [16]; in contrast, the area of corpus callosum decreases significantly with age in men but not women. [17] Computed tomographic studies have reported significant gender differences in age-associated ventricular enlargement. [18,19] A precipitous increase in ventricular volume begins in the fifth decade in men and the sixth decade in women. [18] However, once the atrophy process is started, its velocity increases with age more rapidly in women than in men. [19] Magnetic resonance (MR) imaging studies of sex differences in brain aging are in disagreement. Some found no sex difference, [20] whereas others [21,22] reported that men have a greater age-related loss of brain volume than women, and that age-related atrophy is asymmetric in men but symmetric in women. However, no study has examined sex differences in age-related effects on all brain lobar regions-including parietal and occipital lobes in addition to frontal and temporal lobes and subcortical nuclei (lenticular, caudate, and thalamic)-and examined hippocampus and amygdala as separate structures.

Changes in bulk volume of brain tissue can be measured by MR imaging, and this may not reflect changes in neuronal metabolism and function. In contrast, single photon emission computed tomography and positron emission tomography (PET) allow measurement of cerebral blood flow and regional cerebral metabolic rates for glucose (rCMRglc). Sex differences have been reported in cerebral blood flow by means of single photon emission computed tomography, [23-25] and in cerebral blood flow and rCMRglc by means of PET. [23,26-28] However, there are no published reports on sex differences in age-related effects on metabolism of the healthy human brain.

Our aim was to determine whether the effect of aging differed between sexes on brain morphometry by means of in vivo MR imaging, and on rCMRglc by means of PET and (18F)-2-fluoro-2-deoxy-d-glucose. We previously reported significant and differential effects of the X chromosome and sex steroids on the brain. [29,30] The X chromosome is involved in development and aging of gray matter in association with the neocortex, but sex steroids modulate this effect and are crucial to the development and aging of the hippocampus. Thus, in this study, we hypothesized that sex would significantly influence age-related differences in brain morphometry and glucose metabolism, particularly in areas implicated in higher cognition and neuropsychiatric disorders.

SUBJECTS AND METHODS^

SUBJECTS^

All subjects were participants in a clinical program on brain aging conducted by the Laboratory of Neurosciences of the National Institute on Aging, Bethesda, Md. All were recruited from a relatively affluent area of Maryland; some volunteered because they were already aware of our program from friends and/or media news items, and others were recruited by advertisements in local newspapers. Every subject was rigorously screened [29] to exclude illnesses that could affect brain function, and all had normal results of a structured neurologic and cognitive examination, [31] urine and blood tests (including serology), chest radiography, and electrocardiography. All were medication free for at least 4 weeks before study. Informed consent was always obtained, and the research was approved by the National Institute on Aging institutional review board (National Institutes of Health protocol 80-AG-26).

We studied 69 subjects by MR imaging (34 women and 35 men) and 120 by PET (65 women and 55 men). All subjects were right handed, and men and women did not differ significantly in age or intelligence (Table 1). Recruitment difficulties and scanner availability in the MR imaging study led to relatively few middle-aged volunteers, and so subjects were divided into young (age range, 20 to 35 years) and old (60 to 85 years) groups. Of the young subjects, 15 were women (mean +/- SD age, 27 +/- 4 years) and 21 were men (25 +/- 2 years), and of the old subjects, 19 were women (68 +/- 6 years) and 14 were men (72 +/- 6 years). Our PET data set was larger than our MR imaging set, and, in the PET study, the mean (+/- SD) age of the 65 women was 52 +/- 23 years (range, 21 to 91 years) and that of the 55 men was 54 +/- 22 years (range, 21 to 90 years).

Table 1. Characteristics of Male and Female Subjects*

NEUROPSYCHOLOGICAL TESTING^

The Wechsler Adult Intelligence Scale [32] was administered as an omnibus test of language and visuospatial functions and was scored to yield full-scale IQs.

MR IMAGING^

The MR imaging of the brain was performed on a 0.5-T scanner (Picker Instruments, Cleveland, Ohio) and on a 1.5-T scanner (General Electric Medical System, Milwaukee, Wis).

The 0.5-T scanner was used to quantify volumes of cranium, lobar brain matter, ventricular and peripheral cerebrospinal fluid, and caudate, lenticular, and thalamic nuclei. Volumes of cranium, cerebral hemispheres, lobar brain, cerebellum, and ventricular and peripheral cerebrospinal fluid were acquired from 6-mm-thick contiguous coronal slices (repetition time, 2000 milliseconds; echo time, 20 milliseconds) obtained perpendicular to the inferior orbitomeatal line.

The caudate, lenticular, and thalamic nuclei were measured from 7-mm-thick, contiguous axial slices (repetition time, 2000 milliseconds; echo time, 20 milliseconds) obtained from the foramen magnum to vertex, parallel to the inferior orbitomeatal line. [33]

The 1.5-T MR imaging was used to measure volumes of the amygdala, hippocampus, and parahippocampal gyrus, and data were obtained from 5-mm-thick contiguous coronal slices (repetition time, 400 milliseconds; echo time, 20 milliseconds) obliquely centered at and parallel to the sylvian fissure. Hippocampal sequences were available in 25 men (13 young and 12 old) and 23 women (11 young and 12 old). There were no significant differences in age or intelligence between those who did and those who did not undergo hippocampal MR imaging.

Data were analyzed with a computer system (VAX 11/750, Digital Equipment Corp, Landover, Md) and an image array processor (Gould 8400, Vicom Inc, Fairfax, Va) after being displayed on a television monitor. Scans were analyzed without knowledge of the subject's clinical status. Right and left caudate, lenticular, and thalamic nuclei, hippocampus, amygdala, parahippocampal gyrus, and lobar volumes were traced using a method that has been previously described. [29] Also, a segmentation analysis [33] was used to determine volumes of brain matter and ventricular and peripheral cerebrospinal fluid. The frontal lobe was defined as all supratemporal structures anterior to the aqueduct of Sylvius. Temporal lobe volume was traced from the anterior pole of the temporal lobe to the aqueduct of Sylvius. The superior temporal lobe boundary was defined as a straight line drawn from the angle of the medial temporal lobe, where it attaches to the temporal stem, to the midpoint of the operculum; dura of the middle cranial fossa was then traced around each temporal lobe to complete the region. Parietal lobe was defined as the brain matter posterior to the aqueduct of Sylvius, extending to the medial transverse fissure of striate cortex. The remaining caudal portions of the cerebral hemispheres were defined as parieto-occipital. Hippocampus and amygdala were traced by means of an adaptation of the criteria of Watson et al [34] -namely, we did not trace the hippocampus any further posterior than the aqueduct of Sylvius. Parahippocampal gyrus was also traced anterior to the aqueduct of Sylvius; its inferolateral boundary was defined by the collateral sulcus, its superior boundary by the subiculum, and its medial boundary by the entorhinal cortex.

The volume of each region was calculated by multiplying the summed pixel cross-sectional areas by slice thickness. Women were significantly shorter than men and had a smaller head size. Thus, to control for the relationship of cerebral volume to head size, brain volumes were normalized as a percentage of the traced intracranial volume. Brain asymmetries were calculated by dividing right-left volumes of a structure by total intracranial volume.

Intrarater and interrater reliabilities were determined for all brain regions of interest (ROIs) traced by the operators as part of this analysis. Highly significant interrater and intrarater reliabilities were obtained in all cases. The interrater correlation coefficients were $F>4.0$ and $P<.01$. [35]

PET STUDY^

The rCMRglc values were obtained by means of PET with (18F)-2-fluoro-2-deoxy-d-glucose. Studies were performed on a tomograph (Scanditronix PC-1024-7B, Uppsala, Sweden) that can simultaneously acquire data from seven slices and that has an in-plane resolution of 6 mm and an axial resolution of 10 mm. Before scanning, each subject underwent radial artery catheterization, and arterial blood samples obtained during the procedure were used to measure plasma glucose concentrations and radioactivity.

Scans were carried out with lights dimmed and the patient's eyes and ears covered to reduce sensory input, and a thermoplastic mask was fitted to maintain positioning in the scanner. A multislice transmission scan was performed at two interleaved levels for attenuation correction at the beginning of each scan. Two methods of acquiring transmission data were used. Postprocessing techniques, based on internal standards, were used to ensure comparability. Forty-five minutes after injection of 185 MBq of (18F)-2-fluoro-2-deoxy-d-glucose, two interleaved emission scans were obtained at the same level as transmission scans. Fourteen slices were acquired, parallel to the externally defined inferior orbitomeatal line.

Data from the scans were analyzed with the use of a template of 8-mm-diameter circular ROIs to sample metabolic rates from cortical and subcortical areas. [36] Each template slice was matched to a slice from the patient's scan. Brooks' modification [37] of the operational equation of Sokoloff et al was used to calculate rCMRglc in each ROI, with the use of a lumped constant of 0.418. [38] Scans were analyzed by members of the PET Unit of the Laboratory of Neurosciences; interrater reliability coefficients [35] for the regions analyzed ranged from 0.87 to 0.99.

We previously reported [29,30,39] significant effects of the X chromosome and sex steroids on verbal and visuospatial abilities and on structure and metabolism of parietal, superior parietal, temporal, midtemporal, and occipital cortex, hippocampus, and lenticular, caudate, and thalamic nuclei. Therefore, to decrease the number of statistical comparisons, and thus the chance of generating false-positive (type 1) errors, regional metabolic rates were averaged [36] into total values for these ROIs and Broca's and Wernicke's areas. We have previously defined [36] Broca's and Wernicke's areas on a slice 45 mm above the inferior orbitomeatal line as an inferior frontal region (premotor; ROI 12) and a superior temporal region (superior temporal; ROI 13), respectively. Hippocampus was defined on a slice 35 mm above the inferior orbitomeatal line as a posterior medial temporal region (ROI 10) and was a composite measure including

parahippocampal gyrus. Only absolute metabolic rates (milligrams per 100 g per minute) were evaluated.

Right-left cerebral metabolic asymmetries were examined with the following equation, where R=rCMRglc in a right-sided region and L=rCMRglc in the homologous left-sided region: % metabolic asymmetry={(R-L)/[(R+L)/2]}x100.

Anterior-posterior ratios were calculated for Broca's-Wernicke's area by the same equation but substituting the terms Broca and Wernicke for right and left, respectively.

STATISTICS^

In the MR imaging study, statistical comparisons were carried out only on brain volumes normalized to intracranial volume to correct cerebral volume to head size because men had significantly bigger heads than women-and head size is directly proportional to brain size. Age (young vs old), sex (male vs female), and age x sex interactions were studied by an analysis of variance for unbalanced cells, [40] and a Student-Newman-Keuls multiple range post hoc correction for multiple comparisons. [40] The level of statistical significance was defined as $P<.05$.

Statistical comparisons in the PET study were carried out on absolute metabolic rates and not ratios because the denominator (whole-brain glucose metabolism) changes with age, but there is no uniform relationship between age-related changes in whole-brain glucose metabolism and ROIs. Thus, changes in ratios would not accurately reflect changes in the numerator (regional glucose metabolism). For example, if regional glucose metabolism of caudate does not change with age, but whole-brain metabolism decreases, then an artifactual increase in caudate metabolism would be reported with the use of ratios.

Metabolic activity was compared by means of a univariate multiple regression with age, sex, and age x sex interaction as the predictor variables. [41] This regression method is mathematically identical to a two-way analysis of variance with regard to age, sex, and their interaction as factors. The advantage of the regression equation is that we were able to keep age as a continuous variable because of the wide age distribution of our sample (20 to 91 years). The level of statistical significance was defined as $P<.05$. For brain ROIs that showed significant age-related sexual dimorphism, nonlinear trends were assessed by testing if a quadratic regression equation significantly improved the proportion of variance accounted for compared with a linear regression equation. [41] Also, for brain ROIs that showed a significant age x sex interaction, the Johnson-Neyman technique was used to define regions where the regression lines for the two groups significantly differed. [42]

RESULTS^

Our analysis of variance and regression analysis simultaneously examined sex differences, age-related changes, and age x sex interactions. Interpretation of the

main effects for age or sex are confounded if there is a significant age x sex interaction on the variable in question. [41] Therefore, the results are presented first for variables that showed only a main effect of sex or age without an interaction, and then for measures that showed an age x sex interaction.

MR IMAGING STUDY^

Sex^

Women had a significantly larger volume of thalamic and caudate nuclei than men (Table 2). In contrast, right-left asymmetry of lateral ventricles was significantly greater in men than women.

Table 2. Brain Matter and Cerebrospinal Fluid (CSF) Volumes in Young and Old Subjects*

Age^

There were significant age-related decrements in brain-matter volumes of cerebellum, cerebral hemispheres, parieto-occipital lobe, parahippocampal gyrus, and subcortical nuclei (amygdala, thalamic, and caudate) (Table 2). Furthermore, there were significant bilateral increases in volume of ventricular and peripheral cerebrospinal fluid. In contrast, there was no significant age-related decrease in volume of the temporal lobe.

Age by Sex^

Men had a significantly greater age-related decrease than women in brain-matter volume of cerebral hemispheres and frontal and temporal lobes (Table 2). In contrast, women had a significantly greater decrease than men in volume of the parietal lobes and hippocampus, and a significantly greater increase in volume of the third ventricle. Furthermore, there were significant sex differences in the right-left asymmetry of age-related decreases in frontal lobe volume-the right decreased more than the left in men, but the left decreased more than the right in women.

PET STUDY^

Sex^

Right-left metabolic asymmetry of frontal lobe metabolism was significantly less in women than men. Interpretation of all the other significant sex differences noted in (Table 3) are confounded because of significant age x sex interactions (Table 4).

Table 3. Mean Cerebral Metabolic Rates for Glucose in Men and Women*

Table 4. Age x Sex Differences in Brain Glucose Metabolism*

Age^

There were significant age-related decrements in glucose metabolism of whole-brain, frontal, temporal, and parietal ROIs (Table 4). Also, these metabolic decrements were significantly asymmetric in parietal (left more affected than right) and frontal (right more affected than left) lobes, and language areas (Broca's more than Wernicke's area).

Age by Sex^

Women had a significantly greater age-related metabolic decline than men in thalamus (Table 4) and hippocampus (Figure 1); thalamic metabolism of women was significantly higher than that of men until 24 years of age, whereas their hippocampal metabolism became significantly lower than that of men at 70 years of age. Also, there were significant age-related sex differences in right-left metabolic asymmetry of the temporal lobes until age 26 years ((Table 4), (Figure 1)) and of the parietal lobes and Broca's area from age 60 and 75 years, respectively. Generally, compared with women, age-related declines in metabolism in men were greater in the left than the right (Table 4); whereas, in women, the aging effect was either equal in the two hemispheres or greater in the right than the left (Table 4). A quadratic fit was not significantly better than a linear fit in all brain regions that demonstrated significant age-related sex difference.

Figure 1. Effect of aging on right-left asymmetry of temporal lobe (top) and absolute glucose metabolism of the hippocampus (bottom) as measured by positron emission tomography in male (open circles) and female (solid circles) subjects.

COMMENT^

Our report of age-related brain atrophy and an age-related decrease in glucose metabolism, as well as regional differences in age-related brain atrophy and metabolism, replicate previous results from our laboratory. [33,43,44] Also, our MR imaging finding of significant sex differences in age-related brain atrophy supports, and adds to, the findings of Gur et al [21] and Cowell et al. [22] In the PET study, we found significant sex differences in age effects on metabolism in some of the same regions in which MR imaging demonstrated morphometric

differences. Thus, some metabolic findings may have been influenced by sex differences in brain atrophy. Because not all subjects who underwent MR imaging had PET, we cannot directly address this issue. However, Grady and Rapoport [44] reported that age-related decreases in brain glucose metabolism are still significant after atrophy correction, and in the present study we found that regions that are anatomically close (eg, temporal lobe and Wernicke's and Broca's areas) had significant differences in age- and sex-related effects. Thus, our metabolic findings cannot be fully explained by sex differences in brain atrophy, although this probably accounts for some results.

We found a significant sex difference in age-related hippocampal volume loss, but the groups did not start from an identical baseline-hippocampal volume in young women was larger than that in men but was similar in old women and men. This result will need to be replicated in a larger sample. However, this MR imaging finding of significant sex differences in age-related loss of hippocampal volume is supported by our PET results, in a relatively large sample, which found significant sex differences in age-related decreases in hippocampal glucose metabolism. Thus, women have a significantly larger age-related decrease than men in hippocampal cellular glucose metabolism, and this may lead to greater atrophy and volume loss.

Our subjects were recruited locally, medication free, highly intelligent, and healthy. Thus, they do not represent the whole population, and our findings may not be generalizable. However, the selection of healthy subjects reduces the confounding effect of even mild physical disease on age-related changes in brain morphometry and metabolism. [45-47] Thus, our results may give a better measure of intrinsic age- and sex-related differences in the brain.

Cognitive abilities decline with advancing age, [48-50] but not all capabilities are equally affected. Most verbal capacities are preserved (including memory) until a very advanced age, [51,52] whereas visuospatial abilities and memory decline steadily throughout adulthood. [52-55] Women [4-6] have significantly less age-related decline than men in verbal memory, whereas men have significantly better preservation of visuospatial abilities, including visuoconceptual, constructional, and memory tasks. Performance on recognition tasks for visual stimuli is related to metabolic asymmetry in the parietal lobes, [56] and aging is associated with lateralized effects on cerebral blood flow. [57] Horwitz et al [58] suggested that decreased integration of metabolic function within parietal areas, and between frontal and parietal areas, may be associated with some age-related neuropsychological deficits. In this study, we found significant sex differences in age-related effects on morphometry and metabolism of brain regions involved in cognitive functions that also show significant age-related sex differences, and so these findings may be related. We are currently examining whether sex differences in age-related changes in cognitive ability and changes in brain morphometry and metabolism are related in a longitudinal study.

The timing, and biologic basis, for development of cerebral asymmetry is controversial. Human cerebral asymmetries are present at the 20th week of gestation [59] and well established by the 36th week. [60] However, it is unknown whether human brain asymmetry changes over the life span, and it has been proposed that specification of cerebral dominance is completed by birth, [61] age 5 years, [62] or puberty, [63-65] or continues to develop over the life span. [66] A Y chromosomal responsibility for development of cerebral asymmetry has been suggested, [67] but the X chromosome's importance is implied by studies of sex chromosome aneuploidies. For example, males with 49,XXXXY (Klinefelter syndrome) have better visuospatial than verbal skills, [68,69] girls with 47,XXX have delayed language and cognitive development, [70-73] and females with Turner's syndrome show X chromosome dosage effects on brain morphometry and cognitive ability. [29,30] Moreover, sex steroids are also implicated in the development of brain asymmetry. Some authors [74] proposed that in men testosterone modulates connectivity in an already asymmetric brain, and that low levels of testosterone lead to less functional asymmetry, whereas others [75,76] suggested that high levels of testosterone produce less functional asymmetry.

We found that right-left lateralization and anteroposterior ratios of brain metabolism undergo sex-dependent, age-related linear changes. Age-related changes in sex steroid concentrations are not linear, and we have reported sex chromosome dosage effects on structure and function of human association neocortex [29,30] and sex steroid effects on development of human hippocampus and memory function. [29,30] Thus, lateralized brain metabolism is not static but changes across the life span, and it may be genetically determined. Of course, other factors (such as hormone milieu) may modify aging of particular brain regions (eg, hippocampus and parietal cortex). [30] Also, this study was cross sectional rather than longitudinal and so could only address age-related differences and not changes during the life span of an individual.

Development of asymmetry in brain function is of relevance to human brain disease, eg, Crow [77] hypothesized that schizophrenia is secondary to an arrest of development of the primary asymmetry in Wernicke's area. Also, both aging and sex affect cerebral asymmetry because a lesion in left temporoparietal (Wernicke's) cortex produces different aphasia types by age [66] and aphasic symptoms in right-handed men but not in women. [78] Conversely, left anterior damage [78] causes aphasia more often in women than men.

The significant sex differences we found in age-related effects on the human brain may interact with a superimposed pathologic process and contribute to sex differences in brain disorders, because they occur in regions that are associated with higher cognitive function and that are implicated in age-related brain diseases (including AD and late-onset schizophrenia).

Women may have a higher age-adjusted prevalence and incidence of AD than men. [7,79-85] Furthermore, women with AD perform significantly worse than men

in some visuospatial [86] and memory [87] tests. We found that women had significantly more age-related decline in hippocampal metabolism and parietal lobe volume than men, and both brain regions are involved in memory and visuospatial function and in neuropathologic abnormalities in AD. [88-93] Thus, sex differences in aging of brain regions implicated in AD may contribute to sex differences in its symptoms. Nevertheless, others [94] found that in AD rCMRglc does not differ significantly between sexes-although this may reflect the small number of women older than 65 years they studied (N=5).

In late-onset schizophrenia, the male-female ratio (3:20) in patients older than 75 years exceeds that in the elderly population, [95] and some have proposed that this is secondary to loss of the antidopaminergic effect of estrogens. [96,97] However, schizophrenia is associated with structural and metabolic abnormalities in a number of brain regions (including the hippocampus), [98] and we found that women had a significantly larger age-related decrease in hippocampal metabolism and volume than men. Thus, sex differences in late-onset schizophrenia may be secondary to differences in age-related decreases in volume and metabolism of brain regions implicated in the disease. Furthermore, previous reports of sex differences in the brain structure of schizophrenics (see Castle and Murray [99] for a review) may reflect normal sex differences in the brain rather than the effects of schizophrenia per se.

In conclusion, we found significant sex differences in age-related effects on human brain morphometry and metabolism in regions known to subserve higher cognitive function. Our findings may explain some sex differences in age-related cognitive decline and may interact with superimposed pathologic processes to contribute to sex differences in human brain diseases.

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Aging; Brain Diseases; Cognition Disorders; Frontal Lobe; Gender; Hippocampus; Magnetic Resonance Imaging; Parietal Lobe; Positron-Emission Tomography; Sex; Temporal Lobe; Tomography, Emission-Computed

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