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Dementia is a medical problem of increasingly obvious importance. The most common cause of dementia, Alzheimer's disease (AD) accounts for at least 50% of all cases of dementia, with multi-infarct dementia the next most common cause of the syndrome[1]. While the accuracy of diagnosis of AD may range from 80 to 90%[2], there is currently no laboratory test to confirm the diagnosis. Furthermore, studies of the pathophysiology of AD and other causes of dementia which have utilized anatomic neuroimaging techniques have generally found changes related to cerebral atrophy. While the rate of progression of cerebral atrophy may differ between patients with AD and control subjects[3], this atrophy is usually insufficient to classify a given patient as having AD since the overlap with normal aging and other dementias is so great[4]. Functional imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) offer distinct advantages since brain function is unequivocally disturbed in all dementing illnesses.

Both PET and SPECT have been utilized in the study of dementia. While both techniques rely on principles of emission tomography to produce three dimensional maps of injected radiotracers, the differences between positron and single photon emission have important consequences for the practical applications of the two procedures. This chapter will briefly review the technical differences between PET and SPECT, and discuss how both techniques have been used in our laboratory to elucidate the pathophysiology of dementia.

Emission Tomography: Principles of PET and SPECT

All emission tomographic techniques utilize an injected radiotracer which is detected by a tomograph. The tracer represents a molecule of interest labelled with a radionuclide which can be detected by the tomograph. PET and SPECT tomographs use different

principles to accurately map the distribution of the tracer because of differences in the physical principles of positron and single photon detection. Despite these differences, the ultimate goal of these techniques is similar -- the quantitation of physiological processes. Both tomographic techniques therefore rely upon accurate measurement of the distribution of radioactivity in the brain, a clear understanding of the metabolism of the labelled tracer, and knowledge of the mechanisms responsible for the uptake and retention of the tracer in the brain. Application of mathematical models to the measurements of brain radioactivity allow the quantitation of physiological processes.

When an unstable nucleus decays by positron emission, the positron travels a short distance in tissue and then collides with an electron to produce two photons which travel in 180° opposite directions to each other. PET tomographs consist of a radial array of crystal detectors which are electronically coupled in a coincidence detection circuit in order to detect the simultaneous excitation of the two opposing crystals. Thus, the positron emission can be localized to a line, and the projection of multiple lines can reconstruct an image and map the distribution of the positron emissions. This method has the advantages of potentially high resolution, on the order of several millimeters. In addition, PET scanners also have high sensitivity (generally defined as counts/mCi of activity/sec) which translates into the ability to acquire many counts in a short time period and allows dynamic, time-varying measurements to be made quickly.

In SPECT imaging, tracer distribution is ascertained by utilizing collimation to localize the regions of radionuclide decay. This results in the loss of detection of some decay events, so that sensitivity decreases as resolution increases. At some point, around 10 mm, increasing resolution becomes impractical because of this loss of sensitivity. In addition, lower sensitivity makes acquisition of data in short time periods difficult, and therefore limits time-varying measurements of brain tracer uptake necessary for dynamic studies. The problems of radiation scatter and attenuation by brain and skull are also more difficult to resolve with SPECT imaging than with PET, resulting in less accurate

measurements of brain radioactivity. More detailed analyses of the physics and instrumentation of these two techniques have been recently published[5,6]. Despite these difficulties, SPECT is capable of producing three dimensional images of tracer uptake which contain considerable spatial detail and physiologic specificity.

Another consequence of the difference between positron and single photon emitters affects radiochemical syntheses of tracers. The most commonly used single photon emitters in SPECT studies, ^{99m}Tc and ^{123}I, are not constituents of organic molecules as are commonly used PET radionuclides such as ^{15}O and ^{11}C. Consequently, chemical syntheses and labelling of organic molecules with these single photon emitters may destroy the physiologic behavior of the molecule, while synthesis of PET tracers less frequently suffers from this limitation. The practical consequence of this is that, at the present time, a wider variety of tracers is available for PET studies than for SPECT. Nevertheless, SPECT tracers for the study of regional cerebral blood flow (rCBF) and some neurotransmitter receptors are currently used for human studies. While PET offers considerably more flexibility in the potential to study many different physiological processes, radiochemical syntheses (particularly of new compounds) and quantitative PET studies are technically demanding. Although PET is a more flexible and quantitative tool, technical ease makes SPECT more applicable to larger patient populations. Because of the differences in the techniques, we have utilized PET as a tool to investigate basic pathophysiological mechanisms in dementia, and have used SPECT in order to both assist in the diagnosis and classification of dementing illnesses and to answer other clinical questions necessitating the study of larger numbers of patients.

PET imaging in dementia

The application of PET to the study of AD has delineated changes in regional cortical physiology and thus expanded our understanding of this disease. Frackowiak et al.[7] using the isotope ^{15}O as elemental O_2 to study oxygen metabolism and as H_2O to study regional

cerebral blood flow, found diminished flow and metabolism in temporal and parietal cortex in Alzheimer's disease. Concurrent measurement of flow and metabolism permits the evaluation of the cerebral oxygen extraction ratio (OER), which Frackowiak et al. found to be normal in AD, evidence that the diminished flow is a consequence, and not a cause, of the metabolic deficit. Other laboratories have utilized glucose metabolic tracers, and have also found generally diminished glucose metabolism in temporal and parietal cortex[8,9,10].

We have utilized the glucose metabolic tracer FDG in conjunction with the PET-280, a single-slice tomograph with 8 mm resolution (full-width at half-maximum) and a 10 mm slice thickness. Initial studies of 10 AD patients[11] showed significant decreases in relative FDG uptake in temporoparietal cortex in AD patients. Further investigation of this phenomenon in our laboratory was designed to quantitate these differences and attempt to understand their mechanisms. In order to do this, we utilized dynamic PET scanning to estimate the parameters of the three compartment model developed by Sokoloff et al.[12]. Simultaneous acquisition of dynamic PET data and dynamic blood data permits fitting for the individual parameters of the Sokoloff model: k_1 and k_2 for forward and reverse transport of glucose, respectively, and k_3 for phosphorylation by the hexokinase enzyme.

Dynamic studies were performed in 11 patients who met current research criteria for AD[13] and in 6 age-matched controls. Subjects in both groups were free of any significant medical illnesses and were taking no medications. The AD group averaged 66.6 years of age and the control group averaged 64.2 years. A more detailed report of this study can be found in a recent publication[14].

The dynamic PET experiments were designed to acquire time activity curves for the PET data and the time course of the activity in blood. Immediately following the injection of the tracer, blood was withdrawn from a heated hand vein initially at rapid intervals followed by progressively slower intervals. Simultaneously, PET data were acquired, initially every 2.5 or 5 sec, followed by increasingly long intervals. Regions of interest were then drawn in PET images, and the time-activity curves for each brain region were

calculated. These data were then fit with the blood time-activity curves using an iterative least squares fitting technique to derive the rate constants for glucose transport and phosphorylation.

Although dynamic studies did not reveal differences between controls and AD patients for any of the model parameters k_1 through k_3, the variability of the data was large with coefficients of variation from 18 to 45%. When this variability was reduced by normalizing the data using ratios of the parameter in a given brain region to the value in entire cortex, we found that AD patients showed relatively reduced k_3 in temporal cortex, the brain region which has been consistently most abnormal in AD.

These PET studies demonstrate a disturbance in neocortical glucose metabolism which appears to be due to abnormalities of the hexokinase step of glucose metabolism and not glucose transport. Nevertheless, it remains possible that the disturbed glucose metabolism is a result of loss of neuronal number in the image volume, rather than a primary disturbance of glucose metabolism. Friedland, Brun and Budinger[15] have noted that the regions showing diminished glucose metabolism are also the site of the most severe neuropathologic involvement.

One limitation of PET applications to degenerative disease is the problem of atrophy. Since all PET images suffer from some partial volume artifacts, metabolic rate measurements of convoluted cortical regions contain volume averaged white matter and cerebrospinal fluid which lowers the calculated metabolic rates. This problem may be worsened in patients with cortical atrophy. Thus, Chawluk et al.[16] have found that correction of PET metabolic rates for atrophy produces larger increases in rCMRglc in AD patients than in normal controls. Use of PET instruments with higher resolution also can help mitigate this problem, since cortical convolutions may be more clearly seen and the partial volume artifact minimized. Physical principles discussed above permit increasingly higher PET resolution within the plane of the section by increasing the number of detectors in the scanner with no loss in sensitivity. Our new tomograph, the Donner PET-600, has

an in-plane resolution of 2.6 mm and an axial thickness of 5 mm[17] . Images from a control and AD subject are seen in figure 1. This improved resolution also provides the ability to quantitate physiologic processes in small brain regions, particularly the mesial temporal lobe structures which we suspect are the earliest to be involved in AD.

SPECT Imaging in AD

Initial findings using PET with FDG suggested that the abnormal pattern of glucose metabolism in AD could have diagnostic utility. Technical factors described above, however, largely limit the availability of PET to tertiary care medical centers. SPECT imaging technology is immediately accessible to most community hospital nuclear medicine departments, and tracers for the study of rCBF are now commercially available. Findings that rCBF appears normally coupled to regional metabolism in AD supported the use of this technique in investigations of demented patients.

Studies of rCBF in AD patients have used both ^{123}I-labelled N-isopropyl-p-iodoamphetamine (IMP) and ^{99m}Tc-labelled hexamethyl propyleneamine oxime (HM-PAO) with similar results[18,19,20,21]. Prominent temporal and parietal hypoperfusion is seen using both tracers. Methods of data analysis have included visual inspection and within-patient ratios of regional radioactivity distribution, and generally show some overlap between AD and control subjects. While the frequent asymmetry of the temporoparietal lesions seen in AD has resulted in the misclassification of AD patients as having MID, this problem can be avoided by also studying patients with an anatomic imaging technique.

In our initial series[22] we studied 9 AD patients, 5 controls, and 2 patients with MID using the tracer IMP. Subjects were scanned on a multidetector scanner with a resolution of 14 mm full width at half-maximum[23] using the blood flow tracer IMP. Subjects were

positioned in the scanner in a plane parallel to the canthomeatal line, and were injected with 3-5 mCi of IMP with eyes open and ears unoccluded in a quiet dimly lit room. Scanning began ten minutes following injection, with 20 minutes of data acquired at each of two tomographic levels. These levels corresponded to planes approximately 7 and 5 cm above the external auditory meatus and passed through the middle of the lateral ventricles (level 1) and basal ganglia (level 2), respectively. For the purposes of our initial study, we analyzed data from only the upper tomographic level. Because of the limitations of SPECT for absolute quantitation of radiotracer uptake, we did not model and quantitate rCBF in these patients, but rather used a ratio of the radioactivity in a region of interest to the activity in the entire tomographic slice. Initial results showed that the temporoparietal to whole slice ratio completely discriminated the AD from control and MID subjects. In addition, this ratio strongly correlated with dementia severity as measured using the mini-mental status examination (MMSE)[24]. Other groups have also noted relationships between tracer uptake and dementia severity[25]. Examples of SPECT-IMP images from our laboratory are seen in figure 2.

SPECT studies also parallel the cognitive features of dementia seen in different clinical groups of patients. Some dementia patients are behaviorally quite different from AD patients, showing cognitive deficits which appear to reflect frontal lobe dysfunction. These patients generally suffer from aphasia and mutism, behavioral disinhibition, and apathy, without the severe memory disturbances which are a prominent feature of AD. SPECT imaging studies of these patients show physiological dysfunction (diminished tracer uptake) in the frontal lobes, rather than the temporoparietal abnormalities of AD[26,27]. While such frontal lobe glucose metabolic abnormalities have been seen in autopsy-documented cases of Pick's disease[28], all dementias with frontal lobe symptoms and

perfusion abnormalities cannot be diagnosed as Pick's disease without autopsy confirmation, since some such syndromes are associated with non-specific pathology[29]. It also remains possible that some of these patients have frontally predominant AD. Results using ^{133}Xe inhalation methods to measure rCBF parallel the results obtained with SPECT and PET in patients with frontal lobe dementia syndromes[30]. Thus, while the neuropathological basis of these syndromes is not clear, there is an obvious relationship between clinical syndromes and the location of physiologic dysfunction which reflects current conceptualizations of brain-behavior relationships.

SPECT series of AD patients also show relationships between regions of diminished tracer uptake and cognitive performance[31]. These results are quite similar to results obtained using PET, and demonstrate the pathophysiological basis for the disease's heterogeneity. Indeed, a considerable advantage of SPECT over PET is that its relative low cost and ease of use allows the study of larger subject groups. This is important in illnesses like AD in which biological differences between individuals may be large.

The study of larger patient groups with SPECT has also indicated that the technique is neither completely sensitive nor specific for the diagnosis of AD. We recruited patients in the earliest stages of AD in order to evaluate the sensitivity of SPECT and IMP in diagnosing the cause of dementia[32]. We studied 21 patients, all of whom had SPECT scans and neuropsychological testing. Nine were mildly demented, with scores on the MMSE in the normal range (mean 26.6, SD 1.7) although all complained of memory loss and were felt to have AD, and 12 were moderately demented (MMSE mean score 15.0, SD 5.4). The mildly demented subjects probably represent patients with the earliest stage of AD which is currently clinically detectable. Thirty-six healthy age-matched control subjects were studied -- 14 received SPECT scans, and 22 underwent neuropsychological testing, but no control subject received both. We quantitated SPECT data by calculating an rCBF ratio defined as the ratio of regional radioactivity normalized to occipital cortical radioactivity. We studied four cortical rCBF ratios -- orbitofrontal and dorsolateral frontal

cortex and temporal and parietal cortex -- and found considerable overlap between patients (both mild and moderately demented) and control subjects in all brain regions. Furthermore, when SPECT and neuropsychological abnormalities were defined as scores outside the 95% confidence intervals for the control group means, all AD patients showed memory abnormalities, while only 55% of the mildly demented patients, and 83% of the moderately demented patients showed temporal or parietal perfusion deficits. However, temporal or parietal SPECT abnormalities were seen in only 7% of control subjects, suggesting that its presence may be a more reliable indication of dementia than abnormal memory function, which was seen in 27% of control subjects. Although other methods of SPECT data analysis might be more sensitive for the diagnosis of AD (such as visual inspection by a trained observer), it is clear that a normal SPECT scan does not rule out the presence of AD.

These preliminary results with SPECT provide general guidelines for both the clinical and research uses of the technique. As a diagnostic instrument in dementia, SPECT is clearly not a definitive tool. However, it may be useful in difficult diagnostic cases such as patients with early symptoms, since findings of temporal and parietal hypoperfusion support the diagnosis of AD. It may also be useful in diagnosing patients with unusual dementia symptoms, such as apathy and depression seen in frontal lobe dementia syndromes. As a research tool, SPECT is useful for studying clinical problems in which biological heterogeneity is a limitation of PET studies of small patient groups.

Summary and Conclusions

PET offers both quantitative precision and flexibility in method, allowing accurate measurement of a variety of physiological processes. The study of large patient groups, either for diagnostic reasons or research, is more difficult, however. For this reason we have chosen PET as a tool for the investigation of the pathophysiology of dementia, and have utilized SPECT as a tool for diagnosis and for answering questions about the

heterogeneity of the disease. Future advances in PET technology will improve both its resolution and its ability to quantitate more physiologic processes. Improved resolution may result in the ability to detect cases at an earlier point in the disease, and measurement of more physiological processes, such as new neurotransmitter systems, may provide greater insight into the pathophysiology of dementia. Similar improvements in SPECT technology will allow these studies to be performed on a larger scale.

Figure Captions

Figure 1: PET images taken on the PET-600 tomograph, with 2.6 mm in-plane resolution. Images from a control subject and a patient with Alzheimer's disease (AD) demonstrate regional glucose hypometabolism in bilateral temporal and parietal cortex in the AD patient. The images are taken in a plane parallel to the orbitomeatal line and are 7, 5, and 3 cm (from top image to bottom image, respectively) above this plane. Each image represents 10-15 min of accumulated data, and contains between 1.5 - 2.4 x 10^6 counts.

Figure 2: SPECT regional cerebral blood flow (rCBF) images using the tracer IMP in a control subject and a patient with Alzheimer's disease (AD). Images are 7 and 5 cm above and parallel to the orbitomeatal (OM) line. Results are similar to those seen using PET and glucose metabolic tracers.

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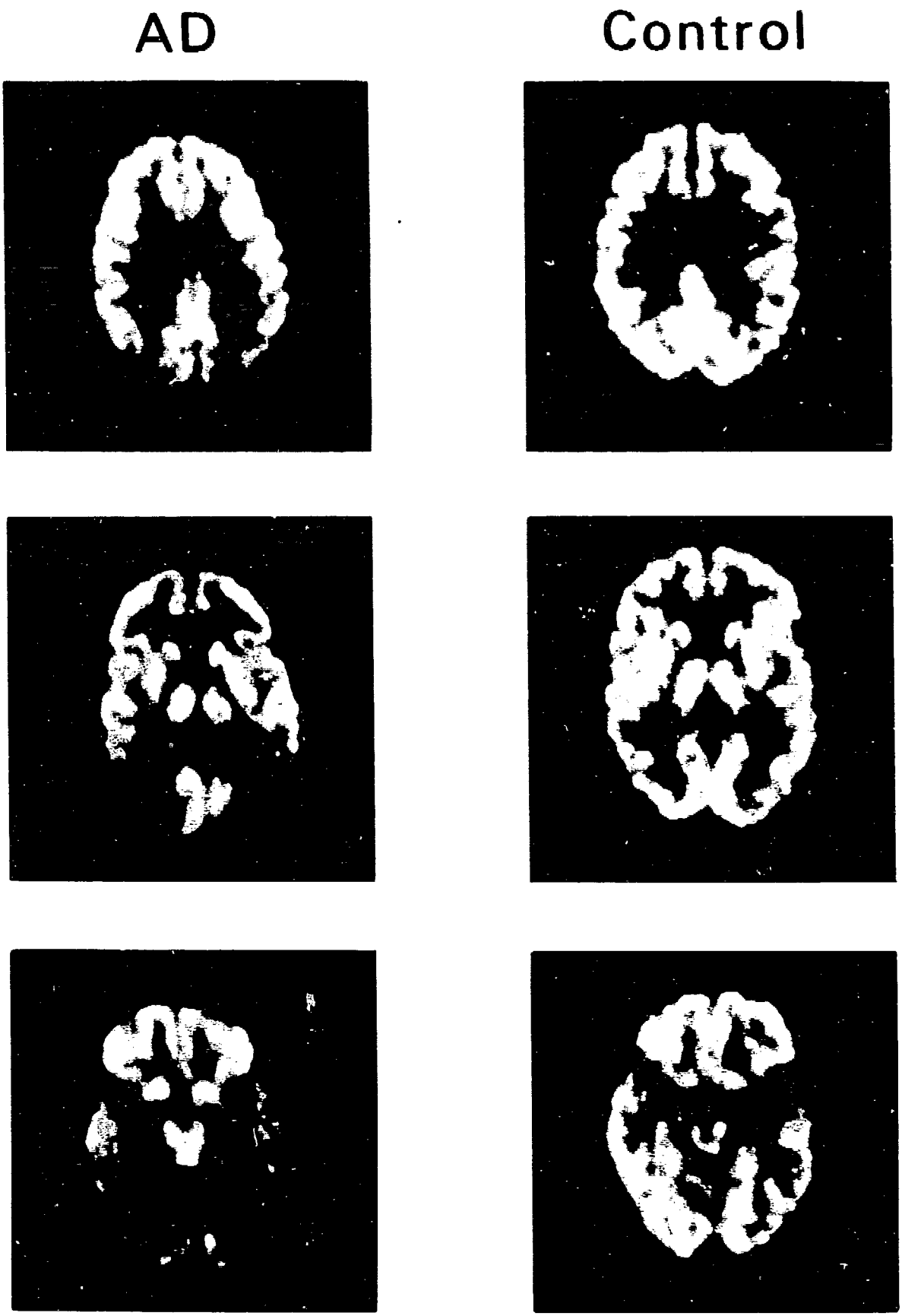

Figure 1

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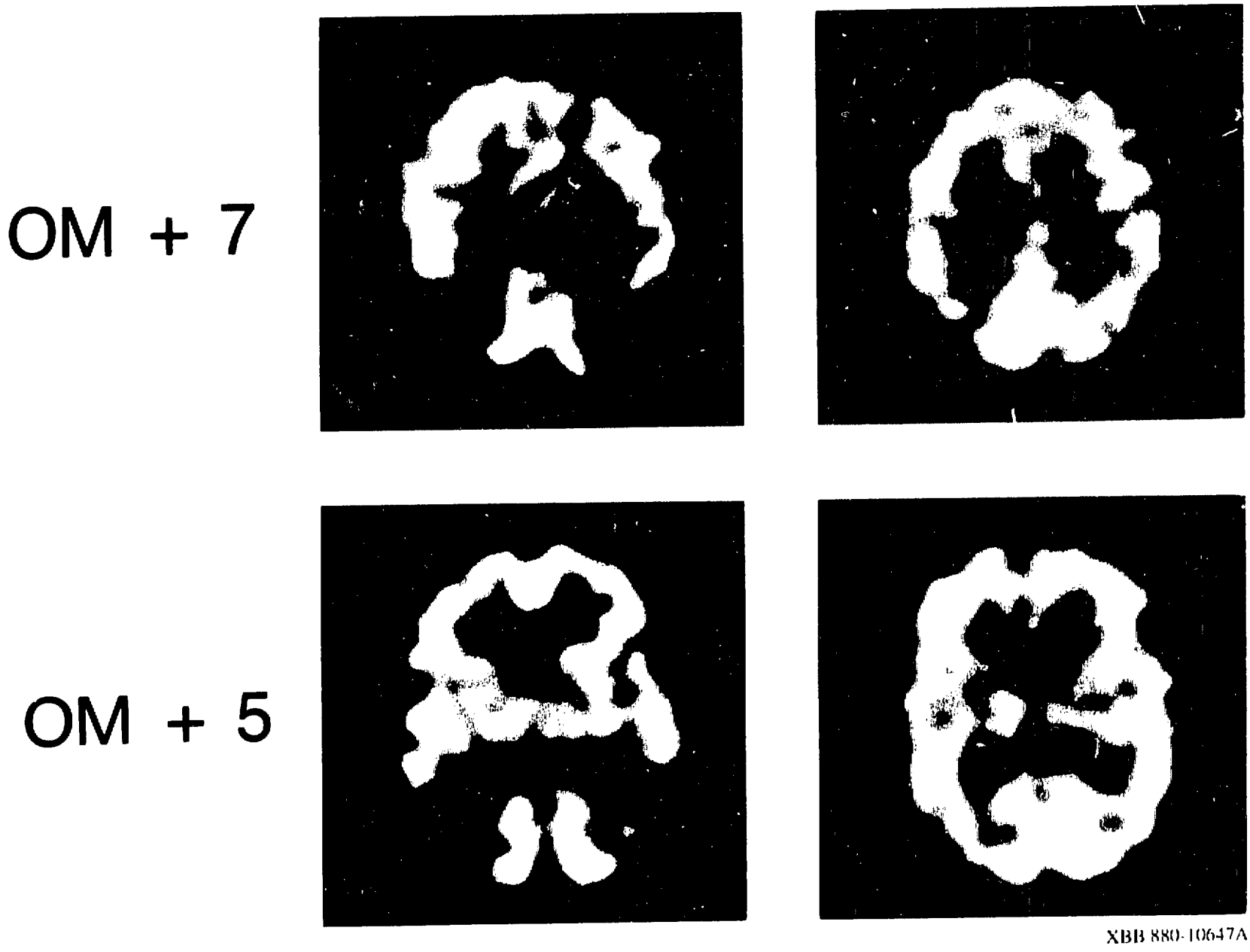

Figure 2