Newsletter

SNM Advancing Molecular Imaging and Therapy

Brain Imaging Council

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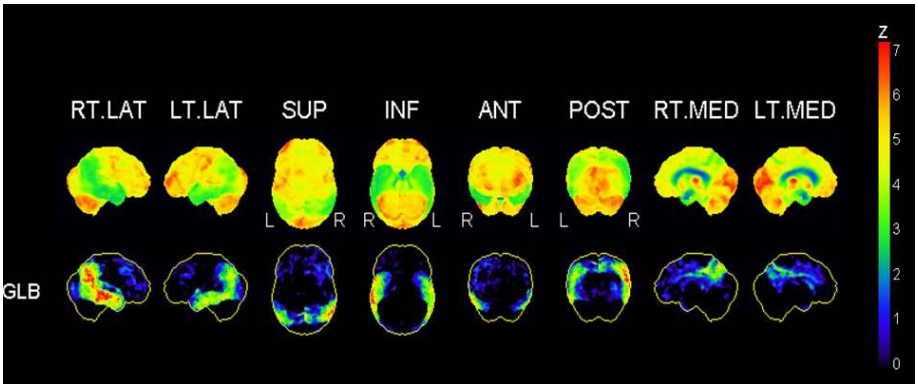


NEUROSTAT 3D-SSP and Its Use in FDG-PET Analysis

The role of FDG brain PET for the diagnosis of Alzheimer's disease (AD) is becoming more widely accepted. In a recent position paper published in *The Lancet Neurology* (2007; 6:734–746), leaders in the field of AD proposed that the research diagnostic criteria—and this will influence clinical diagnostic criteria—should be modified, removing the need for dementia to be present (i.e., marked impairment of functional activities).

Instead, patients with objective memory impairment alone and typical AD type findings on magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis or positron emission tomography (PET) can be diagnosed as AD before the individual is demented. It is therefore becoming increasingly important that the interpretation of fluorodeoxyglucose (FDG) brain studies is reliable, consistent and objective.

In recent years, a number of programs have become available that allow comparison of an individual study to an age-matched, normal database. Some of these are now commercially available or supplied by PET camera vendors. An original program developed by Professor Satoshi Minoshima, a past president of the Brain Imaging Council (BIC), and published in *The Journal of Nuclear Medicine* (1995; 36:1238–1248) is available free-of-charge. This program is called 3D-SSP/NEUROSTAT and was used for the discovery of posterior cingulate hypometabolism in AD and occipital hypometabolism in dementia with Lewy bodies (DLB).

A graphical user interface (iSSP, courtesy of Nihon-Medi Physics) that permits this to run on a PC and produce 3-D surface-extracted images of areas of significant FDG reduction in the form of Z-score maps (the number of standard deviations from the mean of a group of normal subjects) can also be freely downloaded. In conjunction with the effort by the SNM BIC to promote accurate physician diagnosis of FDG-PET scans, my colleagues and I at the Austin Hospital in Melbourne, Australia, have produced a normal database created from 25 healthy elderly persons (mean age of 72 years) with negative PiB PET scans to exclude incipient AD, normal MRI and normal scores on extensive neuropsychology testing.

This database is now available for members of the BIC, and this newsletter contains instructions on how to obtain both the 3D-SSP and Austin normal elderly brain database and install and run them on a PC for research or routine clinical use. We hope these resources will help improve your diagnostic efficacy of brain PET interpretations and promote the field of brain PET imaging.

Once installed on a PC with a DICOM link established to the PET camera work station, transfer of data and processing is quick, easy and requires no manual intervention other than selecting the correct patient file and normal database and then selecting "GO." Processing takes two minutes, and images are ready to print or transfer as TIF files.

In blinded readings of FDG PET at the Austin Hospital, 3D-SSP/NEUROSTAT was found to increase the sensitivity and accuracy of detection of AD of inexperienced readers by 15 percent, allowing them to achieve the same results as an expert brain FDG PET reader. The output is easy to read and can be used to convey results to referring doctors with greater confidence and credibility, resulting in increased clinical referrals.

How to download 3D-SSP / NEUROSTAT

3D-SSP/NEUROSTAT is freely available for download at http://128.95.65.28/~Download/ or http://www.rad.washington.edu/research/our-research/groups/nbl/neurostat-3d-ssp. Versions of NEUROSTAT exist for most operating systems (including Mac OS, Linux and Windows). However, these versions do not include a graphical user interface, and so can be non-trivial to use. The alternative is to use 3D-SSP with a graphical user interface that runs on Windows XP or some older versions of Windows. **This is a much simpler program to use and is what we recommend for routine tasks**. Both software packages can be downloaded from the above Web site.

To run any version of this software, it is necessary to obtain a keycode, which is available for BIC members from Jennifer Mills at SNM at jmills@snm.org. The keycode expires annually, but will be re-issued to active BIC members at no charge upon e-mail request.

To download the Austin Elderly Normal Control Database, please e-mail Gareth Jones at grj@petnm.unimelb.edu.au.

How to install and run 3D-SSP

Once you have downloaded the 3D-SSP zip file (graphical user interface version), uncompress (extract) it into your program files directory. You then need to change properties (File->Properties) of the main folder (iSSP-NMP-us) and all subfolders and filers to read/write/executable. To do this, remove check marks from all attributes and click "apply."

Note that a number of files have default paths (iSSP35.ini, DocExec>cnvttiff.prf, DocExec>stereoSPECT.prf, DocExec>stereoPET.prf) and so will need to be modified if you install 3D-SSP in a location other than c:\Program Files. 3D-SSP reads images in the INTERFILE format. If you need assistance in converting your images to this format, please contact either Gareth Jones grj@petnm.unimelb.edu.au or Tim Saunder at ths@petnm.unimelb.edu.au

For instructions on how to use 3D-SSP, a PDF document is available for download at http://www.petnm.unimelb.edu.au/resources/neurostat.

How to interpret 3D-SSP output

The output consists of two pages with each containing five rows of surface projection images. One page shows increased (INC) uptake in the subject relative to the normal database, and the other shows decreased (DEC) uptake. When looking for reduced metabolism in neurodegenerative disease, the DEC page is the one of interest.

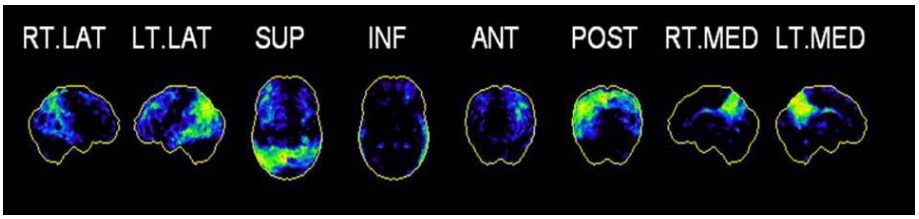
The top row of the page is a surface projection of the brain after conversion to standard space (i.e., warped to a standard size, shape and orientation) showing FDG uptake. The next four rows are surface projections of the difference between the subject and normal brains in the selected database shown by Z-score. Each row shows the result obtained for a specific normalization region (global—whole brain—thalamus, cerebellum, pons). There is no consensus on the best region for brain normalization, and so the program gives you all four. In the examples given below the global normalized Z-score maps are shown.

For those whose statistics are a little rusty, a Z-score is the number of standard deviations away from the mean so that the surface projection images show the areas of cortex with reduced metabolism. Areas showing blue to green or higher on the color scale (Z-score of 1.5 or greater) should be regarded as probably abnormal, but the distribution as well as the severity of hypometabolism (Z-score) must be used for diagnosis. AD is probable when there is hypometabolism in the posterior cingulate and precuneus cortex on the images showing medial cortex plus parietotemporal hypometabolism on the lateral projections.

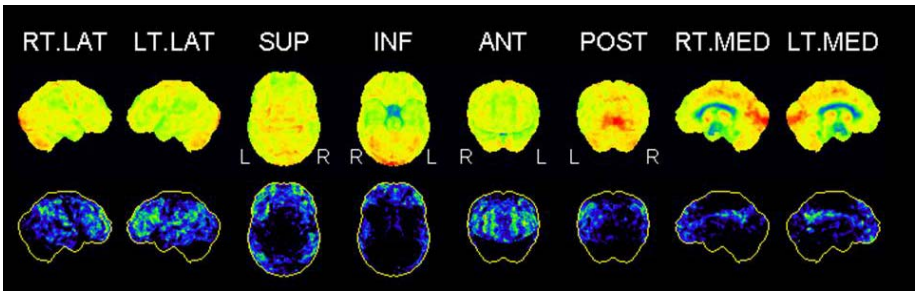
Sparing of the sensory-motor cortex is usually apparent, and there is usually some reduction in the prefrontal cortex. Frontotemporal dementia (FTD) is likely when the degree and extent of hypometabolism is greater in frontal or anterior temporal cortex than in the posterior cortical areas typically affected in AD. This approach was 89 percent accurate for distinguishing FTD from AD in a recently published report where post mortem histopathology was the gold standard. (*Foster NL, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease.* Brain *2007, 130;2616–2635).*

Care needs to be taken, however, not to over-read the effectsof age-related atrophy in the very elderly. This is usually seen in the medial view of the frontal lobe, particularly anterior to the corpus callosum. Lines due to generalized brain atrophy also may be seen along the Sylvian fissures on the lateral images. Patients with dementia with Lewy bodies (DLB) typically show hypometabolism of the occipital cortex (lateral, more than medial).

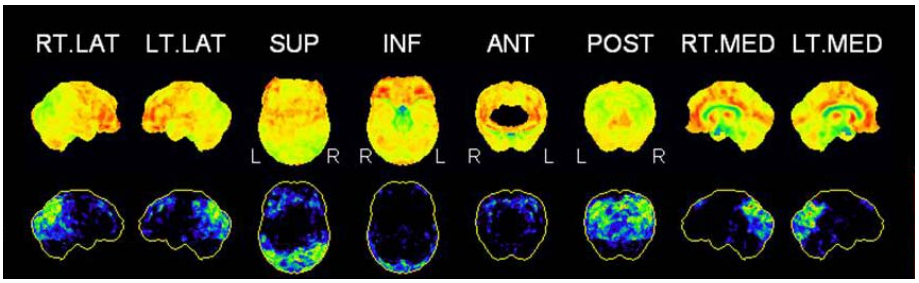
A recent study reported at the 2008 SNM Annual Meeting from the Austin Hospital in Melbourne compared standard visual reporting to reading of the 3D-SSP/NEUROSTAT images while blind to clinical details by four independent readers in 112 subjects, all of whom had extensive neuropsychological assessment, MRI and C-11 PiB amyloid imaging to establish their diagnosis. 3D-SSP/NEUROSTAT substantially improved both the sensitivity and specificity for the less experienced readers. 3D-SSP/NEUROSTAT images were also easier and faster to read than the standard reading of brain slices.



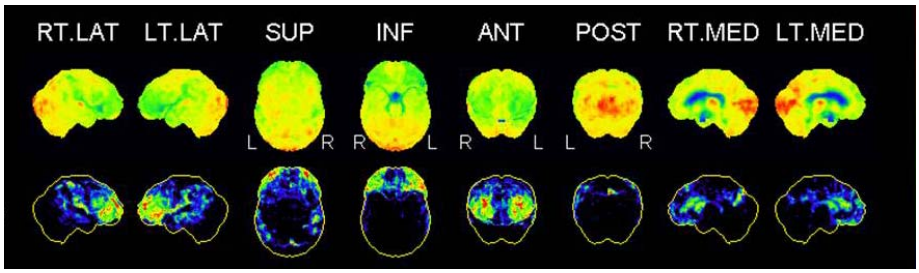
Example 1. Alzheimer's Disease: The lateral views show significant hypometabolism in the parietal and lateral temporal cortex, sparing of the sensori-motor cortex (black) and mild hypometabolism in the prefrontal cortex. The medial views show hypometabolism in the precuneus (posterior medial area of the parietal cortex) and the posterior cingulate gyrus (which lies immediately adjacent to the inferior border of the precuneus but usually cannot be seen as a separate region from the precuneus).



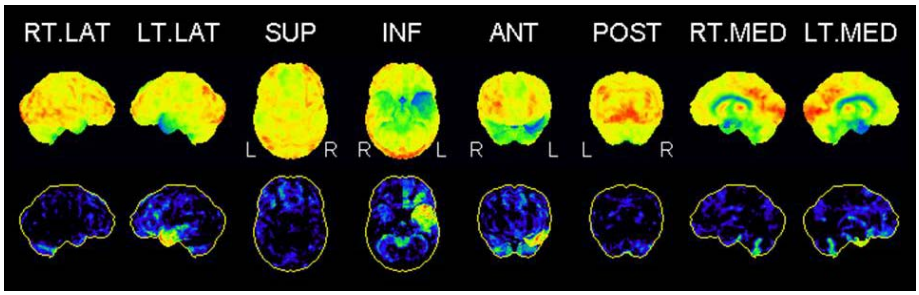
Example 2. Alzheimer's Disease: The top row is the surface rendered FDG image after the brain has been normalized to standard space. The second row shows the areas of reduction compared to the normal database. There is less severe hypometabolism, less precuneus and more frontal involvement than in example 1, but the findings are still consistent with AD. PiB scan for amyloid plaques was positive, confirming AD.



Example 3. Dementia with Lewy Bodies: Hypometabolism is seen in the parietal and lateral temporal regions and the precuneus, similar to AD, but the distinguishing feature of DLB is the involvement of the occipital cortex. A rare variant of AD called posterior cortical atrophy also involves the occipital cortex and should be included in the differential diagnosis.



Example 4. Frontotemporal Dementia (frontal or behavioural variant): There is hypometabolism in the frontal lobes. In other forms of FTD with prominent language disturbance, the hypometabolism is more prominent in the temporal lobes. For example, semantic dementia—a condition where patients lose the meaning of words (i.e., they can say or read a word but cannot tell you its meaning) or lose the meaning of pictures or recognition of faces—the hypometabolism is seen in the anterior temporal lobes and is asymmetric. In progressive nonfluent aphasia, the hypometabolism is seen in the left lateral temporal cortex extending into the parietal cortex. Thirty to 50 percent of these cases are due to AD, the rest to FTD. A good rule of thumb is if it is unilateral, the underlying pathology is FTD; if there is bilateral parietal involvement, AD is more likely.



Example 5. Semantic dementia variant of FTD. ■

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Reimbursement for Brain FDG PET in the United States

Indications for FDG-PET imaging of the brain have expanded to include imaging of dementia, refractory seizures and brain tumors. Dementia imaging constitutes by far the largest number of potential patients; however, coverage by the Centers for Medicare and Medicaid Services (CMS) of FDG-PET for dementia has been severely limited. At this time, CMS requires the following recently approved criteria for reimbursement.

Medicare Coverage of FDG-PET for Alzheimer's Disease

- Minimum of six months of documented cognitive decline from unclear origin;
- Recently established diagnosis of dementia that meets the diagnostic criteria for both Alzheimer's disease (AD) and frontotemporal dementia (FTD);
- Previous evaluation for other neurodegenerative disease or causative factors;
- Comprehensive clinical evaluation by a physician experienced in the diagnosis and assessment of dementia;
- Scan performed in an accredited PET facility, and the reading of the scan done by an expert with substantial experience in interpreting such scans in the presence of dementia; and
- A SPECT scan or previous FDG-PET scan has not been obtained for the same indication.

FDG-PET is also approved for participants in select clinical trials. For more information on the indication criteria, please visit http://www.cms.hhs.gov/ and search for "00088R."

FDG-PET is not currently approved for patients with mild cognitive impairment, and yet this area is perhaps the most valuable in determining which patients have a high likelihood for progression to dementia. If a typical Alzheimer's pattern is detected (biparietal, posterior temporal and posterior cingulate reductions), there is a very high likelihood that the patient will convert to AD within a few years.

Insurance carriers other than CMS also have been paying for these examinations on a case-by-case basis. It is important for the institution performing the studies to consult with the referring physicians and obtain information that could ultimately

lead to reimbursement. In order to do this effectively, it is suggested that a form be developed that is easily filled out by the physicians or designates of the physician ordering the study (*see sample form below).*

Refractory Seizures

FDG-PET scans have been shown to be highly sensitive and specific in the evaluation of patients with suspected temporal lobe epilepsy. The examination is performed in the inter-ictal period. Temporal lobe reductions can be seen in the affected temporal lobe. This test becomes extremely important in determining which patients should undergo surgical removal of the epileptic focus. It is not uncommon to see correlation with an MRI demonstrating mesial temporal sclerosis, although the PET scan appears to be significantly more sensitive than MRI in detecting the epileptogenic focus.

Brain Tumors

It has been demonstrated in numerous peer-reviewed articles that FDG-PET is useful in tumor-grading and determining whether an MRI abnormality is due to tumor recurrence or tumor necrosis. At this time, CMS has chosen not to reimburse for this procedure unless the patient is entered into the National Oncology PET Registry (NOPR) database. Effective reimbursement for FDG-PET functional brain imaging can be accomplished if CMS guidelines for reimbursement are correctly followed. Reimbursement through individual insurance carriers can be negotiated at the local level. Currently, there is an effective reimbursement program in place for AD and FTD as well as refractory seizures, especially of the temporal lobe origin. ■

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BRAIN PET REFERRAL FORM

Patient Name: _____ Date of Birth: _____

Is Patient Diabetic? ☐ Yes ☐ No

Is Patient Covered by Medicare? ☐ Yes ☐ No Reservation Number: _____

Clinical Indication: (Check one)

☐ **Alzheimer's and Fronto-temporal Dementia:** Brain

☐ **Refractory seizures**

☐ **Other:** _____

_____

Mini mental status exam (MMSE) or similar testing: Score: _____ Date: _____

Summary of reports from neuropsychological testing performed: _____

_____

Structural imaging: ☐ MRI ☐ CT Date: _____ Where performed: _____

Names of neurological medications : _____

Previous SPECT or FDG-PET scan for same indication: ☐ Yes ☐ No If Yes, Date: _____

SYMPTOMS: _____

_____

Date of onset: _____

REFERRING PHYSICIAN NAME: _____
PLEASE PRINT

PHONE: _____ FAX: _____

REFERRING PHYSICIAN SIGNATURE: _____ DATE: _____