

# Semiquantitative analysis of FDG PET brain scans using Neurostat and SPM

by

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## Abbreviations

CAD4D	computer-aided diagnosis for dementia
CLI	command line interface
CNS	central nervous system
CT	computed tomography
DICOM	digital imaging and communications in medicine
FDG	fluorine-18 2-fluoro-2-deoxy-D-glucose
GUI	graphical user interface
MRI	magnetic resonance imaging
NS	Neurostat
NIfTI	neuroimaging informatics technology initiative
PET	positron emission tomography
RAMLA	row action maximum likelihood algorithm
SPECT	single photon emission computed tomography
SPM	Statistical Parametric Mapping

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**Publication ready manuscript**

The following manuscript has been prepared for submission to a journal.

## Semiquantitative analysis of FDG PET brain scans using Neurostat and SPM

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## Abstract

### Background:

Positron emission tomography using Fluorine-18 2-Fluoro-2-Deoxy-D-Glucose (FDG-PET) has an established role in the investigation of multiple neurological conditions such as neurodegeneration and epilepsy. FDG PET brain scans are interpreted visually and semi-quantitatively using tools such as Neurostat or SPM. The normal databases used in Neurostat were created over 20 years ago, however since this time there has been a steady advance in camera technology and reconstruction algorithms for semiquantitative analysis. It is possible that results obtained with semiquantitative analysis using Neurostat (old PET databases) are different from results obtained with semiquantitative analysis using SPM (using a new PET database). The aim of this study was to evaluate whether there are differences in study interpretation when the same scans are read in combination with a Neurostat analysis, compared to when they are read in combination with an SPM analysis using a database built with new scan data.

### Methods:

First, a local normal database was built with healthy control data using MATLAB R2014b and SPM12. These scans were obtained from previous research projects and prospectively enrolled participants. All scans were acquired on a Philips Gemini-TF Big bore PET/CT scanner. Second, a test dataset, comprising a mixture of clinical scans and scans of prospectively enrolled participants (other than those included in the normal database), was used to compare interpretation of results when using the SPM-based normal database (SPM) to interpretation results when using Neurostat (NS).

### Results:

A database of normal FDG Brain PET/CT studies for the 19-35 year age group was created from a total of 26 healthy controls (13 men and 13 women – optimally matched for age and gender). The test dataset was comprised of 20 scans in the same age range: 15 clinical cases and 5 controls. Next, two expert readers read scans in the test dataset with the assistance of both the NS outputs and the SPM outputs, in separate reading sessions. There was no statistically significant difference in whether a scan was called normal or abnormal using either Neurostat or SPM. There was also no significant difference when comparing the number of lesions identified. SPM scored lesions as less severe than Neurostat ( $p=0.006$ ).

### Conclusion:

SPM-based analysis using a locally-developed normal database (with scans acquired on a modern PET-CT scanner) yielded similar results to Neurostat, justifying its continued use. Further evaluation to determine if these results are applicable to older patients with neurodegenerative conditions such as Alzheimer's disease is planned.

## Introduction

Positron emission tomography using fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG-PET) has an established role in the investigation of multiple neurological conditions including dementias, movement disorders, neurolupus, and epilepsy <sup>1</sup>.

FDG PET brain scans are generally interpreted in two ways: *visually* (to detect characteristic disease-related metabolic changes) and using *semi-quantitative* tools that compare individual scans to a normal database<sup>2</sup>. Such semi-quantitative techniques (especially when used in combination with visual reading) have been shown to improve accuracy<sup>3,4</sup>. Minoshima and colleagues<sup>5</sup>, have previously designed a PET stereotactic atlas (Neurostat 3D SSP) for the semi-quantitative analysis of functional brain images. This program includes several normal databases (based on FDG scans of numerous healthy subjects) and has been used extensively by clinicians and investigators worldwide. The normal databases used in Neurostat were created over 20 years ago, however since this time there has been a steady advance in camera technology and reconstruction algorithms, leading to substantial improvements in the resolution of PET images. This raises the question of whether scans acquired on modern scanners can still be compared to databases based on scans acquired on scanners from earlier years. There is a possibility that differences in quality between the scans being compared to the databases and the databases themselves may result in artefactual results when performing semi-quantitation.

Our department currently relies on the Neurostat program to supplement visual interpretation of FDG PET brain scans. It is also possible, using a MATLAB (MathWorks) based package, Statistical Parametric Mapping (SPM12, Wellcome Centre for Human Neuroimaging, University College London - <http://www.fil.ion.ucl.ac.uk/spm/>), to create a new database based on scans acquired on a modern scanner, and to statistically analyse individual scans against this database.

We hypothesized that semiquantitative analysis using SPM with a new database also created in that program, would not result in any difference in scan interpretation when compared to analysis in Neurostat using that program's dated, native databases.

The aim of this study was to evaluate whether there are differences in overall study interpretation when the same scans are read in combination with a Neurostat analysis (old PET databases), compared to when they are read in combination with an SPM analysis using a new database built with local scan data.

## Methodology

The study was approved by the health research ethics committee of Stellenbosch University (SU), Ethics Reference number S13/01/011.

First, a local normal database was created using healthy control data. Second, a test dataset, comprising a mixture of clinical scans and scans of healthy research subjects (other than those included in the normal database) was used to compare interpretations based on semi-quantification with SPM and interpretations based on semi-quantification with Neurostat (NS).

### Participant selection

There were 2 sets of participants: participants whose scans were used to create the new normal database, and participants whose scans were used for the test dataset.

#### *Participants for normal database*

Participants for the new normal database were drawn from healthy control subjects enrolled in previously performed research projects<sup>6-8</sup>. Participants for the local normal database were also drawn from patients referred for an FDG PET/CT study at Tygerberg Hospital for a non-neurologic indication (e.g. limited-stage lymphoma). These patients, who were prospectively recruited after providing informed consent, had a low probability of neurologic pathology. Participants for inclusion in the new normal database were age- and gender-matched to closely correspond to one of the existing databases in NS. Criteria for scans to be included in the local database were as follows: age over 18 years; no neurological or psychiatric disease; no major medical conditions such as diabetes mellitus or HIV infection; no history of serious head injury (defined by any loss of consciousness associated with the trauma); no malignancy with high risk of brain metastases such as melanoma; no chemotherapy in the last 3 months; and no use of psychotropic medications. For prospectively recruited participants, screening was performed by asking the patients a series of questions in the form of a questionnaire and by performing a neurological examination (Appendix 1) to assess their suitability for inclusion in the normal database.

#### *Participants for test dataset*

Participants whose scans were used for the test dataset were selected 1) from clinical referrals to the Division of Nuclear Medicine for FDG PET brain studies; and 2) from cases initially recruited for the local normal database but who were later excluded for non-optimal age- and gender matching (negative control cases).

### PET/CT image acquisition

Participant preparation for all scans was according to the EANM procedure guidelines for PET brain imaging using FDG.<sup>1</sup> This involves fasting for at least 4 hours before injection of FDG as well as avoiding caffeine, alcohol, or recreational drugs that may affect cerebral glucose metabolism, and drinking plenty of water. Patients were instructed to not speak, read or be otherwise active 5 minutes before to 20 minutes after FDG administration. The patients reclined in a quiet, dimly lit cubicle 5 minutes before to 20 minutes after FDG administration. All participants had eyes open during the uptake period. Participants were requested to void prior to starting imaging at 28 minutes after FDG injection, to avoid discomfort during image acquisition.

All scans used for the normal database and test dataset were scanned on a Philips® Gemini TF Big Bore PET/CT scanner (Philips, Eindhoven, The Netherlands). Image acquisition involved

the acquisition of a low-dose CT scan for attenuation correction (tube current 20 mAs, voltage of 120 kV) followed by acquisition of PET data for a single bed position in list mode for 30 minutes. All scans were reconstructed using an iterative reconstruction algorithm, row action maximum likelihood algorithm (RAMLA).

### **Pre-processing**

Scans utilised from previous research studies were checked for quality as described.<sup>6-8</sup> For prospectively acquired data, FDG PET scans were excluded if they exhibited excessive participant motion; when there were attenuation or scatter artefacts (see scatter correction artefact in Appendix 2); when there was misalignment with the CT; or had missing data. The following motion thresholds were used to exclude prospectively acquired scans: not more than 5 mm overall translation in any direction, or >3 degrees overall rotation in any direction) Where necessary, a minimum of 2 serial frames for any given scan were selected and the remaining frames discarded. Frames for included scans were then summed. All scans exceeded a minimum of 10 million counts as recommended.<sup>1</sup>

To create the normal database and to generate z-maps in SPM, summed PET frames in DICOM format were first converted to NifTI format using MRIcroGL (<https://www.mccauslandcenter.sc.edu/mricrogl/home>) and then pre-processed using MATLAB R2014b (MathWorks) and Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, UCL, London; <http://www.fil.ion.ucl.ac.uk/spm/>). Pre-processing of these scans involved re-alignment, warping, normalisation and smoothing as performed by Doruyter et al.<sup>6</sup>

Single-frame versions of the multi-frame DICOM files, which were used for Neurostat analyses were generated using the *edit header* option in Hermes Browser (Hermes Medical Solutions).

### **Creation of the new SPM database**

A new normal database was created using custom scripts in MATLAB and SPM and the scans of healthy controls. First, the first (Q1) and third (Q3) quartiles and the interquartile range (IQR) were calculated for each voxel location. Outlier voxels were defined as values below  $Q1 - 1.5(Q1)$  or exceeding  $Q3 + 1.5(Q3)$  and once identified, were excluded. Mean and standard deviation images (in which each voxel represented the mean or standard deviation value for that voxel location) were then calculated.

### **Generating z-maps in SPM**

Pre-processed scans in the test dataset were compared to the new normal database using a customised SPM script. After masking zero-value voxels in the respective subject scan, a z-score was calculated for every voxel location using the formula:

$$z = (x - \mu) / \sigma$$

where  $x$  refers to the value of the voxel in the test scan,  $\mu$  refers to the value of the same voxel in the mean image, and  $\sigma$  refers to the value of the same voxel in the standard deviation image. Voxels with zero values were excluded to avoid undefined results. The final result was saved as a three-dimensional, subject-specific z-map image, an example of which is given in Figure 1.

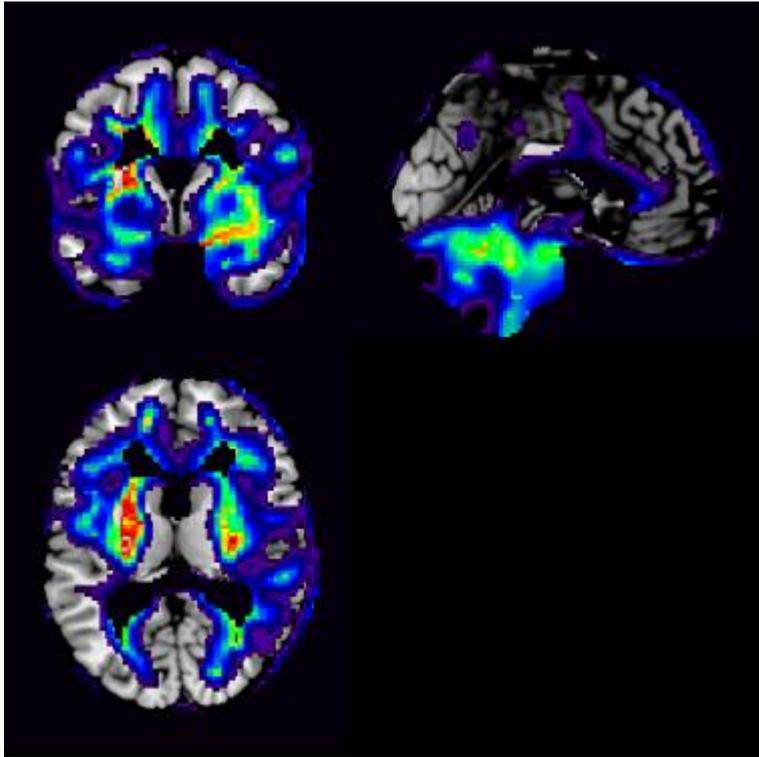


Figure 1. An example of an SPM z-map image overlaid on an MRI template.

### Generating z-maps in Neurostat

The Neurostat program pre-processes brain FDG PET scans by first identifying the mid-sagittal plane. The scan then undergoes linear scaling followed by non-linear warping. This results in spatial normalization with voxels that are then compared to a database. The final results are saved as two-dimensional (subject-specific) stereotactic surface projections (negative and positive z-map images), an example of which is given in Figure 2.

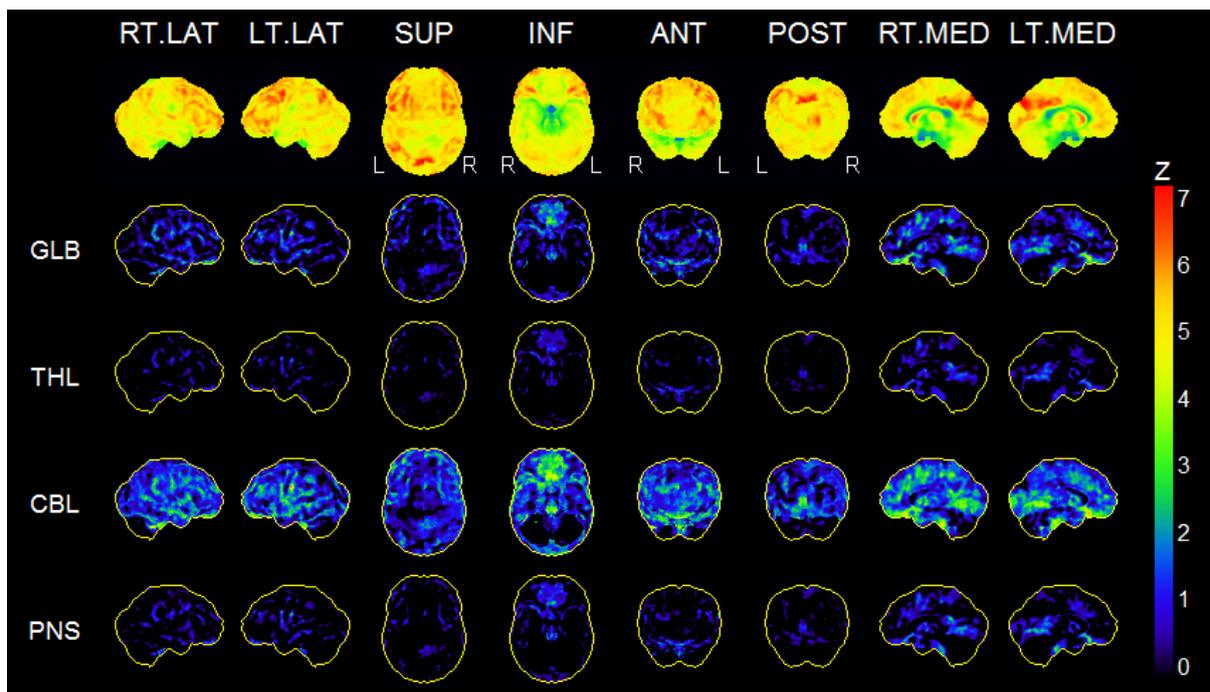


Figure 2. An example of a Neurostat stereotactic surface projection (SSP).

## Reading of test dataset scans

Each scan in the test dataset was interpreted twice, once by combining visual reading with the Neurostat z-maps, and on a separate occasion by combining visual reading and the SPM z-maps.

A process of anonymisation and randomisation was devised to minimise the risk of interpreters remembering their first interpretation when performing the second interpretation. First, two anonymised versions (each with a different unique identifier) of each test case DICOM image were created and allocated unrelated, random N- (to be interpreted together with a Neurostat analysis) and S- (to be interpreted together with a SPM result) numbers. Scans were read in 4 separate reading sessions. S- and N-versions of the same scan were always read in different sessions, a minimum of 4 weeks apart. The intersession scan read order (NS-SPM vs SPM-NS) was varied such that half of the test cases (randomly selected) were read in NS-SPM order, while the remainder were read in SPM-NS order. The intrasession read-order was also randomly varied. Anonymization and randomization were performed by the first author. The process is illustrated in Figure 3.

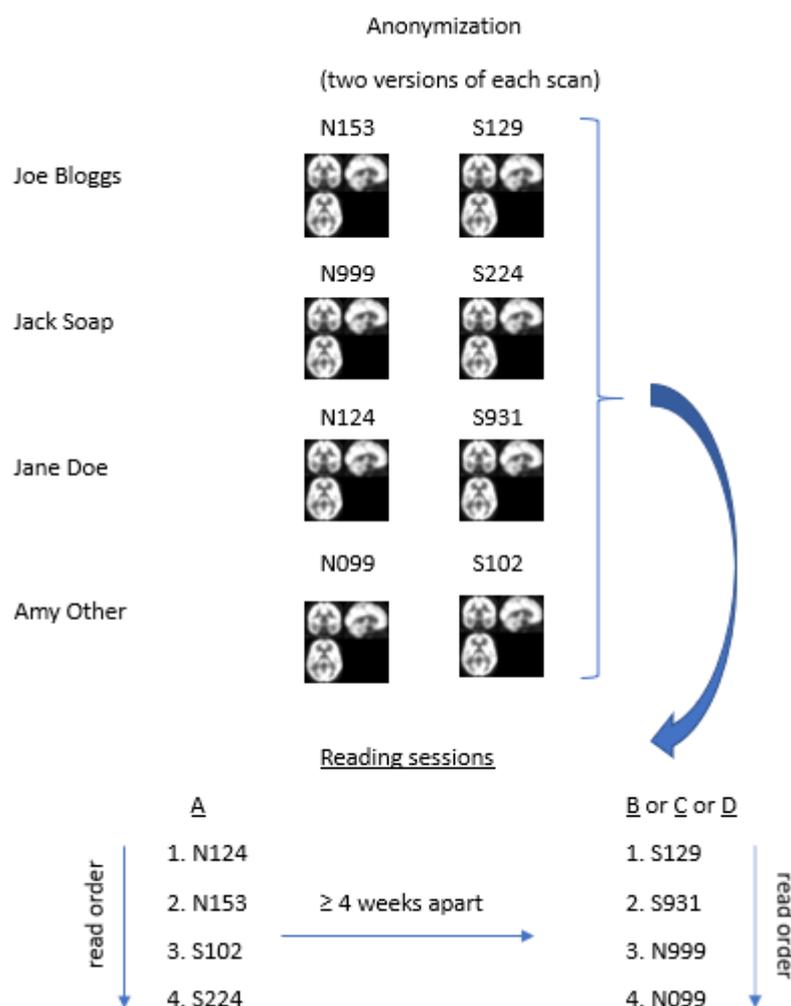


Figure 3. Anonymization and reading of test data scans.

Scans were read visually in Hermes Gold Default Viewer. Neurostat-generated z-maps were viewed in Microsoft Photos (Windows 10 64-bit, Microsoft), while SPM-generated z-maps were viewed in MRICron,<sup>9</sup> a cross-platform NIfTI format image viewer, overlaid on the *ch2bet* MRI template using the NIH colour lookup table at a default scaling of  $\pm 7$ , adjusted manually as needed.

Blinded study interpretation using a standardised datasheet (Appendix 3) was performed by consensus by two experienced Nuclear Medicine physicians with access only to the anonymized PET images and the respective Neurostat and SPM z-maps. For each scan interpretation, readers graded the uptake in 16 regions (left and right frontal, temporal, parietal and occipital lobes; left and right cerebellar lobes and vermis; left and right striatum; left and right thalamus; and pons) as either normal (0), increased (1+ to 3+), or decreased (1- to 3-). In addition, readers recorded any other relevant findings; a one-line conclusion/ diagnosis; and whether they recalled a prior interpretation of the same case (to test for recall bias).

An example of a test case, together with the respective Neurostat and SPM z-maps is given in Figure 4.

### **Statistical analysis**

After data collection, results were unblinded and statistical testing was performed using IBM SPSS Statistics v26. Results were considered statistically significant at a threshold of  $p < 0.05$ .

Age-matching (males vs females) of participants whose scans were used to create the normal database was evaluated using a student t-test.

Analyses were performed to determine whether there was any significant difference between interpretation using Neurostat and interpretation using SPM (with the new database): McNemar's tests were used to detect differences in number of scans reported as normal, and to test for differences in the distribution of abnormalities on both a subject and on a lesion level. Wilcoxon signed ranks tests for paired data were performed to test for differences in the number of lesions identified, as well as the reported severity of lesions identified.

To determine whether interpretation at any reading was influenced by recall of a previous interpretation for the same case, a chi-squared test was performed in which the recall results for the NS-SPM read order subset were compared to those of the SPM-NS subset.

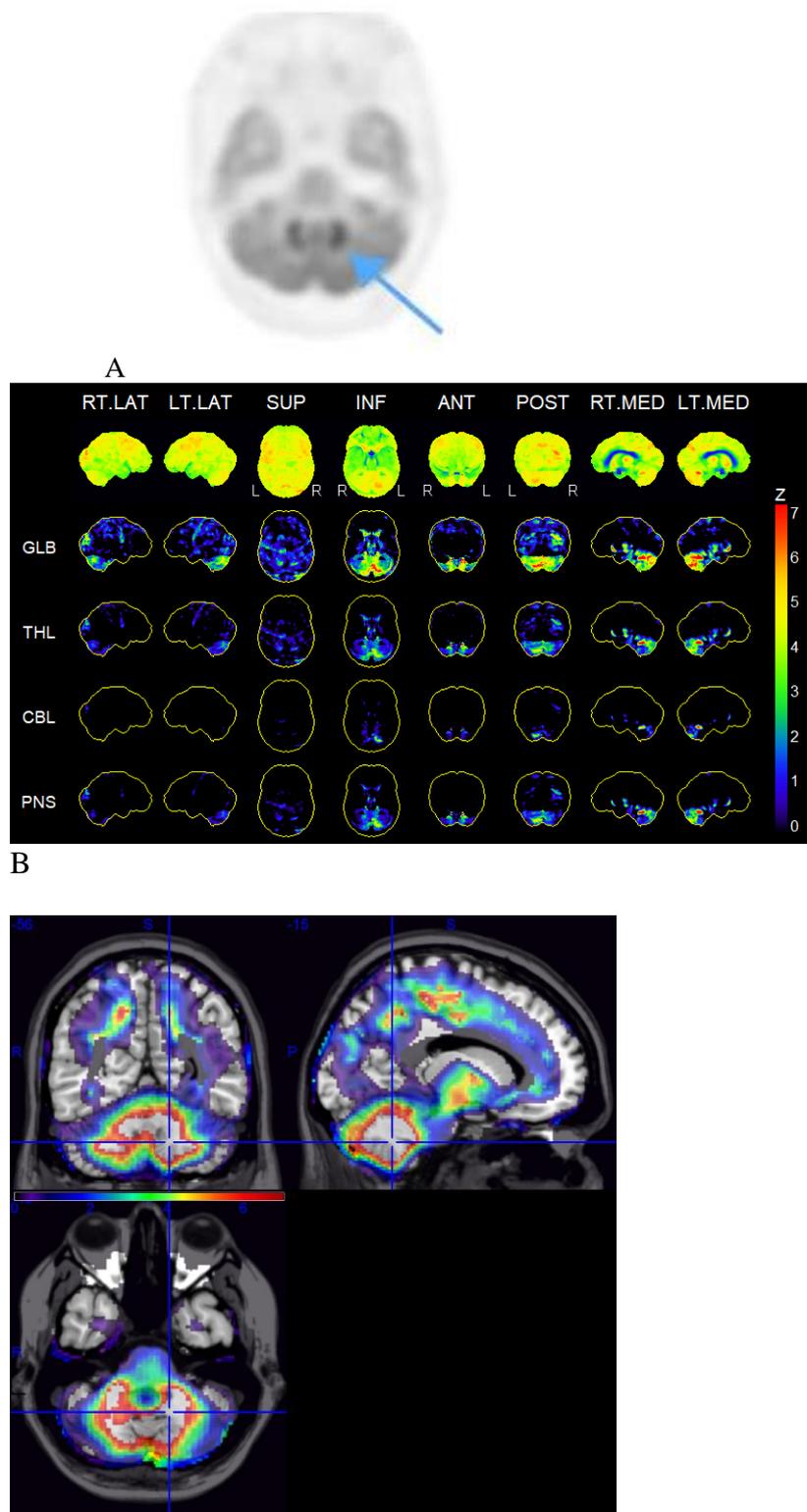


Figure 4. One of the scans from the test dataset. A - Transverse slice of the FDG PET study; B - Neurostat 3D SSP z-map; and C - SPM z-map. The images show increased metabolism in both cerebellar hemispheres, and in the striatum (also bilateral). Abnormalities in metabolism in these regions were scored as 3+ in this case.

## Results

### *Normal database:*

Sixty-five scans eligible for inclusion in the new normal database were identified, of which 24 were from participants who were recruited prospectively. Due to limited scan data, it was decided to limit both the new normal database and the test dataset to cases in the 19 to 35-year-old age range – to match that of one of the existing Neurostat databases. Thirty-eight of the eligible scans fell into this age bracket, of which 4 were excluded due to medical conditions with high-risk for CNS involvement (HIV infection in 2; dermatomyositis in 1; malignancy involving the right orbit in 1); 1 was excluded due to unknown neurological history; and 2 were excluded due to missing raw imaging data. Of the remaining scans, 26 were selected in a manner to optimise age and gender-matching. There were 13 men with a median age of 27.0 years (Range: 19.5 – 34.0 years) and 13 women with a median age 25.3 years (Range: 21.2 – 33.4 years) The difference in age distribution of males and females was not statistically significant ( $p=0.88$ ).

### *Scan interpretation using the two methods:*

The test dataset was comprised of 20 scans: 15 of which were clinical studies, and 5 of which were control cases initially recruited for the local normal database but later excluded due to suboptimal age or gender matching. The demographic and clinical details of these studies are summarised in Table 1.

In terms of classifying a scan as normal or abnormal, interpretations using Neurostat and using SPM were discordant in 2 cases: 1 scan was interpreted as normal with Neurostat and abnormal with SPM, while another scan was interpreted as normal with SPM but abnormal with Neurostat. This was not statistically significant ( $p=1.00$ ). Concordant cases included 7 normal interpretations and 11 abnormal interpretations. The 2 discordant cases were both controls. The scan of an oncology control (N757/S501) was normal on analysis with SPM but abnormal on analysis with Neurostat while the opposite occurred with the scan of a healthy control (N473/S238) which was normal on analysis with Neurostat but abnormal on analysis with SPM.

There was also no statistically significant difference when comparing the distribution of lesions identified on a subject level ( $p=0.289$ , discordance in distribution in 8 participant scans) or on a lesion level ( $p=0.185$ , 28 discordant regions).

Interpretations relying on Neurostat identified 42 lesions, while those relying on SPM identified 34, the difference not being significant ( $p=0.287$ ).

Scans interpreted with SPM tended to score lesions as less severe compared to when the same scans were interpreted using Neurostat ( $p=0.006$ ). Differences in severity scoring are illustrated in Figure 5.

There was no statistically significant difference in the rate of recall bias between the two read orders ( $p=1.0$ ). In one case, during the reading session using SPM, the readers recalled their interpretation of the same scan using Neurostat. For another participant, the readers remembered the clinical case (interpreted months previously) during both the SPM and the Neurostat reading session.

Table 1. Demographic and clinical details of patients in test dataset

Case number	Gender	Age	Scan indication
N571 / S768	F	27.7	Suspected neurolupus
N510 / S510	F	30.0	Suspected neurolupus
N464 / S921	F	18.7	Suspected neurolupus
N451 / S251	F	30.6	Suspected neurolupus
N172 / S353	F	33.9	Suspected neurolupus
N146 / S462	F	34.0	Suspected neurolupus
N926 / S311	F	21.6	Suspected neurolupus
N207 / S610	F	18.0	Suspected neurolupus
N234 / S890	F	25.0	Suspected neurolupus
N525 / S765	M	23.6	Investigation of dysphasia
N189 / S189	F	31.0	Investigation of right hemiplegia
N152 / S908	M	30.2	Suspected paraneoplastic syndrome
N839 / S138	M	26.4	Localisation of epileptogenic focus
N933 / S129	M	30.8	Right-sided tremors
N137 / S173	F	24.0	Investigation of mood disorder
N757 / S501	F	24.0	Oncology control (no CNS pathology)
N473 / S238	F	30.4	Healthy control
N368 / S187	M	21.0	Healthy control
N236 / S736	F	24.2	Healthy control
N494 / S922	F	28.1	Oncology control (no CNS pathology)

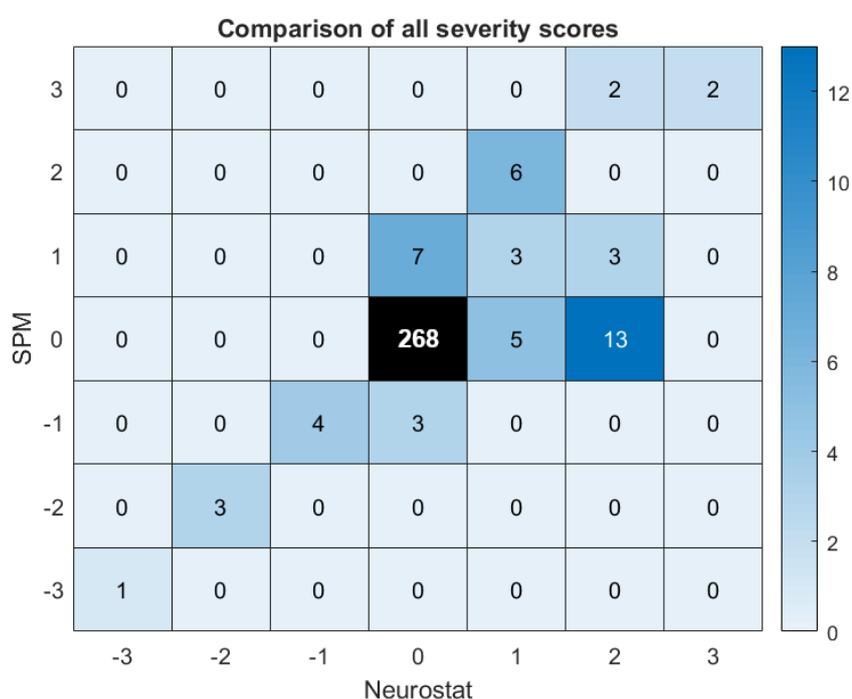


Fig 5. Heatmap illustrating totals of all region severity score combinations. Matrix elements are coloured according to their totals (cases in which regions scored as 0 by both techniques excluded from colour scaling).

## Discussion

In this study, a new SPM database of normal FDG PET brain scans was created using scans of age and gender-matched healthy controls. Interpretations relying on this new tool were then compared to interpretations based on an existing tool (Neurostat) using a test dataset of 20 scans. The study found no significant difference between the two semi-quantitative tools in terms of classifying a scan as abnormal; defining the distribution of abnormal regions on either a subject- or lesion level; or in terms of the number of lesions detected. The study did however identify a tendency for the new SPM-based tool to classify lesions as less severe than the Neurostat tool.

The two discordant cases were both controls and were expected to be identified as normal using analysis with both SPM and Neurostat. However, the methodology of the study differed from a clinical scenario in that FDG PET brain scans are usually interpreted with a clinical history, which was not done in this study to reduce the likelihood of recall bias. The history would have likely resulted in the scans not being done. This emphasizes the importance of a clinical history in approving clinical requests for FDG PET brain scans and in their interpretation.

Previous studies have compared the analysis of brain scans using Neurostat and other software packages. One study<sup>10</sup> evaluated FDG PET brain scans of 20 patients with confirmed Alzheimer's disease and 10 non-Alzheimer's patients using normal databases constructed with three tools: computer-aided diagnosis for dementia (CAD4D), SPM and Neurostat. Their study showed similar patterns of FDG uptake with the three different software packages and reported a tendency for CAD4D and Neurostat to generate larger z-scores than those obtained with SPM which is similar to our findings. A second study<sup>11</sup> compared analysis of brain perfusion SPECT and MRI gray matter images of 61 patients with very early AD and 82 age-matched healthy volunteers using Neurostat, SPM99 and SPM2 with original and common templates and reported similar results from all three packages. Both previous studies focused on Alzheimer's disease in older participants, and comparison of the semiquantitative outputs of Neurostat to other software packages in younger patients has not been performed until now. Such work is important, in that it validates the use of databases created using dated imaging systems, in the modern context, with more advanced technology.

The database in Neurostat for the 19-35 years age group was compiled from 20 scans of participants with a mean age of 26.5 years. This is similar to the participant scans used to create the database in this study, in which the mean age of the participants was 29.4 years.

The similarities in results obtained using the two software packages offer reassurance that the method in use is unlikely to be significantly affected by the advances in camera technology and supports the continued use of the Neurostat tool. The study has also provided a degree of validation for a different method (based on SPM) in our setting should it become necessary to stop using Neurostat.

The only statistically significant difference between interpretations using Neurostat and our own SPM-based tool were in the scoring of lesion severity. The potential clinical implications of this discrepancy are uncertain without the benefit of a gold standard but given that scan indications in our test cohort were more diagnosis-driven than prognosis-driven, our feeling is that this would have made little difference in terms of clinical management. Consequently, the study results do not provide compelling evidence to justify changing from Neurostat to SPM as this will require time to teach the consultants and registrars a new method and to acquire experience with it.

A strength of this study was that scans were anonymised and read in a random order with an interval between readings to avoid recall bias. The clinical history and other relevant information of the test dataset were also not provided to the readers. This reduced the risk of recall bias. The test dataset included all the available scans at our institution in the 19 – 35 year age group and covered a period of 3 years. This is a strength because the results are applicable to our setting.

A limitation of the study is that it involved the comparison of two different z-map formats, generated by different programs. Both programs have been used for semi-quantitative analysis of brain FDG PET scans however SPM generates volumetric (three-dimensional) statistical maps, as opposed to the graphical user interface (GUI) version of Neurostat which generates (two-dimensional) stereotactic surface projections. Another limitation was the difference in reader familiarity with the Neurostat interface (familiar) and the interface used to read the SPM-generated z-maps (unfamiliar).

The Neurostat database was based on scans acquired on an older-generation Siemens PET-CT scanner (model unknown), while those in our database were acquired on a modern Philips Gemini scanner, with better performance characteristics. This is also relevant to the techniques used to reconstruct the scans used in these databases (filtered back-projection, and the more sophisticated RAMLA technique respectively). This might have resulted in a confound (e.g. due to differences in gray-white matter contrast) when comparing outputs derived from the two databases.

The test dataset consisted of 20 scans. A greater number of scans would have made the results more robust. This limitation can be overcome in future research by collaboration with other facilities nationally and internationally.

Future research in our division will focus on additional FDG databases for other age groups using the data acquired from the 29 volunteers who were more than 35 years old. Future research will also involve compiling databases for other tracers and exploration of the command-line interface (CLI) version of Neurostat, which may enable the generation of volumetric statistical maps, as opposed to the statistical surface projections generated by the graphical user interface (GUI) version.

## **Conclusion**

The results obtained with semiquantitative analysis of FDG PET brain scans of patients aged 19 – 35 years using Neurostat are similar to results obtained with semiquantitative analysis using SPM (with a new normal FDG PET database). These findings effectively validate the continued local use of Neurostat software in this age-group and offer a potential alternative.

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**Appendix 1: Screening questionnaire****Receptionist** (day of booking)

Tygerberg and Stellenbosch University are conducting a study on the different methods of reconstructing PET brain scans. As part of this study, we would like to perform an additional brain PET/CT in 40 patients referred for an ordinary PET study. Tumelo Moalosi is the principal investigator.

At the time of booking ordinary PET scans, please book as usual but in addition please check that ALL 5 of these are true:

**1. Table:**

	ü	û
Patient is currently on the hospital premises?		
Patient is 18 years old or more		
Patient does not have diabetes		
No chemotherapy in the last 3 months		
Referring doctor not aware of any brain lesions or neurological disease and has no reason to suspect a brain scan would be abnormal		

2. **Language:** Please check whether the patient can speak ENGLISH or AFRIKAANS or XHOSA

**If the patient meets all criteria (ü) in the Table and can speak one of the languages above, please ask the referring doctor if the patient can come to the PET centre to discuss the preparation for their scan.**

Please **inform the registrar** at PET that a candidate for Tumelo's Brain Recon Study is on their way for clinician screening. And let them know whether patient can speak **English or Afrikaans or Xhosa**.

**NAME:**

**FOLDER #:**

**Provisional booking date for Clinical PET scan:**

**NM PET registrar (day of booking)**

Tygerberg and Stellenbosch University are conducting a study on the different methods of reconstructing PET brain scans. As part of this study we would like to perform an additional brain PET/CT in 40 patients referred for an ordinary PET study. Lionel Munemo & Tumelo Moalosi are the principal co-investigators. The PET secretary will perform an initial rudimentary screen and then ask the patient to come to the PET centre for further registrar screening and informed consent.

**Before the candidate arrives (registrar):**

1. The PET secretary will inform you that a candidate for Tumelo’s Brain Recon study is on the way. Establish whether the candidate is fluent in a language which you speak. If not, either get hold of another NM registrar fluent in that language to perform the informed consent or get hold of an interpreter to assist you:
  - a. Afrikaans: ask one of the radiographers or radiography students
  - b. Xhosa: ask Tumelo (cell phone number: 076 883 2032)
2. Check the ECM and iSite for any clinical or imaging info that would exclude them from the study.
3. As soon as you have the referral form – check for any other factors that might exclude them from the study in which case no further screening is necessary

**Once the patient arrives (radiographer/ receptionist) prepares patient as usual, including:**

1. In women of childbearing potential – **exclude pregnancy** as per departmental protocol. If pregnant they are excluded from the study and the PET.
2. Explain why their doctor has referred them for their clinical PET scan and what the scan entails. Explain that after injection there is a waiting period of 1 hour before the scan is done. Answer any questions they might have about the scan. Explain the preparation they need to follow for their scan.
3. Explain that if their blood sugar is high on the day of the study, we may not be able to do the scan.

**After patient preparation complete:**

Radiographer/receptionist performing patient preparation then hands patient over to registrar explaining that there is something that the doctor would like to discuss with them.

**Introduction (registrar):**

1. Registrar to introduce themselves to the patient
2. Explain that we are doing a study using brain scans and would you mind if we asked you some questions to check whether you qualify for the study? (At this point; if the patient says they are not interested then no further screening is necessary and the patient is free to go.)
3. Explain that what you are about to discuss does not affect their treatment or the PET scan they have already been booked for in any way.
4. If the patient indicates they are willing to hear you out, then proceed as follows:

**Screening (registrar):**

**Table 1: History**

Any condition that is not met excludes the patient from the study and no further screening is necessary.

	<b>YES</b>	<b>NO</b>
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Patient is 18 years old or more? (if no: <b>EXCLUDED</b> – no further screening)		
Diabetes? (if yes: <b>EXCLUDED</b> – no further screening)		
Chemotherapy in the last 3 months? (if yes: <b>EXCLUDED</b> – no further screening)		
Able to give informed written consent? (if no: <b>EXCLUDED</b> – no further screening)		
Any pathology that has a high risk of brain lesions? (if yes: <b>EXCLUDED</b> – no further screening)  <i>Patients with advanced melanoma; small cell lung cancer – should be excluded. (If unsure, ask Dr Doruyter or Prof Warwick)</i>		
Referred for fever of unknown origin (FUO) or vasculitis? (if yes: <b>EXCLUDED</b> – no further screening)		
Previous head injury that resulted in loss of consciousness? (if yes: <b>EXCLUDED</b> – no further screening)		
Current or previous medical condition that affected/affects the brain? (if yes: <b>EXCLUDED</b> – no further screening)  (To check this, ask the following questions: “Have you had or do you currently have any medical conditions?” (list examples) and “Have you ever had any condition that has affected your brain, such as an infection of the brain or a stroke?” and “Have you ever had a scan of their brain and if so, what for? Was it normal or abnormal?” (check the scan if available))  <i>(Any of the following conditions will exclude the patient from the study: Severe medical or neurological illness that could affect the central nervous system, including epilepsy, severe hypertension (requiring more than two agents), brain tumour, paraneoplastic syndrome, severe renal, hepatic, pulmonary, endocrine disease)</i>		
Previous brain operation(s)? (if yes: <b>EXCLUDED</b> – no further screening)		
Does the patient use any psychotropic medications? (if yes: <b>EXCLUDED</b> – no further screening)  (To check this, ask this as an open question and then as a closed question: “Please tell me all the medicines you are on?” and “Are you on any medicines for depression or other psychiatric problems such as bipolar disorder, schizophrenia, etc?”)		
Ever been diagnosed with psychiatric disorder? (if yes: <b>EXCLUDED</b> – no further screening) (To check this, ask as an open question:		

“Have you ever been diagnosed with a severe depression or another psychiatric condition such as bipolar disorder; schizophrenia etc.”?)			
Do you have any of these symptoms? (if yes: <b>EXCLUDED</b> – no further screening)		<b>YES</b>	<b>NO</b>
Ask specifically:	<i>Double vision?</i>		
	<i>Severe headaches?</i>		
	<i>One-sided weakness?</i>		
	<i>Difficulty speaking?</i>		
	<i>Seizures (fits)?</i>		
	<i>Fainting spells?</i>		
	<i>Involuntary movements?</i>		
	<i>Disturbed sensation?</i>		
Do you drink more than one alcoholic drink per day (if you are a <b>woman</b> )? or Do you drink more than two alcoholic drinks per day (if you are a <b>man</b> )? (if yes: <b>EXCLUDED</b> – no further screening)			
Do you use any recreational drugs (dagga; heroin; tik; ecstasy; cocaine)? (if yes: <b>EXCLUDED</b> – no further screening)			

**Table 2: Neurological exam**

Any clear abnormality excludes patient from study.

	<b>YES</b>	<b>NO</b>
While taking the history above, patient seems orientated to time, place, speech? (if no: <b>EXCLUDED</b> – no further screening)		
Patient squeezes both your hands with equal power? (if no: <b>EXCLUDED</b> – no further screening)		
When the patient holds their hands out, is there any gross tremor? (if yes: <b>EXCLUDED</b> – no further screening)		
Can the patient touch their thumbs to each finger of the same hand? (if no: <b>EXCLUDED</b> – no further screening)		
Can the patient, using their index finger, alternately touch their own nose and your finger which you are moving slowly around in front of them? (if no: <b>EXCLUDED</b> – no further screening)		
Sitting directly in front of the patient and looking directly into their eyes; hold out your hands so that they are halfway between you and the patient, stretched		

out so they are the very edge of your own field of view. Ask the patient, without breaking their gaze, to point to the hand that is moving (repeat several times):		
Is there any gross defect in visual fields? ( <i>if yes: <b>EXCLUDED</b> – no further screening</i> )		
Can the patient follow the movement of your finger in front of their face with their eyes? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		
Are the pupils equal and reactive to light? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		
Can they raise their eyebrows? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		
Can they grin to show you their teeth? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		
Can they puff out their cheeks? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		
Can they get out of the chair without using their hands? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		
Can they walk normally? On toes? On heels? Heel-to-toe? ( <i>if no: <b>EXCLUDED</b> – no further screening</i> )		

**Should patient meet all the criteria in the tables then they will be eligible for the study:**

1. Ask the patient if you could discuss their potential inclusion in the study and if they are agreeable, go through the informed consent form with them.
2. Should the patient **consent**:
  - a. Before you end the consent session, explain to them that in the event that they have a high blood sugar on the day of the scan, they might not be included in the study because this will affect the scan. Explain that this is very unlikely because they are not diabetic.
  - b. Inform the receptionist that the patient is a study patient and that they should:
    - i. Book them as the first case on their scan day
    - ii. Not scan more than one study patient per day
  - c. Confirm final date with patient
  - d. Place **study sticker** on the clinical referral form
  - e. Add the **dedicated study protocol** to the PET (plastic) patient folder
  - f. Place the signed consent form in the plastic folder
3. Should the patient **decline**:
  - a. Explain that the clinical PET scan will continue as planned
  - b. Inform the receptionist that the patient will **not** be participating in the study and ask them to confirm the scan date with the patient

**Checklist**

	<b>YES</b>	<b>NO</b>
Patient to be included in study?		
Informed Consent signed and placed in plastic folder?		
Explanation given that may still exclude if blood sugar high?		
Receptionist informed that patient is study participant?		
Scan date: (please insert here)		
Booked as first case of day?		
Study sticker placed on referral?		
Dedicated Study Protocol placed in plastic folder?		

### Registrar/radiographer (day of scan)

#### Instructions: on day of study

1. Check participant is fasting, record medications.
2. Explain the procedure: you will take them through and measure their weight and height and place a small drip in their arm. They will then be taken through to a comfortable chair in a cubicle where they will be asked to sit and wait without talking or sleeping (must keep eyes open: cannot read or use/read mobile phone!) – **just relaxing with eyes open**. After about 25 minutes someone will come and inject the FDG – please keep talking to a minimum if at all! (It affects what we seen on the scan). The FDG has no side-effects. After injection they will continue to sit quietly with eyes open for the next 20 minutes. Then someone will take them through to the bathroom and then to the camera for the scan. The scan takes half an hour: please lie absolutely still (not even a mm of movement!) with eyes open.
3. After the brain scan, we will proceed with the clinical scan.
4. Ask if they have any questions and answer them
5. If female and of child-bearing potential – do pregnancy test (unless a test in the last 10 days was negative – then just record as “NEGATIVE preg test”) and record negative result.
6. At about 08:45 take them through to do weight, height, blood glucose, IV cannula – record time cannula placed and site (make sure it is in! Cannot have even partial misinjection! A registrar should place the cannula and test the blood glucose.)
7. Take them through to injection cubicle – record time (**please make sure there are no signs for them to read in the cubicle! Usually I take them down personally.**)
8. Let them sit quietly in the dimly lit cubicle (eyes open, no reading) for at least 10 minutes before FDG is injected – record time and dose (approx. 150MBq)
9. When time to take through to camera room – remove IV cannula (about 20 min post-injection) – record time
10. Aim to start PET acquisition at 30 min post injection (i.e. can start CT before)
11. 30 minute dynamic PET (15 x 2 min frames) brain – record time started
12. Ask radiographers to copy **all scan files** (including the topograms) except the raw data – to the EBW.

**If blood glucose > 7.0 mmol/l then the patient cannot be included in the study.** Please explain to the patient that the blood sugar is high and that there is a concern that this would affect the images if we were to include their scan in the brain scan project. The decision of whether or not to continue with the clinical PET/CT (as requested by the referring doctor) is to be made as per clinical protocol. If the patient was adequately prepared (i.e. fasting) then the high glucose reading should be communicated to the referring clinician in the final report, i.e.

*“Fasting finger-prick glucose of 9.3 mmol/l in a patient not known with diabetes. Further investigation to exclude diabetes mellitus advised.”*

### **Brain Study: Lionel**

**Procedure:** Brain scan prior to routine clinical scan.

**Brain acquisition:** 30 minute dynamic scan, recon as 15 frames of 2 minutes each.

**Date:**

**NPO except plain water for > 6 hours?**

**Pregnancy test:** Neg/Pos/NA

**Medications:**

**Notes:**

Time IV cannula placed:

Site of IV cannula:

Time in uptake room:

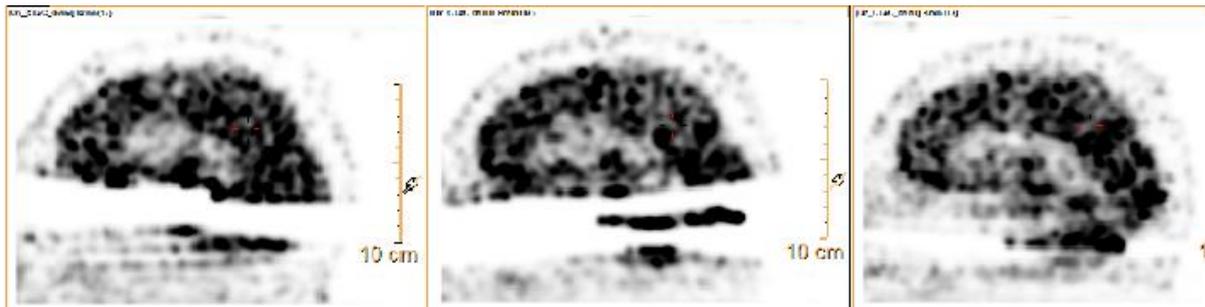
Time of FDG injection (after at least 10 min in uptake room):

Time IV cannula out (20 minutes post-injection):

Time PET acquisition started (30 min post-injection):

Raw data saved to research drive?

## Appendix 2: Scatter artefact



### Appendix 3: Scan findings form

Date:

Patient code:

Findings:

	Left	Right	
Frontal			
Temporal			
Parietal			
Occipital			
Striatum			
Thalamus			
Cerebellum			Vermis
Pons			

(designate any abnormalities as “↑” for increased metabolism or “↓” for decreased metabolism)  
 mildly (↑)      moderately (↑↑)      markedly (↑↑↑)

Diagnosis:

Can you recall the first interpretation of the same case (for second interpretations)?