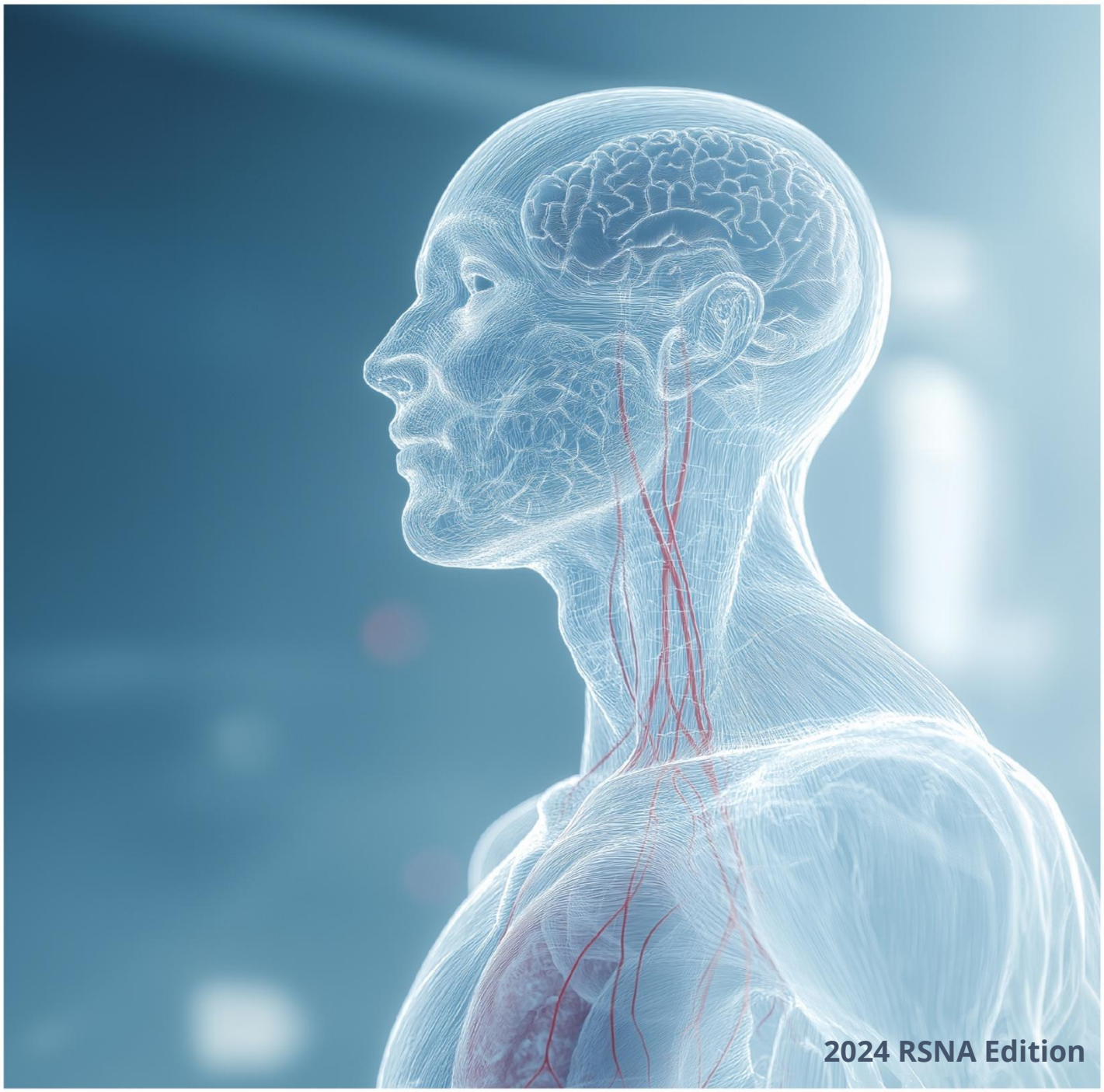
u!nnovation.

UNITED IMAGING



Issue Highlights

Disclaimer

The articles contained in this magazine are provided solely by the authors, and the author(s) of each article appearing in this magazine is/are solely responsible for the content thereof as well as personal data, which is used anonymously or complied with applicable data privacy laws or regulations. United Imaging Healthcare makes no representation or warranties, expressly or impliedly, with respect to the accuracy, timeliness, reliability, legitimacy, applicability, fitness, originality, or completeness of the contents of this magazine. United Imaging Healthcare assumes no legal responsibility or liability for any error, omission, or illegality with respect to the material contained within.

All articles contained in this magazine only represent the opinions and views of the authors and do not implicitly or explicitly represent any official positions or policies, or medical opinions of United Imaging Healthcare or the institutions with which the authors are affiliated unless this is clearly specified. Discussions of any brand, services, or products in the magazine should not be construed as promotion or endorsement thereof.

Articles published in this magazine are intended to inspire further general scientific research, investigation, understanding, and discussion only and are NOT intended to and should not be relied upon as recommending or promoting a specific medical advice, method, diagnosis, or treatment by physicians for any particular individual, nor to replace the advice of a medical doctor or other healthcare professional. Any individual wishing to apply the information in this magazine for the purposes of improving their own health should not do so without consulting with a qualified medical practitioner. All patients need to be treated in an individual manner by their personal medical advisors. The decision to utilize any information in this magazine is ultimately at the sole discretion of the reader, who assumes full responsibility for any and all consequences arising from such a decision. United Imaging Healthcare makes no representations or warranties with respect to any treatment, action, or application of medication or preparation by any person following the information offered or provided within or through the magazine. United Imaging Healthcare shall remain free of any fault, liability, or responsibility for any loss or harm, whether real or perceived, resulting from the use of information in this magazine.

The articles included in this magazine may contain work in progress, which represents ongoing research and development. Such technologies are not available for sale in the United States for clinical use and also may not be available for such sales in other countries around the world.

Please note that the magazine is intended to be distributed only within a limited scope instead of publication.

If you have any questions about the magazine, or simply wish to reach out to us for any other reasons, you are welcomed to contact us at the following email address: compliance@united-imaging.com

Experience with Quantitative Brain PET using the uMI 550 PET/CT at Stony Brook

Paul Vaska[1,2,3]

[1] Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY, United States
[2] Department of Radiology, Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, United States
[3] PET Imaging Core, Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, United States

1. A Brief History of SBU PET Core

The PET Imaging Core of the Renaissance School of Medicine at Stony Brook University (SBU) was created in 2012 by Dean Ken Kaushansky and placed under the leadership of Drs. Ramin Parsey and Mark Slifstein who transitioned from the PET group at Columbia University. PET imaging researchers were initially recruited from Columbia as well as Brookhaven National Laboratory (BNL). Dr. Peter Smith-Jones was recruited to design the PET radiochemistry facilities which are currently led by Dr. Wenchao Qu. The Core facility was constructed in a spacious wing of the new MART building adjacent to the main University Hospital and is now fully functional. It houses a GE PETtrace 800 cyclotron, a research radiochemistry laboratory with 5 hot cells, a Good Manufacturing Practice (GMP) radiosynthesis laboratory with 5 hot cells (2 standard, 2 mini and 1 dispensing), a Quality control (QC) laboratory, and a comprehensive blood analysis lab to generate metabolite-corrected plasma input functions for quantitative brain studies. The first PET scanner dedicated for research studies was a 1990's vintage Siemens HR+ moved from BNL and upgraded by MiE with new electronics and software. Research studies are also performed on a nearby Siemens mMR PET/MRI owned by the Department of Radiology. In 2022, the Core purchased a United Imaging uMI 550 PET/CT which has been the workhorse of our research studies since, with over 140 scans performed. In 2023, SBU and United formalized a research agreement to develop methods to optimize the use of the uMI 550 for brain PET studies, which make up the majority of research studies in the core. Human studies with locally synthesized tracers began in 2015 for ^{18}F tracers, and in 2022 for ^{11}C tracers. Much of the funding for the core was philanthropic, in particular from Kavita and Lalit Bahl and the Laurie family. SBU supports a complete range of imaging facilities for human and animal research, including a small-animal PET core led by Dr. Vaska that provides imaging with a Siemens Inveon PET/SPECT/CT system and access to custom high-resolution PET systems such as the RatCAP (1).

2. Practical Considerations for Quantitative Brain PET on the uMI 550

Like almost all PET/CT scanners, the uMI 550 is optimized for clinical application, primarily whole-body oncology scans. In our experience so far, it is also appropriate for quantitative brain research studies, although there are some important practical issues to consider. For studies without blood sampling, the standard headfirst supine position works best. The head is positioned within the supplied head holder and additionally, expanding foam can be used to give a custom fit to further minimize motion. However, this patient position is not ideal for studies using an arterial line in the arm for blood sampling nor for injection while in the scanner, as in typical dynamic scans used for kinetic modeling, because the PET component is farther from the base of the bed, and the arms are not as accessible due to the CT component. Thus, for these studies we use feet first positioning, allowing shorter tubing (hence less dead volume and less flushing), better ability to monitor the catheter, and a less claustrophobic experience for the patient whose body is mostly outside the bore. While the bed is sufficiently long and sturdy to support this very extended position, it requires considerable space in the room, and this should be considered when constructing the room. Another consideration for the feet first position is that the supplied head holder can't be used (now positioned near the feet), so a custom setup is required - in our case a shaped piece of foam attached to the bed. For studies requiring visual stimulation, we use a small mirror at 45 degrees mounted to a curved 3D printed plastic base which is secured with Velcro

to the top of the bore just outside the PET FOV (thus not affecting the PET data).

3. Physics Considerations

3.1 Spatial resolution

The state-of-the-art resolution of the uMI 550 (2.9 mm FWHM transaxial near center NEMA (2)) is a substantial advance over the previous generation of scanners which provided closer to 4 mm FWHM (eg, Siemens mMR is 4.3 mm (3)) and better even than the Siemens Vision which provides 3.6 mm resolution (4). This is a particular benefit for brain studies by helping to reduce the partial volume effect and distinguish among the large number of nuclei and divisions of the cortex. In order to evaluate the resolution in a way that is more appropriate for brain studies, we used the Joshi method (5) with the Hoffman brain phantom scanned for an hour. Fig. 1 shows the same slice of the phantom reconstructed in different ways and the associated FWHM spatial resolution. As expected, the highest resolution is for OSEM with PSF modeling, which achieves a resolution of 3.4 mm FWHM.

3.2 Axial field of view

The long axial field of view of the uMI 550 (24 cm) is typical of modern PET systems but a big improvement over older systems like the HR+ (15 cm). Even though the whole brain can be captured in a 15 cm FOV, the sensitivity (in 3D mode) drops dramatically from the center to the edge, resulting in substantial differences in noise levels across the brain. The longer FOV reduces this effect and also provides greater overall sensitivity if the brain is positioned in the axial center. Moreover, the long FOV coupled with the improved spatial resolution facilitates the use of an image-derived input function (IDIF) from ROIs on the carotid arteries, although this has not yet been explored by our group. One potential concern we are investigating is the normalization of image slices within 1-2 cm from each axial edge, so axial centering of the brain in the FOV remains important, and IDIF measurements may require additional corrections until this is resolved.

3.3 Sensitivity and Noise Equivalent Count Rate

The NEMA line source sensitivity is 10.24 cps/kBq and NECR peak is 124.4 kcps at 18.85 kBq/mL (2). This is somewhat lower than the Siemens mMR (15 cps/kBq and 184 kcps at 23.1 kBq/mL (3)) primarily due to shorter crystals (16.3 mm vs 20 mm), but we have deemed this to be an acceptable trade-off for the improved spatial resolution and lower cost.

3.4 Time-of-flight (TOF)

Although the uMI 550 may not be at the cutting edge of TOF resolution (372 ps FWHM (2)) and we have not yet fully evaluated its performance, qualitatively the feature performs without artifact and it should be helpful even for brain studies. According to the classical formulation by Budinger (6), the improvement in effective sensitivity is a factor of ~4 for brain, suggesting an SNR improvement factor of ~2.

3.5 Quantitative corrections

Given that the kinetic modeling of dynamic brain PET studies requires quantitatively accurate images, the correction methods need to be accurate, including those for randoms, attenuation, scatter, detector efficiency, deadtime, branching fraction, and overall efficiency (calibration). All corrections are implemented and appear to employ validated approaches, and we are in the process of evaluating their accuracy.

3.6 Data processing

The uMI 550 exclusively uses listmode data and sinograms. Listmode should be optimal for image accuracy because data is not rounded to fit into discrete histogram bins. On the other hand, the absence of sinograms makes it more challenging for the user to detect or diagnose hardware issues. While such issues should be largely dealt with by the QC software and/or service engineers, there would be greater confidence in the data if it could be visually inspected by the user, especially in a research environment. The system supports dynamic studies with time bins as small as 3 sec which is acceptable for quantitative brain studies.

3.7 Image reconstruction

A variety of algorithms are available, including the standard filtered backprojection (FBP) and ordinary-Poisson ordered subsets expectation maximization (OP-OSEM) which have sufficient flexibility for clinical studies. Examples are shown in Fig. 1, including a PSF modeling option which can improve resolution substantially. For research studies, there are some limitations on OSEM parameters including a maximum of 99 iterations and 2 choices for number of subsets (10 and 20, thus a plain MLEM algorithm is not strictly available at this time). There are also options with potential clinical benefit

that should be validated before use in quantitative brain PET studies. For example, AI-based noise reduction approaches are likely trained on common clinical scenarios which may be quite different from research applications, even if the radiotracer is the same. Another example is the ROSEM algorithm which adjusts the regularization (effectively the degree of image smoothing) based on acquired count levels – this should be used with caution in dynamic scans which can have greatly varying count levels across time frames, possibly resulting in varying partial volume effects across time points in the time activity curve.

3.8 Reducing CT dose

The standard attenuation correction protocol provides low noise CT images but in the case of brain PET research, these images are typically not used except for attenuation correction. In order to minimize radiation dose we performed a study using a realistic head CT phantom, and showed that reducing the mAs target from 150 to 40 preserved the value of the attenuation correction factor for each line-of-response (see Fig. 2) while lowering dose by almost a factor of 4 (to <9 mSv CTDIvol for head 16 cm phantom). Subjective PET image quality was also unaffected. The result is an effective CT dose of ~0.4 mSv which represents an almost negligible fraction of the total PET/CT study dose (typically 5-10 mSv).

3.9 Head motion

Dynamic brain studies can be as long as 3 hours, so head motion is more likely than in the clinical situation. Moreover, in order to take advantage of the improved intrinsic spatial resolution of this scanner, greater care must be taken to reduce and/or correct for head motion. United provides an optional motion correction algorithm to detect when significant motion occurs using the PET data itself (based on changes in center of mass of the projection data). It uses these time points to divide the scan into multiple time frames which are reconstructed individually, co-registered, and recombined into a single 3D image. While this may be useful for static clinical studies, it is not available as an option for dynamic scans and in any case would likely be problematic for time frames with low counts due to statistical noise in the projection data (e.g., early time frames after injection).

Thus, we are collaborating with United on evaluating a motion detection/correction approach based on an infrared structured-illumination system, called the United Imaging Healthcare Marker-less Motion Tracking System (UMT), shown in Fig 3. We measured the intrinsic positioning accuracy to be ~0.2 mm as measured by moving a head phantom in known increments, which is far smaller than the PET spatial resolution and thus sufficiently accurate for motion correction. Results from a real human study in head first supine position are shown in Figure 4.

4. Examples of Imaging Studies at SBU

The PET Core currently produces 10 different ^{11}C and ^{18}F based radiotracers for human studies, shown in Table 1, with several more in the pipeline. Many of these studies are fully quantitative, including acquisition of metabolite-corrected arterial input function and kinetic modeling. Some examples are described below.

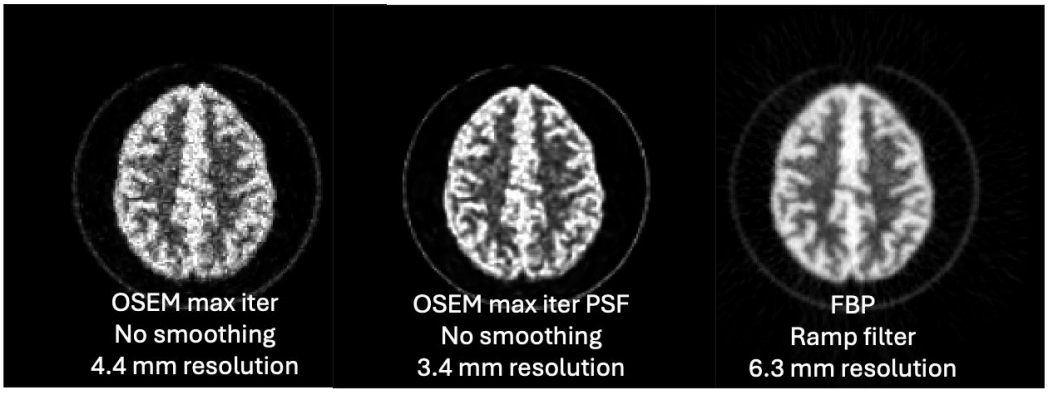


Figure 1. High statistics Hoffman phantom reconstructed with different methods and associated spatial resolutions measured using the method of Joshi et al. (5). Max iterations is 99 (10 subsets) and no post-smoothing is applied. Voxel sizes are the same for all reconstructions, and are almost isotropic at ~1.5 mm.

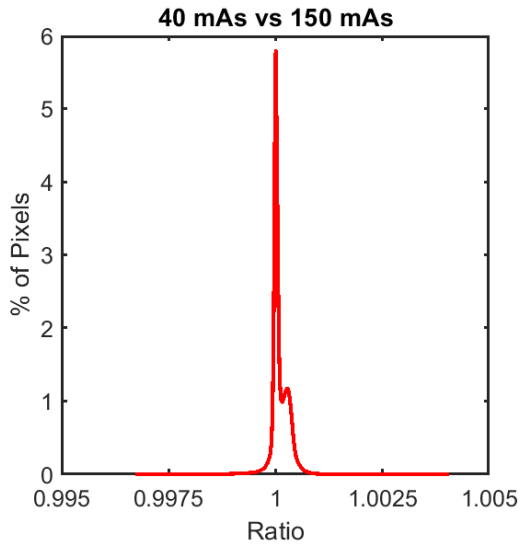


Figure 2. Histogram of ratios of LOR attenuation correction factors measured at 40 mAs relative to those at 150 mAs (default value and assumed to be the most accurate), for a CT head phantom. The ratios fall within a narrow range around 1, indicating that the correction factors are very nearly the same at both settings.

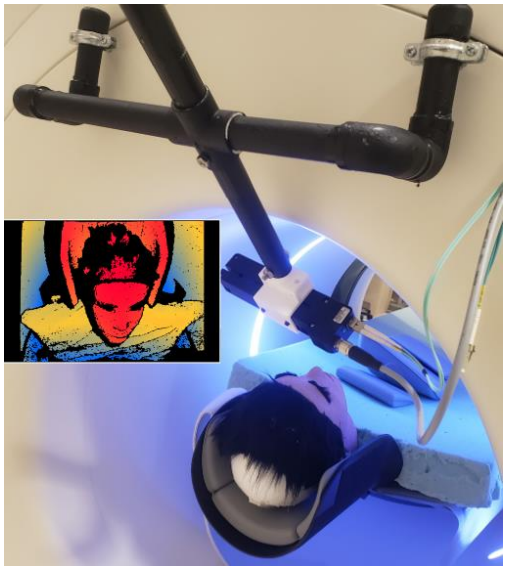


Figure 3. The UMT motion tracking system with custom holder mounted to the back of the uMI 550 PET/CT scanner. Head phantom is in head first supine position and inset photo is the raw data from the system.

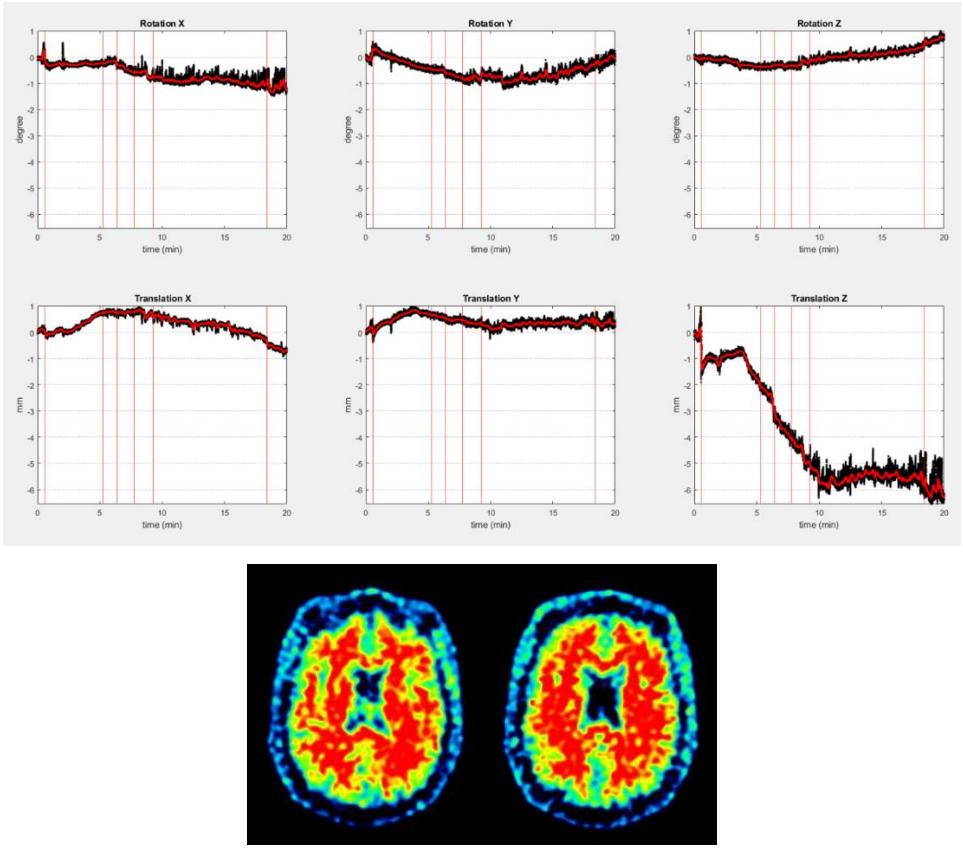


Figure 4. Top - The 6 rigid body motion parameters measured by the UMT system as a function of time during a 20 minute [^{11}C]PiB human brain study of a healthy subject. The predominant motion is a slow shift of almost 7 mm in the z direction. A motion detection algorithm applied to these traces resulted in 6 detections, indicated by the vertical red lines, which were used to define 7 time frames (each with low intra-frame motion). Bottom – the associated brain images without motion correction (left) and after reconstructing each time frame and realigning using the measured motion parameters (right). Note the improved delineation of the white matter pattern that is typical of this tracer in a non-AD subject.

Table 1. List of Radiopharmaceuticals Currently Produced by Stony Brook PET Core

Tracer	Target Molecules or Biological Processes	Application Area(s)
[18F]F-AraG	Activated T cells	Immunotherapy in Oncology
[18F]Florbetaben	Amyloid β plaques in brain	Dementia, Normal Aging
[18F]T807	Tau fibrillary tangles in brain	Dementia, Normal Aging
[18F]LY245	k opioid receptors in brain	Psychiatry (Schizophrenia, Depression, Substance Use)
[18F]VAT	Vesicular acetylcholine transporter in brain	Psychiatry, Neurology, Dementia and Normal Aging
[18F]FEPPA	Translocator Protein in brain	Neuroinflammation; Activated Microglia
[11C]ABP688	Metabotropic Glutamate Receptor 5 in brain	Psychiatry
[11C]PiB	Amyloid β plaques in brain	Dementia, Normal Aging
[11C]UCB-J	Synaptic vesicle protein 2A in brain	Synaptic Density (Psychiatry, Neurology, Epiliepsy)
[11C]PS13	Cyclooxegenase-1 in brain	Neuroinflammation

[^{18}F] FEPPA assesses changes in neuroinflammation after treatment for depression (PI Drs. Parsey and Delorenzo)

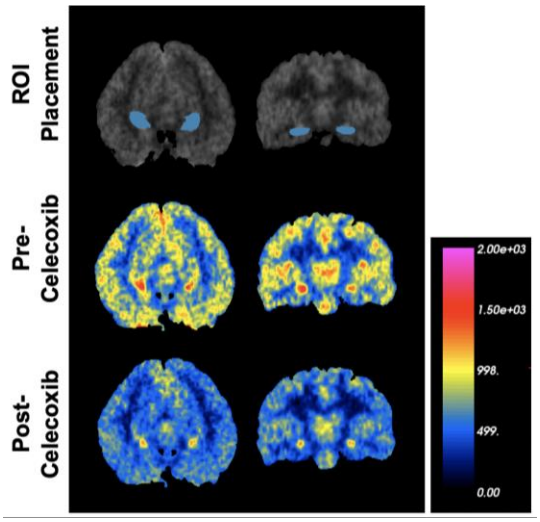


Figure 5. Neuroinflammation is decreased following treatment in major depressive disorder. Center images reflect neuroinflammation prior to treatment and bottom images are post-treatment, showing a ~25% reduction in TSPO density. A structural MRI is shown on the top row for reference. Neuroinflammation was quantified by TSPO volume of distribution (VT, which varies directly with TSPO density) using the PET tracer [18F]FEPPA at Stony Brook PET Core (blue to fuchsia, low to high). (Figure courtesy of Drs. R. Parsey and C. DeLorenzo).

[^{11}C]PiB used to investigate effects of subconcussive injury in college athletes (PI Dr. Vaska)

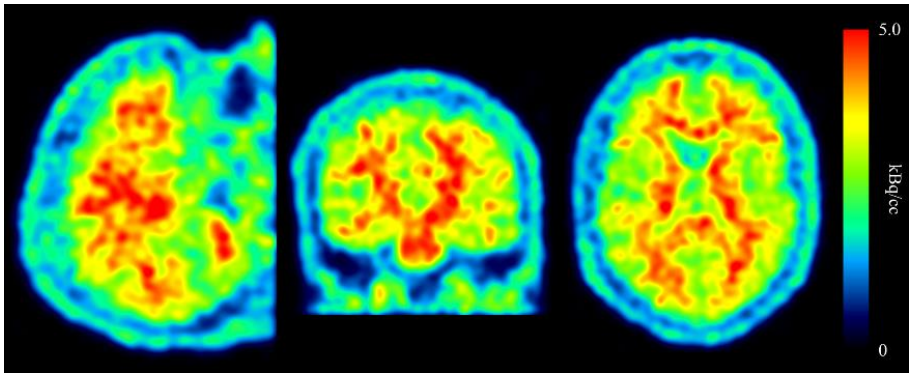


Figure 6. Image of college football player after season of play in this ongoing study. Injection was 11.7 mCi of [11C]PiB, imaged on our UMI 550 PET/CT.

5. Acknowledgements

The author acknowledges the assistance and support of Jaclyn Brunner, Juin Zhou, Lemise Saleh, Tim Cotroneo, Mark Slifstein, Wenchao Qu, Bao Hu, and William Stanley.

6. References

1.Schulz, D., et al., Simultaneous assessment of rodent behavior and neurochemistry using a miniature positron emission tomograph. Nat Meth, 2011. 8(4): p. 347-352.

2.Chen, S., et al., Performance characteristics of the digital uMI550 PET/CT system according to the NEMA NU2-2018 standard. EJNMMI Phys, 2020. 7(1): p. 43.

3. Delso, G., et al., Performance measurements of the Siemens mMR integrated whole-body PET/MR scanner. J Nucl Med, 2011. 52(12): p. 1914-22.

4.van Sluis, J.J., et al., Performance characteristics of the digital Biograph Vision PET/CT system. J Nucl Med, 2019.

5.Joshi, A., R.A. Koeppe, and J.A. Fessler, Reducing between scanner differences in multi-center PET studies. Neuroimage, 2009. 46(1): p. 154-9.

6.Budinger, T.F., Time-of-Flight Positron Emission Tomography - Status Relative to Conventional Pet. Journal of Nuclear Medicine, 1983. 24(1): p. 73-76.

Author Biography

Paul Vaska, Ph.D.
Professor of Biomedical Engineering and Radiology
PET Imaging Core at Stony Brook University
Stony Brook, NY
USA

Dr. Paul Vaska obtained a B.S. in Physics from Clarkson University followed by a Ph.D. in Nuclear Physics from Stony Brook University. He then transitioned to medical applications as Research Physicist for UGM Medical Systems in Philadelphia - a small PET scanner manufacturer led by Dr. Gerd Muehllehner, one of the pioneers of PET, which was affiliated with the University of Pennsylvania and ultimately absorbed by Philips Medical Systems. Dr. Vaska then joined the scientific staff of Brookhaven National Laboratory, in the PET group led by Drs. Joanna Fowler and Nora Volkow (now Director of the NIH National Institute on Drug Abuse). He is currently Professor of Biomedical Engineering and Radiology and one of the directors of the PET Imaging Core at Stony Brook University.

PASSION for CHANGE

If you have any questions about the magazine, or simply wish to reach out to us for any other reasons, you are welcomed to contact us at the following email address: compliance@united-imaging.com