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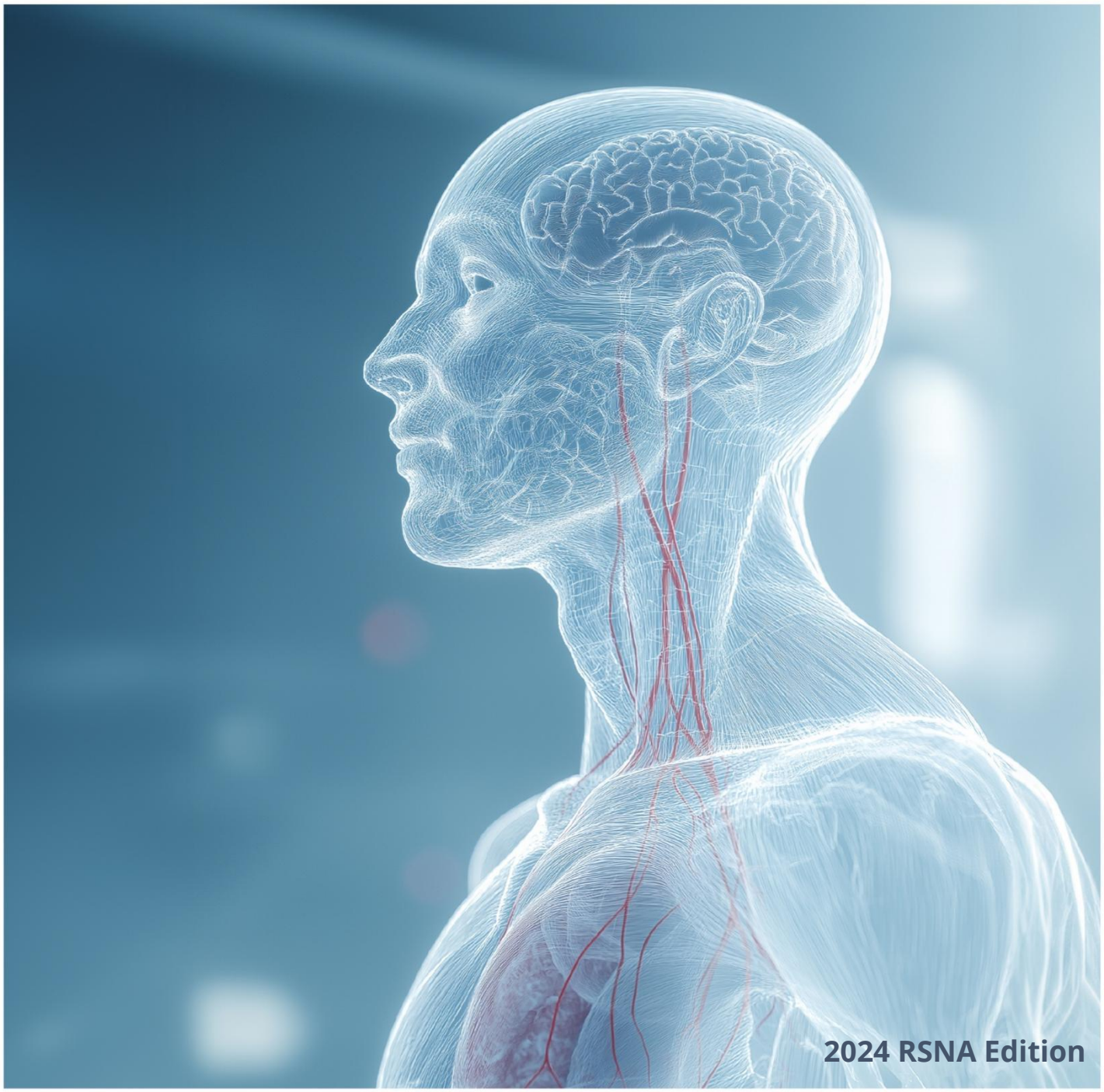

Issue Highlights

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Unveiling the Mind: Journeying through Brain PET with Dr. Richard E. Carson

A United Imaging article by Edwin K. Leung, Ph.D.

E: Dr. Carson, it's a pleasure to have you with us today as we delve into the fascinating world of brain PET imaging. Before we start, congratulations to you and your colleagues for winning the 2024 SNMMI Image of the Year, and for the featured article in the Journal of Nuclear Medicine utilizing the uNeuroEXPLORER[1] system.

R: Thank you so much! It was very exciting to receive the Image of the Year award and really a thrill to be able to share these amazing images with our field.

E: PET imaging is largely utilized today in oncology to detect cancer, despite that early PET imaging applications focused on the brain. Why do you think there was such a shift?

R: I think there are 2 key factors to consider here. Certainly, the brain was a good target, especially for the early generations of PET systems due to the challenges of imaging in the body. Also, there was a large number of molecules already well defined and of interest – especially from the pharmaceutical industry. So, there were many relevant tracers that were broadly relevant in many brain disorders, and the instrumentation at the time was sufficient to image those targets.

The big switch occurred with the advent of PET/CT, when it became evident that FDG PET was incredibly useful in all aspects of tumor assessment. Simultaneously, the clinical utility of PET improved significantly when combined with CT; this was a turning point in the field. At the same time, this shift has led to huge benefits for brain PET, because the clinical demand in oncology has driven significant progress in the quality of PET instrumentation along with the increased availability of cyclotrons and the production of radiopharmaceuticals.

So, we wouldn't have been able to advance brain PET as far as we have without this incredible push for oncology thanks to PET/CT.

E: Many of our colleagues understand that you and your team at Yale have utilized the HRRT, a dedicated brain PET scanner for research over the last 2 decades or so. What were some benefits and limitations you have found with earlier dedicated brain PET systems compared to its clinical whole-body PET/CT counterparts for brain PET imaging?

R: The HRRT was unique – it was meant to be an experimental research system, trying to push the envelope of what could be done with PET based on the technological capabilities of the mid to late 1990s – specifically, what we could do to handle the effects of depth of interaction (DOI).

We knew that as you move closer and closer to the detectors, if you don't measure the DOI, i.e., where the event occurs within the crystal, you're going to increase the blur in the images. Interestingly, in systems at that time – even between the center of the brain and the cerebral cortex on the edge – you have a noticeable loss of resolution. That motivated the design of the HRRT in order to push the envelope in terms of absolute resolution and uniformity of resolution in the brain.

There were 17 HRRT systems manufactured and distributed across sites all around the world, to experts focusing on high resolution brain PET utilizing interesting radiopharmaceuticals. What we all found was that we could do some exceptional research with interesting clinical applications in neuropsychiatric disorders, because the HRRT provided us much better resolution than any system that was available until very, very recently [the uNeuroEXPLORER].

So, we were able to combine great resolution from the HRRT images with specific radiopharmaceuticals – for example – targeting dopamine, norepinephrine, and serotonin receptors and transporters. Many interesting clinically relevant studies were performed with a wide range of dedicated brain-related molecules.

The HRRT allowed us to move forward in terms of understanding both the brain patterns of individual patients as well as characterizing disease etiology. The HRRT also

[1] This product is not available for sale in the U.S. for clinical uses and also may not be available for such sales in other countries.

accelerated the collaborations of PET researchers with the pharmaceutical industry as they understood that they could measure for a particular drug molecule – did the drug reach the brain target, at what levels, and whether it was reaching a point of significant clinical utility without producing adverse effects.

So, it was an exciting period of time – and the HRRT paved the way because of its high resolution and its ability to make these measurements in relatively small structures compared to clinical systems at the time.

E: A lot of folks today are aware of the EXPLORER total-body PET/CT system [now known as the uEXPLORER system] that was co-developed between Dr. Ramsey D. Badawi and Dr. Simon R. Cherry from UC Davis, and United Imaging. And now, you are collaborating with UC Davis and United Imaging to develop the NeuroEXPLORER (NX) dedicated brain PET/CT system [now known as the uNeuroEXPLORER system]. Can you please shed some light on what made you interested in collaborating with United Imaging?

R: The NX journey started back in 2018. As a professor at Yale, I have the opportunity to take sabbaticals from time to time. At that time, I took a sabbatical in the greater San Francisco Bay Area – and my major destination was UC Davis to visit Simon and Ramsey [to see the uEXPLORER]. We had many excellent discussions – including – what was possible for next-generation brain PET system.

Earlier, I mentioned the good features of the HRRT, but its biggest weakness was its sensitivity. The HRRT could identify small structures, but it did not collect enough counts to be able to measure these structures with good reliability. Of course, one of the huge advantages of the uEXPLORER total-body system is its incredible sensitivity.

So, how could we get the best of both worlds – ultra-high resolution – better than the HRRT, and high enough sensitivity to use it? Achieving the right balance led to many wonderful discussions.

Simon and Ramsey have had a very successful relationship with United Imaging. They had the experience that United Imaging was able to deliver on time and deliver what was promised. Therefore, it was the natural next step to reach out to United Imaging to begin the NX collaboration.

We were able to write a grant proposal targeting the NIH BRAIN Initiative, and in September 2019 we submitted the proposal. About one year later, we were awarded that grant. And so, we were all very excited to actually begin the effort of building the new uNeuroEXPLORER system, testing that system, and taking advantage of the combined expertise in the development of novel systems – the system design, optimization, and evaluation skills brought by UC Davis combined with our experience with brain PET imaging at Yale.

E: The one aspect that most people tend to notice at first glance about the uNeuroEXPLORER system is that it has a split PET/CT gantry configuration, in which the CT and the PET gantries are separated by 80 cm. Can you tell us why there is such a gap?

R: One very important part of the kind of brain imaging we do is to also measure the activity in the subject's blood. When you perform an injection of a radiopharmaceutical, how much activity reaches the brain is going to depend on how the rest of the body handles the tracer.

For example, if your liver metabolizes the radiopharmaceutical faster or slower, that's going to affect your brain content. Also, your body mass is a major factor – that's why SUV is normalized by body mass. With that in mind, we needed to have room between the PET and CT gantries so that our technologists and nurses could easily access the subject's arms, so that we perform the injection in one arm and perform arterial sampling in the other arm.

Also, we fully expect – and I think there's already quite a lot of preliminary data – that eventually we may not need a CT for brain PET imaging. So, from a manufacturing viewpoint, it was advantageous to have a separate PET gantry because synthetic CT for PET attenuation correction is becoming more and more widespread – mostly with deep learning methods. But there are also other approaches such as using the lutetium background, that are able to synthesize an appropriate CT for the purpose of PET attenuation correction. It remains to be shown if these methods are as good as what we might need clinically, i.e., CT images.

So, I think the separate gantry setup is well-suited for the long-term goal of the uNeuroEXPLORER system as a standalone PET – something smaller without the CT there. Also, when we're thinking about utilizing the high sensitivity to reduce injected dose, removing the CT will be very important – for example – in pediatric imaging.

E: Many people have commented that the uNeuroEXPLORER has a somewhat large bore, at 50 cm, for a dedicated brain scanner. What advantages does a large bore provide compared to a more conventional bore for brain PET (on the scale of 20 cm)?

R: There is a lot of interest right now in other geometries for dedicated brain systems such as helmet designs, trying to be as close to the head as possible. A smaller bore would increase the raw sensitivity of the system.

The question is whether such systems will have all the advantages of the uNeuroEXPLORER. For example, can those systems produce the same time-of-flight advantage, which produces a large boost in effective sensitivity?

In addition, what we really wanted to enhance with a larger bore was patient comfort, especially in the research world where we perform long scans. Having a very tight bore for what could be 90 min or 2 h of scanning could produce a level of claustrophobia that might not be acceptable.

Being able to position the patient's neck comfortably – especially for our older patients – is crucial. We also believe that our ability to measure head motion is much better with a bigger bore. This larger bore was also an advantage since it allowed us to test the United Motion Tracking (UMT) system on an existing clinical system (which also has a larger bore) starting 2 years before the uNeuroEXPLORER arrived at Yale, and we've gained a lot of good experience in learning how to operate and optimize the UMT system.

E: Speaking of patient comfort, what are your thoughts on brain PET system designs in which the patient is sitting upright at a slight angle?

R: Several of these designs have been presented at SNMMI over the years, and there are certainly tremendous advantages for patients who can remain comfortable when sitting and leaning back. Upright designs can be very relevant for applications that just require a short scan, such as in Alzheimer's Disease (AD), Parkinson's Disease (PD), and other disorders where a short scan is paired with a well-established tracer.

So, I think there is merit and relevance to upright designs, and we look forward to seeing more data in the coming years to understand the relative advantages of that design in terms of patient comfort. I think these upright designs are focused on a different type of application than our focus with uNeuroEXPLORER. For example, if you utilize the helmet geometry to provide sensitivity, you cannot readily have a long axial field of view – otherwise the scanner bore will be right in front of the patient's face, and that's never comfortable for long scanning periods.

E: What were some additional distinct aspects and design considerations you had when developing the uNeuroEXPLORER system with United Imaging?

R: I think the biggest factor is the great DOI. The ability to measure where in the detector the event occurs so that you can more correctly position the line of response makes a huge difference with regards to the accuracy of event localization, both for in-plane and axial parallax effects. This is a critical feature for any system that targets ultra-high resolution.

So, DOI was a critical design factor right from the beginning. It did not allow us to produce ultra-small crystals, but I think based on the results that we've have, it is clear that the uNeuroEXPLORER is providing us with exceptional resolution. This approach also impacts the time-of-flight capability of the system. Our slightly larger crystals (compared to ultra small crystals) mean more light output which is needed to obtain a very good time of flight measurement, at 236 ps. The systems that currently have the best time of flight values generally have larger crystals, which leads to resolution tradeoffs.

We are very satisfied with the balance of sensitivity and resolution that has been achieved. We were targeting a 10-fold net sensitivity increase from the HRRT with smaller crystals, longer axial field of view, and time-of-flight. And so far, the data are showing that we are hitting these targets.

E: The time between the funding notification of the NX project to the imaging of the first human subject took under 2.5 years. What made this rapid progress possible?

R: I think the rapid progress can certainly be attributed to the great discussions and planning that we did during the writing of the NIH grant. There is always that waiting period after the submission of a grant when you're not making much progress because the funding has not yet arrived. But honestly, the relationship with United Imaging was absolutely

the key. United laid out the manufacturing timeline and basically finished the system on time. By far, the biggest delay was the time for renovation of the scanner room at Yale.

I also think that all the ongoing discussions within the NX consortium were essential. We were trying to anticipate what kind of problems we would have and what surprises there might be; this is all part of building a new system. We had lots of discussions on whether there would be issues related to cooling, for example, and just really focused as much as possible on the nitty gritty details of the design.

Another good example mentioned earlier is that of working on the UMT camera with a different clinical PET/CT system to gain experience prior to system delivery. We were ready to use that camera as soon as possible, and the camera was used on the very first scan that was acquired on the uNeuroEXPLORER – all thanks to planning ahead.

The bottom line is that if you're going to try to build a new system well, you must have an experienced industry partner, and that's exactly what we had working with United Imaging.

E: Now that the uNeuroEXPLORER system has been operational at Yale University for almost a year, what are some ongoing projects that you and your team are working on that were made possible using the uNeuroEXPLORER system?

R: Some original projects that were planned in the original grant include comparing the uNeuroEXPLORER to the HRRT, and we were able to show those images at SNMMI recently. Now, we are focusing on using our tracers with focal brain uptake to look at small regions, such as the substantia nigra (very relevant in PD) and the locus coeruleus, which might be a key brain region in the development of dementia, including AD.

Other projects starting soon will be looking at pre-clinical AD, trying to visualize and quantify deposition of tau protein in very small regions in the entorhinal cortex. And in PD, there is great excitement surrounding the first generation alpha synuclein tracers. The signals to be imaged will be extremely small, and the uNeuroEXPLORER is going to be the natural system for those studies; we'll be beginning those scans in the coming weeks.

Some of the other areas we're looking into are the potential applications in head and neck tumors, and that's that is also very exciting. So far, the initial comparisons of patients scans on the uNeuroEXPLORER against a state-of-the-art conventional whole-body PET/CT are very encouraging – our oncologists are very excited about seeing how we can really push the envelope with the uNeuroEXPLORER.

We're also beginning scans in adolescents where we're dramatically dropping the radiation dose. Thanks to the high sensitivity of the uNeuroEXPLORER, we're going to aim for as much resolution as possible with reduced counts compared to a standard dose, and I think that's going to open tremendous opportunities. Also, we have the very good UMT camera to handle motion correction, and of course, adolescents do tend to move more than adults.

Also, many of our investigators at Yale are very excited about being able to apply and use the uNeuroEXPLORER. For example, if we're following subjects longitudinally, we expect to be more sensitive in detecting small changes. Certainly, that increased sensitivity of the uNeuroEXPLORER is going to provide an advantage in that area. Alternatively, we can lower the dose to perform more scans in the same subject with one tracer or perform multi-tracer PET, such as combining a synaptic marker with a dopaminergic marker in PD.

E: For some time, clinicians have primarily focused on the use of standardized uptake value (SUV) as a means of performing semi-quantitative analysis of PET images. What could serve as the pivotal point to encourage clinicians to adopt more sophisticated analysis with high-performance systems such as the uNeuroEXPLORER?

R: Let's start with FDG. Many sites are evaluating the impact of using SUV or a more quantitative measure such as the Patlak net uptake value (Ki). With the current generation of machines, the sensitivity of the system can be a crucial limiting factor. In Patlak analysis, you're trying to measure a slope, and in SUV you're measuring the mean value. Intrinsically, slopes are more variable than the mean value. The subtlety is that, in many cases, the slope is more important than the mean value; this is shown most dramatically if we're looking at metastases in the liver where the kinetics of the tumor are rising, and the kinetics in the normal liver are flattening out. If you measure the slope, you can easily identify liver tumors compared to normal liver.

To address this, we need the higher statistical quality. Right now, to get a good Patlak image on most systems, you need

a reasonably long period of scan time – longer than what you'd like to do, especially if you're trying to do whole body imaging.

The uEXPLORER is already showing that you can perform whole body scans within 10 min, and you're starting to get reasonable Patlak images in that short time. We're going to be able to see those same kind of advantages for the head and neck patients, to see how much shorter those scans could be, and what advantages will be provided by a Patlak uptake image over SUV.

The requirements of clinical reimbursement certainly push for short scans that can adapt easily into normal clinical throughput. One approach for other tracers is a "coffee break" protocol which is composed of an early image and a late image, with a break in between. For now, only a few facilities can handle such a protocol, so we'll need to see the data from these sites to assess the clinical utility. So, for now I think the main step forward will be to take advantage of the huge sensitivity advantage of the uNeuroEXPLORER, like what we're seeing already with the total-body uEXPLORER.

There is one other subtlety when you have very good resolution. There could be cases where you choose to not use all the resolution. If we blur the images a bit, we can get much lower noise, and that can produce other advantages. So, I expect that there'll be some interesting dynamic analyses that might operate at different resolution levels to achieve the best balance of image resolution and quantification from the dynamics within a short scan.

E: What are your thoughts on the future of brain PET imaging in clinical and in research over the next 20 years, and how can industry help accelerate the progress?

R: Great question.

In research, we've been exploring the brain with pharmacology for many years, and the uNeuroEXPLORER is now putting us at a level where we can dive down and look at very small brain nuclei to begin to understand their effects in various diseases. One of the exciting results that we've seen already was being able to visualize some small nuclei within the thalamus, specifically the anterior thalamus, with a dopaminergic marker. This nucleus had not been imaged with PET reliably before. As we look at every new scan now, the image quality matters to identify something new that we can evaluate. The brain is so complex, and the range of neuropsychiatric disorders is so broad that being able to make a reliable measurement in these tiny regions with the right tracer is going to open up a lot of opportunities, both in patient identification drug development, and treatment evaluation.

Clinical impact will take longer, in part because of how many different relevant molecules there are in the brain. We're seeing how, in the cancer world, FDG was the only tracer for so long – and of course FDG was extremely valuable for looking at tumors. But, as the PSMA compounds are now readily available for prostate cancer, how FAPI's applications are exploding, and the value of these tracers is that they can be applied in a large number of patients.

In the brain, the biggest clinical target, of course, is dementia. But there are so many questions: which targets are we going to be imaging to identify which patients would be suitable for the new treatments? Will the imaging agents be better than samples of cerebral spinal fluid (CSF) or plasma? Identifying patients as early as possible in the disease progression is critical to be able to clear amyloid and other proteins from the brain. I believe that the imaging agents, at early disease when the changes in the blood and CSF are small, are going to be more valuable.

Overall, I think that the neurological disorders – in AD, PD, and related disorders – are going to be the main focus, where targeted tracers can help you pick the patients who are suitable for the drug treatment and to then monitor the success of those treatments.

E: Is there anything else you would like to share with the readers regarding the NX project?

R: Perhaps, I would like to send a message to people interested in doing brain research with imaging.

I've been fortunate to be in this field since I was a graduate student at UCLA starting 45 years ago. The images of that era were a far cry from those the uNeuroEXPLORER, but it was also an exciting time then to learn about the potential of PET to image virtually any physiological process, to bring quantification into the mix, and then watch this technology turn into routine clinical practice.

So, for me, that excitement has not gone away in 45 years, and it's incredibly fun to be able to continue to study the brain with PET, and now be able to do that with a system of the

quality of the uNeuroEXPLORER.

Working with partners like UC Davis and United Imaging has made this journey an exceptional ride and it has been really fun to be able to do this work that at this phase of my career. It's truly exciting to show these incredible images and start looking at the brain in ways that have never been done before.

E: With that, Dr. Carson, thank you very much for your time, and we look forward to making more history with you in the mind-blowing world of brain PET imaging 😊

R: Thank you so much for the opportunity.

Expert's Biography

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Dr. Richard E. Carson is Professor of Radiology and Biomedical Imaging and of Biomedical Engineering at Yale University. He is a world-leading researcher in brain PET imaging and is the pioneer who partnered with the University of California, Davis (UC Davis) and United Imaging to develop the next-generation dedicated brain PET/CT system, the uNeuroEXPLORER, through a $10.2M USD U01 academic-industry partnership grant funded by the National Institutes of Health (NIH) in late 2020. Dr. Carson has received many prestigious awards, has published over 400 papers in peer-reviewed journals, and has given over 175 invited lectures, including the Henry N. Wagner Jr. Lectureship at the SNMMI Annual Meeting in 2018. Together with the NeuroEXPLORER consortium, Dr. Carson and his colleagues have been honored with the 2024 SNMMI Image of the Year award. Their publication has also been highlighted as a "Featured Article" in the Journal of Nuclear Medicine (DOI: https://doi.org/10.2967/jnumed.124.267767). Additionally, their work has garnered attention across multiple media outlets, including AuntMinnie.com and The Imaging Wire.

PASSION for CHANGE

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