2018 SNMMI Highlights Lecture: Brain Nuclear and Molecular Imaging

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2018 Highlights Lectures were delivered on June 26 at the SNMMI Annual Meeting in Philadelphia, PA. In this issue we feature the lecture by Henryk Barthel, MD, PhD, a professor in the Department of Nuclear Medicine at the University of Leipzig (Germany), who spoke on neuroscience highlights from the meeting. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2018;59[suppl 1]).*

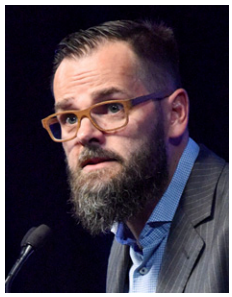
These are most exciting times for nuclear brain imaging researchers. A number of different neurologic disorders, new diagnostic concepts, and therapeutic opportunities have emerged in recent times. These new developments have provided an extraordinary stimulus for our research efforts to improve molecular brain imaging—as seen across a broad spectrum of presentations on high-quality brain imaging at this meeting.

The neuroscience-related portions of this year's meeting were, once again, full of amazing highlights. High-quality talks and posters were presented by leading national and international brain imaging scientists, including excellent representation from this year's SNMMI partner country, China. We owe a special thank you to our Chinese colleagues for their valuable contributions in making this meeting such a great success under what were (at least for some of them as well as for some attendees from other countries) difficult circumstances. I also want to thank all the authors who generously shared their valuable results and images and to offer my apologies to those whose valuable results I cannot include here because of space limitations.

This year's SNMMI Annual Meeting featured exciting clinical brain imaging research, innovative basic science neuroimaging, and also new developments in instrumentation and data analysis. Perhaps most exciting were the numbers of presentations on new brain imaging probes.

Brain Imaging Council Awards

As always, one of the highlights for the nuclear medicine neuroscience community was the presentation of the annual Brain Imaging Council awards. These include both the heroes and the future research leaders of our field. Victor Villemagne, MD, from Austin Health (Melbourne, Australia) was the 2018 Kuhl–Lassen awardee. His groundbreaking research in detangling Alzheimer brain pathologies and neurodegeneration, with relevance to many other areas of nuclear neuroscience, continues to be productive and innovative. He is, without a doubt, a worthy recipient of this prestigious award.



Henryk Barthel, MD, PhD

This year's Brain Imaging Council Young Investigator Award session again provided both hope and evidence that the future of nuclear medicine is bright. Ensuring that future, however, requires the provision of attractive research and career opportunities for our young colleagues. The first prize was won by Willekens et al. from University Hospitals Leuven and KU Leuven (Belgium), who reported on "Regional FDG decreases in healthy aging are associated with white matter integrity changes: A simultaneous PET-MR study" [83]. In this excellent basic science study, the group applied hybrid brain PET/MR imaging to investigate the relation between age-dependent brain glucose consumption and structural connectivity in healthy individuals. They found that partial volume effect–corrected cerebral glucose metabolism data and white matter fractional anisotropy declined in healthy aging, whereas white matter mean diffusivity increased. They also noted that the decline in cerebral glucose metabolism was related to microstructural integrity changes in the connecting white matter tracts, indicating a relationship between deterioration of specific vulnerable networks and healthy aging. The authors concluded that "simultaneous FDG PET and diffusion tensor imaging allow a more refined picture of aging, which may also be important in brain disorders."

Haywood et al. from Stanford University/Stanford University School of Medicine (CA) reported on "A novel PET reporter gene/reporter probe for the central nervous system (CNS)" [78]. This group received the second Young Investigator Award, in recognition of promising research with a novel PET probe that binds to the pyruvate kinase M2 (PKM2) reporter gene and can be coupled to specific therapeutic genes to treat brain diseases. The study included both in vitro experiments and in vivo studies in mice with the tracer ^{18}F-DASA-23, which freely crosses the blood–brain barrier (BBB), allowing imaging in the CNS. They concluded that PKM2 and similar tracers have "the potential to be further developed into a PET reporter gene system for the imaging of gene therapy in the CNS."

Lu et al. from Yale University (New Haven, CT) reported on "Partial volume correction for PET synaptic density imaging with ^{11}C-UCB-J" [77], winning the third Young

Investigator Award. These researchers applied an innovative method in patients with Alzheimer disease (AD). They observed that ^{11}C-UCB-J binding was significantly reduced in the hippocampus in patients with AD and that partial volume effect correction had the greatest effect on cortical regions. They concluded that ^{11}C-UCB-J binding in the hippocampal region is more sensitive than MR in differentiating AD patients from healthy individuals.

I would like to congratulate all those responsible for the impressive research presented at this meeting by junior scientists in the neurosciences.

Novel PET Imaging Probes

In the main scientific program, reports on novel PET imaging probes to visualize and quantify neuroinflammation were an important component. One notable current trend focuses on identifying alternative targets to the 18 kDa translocator protein (TSPO) in neuroimaging. Frankland et al. from the National Institutes of Health/National Institute of Mental Health (Bethesda, MD) and Stanford University (CA) reported on "Evaluation of a novel PET radioligand to measure cyclooxygenase-2 (COX-2) in a model of neuroinflammation in rhesus macaque" [71]. These researchers tested the PET tracer ^{11}C-MC1 in a nonhuman primate model of local neuroinflammation caused by lipopolysaccharide injection. This led to significant increases in brain tracer uptake, which could be blocked by cold compound. Brain uptake increased by 60% with the first lipopolysaccharide injection and by more than 200% after the second (Fig. 1). This effect was specific to COX-2, meaning that COX-1 was not affected. This promising tracer is now under further evaluation in patients with neuroinflammation to measure COX-1 in healthy conditions and COX-2 in inflammatory disorders, with the potential to evaluate the selectivity of nonsteroidal anti-inflammatory drugs.

Solingapuram Sai et al. from the Wake Forest School of Medicine (Winston-Salem, NC), Columbia University Medical Center (New York, NY), and the New York State Psychiatric Institute (NY) reported on "Development of ^{11}C-HD800, a high affinity tracer for imaging microtubules" [6]. Microtubules are important components of the cytoskeleton that can be dysfunctional in several malignancies, neurodegenerative disorders, and brain injuries. Currently available microtubule tracers are limited for brain imaging by insufficient BBB penetrance. The authors' biodistribution and microPET imaging studies in healthy mice showed that this tracer rapidly entered the brain and was very quickly washed out. The tracer binding was also blocked by cold compound, suggesting specific binding to microtubules (Fig. 2). These favorable properties encourage further testing of this tracer in mice and other species, as well as in specific disease models.

Neelamegam et al. from the Massachusetts General Hospital/Harvard Medical School (Boston, MA), the National Heart, Lung, and Blood Institute (Bethesda, MD), the National Institutes of Health Clinical Center (Bethesda, MD), the National Institute of Neurological Disorders and Stroke (Bethesda, MD), and the University of Chicago (IL) reported on "Evaluation of ^{18}F-3F4AP in nonhuman primates: A PET tracer for K^+ channels to image brain demyelination" [545]. ^{18}F-3F4AP is known to bind to voltage-gated potassium channels. It is also known that the number of traceable potassium channels increases in the brain during demyelination, so that ^{18}F-3F4AP binding is increased in areas of demyelination. Using this PET tracer could, in principle, allow visualization of demyelination in positive image contrast. In this study the authors added to previous work in a rat model of multiple sclerosis by evaluating the biodistribution of this tracer in nonhuman primates to approximate human dosimetry and characterize pharmacokinetic properties. They demonstrated promising results, as well as the

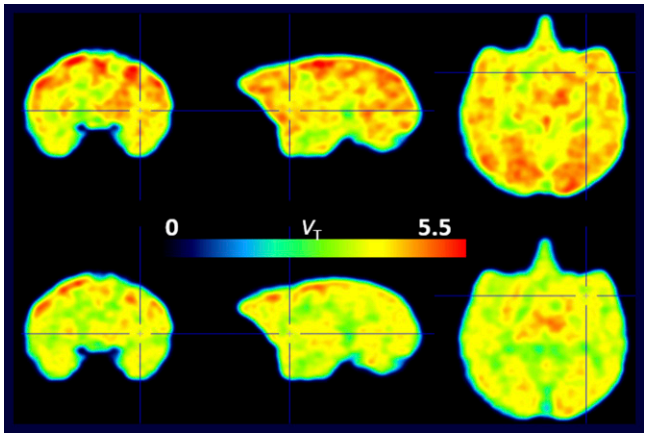


FIGURE 1. ^{11}C-MC1 PET for measuring cyclooxygenase-2 (COX-2) in a model of neuroinflammation in rhesus macaques. Left to right: coronal, sagittal, and axial ^{11}C-MC1 PET images. Top: Baseline imaging uptake showed COX-2 upregulation globally after a single lipopolysaccharide injection. Bottom: Nonradioactive MC1 (cold compound) (0.3 mg/kg, IV) blocked uptake. This effect was specific to COX-2; COX-1 was not affected.

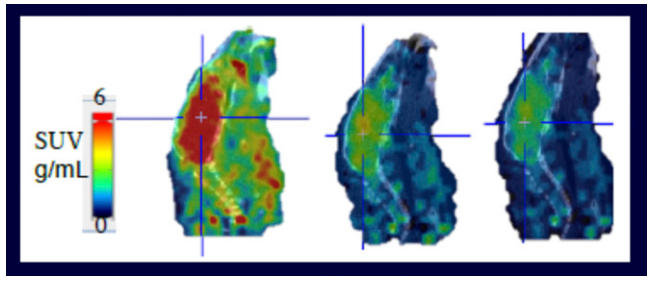


FIGURE 2. ^{11}C-HD800 PET imaging of microtubules. Sum of 0–60-minute fused sagittal images of ^{11}C-HD-800 in a representative mouse brain (left, baseline; middle, blocking with 5 mg/kg HD-800; right, blocking with 5 mg/kg MPC-6827). Intersections of blue lines represent center of brain. Current available microtubule tracers are limited for brain imaging by insufficient blood–brain barrier penetrance. This tracer showed favorable characteristics for overcoming some of these limitations.

possibility of modeling brain kinetics with a 2-tissue compartment model (Fig. 3). The researchers concluded that this first tracer for K^+ channels has high penetration into the brain, excellent stability, and good overall properties for PET imaging. They added that translation into humans is warranted. I eagerly anticipate the first-in-human results.

Brain Imaging Instrumentation and Data Analysis

With regard to improved analysis of TSPO neuroinflammation PET data, an innovative approach was presented by Zhou et al. from the Johns Hopkins University School of Medicine (Baltimore, MD), who reported on "A genetic polymorphism-based kinetic analysis of ^{11}C-DPA-713 dynamic PET for precision imaging of brain injury in National Football League players" [498]. For many TSPO tracers, like ^{11}C-DPA-713 as employed in this study, consideration of individual genetic TSPO polymorphism is important. These authors looked at retrospective ^{11}C-DPA-713 PET data from 62 individuals: 37 healthy controls (23 with the CC TSPO genotype and 14 with the CT genotype), 19 professional football players (9 CC, 10 CT), and 6 other individuals (3 healthy controls, 1 football player, and 2 patients diagnosed with schizophrenia) and evaluated a constrained compartment modeling approach for estimation of ^{11}C-DPA-713 TSPO specific and nonspecific binding on the individual level. With these population-based TSPO polymorphism data, they showed that, in subjects with the CC but not the CT TSPO genotype, tracer binding potential as a measure of neuroinflammation was increased in certain brain areas of the football players. When this TSPO polymorphism consideration method can be reproduced in larger patient cohorts, it may prove helpful in simplifying data acquisition and quantification of ^{11}C-DPA-713 in future PET neuroinflammation imaging.

Another promising approach to simplifying brain tracer kinetic modeling was presented by Petibon et al. from the Massachusetts General Hospital (Boston) and the McLean Hospital (Belmont, MA), who reported on "Direct parametric reconstruction for improved characterization of neurotransmitter release using dynamic PET" [497]. In this study, dopamine release was determined by ^{11}C-raclopride dopamine D2 receptor PET as modeled directly from the raw dynamic PET projection data, rather than the standard indirect method of fitting time–activity curves. Using phantom simulation and human PET imaging it was shown that this novel direct method reduced bias and variance and increased the signal-to-noise ratio in parametric imaging (Fig. 4). This direct parametric reconstruction approach is extremely promising. The authors concluded that in the future it may "improve the characterization of local neurotransmitter release, potentially allowing detection of weaker effects, reducing the needed sample size, or reducing radioactivity dose to facilitate repeated experiments or minimize radiation exposure."

Basic Science Brain Imaging

The possibilities associated with the ability to determine neurotransmitter status in the living human brain with nuclear imaging techniques has also stimulated new research in basic science. Liu et al. from the Washington University School of Medicine/Washington University in St. Louis (MO) and Sun Yat-sen University (Zongshan, China) reported that a "Dopaminergic D2 antagonist modulates expression of vesicular acetylcholine transporter (VAT) in the brain of nonhuman primates" [340]. The authors were interested in the so-far poorly understood interplay between dopaminergic and cholinergic neurotransmission. They used the recently developed tracer ^{18}F-VAT for PET studies in cynomolgus macaques. They found that pretreatment with the dopamine D2 receptor antagonist eticlopride significantly increased tracer binding in the striatum but not in the cerebellar hemispheres, indicating that the latter can serve as suitable reference regions for this tracer (Fig. 5). They concluded that their results suggest that ^{18}F-VAT PET "provides a useful tool for

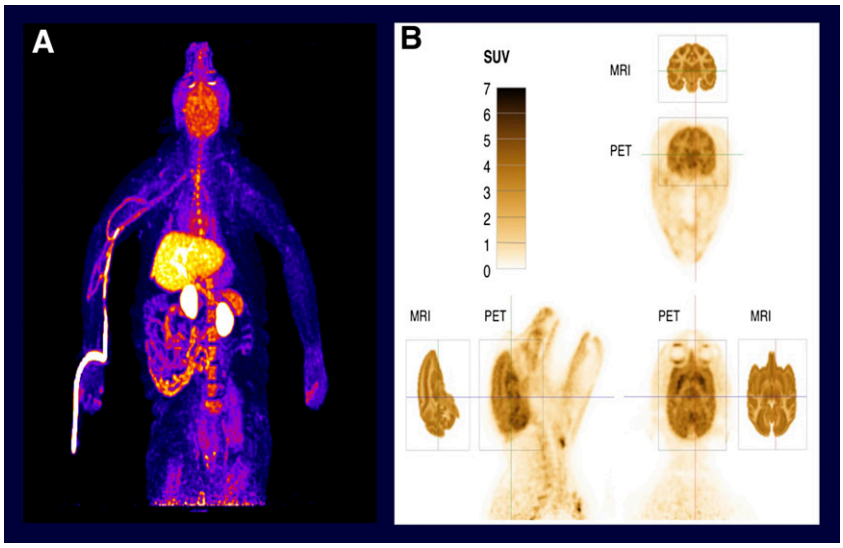


FIGURE 3. ^{18}F-3F4AP PET imaging of demyelination in nonhuman primates. The study evaluated the biodistribution of this tracer in nonhuman primates (left) to approximate human dosimetry and characterize pharmacokinetic properties. They demonstrated promising results. Time–activity curves showed fast entry into the brain (right) followed by fast-to-moderate washout. Brain data fitted well an unconstrained 2-tissue compartment model using arterial input function (V_T range: 1.8–2.5 mL/cc). This first tracer for K^+ channels has high penetration into the brain, excellent stability, and good overall properties for PET imaging.

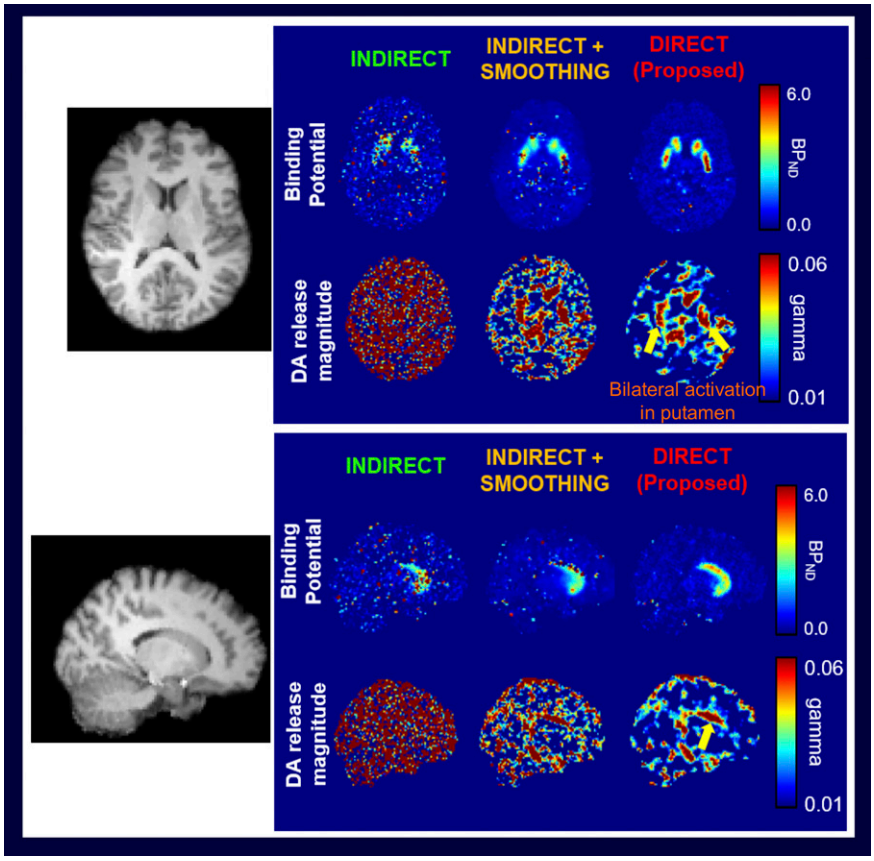


FIGURE 4. Direct parametric reconstruction for improved characterization of neurotransmitter release using dynamic ^{11}C-raclopride PET. In this study, dopamine release was determined by ^{11}C-raclopride dopamine D2 receptor PET as modeled directly from the raw dynamic PET projection data. A 45-minute human study was conducted on a hybrid PET/MR system using ^{11}C-raclopride for construction of parametric maps (top block, axial; bottom block, sagittal). A reward task was started ~27 minutes after tracer injection to induce striatal dopamine release. Linear extension of the reference region model maps of BP_{ND} and magnitude of dopamine release were estimated with 3 methods (left to right): indirect (standard): dynamic OSEM + TAC fitting; indirect + smoothing: dynamic OSEM + Gaussian smoothing + fitting; and direct (proposed): estimation directly from dynamic sinograms. This novel direct method reduced bias and variance and increased the signal-to-noise ratio in parametric imaging.

investigation of dopaminergic modulation on VAT expression in the brains of living animals." If transferrable to humans, these impressive data could stimulate development of novel treatment concepts or new imaging agents for movement or dementia disorders.

Toyonaga et al. from Yale University (New Haven, CT) reported that "Synaptic density imaging with ^{11}C-UCB-J detects treatment effects of a Fyn tyrosine kinase inhibitor on AD mice" [197]. Novel synaptic density PET tracers, like ^{11}C-UCB-J, as employed by the Yale group in this study (and also in the Young Investigator awards), recently emerged as promising tools with the potential to improve imaging of epilepsy, dementia, and other brain disorders. These researchers determined in wild-type mice (controls) and AD model mice the extent of tracer uptake in the hippocampus and monitored the effect of a Fyn tyrosine kinase inhibitor on this uptake. Mice underwent ^{11}C-UCB-J PET imaging at baseline, after about 40 days of saracatinib (an inhibitor of Src family kinases that also has activity against Fyn), and during drug washout (Fig. 6). Reduced hippocampal ^{11}C-UCB-J binding was demonstrated in AD mice at baseline. These deficits were normalized during Fyn inhibitor treatment. If these promising findings are reproducible in larger studies and correspond with histopathologic and cognition data, they would not only imply a potential new therapeutic strategy for AD but also the ability of synaptic density PET imaging to monitor treatment effects.

One group reported on research into the unique capability of nuclear imaging to monitor treatment effects not only in the brain but on a molecular level. Drug resistance is a major challenge in neuropharmacology and is often mediated by p-glycoprotein, which limits the permeation of many drugs across the BBB. Auvity et al. from Commisariat

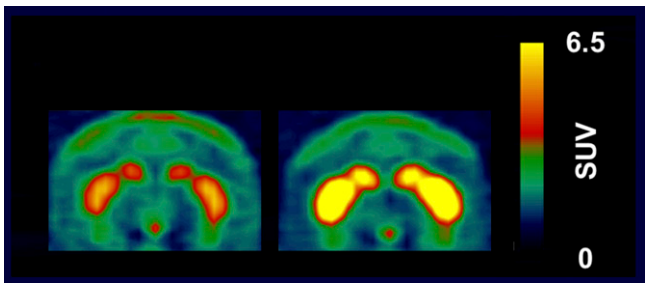


FIGURE 5. Dopaminergic D2 antagonist and modulation of vesicular acetylcholine transporter (VAT) expression in nonhuman primate brain. Using ^{18}F-VAT PET in cynomolgus macaques, researchers found that pretreatment with the dopamine D2 receptor antagonist eticlopride significantly increased tracer binding in the striatum but not in the cerebellar hemispheres, indicating that the latter can serve as suitable reference regions. Representative ^{18}F-VAT PET images: (left) ^{18}F-VAT PET at baseline without pretreatment; (right) after pretreatment with (–)-eticlopride. These findings could stimulate development of novel treatment concepts or new agents for movement and dementia disorders.

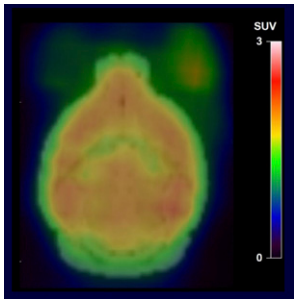


FIGURE 6. Synaptic density imaging with ^{11}C-UCB-J PET. Figure shows a 30–60-minute summed ^{11}C-UCB-J PET image in a control mouse after injection of a Fyn inhibitor. These investigations not only could support potential new therapeutic strategies for Alzheimer disease but also the ability of synaptic density PET imaging to monitor treatment effects.

à l'Energie Atomique/Service Hospitalier Frèdèric Joliot/Imagerie Moléculaire In Vivo (Orsay, France) and the Medical University of Vienna (Austria) reported that "P-glycoprotein (ABCB1) function at the BBB drives the clearance of its substrates from the brain back to the blood: A ^{11}C-metoclopramide PET study in baboons" [200]. These researchers employed ^{11}C-metoclopramide as the tracer in this nonhuman primate brain kinetics study because its p-glycoprotein-binding characteristics are quite similar to those of other agents with limited permeability across the BBB. Using controlled administration of the potent p-glycoprotein inhibitor tariquidar, the researchers found that p-glycoprotein inhibition not only affected tracer influx into the brain (the so-called K_1 effect) but also the efflux rate constant K_2 (Fig. 7). These and other results led the authors to conclude that "p-glycoprotein does not solely act as a 'barrier' to limit the brain penetration of xenobiotics from the blood" but also "mediates the clearance of its substrates back to the blood, thus providing an additional dynamic system to limit overall brain exposure." If these convincing nonhuman primate data are successfully validated and translated to humans, these findings could substantially improve our understanding of the ways in which drugs behave at the BBB.

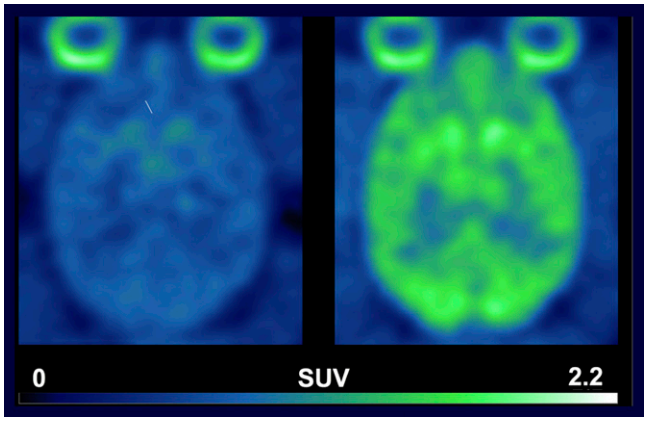


FIGURE 7. ^{11}C-metoclopramide PET, p-glycoprotein binding, and resistance at the blood–brain barrier (BBB). Left: ^{11}C-metoclopramide PET baseline imaging in a baboon brain; right: after controlled administration of the potent p-glycoprotein inhibitor tariquidar. P-glycoprotein inhibition not only affected tracer influx into the brain (K_1 effect) but also the efflux rate constant K_2. Development of these findings could substantially improve understanding of the ways in which drugs behave at the BBB.

Clinical Brain Imaging

Bischof et al. from University Hospital Cologne (Germany), Research Center Jülich (Germany), Austin Health (Heidelberg, Australia), Austin Hospital (Melbourne, Australia), Commonwealth Scientific and Industrial Research Organisation (Heidelberg, Australia), Institute for Neurodegenerative Disorders (New Haven, CT), Klinik und Poliklinik fur Nuklearmedizin (München, Germany), Universität Technische München (Germany), University of Leipzig (Germany), University Hospital of Cologne (Germany), Neurology Hospitals Leuven (Belgium), University of Utah (Salt Lake City), and VU University Medical Center (Amsterdam, The Netherlands) reported on "Comparing amyloid PET tracers and interpretation strategies: First results from the CAPTAINS study" [485]. While ongoing multicenter efforts are underway here in the United States and in Europe to provide high-level evidence for the assumption that amyloid imaging has clinical utility, this multicenter project led by the group in Cologne wanted to determine how visual interpretation protocols for the 3 established ^{18}F-labeled amyloid tracers compared. In a cross-over design, they found that rater agreement and accuracy were high for all 3 tracers, with some slight differences. These differences, when defined in more detail, might point the way to more successfully standardizing protocols in future multitracer trials in which amyloid imaging is employed. The authors are currently developing and evaluating a unified visual rating scheme that may enhance interrater reliability and simplify interpretation of amyloid scans, including advantages for the less experienced reader.

Characterization of the disturbance of cholinergic transmission in relation to the severity of differing cognitive function in patients with AD was the focus of a study by our group in Leipzig, Germany. Meyer et al. from ABX Advanced Biochemical Compounds (Radeberg, Germany), ZEA-2 Forschungszentrum Jülich (Germany), Institute of Radiopharmaceutical Cancer Research Helmholtz-Zentrum Dresden-Rossendorf (Leipzig, Germany), and the University of Leipzig (Germany) reported on "Associations between α4β2 nicotinic acetylcholine receptor (α4β2 nAChR) availability and memory, executive function, and attention in mild AD: A (–)-^{18}F-flubatine PET investigation" [414]. To investigate this feature, (–)-^{18}F-flubatine, a novel nAChR PET tracer, was used. We observed that regional distribution volumes correlated with the status of distinct cognitive domains. Specifically, we found that in individuals with mild AD, α4β2 nAChR deficiencies were identified in the basal forebrain–cortical and septohippocampal cholinergic projections. A relationship was also identified between subcortical α4β2 nAChR availability and impaired episodic memory, executive function/working memory, and attention (Fig. 8). We concluded by pointing to the potential of (–)-^{18}F-flubatine "as a PET biomarker of cholinergic vulnerability, specific cognitive decline, and disease progression in AD." These data also indicate that this tracer could be useful in other

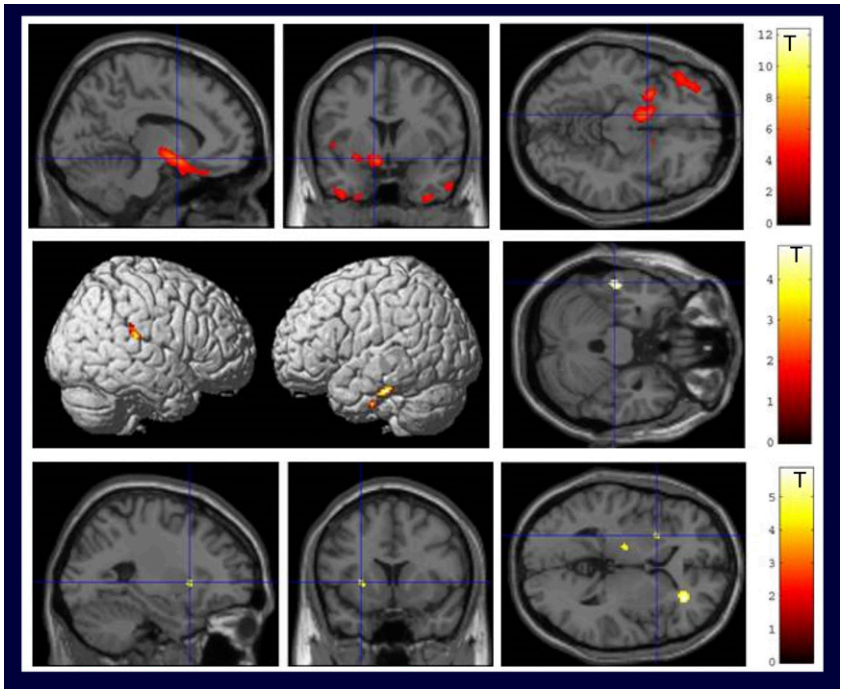


FIGURE 8. Characterization of disturbance of cholinergic transmission in relation to differing cognitive function in patients with Alzheimer disease (AD). Use of (–)-^{18}F-flubatine, a novel α4β2 nicotinic acetylcholine receptor (nAChR) PET tracer, found regional distribution volumes to be correlated with the status of distinct cognitive domains. Statistical parametric mapping shows positive correlations between α4β2 nAChR availability (V_T) and cognitive partial functions (Z scores) in AD in (top to bottom): episodic memory (basal forebrain, inferior temporal cortex, parahippocampus), executive function/working memory (temporal cortex, parietal cortex), and attention (frontal cortex, putamen, thalamus). The results support the potential of (–)-^{18}F-flubatine as a PET biomarker of cholinergic vulnerability, specific cognitive decline, and disease progression in AD.

dementia disorders, as well as for selection of patients who might profit from cholinergic drugs.

Second-generation tau tracers are now being assessed by many researchers as having great promise for rapid clinical translation in the nuclear brain imaging field. I will highlight 2 examples from this meeting. Villemagne et al. from Austin Health (Melbourne), Commonwealth Scientific and Industrial Research Organisation (Brisbane and Melbourne), and the Florey Institute of Neuroscience and Mental Health (Melbourne, all in Australia) reported on "Evaluation of ^{18}F-PI-2620, a second-generation selective tau tracer for the assessment of Alzheimer's and non-Alzheimer's tauopathies" [410]. This group looked at ^{18}F-PI-2620, which in previous in vitro studies appeared to bind to different types of tau deposits. Participants in the study included individuals with clinical diagnoses of probable AD, progressive supranuclear palsy, and frontotemporal lobar degeneration, as well as healthy age-matched controls and a group of patients with mild cognitive impairment. No tracer retention was observed in the healthy controls, and no off-target binding in the choroid plexus or basal ganglia was observed in any participant. In typical AD patients, however, elevated tracer uptake was seen in classic tau regions such as the temporoparietal and posterior cingulate cortices (Fig. 9). The authors concluded that ^{18}F-PI-2620 is a sensitive tool to detect tau deposits in the

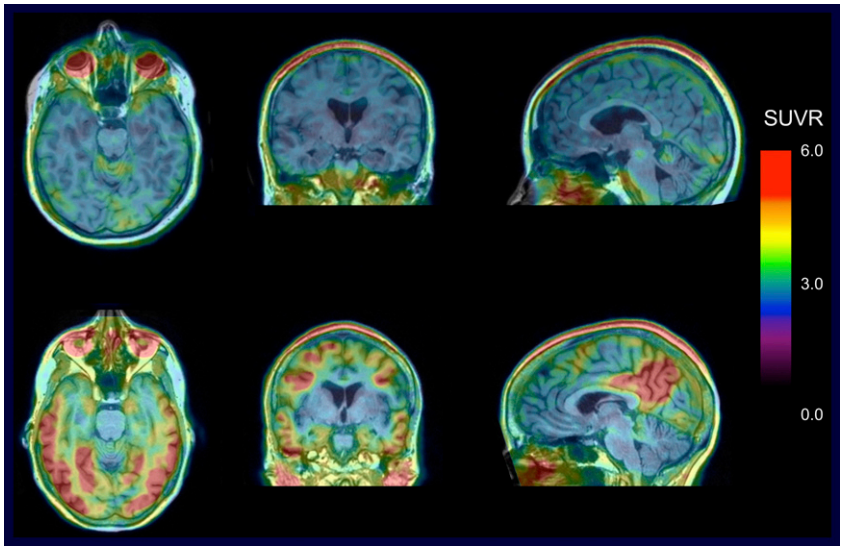


FIGURE 9. ^{18}F-PI-2620, a second-generation selective tau tracer for assessment of Alzheimer and non-Alzheimer tauopathies. ^{18}F-PI-2620 PET imaging in (top) a healthy control participant (61-year-old woman; Mini Mental State Exam [MMSE] score of 29) and (bottom) a 58-year-old woman (MMSE 23) with diagnosed Alzheimer disease (AD). In typical AD patients elevated tracer uptake was seen in classic tau regions such as the temporoparietal and posterior cingulate cortices. Imaging with this tracer was not affected by potentially confounding off-target binding.

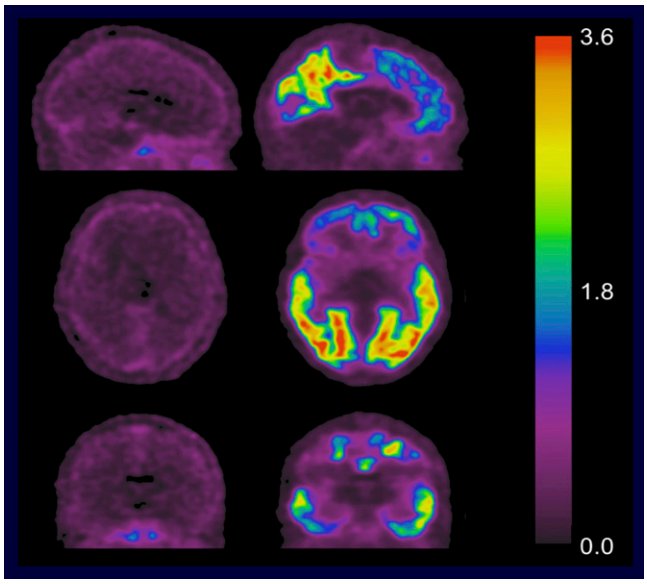


FIGURE 10. ^{18}F-MK6240, a second-generation selective tau tracer. ^{18}F-MK6240 PET was found to discriminate with high accuracy between healthy controls (left column) and individuals with Alzheimer disease (right column). ^{18}F-MK6240 shows promise for integration of tau imaging into clinical practice and therapeutic trials.

brain and is not affected by potentially confounding off-target binding.

The second example came from Rowe et al., also from Austin Health (Melbourne) Commonwealth Scientific and Industrial Research Organisation (Brisbane and Melbourne), and the Florey Institute of Neuroscience and Mental Health (Melbourne, all in Australia), who reported on "Tau imaging in AD with ^{18}F-MK6240, a second-generation selective tau tracer" [409]. The participants included individuals with probable AD, mild cognitive impairment, and other dementias, as well as healthy age-matched controls. The tracer was found to discriminate with high accuracy in this so-far limited cohort between individuals with AD and healthy controls (Fig. 10). In addition, it was possible to establish relationships between accumulation of this PET tracer, severity of cognitive phenotype, and age. The authors noted that ^{18}F-MK6240 should "facilitate integration of tau imaging into clinical practice and therapeutic trials."

All these data are in support of the goal to develop accurate means to determine brain tau load in vivo. Future research with these promising second-generation tau tracers should define optimal imaging protocols, deal with the question of whether other tauopathies (such as progressive supranuclear palsy) are likewise approachable, and—as the ultimate proof—correlate the resulting PET data with histopathology results. We have learned from previous research with tau PET that a careful characterization of novel tracers is essential. This is of special importance in applications in which the target is less abundant in the brain and in which it is challenging to develop specifically binding tracers.

Conclusion

We can learn much from past activities in our field, as well as from its esteemed pioneers. As I attended sessions and visited the poster presentations at this meeting, I was, as always, impressed by the tremendous synergy that occurs when scientists from all over the world with similar interests meet to share their research and ideas. I was reminded of the 2 Peace Through Mind/Brain Science conferences organized by Henry N. Wagner, Jr., MD, and colleagues and held in Hamamatsu, Japan, in May 1988 and February 1989. These meetings launched a series of collaborations, many of which persist to this day, among North American, Asian, and European scientists. I am mentioning this meeting not only in deep admiration of Dr. Wagner's tremendous impact on the field of nuclear medicine and my open-mouthed amazement (now based on practical experience in preparing this lecture) at his extraordinary overview of and visionary thinking across the spectrum of our specialty's activities. The Hamamatsu meeting also reminds me that a peaceful and tolerant intercourse, one that allows researchers to travel to conferences without restrictions, is an important prerequisite for a prospering international science community from which physicians, other scientists, and patients can benefit. Thank you for the honor of delivering this summary of the neuroscience highlights at this meeting.