

2015 SNMMI Highlights Lecture: Neurosciences

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and delivered 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. The 2015 Highlights Lectures were delivered on June 10 at the SNMMI Annual Meeting in Baltimore, MD. Nicolaas I. Bohnen, MD, PhD, professor of radiology and neurology at the University of Michigan Medical School (Ann Arbor), spoke on neuroscience highlights from the meeting's sessions. The first 2015 highlights presentation appeared in the September issue of Newsline, and the remaining 2 will follow in November and December. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine (2014;57[suppl 3]).

This was a very exciting meeting in Baltimore, especially for the neurosciences. This summary of the neuroscience highlights from the meeting provides the opportunity to pay homage to one of the giants of nuclear medicine, Henry N. Wagner, Jr., MD, who for more than 30 years presented the annual Highlights Lecture and also catapulted the field of neurosciences to higher levels with the introduction of dopamine receptor imaging in 1983.

The highest award from the SNMMI Brain Imaging Council is the Kuhl–Lassen Award, which was presented on June 7 to John P. Seibyl, MD, Executive Director and Senior Scientist at the Institute for Neurodegenerative Disorders (New Haven, CT). Seibyl was a pioneer in dopamine transporter SPECT imaging in the early days and subsequently moved on to study and develop early-stage imaging methods to identify Parkinson disease (PD), Alzheimer disease (AD), and Huntington disease (HD). His Kuhl–Lassen lecture was titled “Molecular phenotyping individuals at risk for neurodegenerative disorders: imaging preclinical PD, AD, and HD.”

The winners of the Brain Imaging Council Young Investigator Awards, also presented on June 7, were all from outside the United States, emphasizing the continued growth of SNMMI from a national to an international society. The first-place winner was Matthias Brendel, MD, from Ludwig-Maximilian University in Munich (Germany), who reported with colleagues on “Glucose metabolism and glial activation in a transgenic AD mouse model: a triple-tracer PET study” [30]. The second-place winner was Flavia Niccolini, MD, MSc, from King’s College London, who, with colleagues from University College London, Imanova (London), and Imperial College London (all in the UK), reported that “Loss of phosphodiesterase 10A signaling is associated

with progression and severity in patients with PD” [31]. The third-place winner was Mandy Drabe, from the University of Leipzig (Germany), who reported with colleagues that “Serotonin transporter (SERT) gene methylation is associated with in vivo SERT availability and body mass index (BMI) in obese subjects” [34].



Nicolaas I. Bohnen, MD, PhD

Dementia and Neurodegenerative Conditions

AD remains a major theme in neuroscience across the broad spectrum of presentations at this meeting. We have made major advances in imaging amyloid- β and tau proteins in AD and now have 3 amyloid- β PET ligands approved by the U.S. Food and Drug Administration (FDA): ^{18}F -florbetapir, ^{18}F -flutemetamol, and ^{18}F -florbetaben. We are also pleased with the recent Centers for Medicare & Medicaid Services funding of the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study under a coverage with evidence development mechanism for almost 18,500 patient scans.

Farrar et al. from GE Healthcare/Amersham (Little Chalfont, UK) and the University of Pittsburgh (PA) reported on “Amyloid PET imaging: understanding the diagnostic accuracy of ^{18}F -flutemetamol derived from a large autopsy cohort” [609]. They presented a comprehensive study in which more than 100 patients were imaged and later followed up with postmortem assessment. The researchers found a >90% accurate correlation between ^{18}F -flutemetamol PET results and postmortem assessment of neuritic amyloid plaque density. Of 106 subjects, only 10 were assessed incorrectly by PET: 7 false-negatives and 3 false-positives. Eight of these subjects were classified at autopsy as having borderline pathology.

Although Alzheimer pathology is present in normal aging, the continuum of amyloid- β deposition in nondemented individuals is poorly understood. Nearly all individuals with Down syndrome will accumulate amyloid- β plaques by the age of 40 years, preceding dementia or cognitive changes. Lao et al. from the University of Wisconsin–Madison and the University of Pittsburgh (PA) reported on “ ^{11}C -PIB imaging in a nondemented Down syndrome population to determine the natural relationship between amyloid- β deposition and aging” [196]. They found that ^{11}C -PiB PET imaging could detect the appearance of elevated tracer binding in individuals as young as 36 years old, and that in many individuals, amyloid- β plaque deposition was most marked in the striatum, sometimes appearing without elevated cortical binding (Fig. 1). The pattern of amyloid plaque buildup in individuals with Down syndrome was different from that

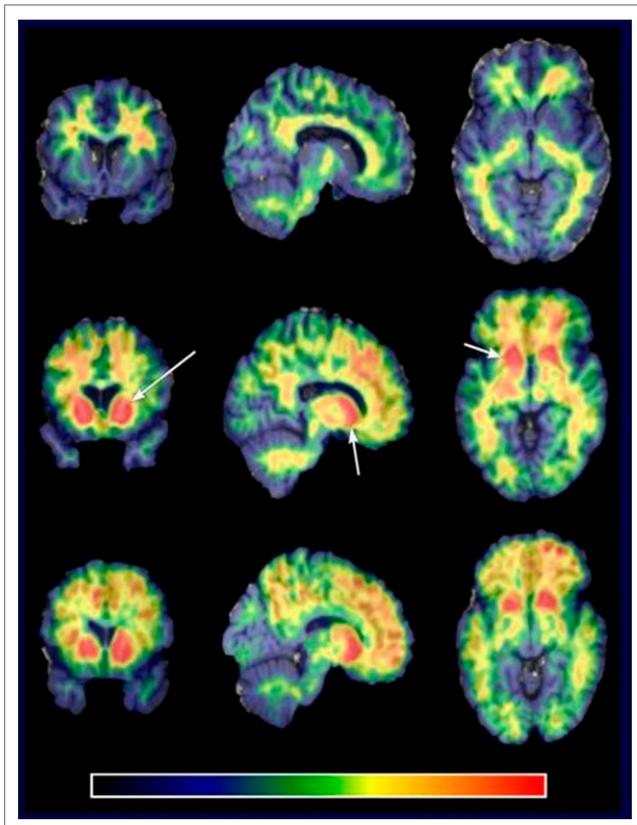


FIGURE 1. ^{11}C -PiB PET imaging in Down syndrome. Elevated tracer binding in individuals as young as 36 years old was noted, with amyloid- β plaque deposition marked in the striatum, sometimes appearing without elevated cortical binding (middle row).

seen in individuals with AD. In old-age onset AD, we typically see amyloid- β plaques first in the cortex, with subsequent spreading to other areas of the brain, including the limbic cortex, striatum, etc. In Down syndrome we see the reverse pattern: patients often develop amyloid- β deposition in the striatum before it is detected in the cortex.

Although we have several FDA-approved amyloid- β ligands available for clinical use, others are under investigation, as we recognize the need for innovation and continuous improvement in this field. Guruswami et al. from Washington University School of Medicine (St. Louis) reported on “Novel PET tracers for molecular imaging of AD” [412]. They reported on investigational ^{18}F -AI 182 and ^{18}F -AI 187 PET tracers, which show high affinity for AD homogenates ($K_d = 1.7$ nM), with fluorescent counterparts that do not interact with other biomarkers of neurodegenerative diseases. These agents bind to both diffuse and fibrillar amyloid plaques in tissues from humans with AD and traverse the blood-brain barrier to label parenchymal plaques in transgenic mice. The authors showed high initial brain uptake followed by retention in brains of transgenic mice and clearance in normal mice brains. These tracers have properties that are desirable for translational imaging agents, and the results suggest that they may be useful for imaging amyloid- β plaques at an earlier stage than current ligands.

Amyloid- β is playing a role in cognitive impairment not only in AD but also in PD. Meyer et al. from the University of Leipzig and the Hannover Medical School (both in Germany) reported on the “Influence of apolipoprotein-E (APOE) $\epsilon 4$ genotype on $\alpha 4\beta 2^*$ -nicotinic acetylcholine receptor ($\alpha 4\beta 2^*$ -nAChR) binding and cognitive dysfunction in PD:

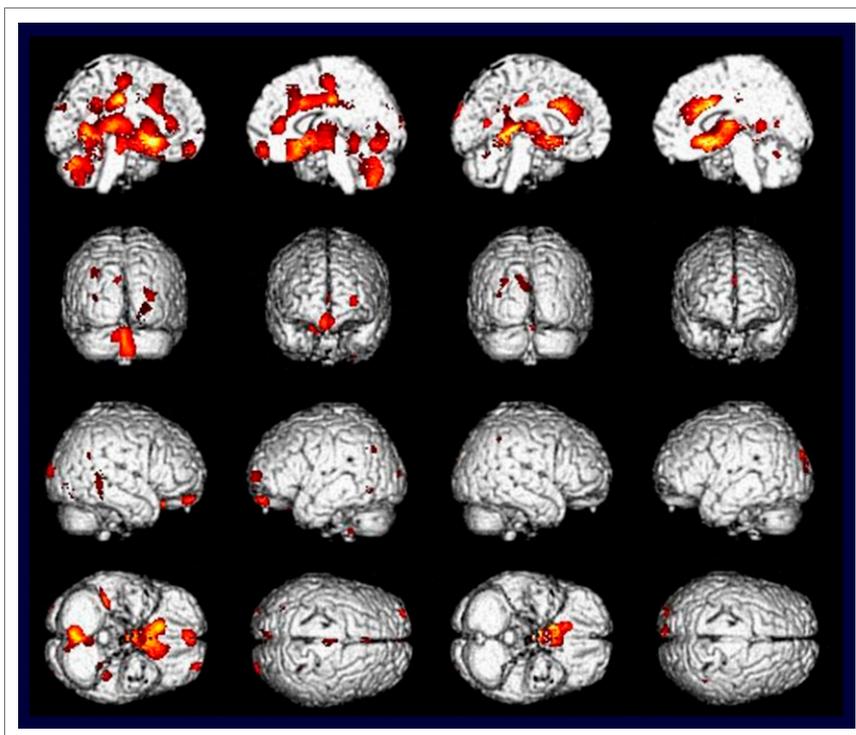


FIGURE 2. Apolipoprotein-E- $\epsilon 4$ (APOE- $\epsilon 4$) genotype, $\alpha 4\beta 2^*$ -nicotinic acetylcholine receptor ($\alpha 4\beta 2^*$ -nAChR) binding, and cognitive dysfunction in Parkinson disease (PD). Images constructed from $2\text{-}^{18}\text{F}$ -F-A-85380 PET findings. Columns 1 and 2 show statistically significant reductions in $\alpha 4\beta 2^*$ -nAChRs in APOE- $\epsilon 4$ -positive PD subjects compared to healthy controls; columns 3 and 4 show less severe reductions of $\alpha 4\beta 2^*$ -nAChRs in APOE- $\epsilon 4$ -negative PD subjects compared to healthy controls. More pronounced cognitive impairment in APOE- $\epsilon 4$ -positive PD patients may be an expression of more widespread subcortical and cerebellar $\alpha 4\beta 2^*$ -nAChR reductions.

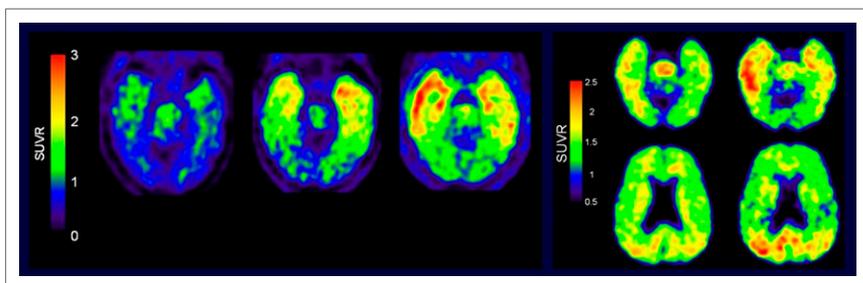


FIGURE 3. ^{18}F -THK-5351 PET and tau pathology. Left block: In elderly normal (left), mild Alzheimer disease (AD; Mini Mental State Examination [MMSE] = 25); middle), and severe AD (MMSE = 13; right). Right block: ^{18}F -THK-5351 (right) was superior to ^{18}F -THK-5117 (left) for PET visualization of tau deposition.

a 2- ^{18}F -F-A-85380 (2-FA) PET study” [82]. These researchers found that when PD patients and healthy controls were stratified according to APOE- ϵ 4 genotype status, significant differences in α 4 β 2*-nAChRs characterized the groups and that these differences correlated with cognitive impairment (Fig. 2). Findings suggest that more pronounced cognitive impairment in PD APOE- ϵ 4-positive patients may be an expression of more widespread subcortical and cerebellar α 4 β 2*-nAChR reductions.

Emerging tau protein ligands provided some of the most exciting neuroscience findings at this SNMMI meeting. In 2014 the SNMMI Image of the Year came from Okamura et al. at the Tohoku University School of Medicine (Sendai, Japan), who used ^{18}F -THK-5117 PET to image tau pathology. This year the group returned with an even better ligand, showing higher target-to-background ratios and less white matter uptake. The group reported on “PET imaging of tau pathology in mild cognitive impairment (MCI) and AD with ^{18}F -THK-5351” [138]. ^{18}F -THK-5351 binding was observed in common sites of tau pathology in AD, achieved a wider dynamic range than ^{18}F -THK-5117, and correlated with neurodegeneration and cognitive impairment in AD patients (Fig. 3).

Wooten et al. from Harvard Medical School, Massachusetts General Hospital, and Spaulding Rehabilitation Hospital (all in Boston) reported on “Pharmacokinetic evaluation of the tau radiotracer ^{18}F -T807” [414]. They presented initial pharmacokinetic characterization and modeling using the metabolite-corrected arterial input function, an approach that allows us to move forward with quantitative tau PET imaging. They found that the tau PET ligand ^{18}F -T807 metabolized primarily in polar metabolites (with a half-life of \sim 14 minutes using radio-high performance liquid chromatography methods) and resulted in rapid clearance from arterial plasma. Parametric images of this tau ligand in a patient with traumatic brain injury (TBI) and a patient with MCI are shown in Figure 4.

These findings suggest that ^{18}F -T807 may be a promising agent for expanding our abilities to clinically quantify tau deposition.

Pontecorvo et al. from Avid Radiopharmaceuticals (Philadelphia, PA) reported on “Relationships between ^{18}F -AV-1451 (aka ^{18}F -T807) PET tau binding and amyloid burden in cognitively normal subjects and patients with cognitive impairments suspected of AD” [245]. They reported on imaging findings from 220 individuals in clinical trials and included amyloid status, cognitive decline, and aging as factors in their analysis. After imaging and clinical assessment, individuals were assigned to different groups: young controls ($n = 16$); older cognitively normal, amyloid-negative ($n = 53$); older cognitively normal, amyloid-positive ($n = 5$); older cognitively impaired, amyloid-negative ($n = 49$); older, dementia, amyloid-negative ($n = 16$); older, cognitively impaired, MCI, amyloid-positive ($n = 47$); and older, cognitively impaired, AD, amyloid-positive ($n = 34$) subjects (Fig. 5). The researchers observed patterns of uptake spreading from the mesiotemporal lobe to the temporal cortex that correlated with group assignments and were consistent with the Braak et al. hypothesis of spreading of tau pathology. Also very intriguing was that fact that when comparing results from cognitively impaired amyloid-negative patients with those from amyloid-positive patients, it was clear that more significant tau binding correlated with positive amyloid binding status. Although the group analysis appears to conform to the Braak et al. staging of tau pathology in the brain, this does not appear to be the case at the individual level. For example, all participants whose images are shown in Figure 6 were both amyloid- β -positive and tau positive, but significant heterogeneity of regional tau deposition was seen, ranging from a more diffuse posterior cortical uptake to more isolated uptake in the temporal lobes. Michael Devous, PhD, also from Avid Radiopharmaceuticals, reported on “Identifying the topology of ^{18}F -AV-1451 (also known as

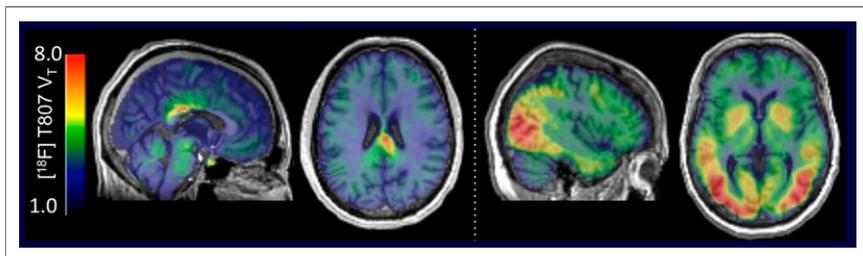


FIGURE 4. Parametric ^{18}F -T807 PET images showing tau pathology in traumatic brain injury (left 2 images) and mild cognitive impairment (right 2 images). This tracer appears to be promising for clinical quantification of tau deposition.

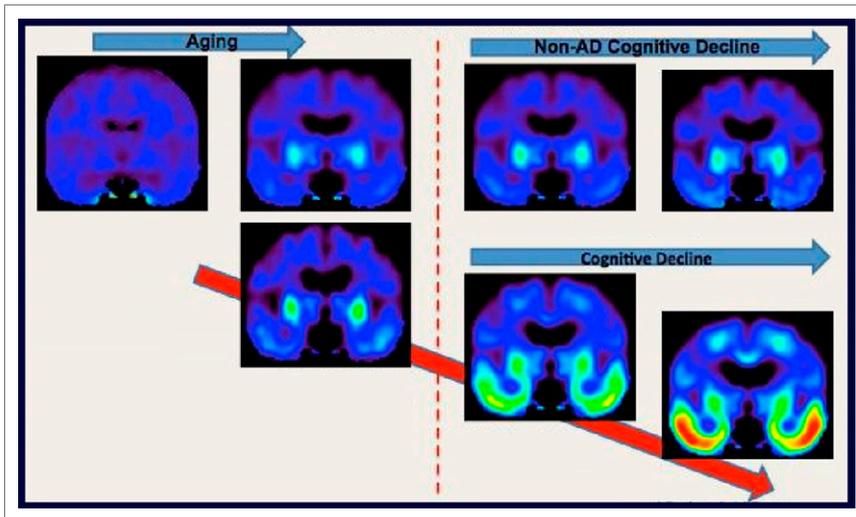


FIGURE 5. ^{18}F -AV-1451 (aka ^{18}F -T807) PET tau binding, amyloid burden, and aging. Top row represents tau PET group averages of amyloid- β -negative (left to right): young healthy (no abnormal tau binding), older cognitively normal (faint temporal lobe uptake), cognitively impaired (minimal temporal lobe uptake), and demented individuals (mild levels of tau deposition). Bottom images represent tau PET group averages showing increased tau deposition in the following amyloid- β -positive groups (left to right): older cognitively normal individuals (mild uptake), patients with mild cognitive impairment (moderate uptake), and patients with Alzheimer disease (most severe uptake).

T807) PET tau images for diagnosis and prognosis in neurodegenerative disorders” [139] and showed interesting data confirming that regional cerebral buildup of tau proteins correlated well with specific cognitive symptoms.

Traumatic Brain Injury

TBI is the focus of much current interest in the United States, with multiple well-publicized sports injuries and both acute and long-term concerns in the care of injured military personnel. One of the exciting applications of tau tracers developed for AD may be in TBI. Normandin et al. from Harvard Medical School, Massachusetts General Hospital, and Spaulding Rehabilitation Hospital (all in Boston) reported on “Tau deposition and white matter fiber integrity in TBI: an ^{18}F -T807 PET and diffusion tensor imaging study” [141]. The researchers showed data from past sustained concussions in football players and found

random uptake in various areas in the brain (Fig. 7, middle row). These data suggest that tau imaging could be used to study the pathophysiology of post-TBI symptoms. The researchers also showed that sites of tau deposition correlated locally with fiber tract disruptions of network connectivity in the brain using MR diffusion tensor imaging (Fig. 7, bottom row). These findings suggest the possibility of investigating anti-tau drug treatment applications in the management of patients with TBI.

Imaging Inflammation in the Brain

Inflammation imaging was another major focus at the meeting and is also of interest in AD and other neurologic disorders. Sandiego et al. from Yale University (New Haven, CT) and UCB Pharma SA (Braine-l’Alleud, Belgium) reported on an exciting study with findings that indicated that infusion of a “Systemic endotoxin induces a robust

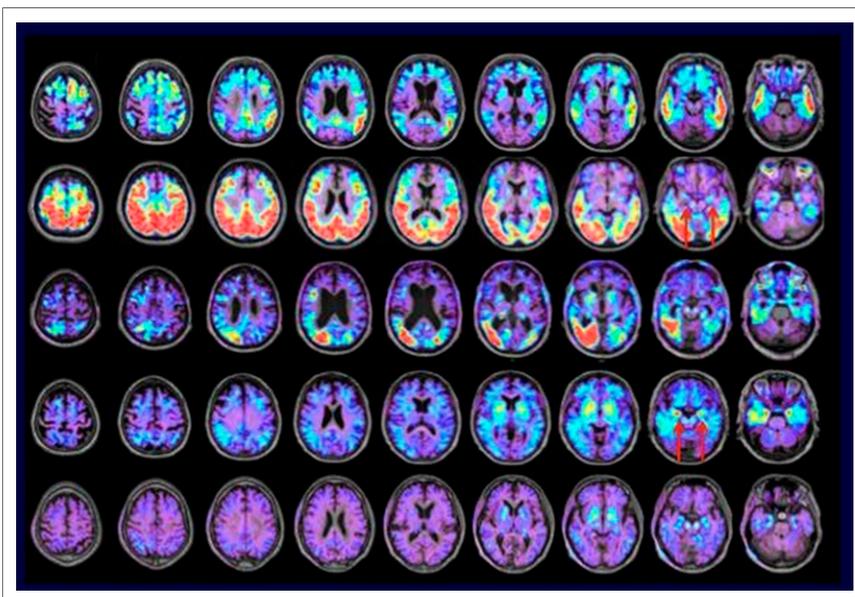


FIGURE 6. ^{18}F -AV-1451 (aka ^{18}F -T807) PET showed significant heterogeneity of tau distribution in amyloid- β -positive individuals with possible or probable Alzheimer disease. Top row: 81-year-old, Mini Mental State Examination (MMSE) = 21. Second row: 54-year-old, MMSE = 23. Third row: 82-year-old, MMSE = 23. Fourth row: 77-year-old, MMSE = 22. Bottom row: 65-year-old, MMSE = 23.

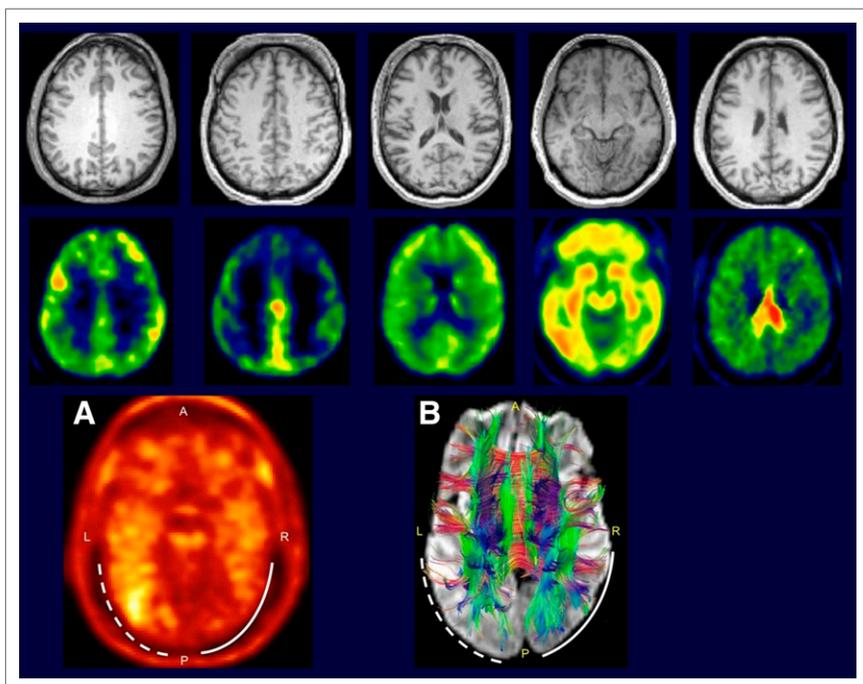


FIGURE 7. Tau deposition and loss of white matter integrity in traumatic brain injury (TBI) assessed by ^{18}F -T807 PET and diffusion tensor MR imaging. Top row: T1-weighted MR imaging from individual TBI patients, showing no gross deficits. Middle row: ^{18}F -T807 PET distribution volume ratios from individual TBI patients, showing heterogeneous uptake patterns ranging from very focal to more diffuse cerebral areas of tau deposition. Bottom row: (A) tau PET image of a TBI patient with more focal right parietal uptake corresponding to (B) regionally more pronounced fiber tract disruption on diffusion tensor MR imaging.

increase in microglial activation measured with ^{11}C -PBR28 and PET in humans” [468]. The study included 8 healthy male volunteers (24.9 ± 5.5 years old) who underwent ^{11}C -PBR28 PET imaging at baseline and then were infused intravenously with a systemic immune endotoxin that induced neuroinflammation. Patients reported fatigue, fever, and shivering. The researchers also collected peripheral inflammatory markers, and PET imaging was repeated at the peak of peripheral cytokine levels and clinical symptoms. Results indicated that this systemic endotoxin induces a robust increase in microglial activation and that this can be

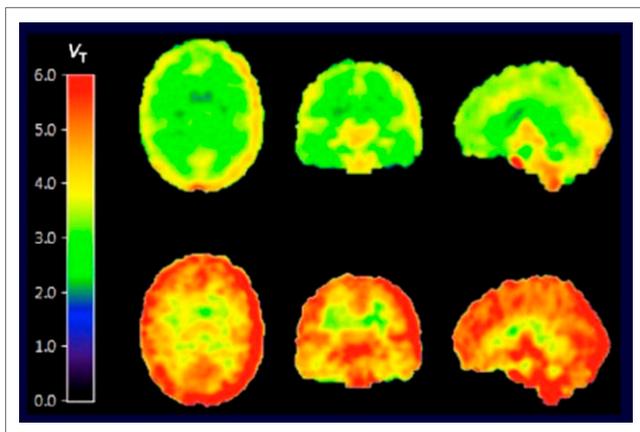


FIGURE 8. ^{11}C -PBR28 PET and microglial activation in inflammation in the human brain. Endotoxin significantly increased microglial activation, peripheral inflammation, and sickness symptoms from baseline (top row) to time of peak serum inflammatory cytokine and sickness symptom levels (bottom row).

effectively measured with ^{11}C -PBR28 PET (Fig. 8). An interesting observation was that brain radiotracer uptake correlated with the peak of peripheral inflammatory immune markers (e.g., TNF- α , IL-6, and IL-8) as well as clinical symptoms. This ability to measure brain microglial activation with ^{11}C -PBR28 PET imaging and the documented association with inflammation provides a novel approach to test the efficacy of neuroprotective and anti-inflammatory drugs for neurodegenerative central nervous system diseases.

New Neuroscience Ligands

We have focused for many years on visualizing amyloid- β buildup or production in the brain, and we now know that this is a very slow process that may begin decades before the appearance of clinical symptoms. This buildup is the result not only of increased production but also of decreased clearance of soluble amyloid- β . Amyloid- β is naturally

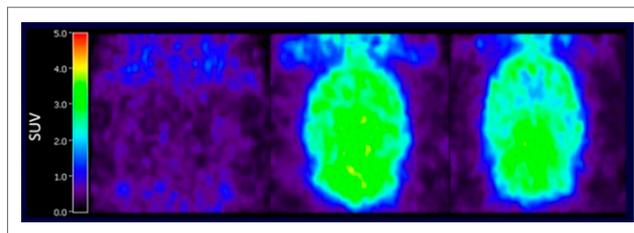


FIGURE 9. ^{18}F -MC225 PET imaging of P-glycoprotein (P-gp) in rats. Distribution volume at baseline (group 1, left) increased 2–4-fold after blocking P-gp with tariquidar (group 2, middle). Blocking both P-gp and breast cancer resistance protein (BCRP) with tariquidar and the BCRP inhibitor Ko143 (group 3, right) did not significantly increase the distribution volume compared to group 2, indicating selectivity of the ^{18}F -MC225 radioligand for P-gp over BCRP.

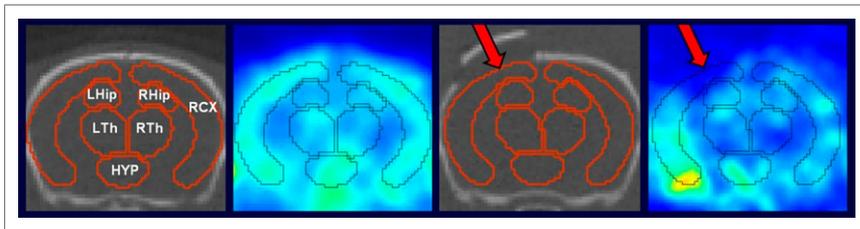


FIGURE 10. ^{18}F -ASEM of $\alpha 7$ -nicotinic acetylcholine receptors ($\alpha 7$ -nAChRs) in a traumatic brain injury model. Left block: CT (left) and ^{18}F -ASEM PET (right) imaging in a control rat. Right block: 1 day after controlled cortical impact; CT (left) and ^{18}F -ASEM PET (right). PET imaging showed acute reductions in $\alpha 7$ -nAChRs at the trauma site (arrow).

present in the brain, and by identifying ways to affect routine clearance of this peptide we may be able to prevent future buildup of amyloid plaques. We also know that specific proteins at the blood–brain barrier, like P-glycoproteins (P-gps), breast cancer resistance proteins, or multidrug resistant protein–1, can function as efflux carriers for soluble amyloid- β peptides. Hence, activation of these efflux carriers is an interesting target for future treatments that might potentially prevent the buildup of amyloid- β in the presymptomatic stages of AD. Therefore, ligands to visualize those efflux carriers could become very important. Savolainen et al. from University Medical Center Groningen (The Netherlands), University of Bari (Italy), and the VU University Medical Center (Amsterdam, The Netherlands) reported on “Preclinical evaluation of a P-gp substrate ^{18}F -MC225 in rats” [472]. The investigators found that the metabolism rate was moderate: 1 hour after injection, 15% of the parent compound was intact in the plasma and 76% in the brain. Using appropriate blocking studies, the researchers were able to successfully visualize P-gp activity in the brain (Fig. 9). Efflux carrier imaging approaches like this may have the potential to aid the development of new treatment approaches in AD aimed at facilitating clearance of soluble amyloid- β .

Hillmer et al. from Yale University (New Haven, CT) and Helmholtz-Zentrum Dresden–Rossendorf (Leipzig, Germany) reported on “A comparative study of ^{18}F -ASEM and ^{18}F -DBT-10, 2 novel PET tracers for the $\alpha 7$ -nAChR in nonhuman primates” [33]. Full validation chemistry and

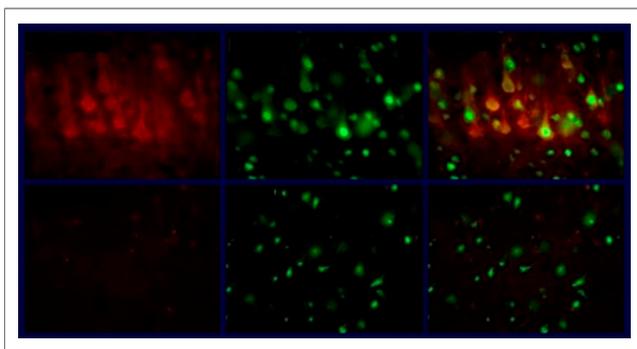


FIGURE 11. Immunofluorescence staining 2 days after sham operation (top row) or controlled cortical injury (bottom row) showed significant reductions in neuronal anti- $\alpha 7$ -nicotinic acetylcholine antibodies (left) and anti-NeuN neuronal markers (middle) in injured mice. Staining results are merged in images at right. These findings correlated closely with ^{18}F -ASEM PET imaging of $\alpha 7$ -nicotinic acetylcholine receptors in a rat model of traumatic brain injury.

modeling studies were performed in rhesus monkeys. Findings showed that the 2 radiotracers have similar kinetic properties and are both suitable candidates for PET assay of $\alpha 7$ -nAChRs. An example of the ^{18}F -ASEM tracer in preclinical studies was provided by Horti et al. from Johns Hopkins University (Baltimore, MD), who reported on “PET imaging of $\alpha 7$ -nAChR with ^{18}F -ASEM in a TBI model” [471]. Figure 10 shows CT and PET imaging at 1 day after controlled cortical impact in a rat. ^{18}F -ASEM PET shows acute reductions in $\alpha 7$ -nAChRs at the trauma site. The researchers also found that ^{18}F -ASEM binding was time dependent, decreasing bilaterally on days 1 and 3 post-injury but increasing at day 26, indicating that $\alpha 7$ -nAChRs were normalizing over time. They confirmed this with immunofluorescence staining comparing sham-operated and cortically injured rats (Fig. 11) and concluded that ^{18}F -ASEM holds promise for studying the cholinergic pathway of the post-TBI biochemical cascade in humans.

Brain Tumors

Several interesting presentations at the meeting focused on brain tumors. Nioche et al. from the Hôpital d’Instruction des Armées du Val-de-Grâce (Paris, France) and INSERM/Commissariat à l’Énergie Atomique et aux Énergies/ Université Paris-Sud/Le Service Hospitalier Frédéric Joliot (Orsay, France) reported that “Coanalysis of textural pattern and peak standardized uptake value (SUV_{peak}) in

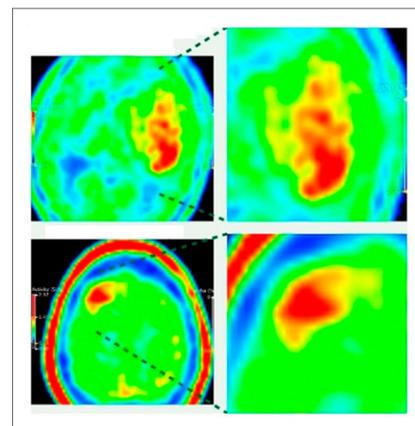


FIGURE 12. Coanalysis of textural pattern and SUV_{peak} in ^{18}F -DOPA PET/CT in glioma staging. Top row: anaplastic oligodendroglioma (WHO grade 3; homogeneity = 0.76; entropy = 1.22; short-run emphasis [SRE] = 0.60; metabolic volume [MV, cm^3] = 106; SUV_{peak} = 1.8). Disease was staged as low-grade with

SUV_{peak} data alone but was changed to high-grade with addition of entropy data. Bottom row: oligodendroglioma (WHO grade 3; homogeneity = 0.81; entropy = 0.83; SRE = 0.60; MV [cm^3] = 8; SUV_{peak} = 1.3). Disease was staged as low-grade with SUV_{peak} data alone, which was confirmed with addition of entropy data.

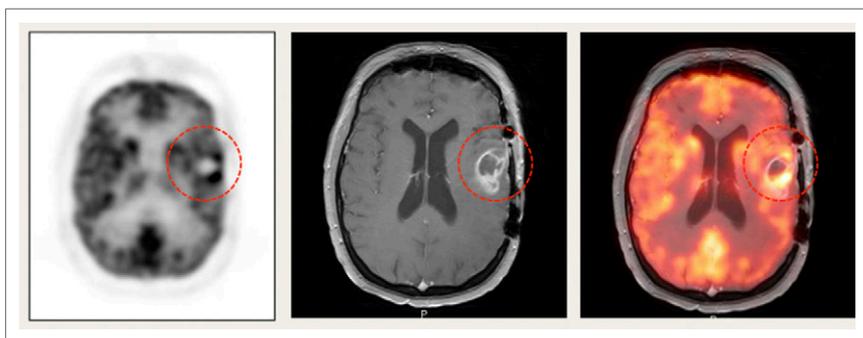


FIGURE 13. ^{18}F -FDG PET/MR and ^{18}F -FDG PET/CT in differentiation of radiation necrosis from tumor recurrence in high-grade gliomas. Postoperative image analysis included (left to right) ^{18}F -FDG PET with MR-based attenuation correction (left); T1-weighted gadolinium-enhanced MR imaging (middle); and fused ^{18}F -FDG PET and T1-weighted gadolinium-enhanced MR images (right).

^{18}F -DOPA PET/CT significantly improves glioma staging” [327]. The study included 81 patients with gliomas (52 newly diagnosed and 29 recurrent). The investigators were not only looking at the typical ^{18}F -DOPA parameters, such as SUV and metabolic volumes but also at tissue/tumor textural analysis parameters (such as entropy and homogeneity). They found that in recurrent tumors SUV_{peak} alone could discriminate low- from high-grade gliomas (86% of tumors accurately classified) but that in newly diagnosed tumors, neither SUV nor metabolic volume could make this distinction (only 58% of tumors accurately classified). By combining SUV and entropy, however, significant improvement in low- from high-grade glioma differentiation was possible (67% of tumors accurately classified) (Fig. 12). The authors concluded that coanalysis of ^{18}F -DOPA PET SUV_{peak} and well-selected tumor texture parameters has the potential to improve classification of newly diagnosed gliomas.

Badve et al. from University Hospitals Case Medical Center (Cleveland, OH) reported on a “Comparison of ^{18}F -FDG PET/MR to qualitative and semiquantitative ^{18}F -FDG PET/CT in differentiation of radiation necrosis from tumor recurrence” in high-grade gliomas after surgery [1607]. They studied patients not only with PET/CT but also with MR imaging with enhancement. Data were analyzed in 2 ways: (1) conventional PET/CT quantitative uptake data, where SUV_{max} , SUV_{mean} , and $\text{SUV}_{\text{median}}$ were considered; (2) and with MR used for attenuation correction, with additional information added from gadolinium-enhanced T1-weighted MR images (Fig. 13). PET/MR analysis

was found to be superior to either qualitative or semiquantitative traditional PET/CT analysis in distinguishing radiation necrosis from tumor recurrence.

Psychiatry

Wong et al. from Johns Hopkins University (Baltimore, MD) and the University of Pittsburgh (PA) reported on “Interactions of dopamine and serotonin in subtypes of Tourette syndrome and obsessive-compulsive disorder (OCD)” [304]. This group previously showed that striatal dopamine release is increased in Tourette syndrome. In the new report at the SNMMI meeting, they showed that striatal dopamine release is increased even more when Tourette syndrome is present with OCD. Furthermore, the investigators showed data suggesting that increased striatal dopamine release correlates with specific clinical OCD subtypes, implicating an intriguing interaction between the dopamine and serotonin systems in OCD. The authors speculated that an increase in SERTS in coexisting Tourette syndrome and OCD may reflect a dopamine-serotonin interaction whereby SERTS fail to maintain intrasynaptic serotonin levels and cause an increased release of dopamine in these patients.

Obesity continues to be a major health problem, and more sophisticated scientific insights in this area are greatly needed. Vettermann et al. from the University of Leipzig (Germany) and the Max Planck Institute (Leipzig, Germany) reported on “Changes of human SERT availability in human obesity prior and 6 months after an integrative treatment approach” [528] (Fig. 14). The study included 27 obese

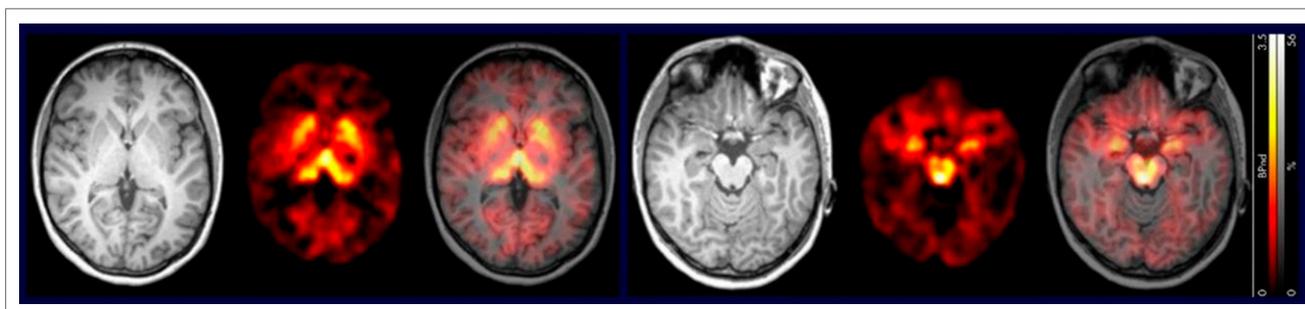


FIGURE 14. ^{11}C -DASB serotonin transporter (SERT) PET/MR imaging in human obesity. Parametric maps of SERT binding potential (middle images) and coregistered individual MR images at the striatum/thalamus (left set of images) and brainstem (right set of images) anatomic levels. After weight loss, decreases in SERT occurred in key brain areas of appetite control.

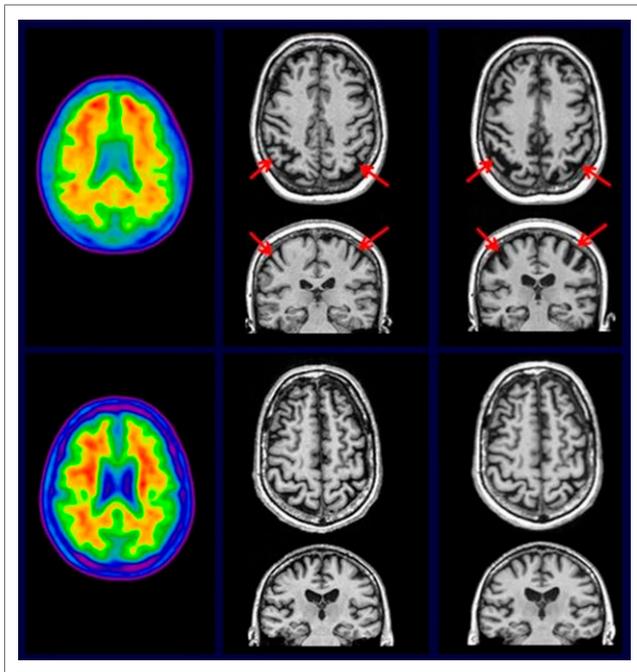


FIGURE 15. ^{18}F -AV45 amyloid- β PET and MR in patients with mild cognitive impairment and subsyndromal depression symptoms. Top block, individuals not on selective serotonin reuptake inhibitors (SSRIs); left to right: amyloid-positive baseline ^{18}F -AV45 PET; baseline T1-weighted MR imaging; repeat MR imaging at 2-year follow-up, showing a gray matter volume loss of 10.3%. Bottom block, individuals on SSRI therapy; left to right: amyloid-positive baseline ^{18}F -AV45 PET; baseline T1-weighted MR imaging; 2-year repeat MR imaging at follow-up, showing a gray matter volume loss of 1.2%. These results suggest that antidepressant SSRI drugs use may potentially slow progression of AD.

but metabolically healthy individuals ($\text{BMI} > 35 \text{ kg/m}^2$) and 15 lean healthy controls ($\text{BMI} < 25 \text{ kg/m}^2$). At baseline all participants underwent SERT-selective ^{11}C -DASB, atlas-based, volume-of-interest PET/MR image analysis to obtain regional cerebral SERT binding potential data. Obese participants were then treated with integrative weight-reduction therapy. Scans were repeated at 6-month follow-up. The investigators found that the integrative weight-reduction therapy resulted in a significant decrease in BMI in the obese persons. The researchers also found that the higher the reduction in BMI, the greater was the decrease in brain SERT binding (i.e., representing increased serotonin synaptic activity). These changes occurred in key brain areas of appetite control, such as the dorsolateral prefrontal cortex, anterior cingulate cortex, insula, and amygdala. Findings suggest a central neuromodulatory role for serotonin in appetite control and may provide a therapeutic target for management of obesity.

An interesting and important study came from Weinstein et al. from Columbia University and NY State Psychiatric Institute (New York, NY), who reported on “Blunted striatal dopamine release in cannabis dependence” [32]. Study participants included healthy controls

and young adults who had been using cannabis on a nearly daily basis since their teens (for >10 years). The researchers found that dopamine release in the striatum was blunted in these long-term cannabis users. Even more worrisome was the finding that these decreases in dopamine release in the striatum correlated with lower working memory and learning performance.

Another interesting study came from Leurquin-Sterk et al. from University Hospital Leuven (Belgium), who reported on “Age dependency of type 5 metabotropic glutamate receptor (mGluR5) and its relationship to novelty seeking and MR spectroscopy (MRS)-derived glutamate concentration: a ^{18}F -FPEB PET study in healthy volunteers” [305]. They found that mGluR5 activity in the thalamus correlated with the tendency of individuals to seek novelty. In the anterior cingulate cortex, mGluR5 binding was negatively associated with glutamine concentration as determined by MRS. They also found that mGluR5 uptake appeared to decrease with age across most brain regions, perhaps explaining why, as we get older, we seem to have less inclination for thrill-seeking behaviors than we did as teenagers.

Brendel et al. from Ludwig-Maximilian University in Munich (Germany) reported on “Amyloid PET in MCI patients with subsyndromal depressive symptoms” [525] (Fig. 15). These researchers used data from the Alzheimer’s Disease Neuroimaging Initiative collective to perform a longitudinal analysis of amyloid plaque burden, brain atrophy, and cognition over a 2-year follow-up duration in amyloid-positive MCI subjects with subsyndromal depressive symptoms. We know that serotonin is not only important in OCD and obesity, as we have seen, but also in AD. We also know from cross-sectional studies that cognitively normal elderly individuals who take selective serotonin reuptake inhibitors (SSRIs) may have less amyloid- β buildup in the brain than those who are not taking these antidepressant drugs. This study included 412 patients with MCI and subsyndromal depressive symptoms who underwent ^{18}F -AV45 amyloid- β PET and MR imaging at baseline and 2-year follow-up. The researchers compared imaging changes between those individuals on SSRIs and those who were not. Amyloid- β -positive patients ($n = 210$) were stratified according to baseline amyloid- β PET findings. The investigators found that amyloid-positive patients with subsyndromal depression and SSRI treatment showed distinctly less cognitive interval worsening compared to individuals without SSRI treatment. Longitudinal MR imaging findings identified less pronounced brain atrophy progression in subjects on SSRIs compared to those without this anti-depressant treatment. These results suggest that serotonergic antidepressant drugs may potentially slow the progression of AD.

Conclusion

This was an exciting meeting, with many presentations that have direct relevance to today’s practice and even more striking implications for the future of the neuroscience field.