2017 SNMMI Highlights Lecture: Neuroscience

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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 2017 Highlights Lectures were delivered on June 14 at the SNMMI Annual Meeting in Denver, CO. In this issue we feature the lecture by Alexander Drzezga, MD, a professor in the Department of Nuclear Medicine at University Hospital of Cologne/University of Cologne, Germany, who spoke on highlights in the neurosciences. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine (2017;58[supp 1]).

Before I begin this presentation I would ask everyone to spend a minute with me in remembering David E. Kuhl, MD. Dr. Kuhl passed away only 2 weeks before this meeting. He was not only a pioneer in nuclear medicine and PET imaging but also an extraordinary innovator across the spectrum of brain imaging. His group was the first to perform 18F-FDG PET imaging of the brain in the 1970s, and he continued to develop medical applications of PET and other tracers and technologies for more than 4 decades. I hope that his dedication and enthusiasm for the field of nuclear medicine will continue to inspire all of us in this exciting field.

Neurodegenerative Disorders

When we look at pathologies of the central nervous system (CNS), neurodegeneration and associated protein aggregation pathologies are clearly the most frequent current targets of imaging. Other CNS disorders are associated with different specific imaging targets: neuropsychiatric disorders with receptor/transmitter changes, vascular disorders with perfusion and metabolic changes, immunologic disorders with inflammatory changes, tumors with proliferation markers, and trauma with neuronal/synaptic loss. What stands out in this pairwise assignment, however, is that neurodegeneration as a complex multifactorial process is associated with almost all of these specific pathologies and their corresponding imaging biomarkers. Research in this field may thus provide insights on various pathologies as well as on the value of different novel modalities, tracers, and analytic approaches that may well extend to have near-term relevance in other disorders. Once again neurodegeneration was a major focus of presentations at the SNMMI Annual Meeting.

Villemagne et al. from Austin Health (Melbourne), CSIRO Preventative Health Flagship (Melbourne and Brisbane), Edith Cowan University (Perth), the Florey Institute (Melbourne), and the University of Melbourne (all in Australia) reported on “Assessing the natural history of Aβ-amyloid deposition with 4 different amyloid tracers using the Centiloid transformation” [560]. They have enrolled more than 200 participants (with mild cognitive impairment, Alzheimer disease [AD], and controls) in this study, in which they performed repeated amyloid scans with several of the available amyloid tracers (11C-Pittsburgh compound B, 18F-flutemetamol, 18F-florbetapir and 18F-NAV4694). They assessed rates of global and regional Aβ deposition and normalized these data using the Centiloid scale, which allows expression of Aβ quantitative values as universal units for more standardized imaging comparisons. They have now been following this population for more than 10 years. Perhaps the most interesting finding is that amyloid may be accumulating in the brain over a period of as much as 30 years before characteristic symptoms appear. They also demonstrated that longitudinal data can be pooled from different tracers through application of the Centiloid conversion. Rates of amyloid accumulation varied in different regions of the brain, and in AD the rate of Aβ deposition seems to slow, approaching a plateau. Knowledge about these nonlinear dynamics of amyloid deposition in the brain will not only be instrumental in diagnosis and prediction of neurodegeneration but, in the future, will be important for initiation and monitoring of therapeutic studies.

Ceccaldi, from the Hôpital de la Timone (Marseille, France), a consortium of researchers from hospitals and tertiary memory centers in France and Germany, and investigators from Piramal Imaging GmbH (Berlin, Germany) reported on the “Impact of florbetaben PET imaging on diagnosis and management of patients with suspected AD eligible for cerebrospinal fluid (CSF) analysis in France” [561]. They evaluated 205 individuals in whom neurodegenerative disease was suspected but for whom CSF analysis was not feasible or had been inconclusive. These patients underwent 18F-florbetaben PET imaging. The researchers found that a remarkably high proportion (67%) of diagnoses were changed after evaluation of PET results, with much higher confidence in final diagnoses (81.5% with improved confidence). Management was changed in 80% of patients after PET. These kinds of data are of great value with regard to approval, acceptance, and reimbursement of amyloid imaging in our field.

Tau imaging: Tau imaging continued to be a major neuroscience focus at this meeting. Pascual et al. from University...
of Texas Physicians, Houston Methodist Neurological Institute, and Houston Methodist Research Institute (all in Houston, TX) reported that “Tau deposition in nonfluent primary progressive aphasia follows the language network” [627]. The study included 6 individuals with this rare aphasia who were amyloid-negative (therefore not suffering from AD) and 8 healthy controls, all of whom underwent tau imaging with ¹⁸F-AV-1451 PET. The aphasia patients also underwent MR tractography. A separate group of 35 healthy controls underwent functional blood oxygenation level-dependent MR imaging to establish normal network connectivity using as seed the volume with the greatest tau load in the patient group. They found tau deposits in the anterior and posterior neuronal clusters of the syntactic language network, areas we know to be involved in nonfluent aphasia. Using functional MR analysis in controls, they demonstrated that these regions are usually interconnected. They also identified a thinning (most pronounced anteriorly) of the left arcuate fasciculus, which connects the 2 clusters of the language network. The analogous contralateral fiber tracts in the right hemisphere were entirely intact. This in vivo evidence supports the neuronal network hypothesis, suggesting that tau propagates in a prion-like matter across the brain, progressively affecting neural function.

One focus of several presentations at this meeting was “off-target” binding of tau tracers, with the investigation of observations of tracer binding in regions not usually affected by tau pathology. In particular, much discussion has centered around monoamine oxidase B (MAO-B), an enzyme in the outer mitochondrial membrane to which some of the tau tracers appear to bind. Villemagne et al. from Austin Health (Melbourne), the Australian eHealth Research Center (Brisbane), CSIRO Health and Biosafety (Melbourne), and the Florey Institute (Melbourne; all in Australia) reported on “Combining categorical and continuous tau burden measures from 4 different tau tracers: ¹⁸F-AV1451, ¹⁸F-THK5317, ¹⁸F-THK5351, and ¹⁸F-MK6420” [626]. Figure 1 shows ¹⁸F-THK5351 PET images before and after administration of selegiline (5 mg, twice daily for 5 days), an MAO-B inhibitor. Tracer uptake decreased strikingly on the left side in this AD patient after application of the MAO-B inhibitor. This provides evidence that this tracer is also binding to a relevant extent to MAO-B, meaning that the tracer is nonspecific to tau.

As a result of similar observations, several studies at this meeting addressed “second generation” tau tracers, and I will briefly highlight 2 of these. Lohith et al. from KU Leuven (Belgium), Merck & Co. (West Point, PA), and Merck Sharp & Dohme (Brussels, Belgium) reported on “Quantification of ¹⁸F-MK-6240, a new PET tracer targeting human neurofibrillary tangles in brains of healthy elderly and subjects with AD” [277] (Fig. 2, top). Barret et al. from AC Immune (Lausanne, Switzerland), the Institute for Neurodegenerative Disorders (New Haven, CT), Molecular Neuroimaging (Woodbridge, CT), and Piramal Imaging GmbH (Berlin, Germany) reported on “Initial clinical
PET studies with the novel tau agent 18F-PI-2620 in AD and controls" [630] (Fig. 2, bottom). In both studies, images show clear uptake in AD patients in regions affected by tau pathology, with no nonspecific uptake in healthy subjects, indicating that this kind of second generation of uptake tracers may be worthwhile for applications in the future and also for longitudinal studies.

**Phosphodiesterases**: One highly interesting target in the brain with regard to CNS disorders may be the phosphodiesterases (PDEs). These are enzymes that metabolize second messengers, such as cAMP/cGMP, to their inactive types, AMP/GMP. These enzymes play a role in Parkinson disease (PD), depression, and schizophrenia and may offer potential therapeutic targets. Two key factors that may influence the activity of PDEs are protein kinase A, which may increase activity, and DISC1, which may decrease activity and is disrupted in schizophrenia. Ooms et al. from the University of Fukui (Japan), Johns Hopkins University (Baltimore, MD), Kyoto University (Japan), Merck & Co. (West Point, PA), and the National Institute of Mental Health (Bethesda, MD), reported on “Optimization and use of a bolus infusion protocol to quantify in vivo changes of PDE4 binding in a DISC1 knockout mouse model” [654]. They investigated 11C-(R)-rolipram binding (as a measure of PDE4 activity) using PET in C57BL/6 mice. They showed that 11C-(R)-rolipram binding increased, consistent with increased activation of PDE4 in this DISC1-deficient mouse model. Their findings were confirmed by results from enzyme assay. In addition to providing evidence that PDE4 is regulated by DISC1, they also concluded that PET imaging can be used to monitor PDE4 activity and associated changes in the brain.

Pagano and colleagues from King’s College London and researchers from Imanova Ltd. (London), the UCL Institute of Neurology (London), and the University of Manchester (all in the UK) reported on “PDEs and striatal pathways in PD” [418]. They examined 12 patients with PD and 12 controls using 11C-IMA107 to assess PDE10A activity and 11C-(R)-rolipram to assess PDE4 activity. They also applied diffusion tensor imaging–based MR fiber tracking to measure PDE expression in direct and indirect striatal output pathways in PD. They found that PDE10A was decreased in PD patients in the direct striatal output pathway, whereas PDE4 activity was decreased in both striatal pathways (Fig. 3). This is interesting, because it suggests the possibility for development of therapeutic interventions to reestablish these pathways and potentially have an effect on performance and outcome in PD patients.

**Inflammation**

Inflammation also was the focus of much interest at the SNMMI meeting, across the range of disease entities and anatomic sites. Earlier in my talk I listed the various disorders and pathologies we can now image. Just as neurodegeneration may exhibit various neuropathologies, inflammatory changes can have effects on various types of disorders of the brain: neurodegeneration, neuropsychiatric disorders, vascular disorders, immunologic disorders, tumors, and trauma. This, in turn, means that inflammation is a promising and already fruitful target for imaging, with significant consequences for expanding our knowledge of the CNS.

Zanotti-Fregonara et al. from the Houston Methodist Research Institute (TX), Janssen Research and Development (Titusville, NJ), Johnson & Johnson (San Diego, CA), and the National Institute of Mental Health (Bethesda, MD) reported that “Unmedicated major depressive disorder is associated with neuroinflammation” [139]. They studied translocator protein (TSPO) binding of 11C-PBR28, which measures activated microglia, in the subgenual prefrontal and anterior cingulate cortices. The study included 12 patients with unmedicated major depressive disorder, 16 with medicated disease, and 20 healthy controls. All patients underwent 11C-PBR28 PET imaging and arterial blood sampling. The researchers found in these relatively small groups that TSPO binding was significantly increased in unmedicated patients with depression, by 31% compared with healthy controls and by 27% compared with medicated patients. This, of course, has a number of implications. It suggests that depression is influenced by inflammation in the brain and that perhaps targeting inflammation with specific drugs could be beneficial.

Petrulli and colleagues from Yale University (New Haven, CT) and Denali Therapeutics (South San Francisco, CA) reported that “Systemic inflammation enhances stimulant-induced striatal dopamine elevation” [132]. They showed...
conducted a very complex study in which $^{11}$C-raclopride PET was used to assess striatal dopamine levels. In 8 healthy volunteers, the researchers used methylphenidate, a dopamine reuptake inhibitor, as a stimulus to increase synaptic dopamine levels. They also used intravenous injection of lipopolysaccharide (LPS), which is known to induce a neuroinflammatory environment. The subjects were scanned 4 times to determine methylphenidate-induced dopamine elevation under both LPS and placebo pretreatment conditions. They found that dopamine elevation induced by methylphenidate was significantly greater when subjects were pretreated with LPS than with placebo. This was reproducibly true in 7 of the 8 subjects (Fig. 4). The authors concluded that the amplification of stimulant-induced dopamine signaling in the presence of systemic inflammation may have important implications for studies of addiction and other diseases of dopamine dysfunction.

Fujita and colleagues from the Uniformed Services University, the National Institutes of Health, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (all in Bethesda, MD) reported that “PET imaging of TSPO detects inflammation after traumatic brain injury (TBI) in the areas with no MRI change” [205]. They examined 23 individuals with TBIs (7 extra-axial hemorrhage, 8 microhemorrhage and diffuse axonal injury, and 8 contusion) who showed TBI-related changes on MR imaging. Participants were followed for up to 2 years after the traumatic event. TSPO PET imaging was performed using $^{11}$C-PBR28 at an average of 383 days after injury, and PET scans were also performed in a group of healthy age-matched controls. Measurement using arterial input showed widespread increase in TSPO after extra-axial hemorrhage, even long after the injury (Fig. 5). Highly interesting was the fact that PET detected increases in TSPO in brain areas that showed no detectable MR changes. This suggests that the inflammatory process may be ongoing well after brain trauma and that PET may identify patients in whom posttraumatic neuroinflammation is a significant component of tissue response to injury that cannot be identified with MR alone. TSPO PET could be useful as a biomarker of chronic inflammation for future research, again with potential therapeutic implications.

Bankstahl et al. from the Hannover Medical School and the University of Veterinary Medicine Hannover (Germany) reported on “Multimodal evaluation of neuroinflammation-associated changes during epileptogenesis using small animal PET and MRI” [206]. They performed longitudinal multimodal neuroimaging studies in the lithium–pilocarpine rat model of epilepsy, where injection of lithium and pilocarpine induces an epileptic focus. They assessed these animals longitudinally with PET tracers for glucose ($^{18}$F-FDG) and amino acid ($^{18}$F-FET) turnover and microglia activation ($^{11}$C-PK11195) and with contrast-enhanced MR for blood–brain barrier integrity. The results are summarized in Figure 6 and show that, with repeated examinations after inducing the epileptic focus, $^{18}$F-FDG was increased on PET after 24 hours and edema shortly later, but the inflammatory reaction imaged with $^{11}$C-PK11195 was apparent up to 1 week after the original insult. This is an excellent example of the value of preclinical imaging with PET to allow identification of longitudinal interactions of specific pathologies in the brain, information previously accessible at best by serial sacrifice of numerous animals at each time point.

Kim et al. from the National Institute of Mental Health (Bethesda, MD) and Stanford University (CA) reported that...
“Novel PET radioligands show that, in rhesus monkeys, cyclooxygenase 1 (COX-1) is constitutively expressed and COX-2 is induced by inflammation” [203]. We know that TSPO imaging in the brain is not the optimal method for addressing inflammation, because it is variable depending on genetic type, with high and low binders. The search is on for new inflammatory tracers. Much interest is focused on cyclooxygenase inhibition and function, with which we are all familiar in nonsteroidal anti-inflammatory medications. The researchers studied 2 PET tracers developed in their lab, 11C-PS13, targeting COX-1, and 11C-MC1, targeting COX-2, in normal rhesus monkeys before and at days 1, 3, and 8 after injection of LPS (Fig. 7). They found that COX-1 seems to be expressed constitutively in major organs such as the spleen, gastrointestinal tract, kidney, and brain. After inflammatory challenge, no brain changes were noted in COX-1, whereas significant COX-2 changes were noted. The authors concluded that these radioligands have potential as biomarkers for measuring neuroinflammation in various disorders and as targets for therapeutic drugs.

Brain Tumors

Inflammation also plays a role in brain tumors. Unterrainer et al. from the Ludwig-Maximilians University (Munich) and the University of Regensburg (both in Germany) reported on “TSPO PET for glioma imaging using the novel ligand 18F-GE-180: first-in-human results in high-grade glioma patients” [204]. TSPO expression has been reported to be upregulated in gliomas. The 18F-GE-180 tracer is a novel third-generation TSPO receptor ligand with improved target-to-background contrast. The study included 12 patients with high-grade gliomas who underwent 18F-GE-180 PET imaging at initial diagnosis or recurrence prior to radiotherapy. Patients were divided on the basis of TSPO-polyorphism genotyping into high- and low-affinity binders (6 each). Eight of the 12 patients underwent follow-up PET at 5–6 weeks after radiotherapy termination. The resulting images (Fig. 8) showed extraordinarily high tumor-to-background contrast (median SUVmax, 2.1; range, 2.5–5.8) in all gliomas. Tumoral and background uptake values did not differ between high- and low-binders. Volumetric comparisons with MR images showed significantly larger biological tumor volumes on PET than MR-based gross tumor volumes, with high 18F-GE-180 binding even in areas without contrast enhancement on MR imaging. Reductions in
TSPO expression seemed to mirror responses to radiation therapy, and reductions in biological tumor volumes were also apparent. The authors concluded that $^{18}$F-GE-180 PET is a promising tool for high-grade glioma delineation with the potential for influencing radiotherapy planning and possibly also response assessment, because pronounced and differing changes of tumoral TSPO expression could be observed after radiotherapy.

The same group presented a study that addresses brain tumor volume in early and late acquisition phases with amino acid PET. Winkelmann et al. from the Ludwig-Maximilians University (Munich, Germany) reported on “$^{18}$F-FET PET-based biological tumor volume of glioma: comparison of early vs. standard summation images” [72]. They compared PET-derived biological tumor volumes in early and “late” standard summation images and evaluated the influence of the World Health Organization (WHO) tumor grade and individual molecular genetic profile on volume delineation in 222 newly diagnosed and untreated glioma patients. It is known that more malignant tumors have an early uptake peak and less malignant tumors seem to have a slower increase, but the effects of different phases of acquisition on measured tumor volume had not been studied. Dynamic $^{18}$F-FET PET imaging was acquired for clinical reading at 20–40 minutes after injection and also at 5–15 minutes after injection to differentiate high- from low-grade tumors. In 53% of the cases a significant volume difference of $>20\%$ between the biological tumor volumes in early and standard summation images was found, with correlations to the WHO grade. In addition, the molecular genetic profile was associated with biological tumor volume delineation in early vs. standard summation images, where 46% of isocitrate dehydrogenase (IDH)–wildtype gliomas had significantly larger volumes in the early summation images. IDH-wildtype tumors are known to be more aggressive, and we see in imaging from this study that early acquisition in the IDH-wildtype resulted in larger biological tumor volumes, whereas in the IDH mutation late acquisition resulted in larger volumes (Fig. 9). This is most intriguing and requires further evaluation, because it may have a number of practical implications for everyday use, particularly in integrating individualized quantification of PET parameters into treatment planning and therapy monitoring.

Neuropsychiatry/Addiction

Ceccarini et al. from KU Leuven and the University of Antwerp (Wilrijk; both in Belgium) reported on “Recovery of decreased metabotropic glutamate receptor 5 (mGluR5) availability in abstinent alcohol-dependent subjects” [14]. This presentation received the SNMMI Brain Imaging Council Young Investigator Award. They used dynamic $^{18}$F-FPEB PET to determine whether decreased mGluR5 availability in alcohol-dependent individuals normalizes during longer term (6 months) abstinence and whether initial mGluR5 imaging parameters can predict relapse. Sixteen patients were imaged at 2 weeks of medically supervised abstinence (baseline) and at 2 and 6 months of a detoxification program. Controls were imaged at the same time points.
timepoints. They found that during abstinence, alcohol-dependent participants showed gradual increases in mGluR5 availability in cortical and subcortical brain areas compared to baseline, up to levels observed in healthy controls after 6 months, except in the hippocampus, nucleus accumbens, and thalamus, which had not recovered fully (Fig. 10). Notably, higher striatal mGluR5 availability at baseline was observed in patients who relapsed during the 6-month follow-up period. Better recovery of mGluR5 in the striatum was also associated with higher reduction in 2 different aspects of questionnaire-assessed alcohol craving. Their finding of lower mGluR5 availability at baseline in abstainers and less availability in relapsers led them to conclude that this downregulation of glutamate receptors may be a compensatory effect, perhaps protecting from glutaminergic excesses in alcoholism, so that individuals with higher neuroplasticity might be better protected from relapsing. This is interesting because, once again, it may have therapeutic implications.

Summary

Neurodegeneration and inflammation were clearly dominant topics in the neuroscience track at this year’s SNMMI meeting. Neurodegeneration is characterized by multiple pathologies, many of which are already accessible to molecular imaging procedures. The development of novel tau tracers with less nonspecific binding was also a focus. Inflammation is present in many CNS disorders and, therefore, represents an ideal target for imaging in general, with the caveat that we do not, as yet, have ideal tracers. Evidence presented at this meeting indicates that this may be changing. New and very promising tracers (for example, for COX inhibition) were introduced. Altogether my impression was that the nuclear neuroimaging field is thriving and holds tremendous and rapidly growing potential for development, selection, and monitoring of novel therapeutic approaches in the neurosciences.

I would like to conclude this presentation, as I did last year, with a reference to Henry N. Wagner, Jr, MD. In his book, A Personal History of Nuclear Medicine (2006), Dr. Wagner mentioned that his most influential teacher was Curt P. Richter, PhD (1894–1988), who was a biologist, psychobiologist, and geneticist at Johns Hopkins for many years. Dr. Richter is known today for advancing the concept of the biological clock. (I should note that Dr. Richter was born in Denver, CO, site of this year’s SNMMI meeting, and studied engineering in Germany, this year’s SNMMI highlight country). Dr. Wagner recalled that Dr. Richter’s metaphor for his scientific life of discovery and insight was that of “walking along the shoreline, picking up the interesting shells.” I hope that this lecture was able to offer a few “interesting shells” from the broad and diverse array of neuroscience presentations at this year’s meeting. I want to thank all of you in attendance and all those who submitted interesting and innovative data, of which, unfortunately, I could show only a small proportion.

FIGURE 10. 18F-FPEB PET imaging and recovery of decreased metabotropic glutamate receptor 5 (mGluR5) in abstinent alcohol-dependent individuals. Controls (far left) underwent imaging, as did abstinent alcohol-dependent participants at (second left to right): alcohol cessation baseline and 2- and 6-month alcohol abstinence follow-up. During abstinence, alcohol-dependent participants showed gradual increases in mGluR5 availability in cortical and subcortical brain areas compared to baseline, up to levels observed in healthy controls after 6 months, except in the hippocampus, nucleus accumbens, and thalamus, which had not recovered fully.
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J Nucl Med. 2017;58:9N-15N.

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