QIBA SPECT Biomarker Committee: Overview and Status Update

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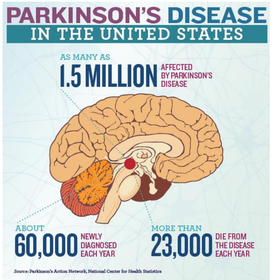
Quantitative Imaging Biomarkers Alliance® RSNA

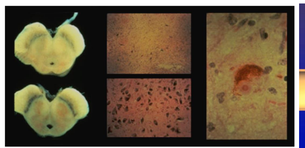
Parkinson's Disease

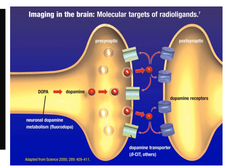
Facts & Societal Impact



Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive bradykinesia, rigidity, tremor, and loss of balance. A significant minority of \patients with idiopathic PD will become demented. There are an estimated 1-1.5 million Americans with PD, with approximately 60,000 new diagnoses per year. Men are 1.5 times more likely to develop PD than women. The average age of onset is 61 years old, although 4% who develop PD are younger than age 50. There have been significant advances in the scientific understanding of the pathophysiology of the disease, but there is yet much to learn. The pathologic hallmark of the disease is the α-synuclein-containing Lewy body.

Histopathology



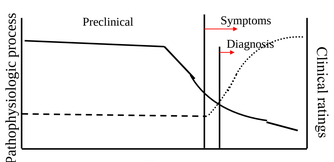


BRAAK Staging- Spread of Lewy Bodies
Stage 1: Dorsal motor nucleus of the vagal nerve; anterior olfactory structures
Stage 2: Lower raphe nuclei; locus coeruleus
Stage 3: Substantia nigra; amygdala; nucleus basilis of Meynert (clinical diagnosis made at this stage)
Stage 4: Temporal mesocortex
Stage 5: Temporal neocortex; sensory association and premotor areas
Stage 6: Neocortex; primary sensory and motor areas

The primary neuropathic event in PD is the progressive accumulation of synuclein containing inclusions called Lewy bodies. By Braak stage 3 these involve nigrostriatal dopamine pathways resulting in motor symptoms Neuronal loss results in decreased presynaptic markers projecting to striatum, like the dopamine transporter, DaT.

Imaging Biomarkers

Further investigations are needed to better understand the relationship between DaT and α-synuclein deposition in the brain relative to the clinical symptoms of PD. Critical to these investigations is the use of biomarkers to assess the natural history of the disease as well as to assess the effect of therapies to prevent or slow disease incidence and progression.



Imaging of Parkinson's Disease has been directed at changes in brain anatomy (global and regional), glucose metabolism, cerebral perfusion and neurochemistry (neurotransmitters, receptors, enzymes, and markers of neuroinflammation), as well as deposition of abnormal proteins. There is currently one FDA approved I-123 labelled DaT tracer with additional candidate radiotracers under investigation.

RSNA 2016

Profile Status

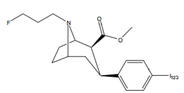
DaT Profile for Quantitative SPECT

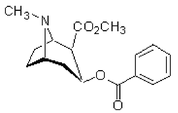
The Profile addresses each of the tasks in the workflow from technical preparedness of the SPECT scanner and the process at the imaging facility to preparing for and performing the DaT SPECT exam to the analysis and interpretation component. Below and to the left is a time sequenced presentation (top to bottom) of the workflow tasks to which technical specification thresholds are set by the Profile. To the right is an outline of some specific items applicable to the DaT Profile.

- **Prep**: • Equipment Calibration • Patient
- **Acquisition**: • Timing • Longitudinal Consistency
- **Reconstruction**: • Optimized for Image Quality • Consistency across scanners
- **Analysis**: • Assure accuracy and consistency
- **Reporting**: • Common measurand • Statistical significance

Decisions made for first version of the Profile:
- Same scanner, same analysis tool and same radiotracer across time points as requirement
- Includes use of free standing SPECT and SPECT/CT, but not SPECT/MR
- Cross sectional measurand is specific binding ratio, SBR (SUVR-1)
- Longitudinal masurand is change in SBR
- Phantom scanning requirement includes use of anthropomorphic phantom to assess striatal uptake
- No partial volume correction to be used

Items under active committee discussion:
- Discriminatory Claim: can current Profile really distinguish patients with neurodegenerative disorders from matched controls?
- Absolute quantification, where the measurand becomes the concentration of radioactivity in each voxel.
- Several technical and biological sources of variability and bias, such as normal variations in regional cerebral perfusion influencing delivery of the radiopharmaceutical



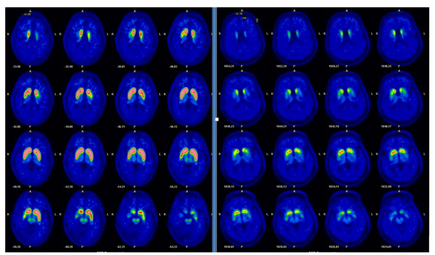


DaT Radiopharmaceuticals. Left: ^{123}I ioflupane for SPECT; right: unlabeled cocaine. Tropanes like ioflupane are more metabolically stable in vivo resulting in better imaging characteristics than ^{11}C radiolabeled cocaine.

DaT SPECT Imaging Interpretation

Radiotracers are currently used to estimate DaT density in patients with movement disorders. The QIBA group is defining technical performance requirements to use ioflupane quantitatively. The current Claim will be used to help assess new patients during their initial presentation, as well as across time points (longitudinal claim) to assess the degree of change necessary to be considered significant.

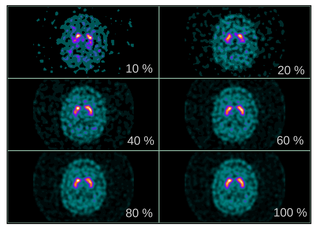
Axial images to the right, first panel, shows the distribution of DaT in a 76 year old healthy volunteer with relatively symmetric uptake in the striata. The panel on the far right is a 77 year old PD patient demonstrating left-right asymettry, and more signal reduction in putamen (posterior) than caudate (anterior). The putamen contralateral to side of symptom onset is the most severely reduced with approximately 50% of age-expected uptake when first motor symptoms manifest



Phantom Projects: Physical & DRO

Acquisition & Reconstruction

Objective: To determine the acquisition parameters and reconstruction methods for measuring SBR in ^{123}I ioflupane SPECT with higher precision and reduced bias.



Question 1:
What is an adequate count level for good quantification?

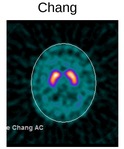
When does accuracy and precision break down?

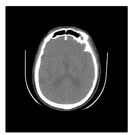
- Is this the same for FBP and OSEM?
- What about the OSEM non-negativity constraint?

Question 2: What are the effects of physical corrections?

Attenuation Correction

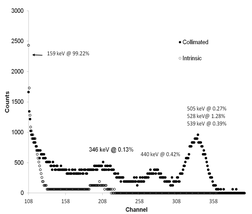
Chang CT





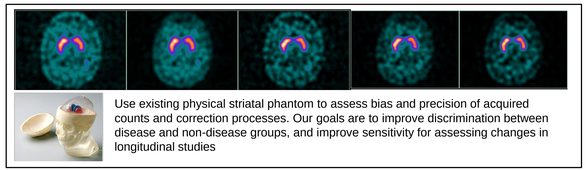
- readily available
- operator dependent
- SPECT/CT only
- Radiation dose

Correction for Scatter (Septal Penetration)



- Septal penetration of higher energy emissions are problematic with I123
- Triple Energy Window correction produces noisy projections

Resolution Modelling
- How will it control noise?
- What are the effects of overshoot (Gibbs) artefact?
- Will noise control and 'resolution recovery' allow a move to MEGP collimators?

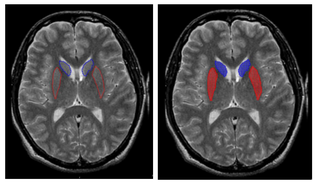


Use existing physical striatal phantom to assess bias and precision of acquired counts and correction processes. Our goals are to improve discrimination between disease and non-disease groups, and improve sensitivity for assessing changes in longitudinal studies

Various QIBA projects and activities have been funded in whole or in part with Federal funds from the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Department of Health and Human Service, under Contracts Nos. HHSN268201000050C, HHSN268201300071C, and HHSN268201500021C.

SPECT DaT Uptake Digital Reference Object (DRO)

Goal: Design and construct a prototype brain Digital Reference Object (DRO) phantom with properties appropriate for testing software used to characterize SPECT DaT uptake patterns in a quantitative fashion.



Section through a T2w MRI patient image

ROIs representing the caudate and putamen

This patient was from the UW database and illustrates anatomical characteristics of caudate and putamen

In the first phase of the project, the processed T2w image will be converted to a SPECT DaT uptake image by defining uptake values in each region (i.e., caudate, putamen and reference region). Images with and without noise and spatial blurring will be produced.

In the second phase of the project, the SimSET software package will be used to produce projection sinograms representing clinical imaging studies and data will be reconstructed to produce realistic levels of noise and spatial resolution blurring.

DRO will then be used to (1) evaluate software used to characterize SPECT DaT uptake patterns, and (2) provide a base for construction of a physical phantom.

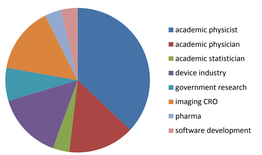
Planned Activities 2017

Profile: Writing the Profile has been the DaT SPECT Biomarker Committee's (BC) primary activity to date. The document has been released for public comment. Each suggested revision will be addressed by the BC and resolved. The committee's goal is to provide a published Profile by early 2017.

Checklist: Each of the performance requirements in the Profile has been compiled as a checklist. This list has been developed as a tool whereby an imaging site can be evaluated for conformance with the Profile.

Feasibility Testing: The checklist can also be used as a quality control tool to assess the ability (or practicality/willingness) of a site to perform each of the Profile's performance specifications. The results of this feasibility test will then be used to streamline and tighten the Profile performance requirements. Subsequently, it is envisioned that an organizational effort will support this qualification process built around checklists in turn based on the Profile.

DaT SPECT Biomarker Committee



The DaT SPECT Biomarker Committee is composed of volunteers who work together in a pre-competitive, international forum. The current composition of the of the group is indicated by stakeholder category in the pie chart at left. Membership is open to qualified and interested individuals. Questions or comments about QIBA or regarding material on this poster should be addressed to qiba@rsna.org

The SPECT Biomarker Committee is deeply grateful for all the help and support from the professional staff at the RSNA who made this work possible by mediating about 4 meetings each month for over a year among many other things that were essential for any success that results..