

## DaTQUANT: The Future of Diagnosing Parkinson's Disease

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**Brief Title:** DaTQUANT: Diagnosing Parkinson's Disease

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## Abstract

Idiopathic Parkinson's disease (PD) is a progressive neurological condition which affects the dopamine transporters in the substantia nigra of the brain. Currently, over ten million people are living with this disease world-wide, with thousands of newly diagnosed and undiagnosed cases added every year. The disease is difficult to differentiate from other similar disorders, as symptoms widely vary and can mimic other conditions. Classic Parkinson's disease symptoms may look similar to essential tremor and other parkinsonian syndromes. The 123I Ioflupane dopamine transporter protocol differentiates Parkinson's disease from essential tremor through in-vivo testing with single-photon computed tomography (SPECT) imaging. The dopamine transporter (DaT) protocol commonly relies on a semi-quantitative analysis and visual interpretations of the images, which may produce inaccurate results due to human error. DaTQUANT software (General Electric Healthcare) was created in 2013 as an adjunct processing tool with advanced quantitative uptake methods and a designated normals database for a more accurate assessment of a patient's case. DaTQUANT has proven to be a vital protocol component for an accurate differentiation of Parkinson's disease from essential tremor. Current use of the software has been rather limited, so a greater push for education and implementation will be key for its success.

**Key words:** Parkinson's disease, 123I Ioflupane, dopamine transporter, DaTQUANT®

As many as one million Americans live with Parkinson's disease, which is more than the combined number of people diagnosed with multiple sclerosis, muscular dystrophy and Lou Gehrig's disease. Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this number does not reflect the thousands of cases that go undetected (1). In correlation to the ten million cases world-wide, this statistic brings attention to the critical issue of diagnosing and managing the disease. Presently, there are no definitive blood tests or imaging modalities that can diagnose Parkinson's disease per se, as the cause remains largely unknown and symptoms widely vary. In trying to understand what Parkinson's disease is, researchers have discovered the origins of symptom causation within the substantia nigra region of the brain. This information has been primarily gained through post-mortem autopsies of patients who lived with symptoms related to parkinsonian syndromes. Existing diagnostic practices need to be improved upon to better treat those living with the disease before it is too late. This continuing education article will provide an overview of Parkinson's disease, current diagnostic practices, the 123I Ioflupane dopamine transporter scan, and the processing tool known as DaTQUANT. The protocol has been shown to effectively rule out Parkinson's disease from essential tremor, providing a patient with more information towards a diagnosis and symptom management.

**Parkinson's disease:** Parkinson's disease is categorized as a paralysis agitans, or disorder of movement control due the degeneration of neurons within the substantia nigra (2). Located in the ventral midbrain, the substantia nigra is lined with an extensive network of axonal processes that innervate the basal ganglia (2). The basal ganglia regulates motor control, together with a wider variety of roles such as motor learning, executive functions, behavior, and emotions (2). The substantia nigra is a distinct region within the basal ganglia, consisting of the substantia nigra pars compacta and the substantia nigra pars reticulata (2). Both sections are characterized

by a blackened appearance from a dark polymer pigment known as neuromelanin (2). FIGURE [1A and 1B]. The dopamine transporter neurons reside in the substantia nigra pars compacta, while gamma aminobutyric acid neurons fill the pars reticulata portion. The substantia nigra region communicates with the caudate nucleus and putamen regions of the basal ganglia through the release of dopamine, the neurotransmitter responsible for an organism's fluid movements. Parkinson's disease manifests as the deterioration of the substantia nigra dopamine neurons which ultimately slows the release of dopamine needed for seamless movement. A patient experiencing parkinsonian-related symptoms may notice a slight resting tremor, rigidity, bradykinesia, hypokinesia, and loss of postural reflexes (2). These cardinal symptoms are common to other clinical parkinsonian syndromes such as progressive supranuclear palsy, multiple system atrophy, vascular parkinsonism, cortico-basal ganglionic degeneration, and dementia with Lewy bodies (2). These disorders are categorized as parkinsonian syndromes due to the relative symptoms experienced which may appear as idiopathic Parkinson's disease. This makes for a difficult diagnosis and ultimately symptom management, as several of these are considered drug-resistant parkinsonian syndromes. The drug commonly prescribed for symptom management is a chemical precursor of dopamine known as levodopa, which is combined with the enzyme inhibitor carbidopa (3). The medication is a natural chemical that crosses the blood brain barrier and is converted to dopamine to replenish the low or non-existent levels present. Levodopa is combined with carbidopa, which protects levodopa from early conversion to dopamine outside the brain, which prevents or lessens side effects such as nausea (4). There are several symptom treatment options for Parkinson's disease, but levodopa has been shown to be most efficacious in managing day to day symptoms experienced by the patient.

The timeline of disease indication to a definitive diagnosis can range from two months to

18 years depending on the clinical presentation (5). According to Ba and Martin (2015), “...misdiagnosis of conditions such as essential tremor, vascular parkinsonism, multiple system atrophy, and progressive supranuclear palsy implies that 5-25% of patients with an initial diagnosis of Parkinson’s disease may be inappropriately managed” (5). This issue leads the discussion to what is currently practiced for an accurate evaluation of Parkinson’s disease from the other common syndromes.

**Current Diagnostic Practices:** Neurologists have developed a method for initial assessment and monitoring Parkinson’s disease progression through a symptom-based diagnosis. The technique includes a timeline of physical and neurological symptoms in conjunction with a medical history and existing physical capabilities and/or limitations. This has been the standard of diagnosis since the 1950’s when Parkinson’s disease was delineated from other neurologically debilitating conditions across the spectrum of diseases (6).

Another tool utilized is the Unified Parkinson’s Disease Rating scale, which is the most well-established scale for assessing patient disability and impairment (7). This evaluative tool was created by the Movement Disorder Society Task Force of the International Parkinson and Movement Disorder Society (7). The scale was formulated with a quantification of symptom severity, numbering zero as normal to four as the most acute disease symptoms experienced (7). The results of scale may be included during the initial clinical assessment of a patient’s symptoms.

Other potentially useful diagnostic imaging studies include high field strength (1.5 Tesla) heavily T2 weighted Magnetic Resonance Imaging, 18Fluorine-fluorodopa positron emission tomography, 11Carbon-raclopride imaging of dopamine D2 receptors, and brain parenchyma sonography (7). Although these neuroimaging techniques are promising, further refinement in

resolution and improvement in sensitivity are needed before their diagnostic potential is fully realized (7).

**123I Ioflupane Mechanism of Action:** In current practice, the 123I Ioflupane dopamine transporter protocol is the only diagnostic imaging modality approved by the United States Food and Drug Administration for the evaluation of Parkinson's disease (8). On January 14<sup>th</sup>, 2011, General Electric (GE) Healthcare announced the approval of the 123I Ioflupane injection: "the DaT scan Ioflupane 123I injection is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes. In these patients, DaT scans may be used to help differentiate essential tremor from tremor due to idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The DaT scan is an adjunct to other diagnostic evaluations" (8).

123I Ioflupane is used to demonstrate the location and concentration of dopamine transporters in the synapses (9). Dopamine transporters refer the transmembrane proteins in the presynaptic membrane of the dopaminergic synapse that transport dopamine from the synaptic cleft to the postsynaptic dopamine receptors. FIGURE [2]. They can also transport dopamine back into the nigrostriatal nerve terminals for either storage or degradation (9). The 123I Ioflupane tracer specifically tags to this component of the nigrostriatal dopaminergic pathway located on the presynaptic nerve terminals to determine the integrity of the system's functionality in releasing dopamine.

According to the Society of Nuclear Medicine Practice Guideline for Dopamine Transporter Imaging, "DaT concentrations are lower in presynaptic Parkinsonian syndromes, which include Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy,

and are also lower in dementia with Lewy bodies” (9). Parkinsonian syndromes such as essential tremor, drug-induced parkinsonism, and psychogenic parkinsonism will have relatively normal presynaptic dopaminergic loss. In differentiating the levels of dopaminergic loss, the tracer can demonstrate a significant variance between Parkinson’s disease from essential tremor. However, the protocol cannot discriminate idiopathic Parkinson’s disease from multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, or any other parkinsonian syndromes so far mentioned. Despite this limitation, a DaT scan can adequately provide a patient with an accurate in-vivo assessment at the striatal level.

**Dopamine Transporter Protocol:** The DaT scan protocol begins with obtaining the patient’s clinical history and contraindications, followed by the administration of a thyroid blocking agent such as Lugol’s solution. After the thyroid blocking agent is given, there is an hour wait before the intravenous tracer injection. The adult dose is generally 185 MBq (5 mCi), with a range of 111–185 MBq (3–5 mCi) (9). Imaging occurs three to six-hours after tracer injection to allow the maximum uptake into the dopamine transporters. After the three to six-hour period, the patient is imaged with SPECT on a multiheaded nuclear medicine gamma camera. Images of the patient’s entire brain are taken over a 35 to 40-minute scan time, with proper head positioning. Accurate head placement will provide precise visualization of the basal ganglia and specific regions involved such as the caudate nucleus and putamen. Head placement can be achieved with positioning devices such as a head cradle, straps, and cushions.

Minor variations in the protocol are allowable and are usually site-specific, however this outline serves as a general guideline to what is typically performed. Detailed image acquisition techniques may be found in the Society of Nuclear Medicine Practice Guideline for Dopamine Transporter Imaging with <sup>123</sup>I-Ioflupane SPECT 1.0 (9).

After images are obtained, the processing steps begin with a sinogram of the data as well as motion correction and image reformatting into coronal, sagittal, and transaxial slices. The slices for diagnostic interpretation are chosen based on a visual selection of the most intense tracer uptake. The slices of the transaxial plane with the highest striatal activity in the basal ganglia are used in a process known as semi-quantification. The Society of Nuclear Medicine Protocol defines this as “the ratio of activity in a structure of interest to activity in a reference region” (9).

For semi-quantification of <sup>123</sup>I-Ioflupane DaT SPECT, binding ratios are calculated by comparing activity in the striatum with activity in an area of low DaT concentration (usually the occipital area) (9). To obtain these ratios, regions of interest for the putamen and caudate nucleus of each hemisphere need to be designated. There are four regions of interest (ROI) methods: manual ROIs, manual volumes of interest (VOIs), more advanced automated systems using VOIs, and voxel-based mathematic systems (9). The manual ROI method is most often used and will be discussed as the principle method when processing the image slices in this article. However, this technique usually leads to the highest instance of interobserver variability which may translate into an inaccurate interpretation of the data.

In visual interpretation, the striatal shape, extent, symmetry, and intensity differentiate normal from abnormal. The normal striata on transaxial images should look crescent or comma-shaped and should have symmetric well-delineated borders. Abnormal striata will have reduced intensity on one or both sides, often shrinking to a circular or oval shape (9).

These observations of normal versus abnormal help delineate essential tremor from idiopathic Parkinson’s disease and the other parkinsonian syndromes. In the final interpretation, those with normal uptake images are assumed to have essential tremor, whereas any

abnormalities will be deemed Parkinson's disease or the other parkinsonian syndromes. In conjunction with the semi-quantification analysis from the ROI selections, the visually-ascertained results often present a general estimation of tracer uptake in the images.

Despite these results, there is the on-going issue of interobserver variability in ROI selection as well as the lack of an established normals database to compare with individual scan results. The ROI selection methods, varying camera models in use, and processing tool variations all contribute to the lack of a recognized standard of image interpretation for the DaT scan protocol. Here the GE Healthcare software program known as DaTQUANT is recognized as a key processing component to remedy these issues at hand. Other helpful components of the software will be discussed as additional features to promote widespread use.

**DaTQUANT:** Launched in 2013 by GE Healthcare, DaTQUANT is available for use with any GE Healthcare DaT scan protocol and approved SPECT camera. According to GE Healthcare (2018): “an aid in the assessment of the degree of in-vivo expression of the dopamine transporter (DaT), DaTQUANT assists in the detection and quantification of the loss of functional striatal dopaminergic neuron terminals, a loss correlated with Parkinson's disease. Quantitative analysis may help assess the extent and intensity of the striatal <sup>123</sup>I Ioflupane signal” (10).

Instead of manually selected ROIs, the software uses a predefined voxel of interest (VOI) template for automatic asymmetry measurements and putamen:caudate uptake ratios. Here the degree of variation in the regions of uptake can be quantified in a volumetric measurement, including the ratio of uptake between the distinct portions. The software is over 95% accurate in automatic VOI placement, with the option of manual adjustments as needed (10). DaTQUANT eliminates the need for manual ROI selection and potentially eliminates interobserver variability with programmed VOI selections.

A critical issue within the DaT scan is the head-tilt artifact that can occur when positioning patients. Per protocol, the patient lays supine on the imaging table with their head placed in a supportive device to prevent any cranial movement or tilt. Any involuntary tremors during the scan or improper securing can lead to the head-tilt artifact FIGURE [3]. DaTQUANT can redirect any image automatically back to the optimal orientation of the anatomy within the images, which can remove the head-tilt artifact as well as the potential problem of inaccurate VOI placement.

The software reports the putamen:caudate ratios and left:right asymmetry ratios. The software analysis can determine the remaining presence of functional striatal dopaminergic neuron terminals for the differentiation of essential tremor from Parkinson's disease. Other values provided when using DaTQUANT include: a calculated mean of uptake, a specific deviation of uptake expressed as a percentage (standard deviation of 1), and a VOI thickness (known as 'z-score') value. These values are based on a normals database from the Parkinson's Progression Markers Initiative, a comprehensive study of patients with diagnosed Parkinson's disease (10). In using the data from this study, GE Healthcare was able to generate an age-matched normals database across a spectrum of ages, providing each individual case a nearly exact representation of their results in comparison to their counterpart from the database FIGURE [4].

In the latest iteration, the software provides longitudinal image analysis to aid in the monitoring of disease advancement and enables access to both a visual and quantitative comparison of a patient's images over several scans. Patients who require multiple scans due to symptom changes or medication issues can benefit from this capability. In terms of clinical data, a dopaminergic transporter density report is available for interpreting physicians to review. GE

Healthcare offers the software to any site utilizing the 123I Ioflupane protocol with approved SPECT cameras. Despite limited use in the last five years, this emerging technology holds the key to Parkinson's disease evaluations with a better understanding of the patient's condition at the striatal level. Providing conclusive answers to those experiencing parkinsonian syndromes means one step closer to a final diagnosis and better symptom management.

**Conclusion:** In the differentiation of Parkinson's disease from essential tremor, the DaT scan protocol utilizing DaTQUANT provides a patient with an accurate in-vivo evaluation of brain physiology. The current diagnostic practices have been improved upon with this modality, leading to better symptom management and treatment. The latest enhancements of the software continue to expand the capabilities of the protocol, providing a patient with more answers regarding their results. Overall, the GE Healthcare 123I Ioflupane protocol with DaTQUANT has led to many advancements with more diagnostic information, which someday, may help in discovering a cure.

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FIGURE 1A: Control sample of healthy brain tissue of substantia nigra. Darkened areas (arrow demonstrating portion of darkened outline) show pigmented neuromelanin portions of substantia nigra pars compacta.

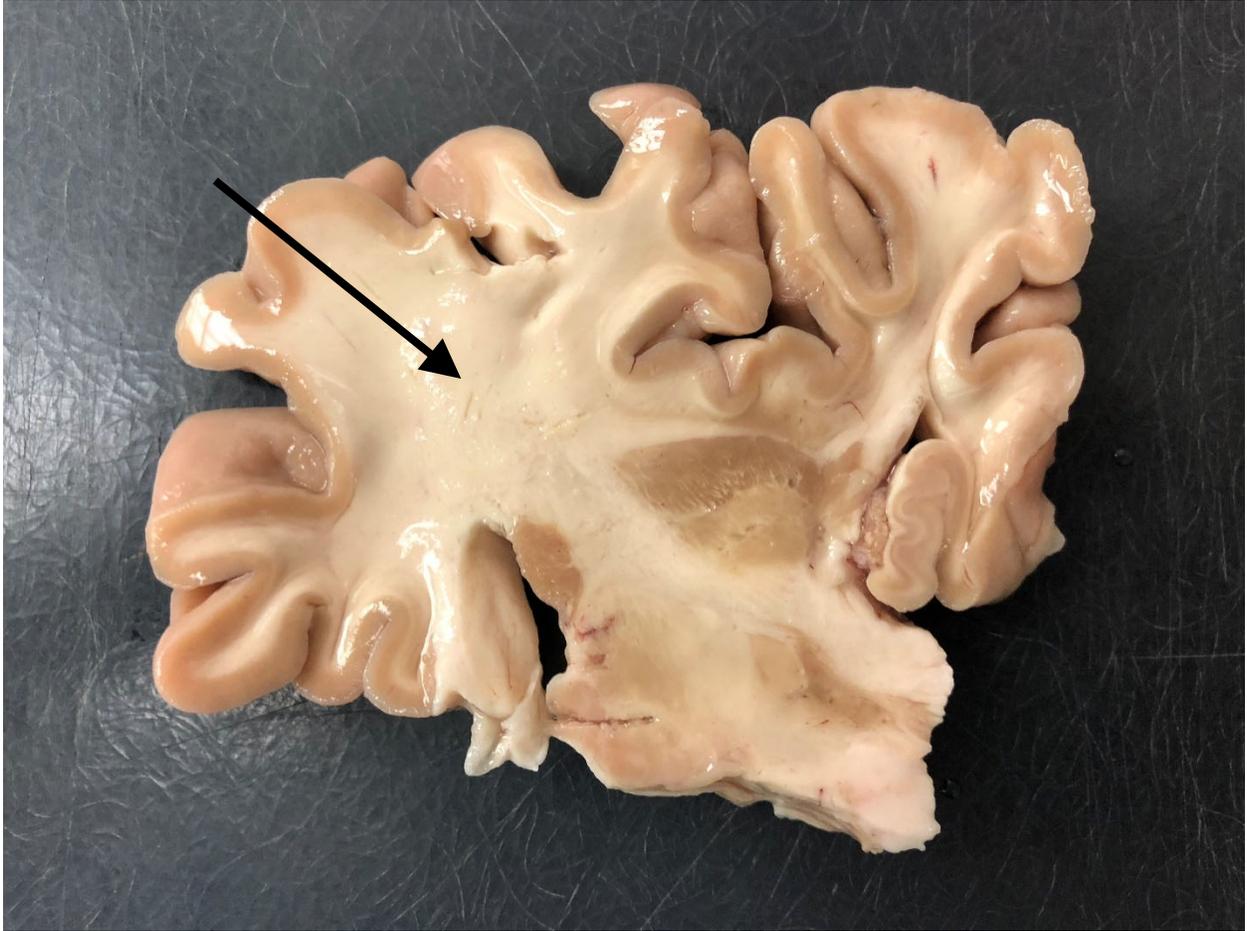


FIGURE 1B: Positive Parkinson's disease tissue sample. Lightened areas demonstrate lack of neuromelanin.

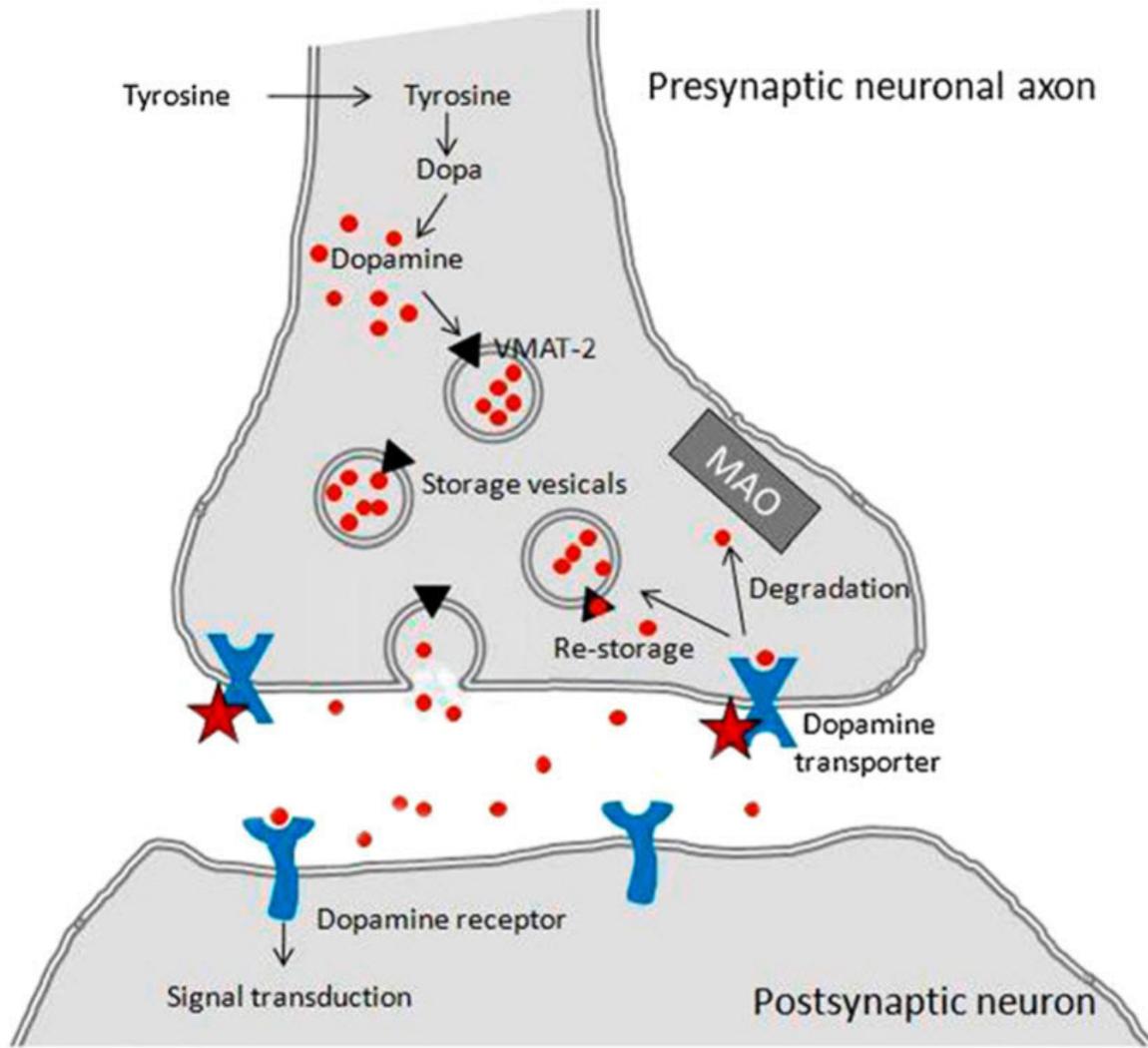


Figure 2: Dopamine transporter synaptic cleft.

The stars represent where the I-123 Ioflupane binds to the transporters.

This image was originally published in JNM. Djang. SNM Practice Guideline for Dopamine Transporter Imaging with 123I-Ioflupane SPECT 1.0\*. J Nucl Med. 2012;53:154. © SNMMI. [http://snmmi.files.cms-plus.com/docs/123I\\_ioflupane\\_SPECT\\_Practice\\_Guideline\\_JNM\\_Edit\\_FINAL.pdf](http://snmmi.files.cms-plus.com/docs/123I_ioflupane_SPECT_Practice_Guideline_JNM_Edit_FINAL.pdf)

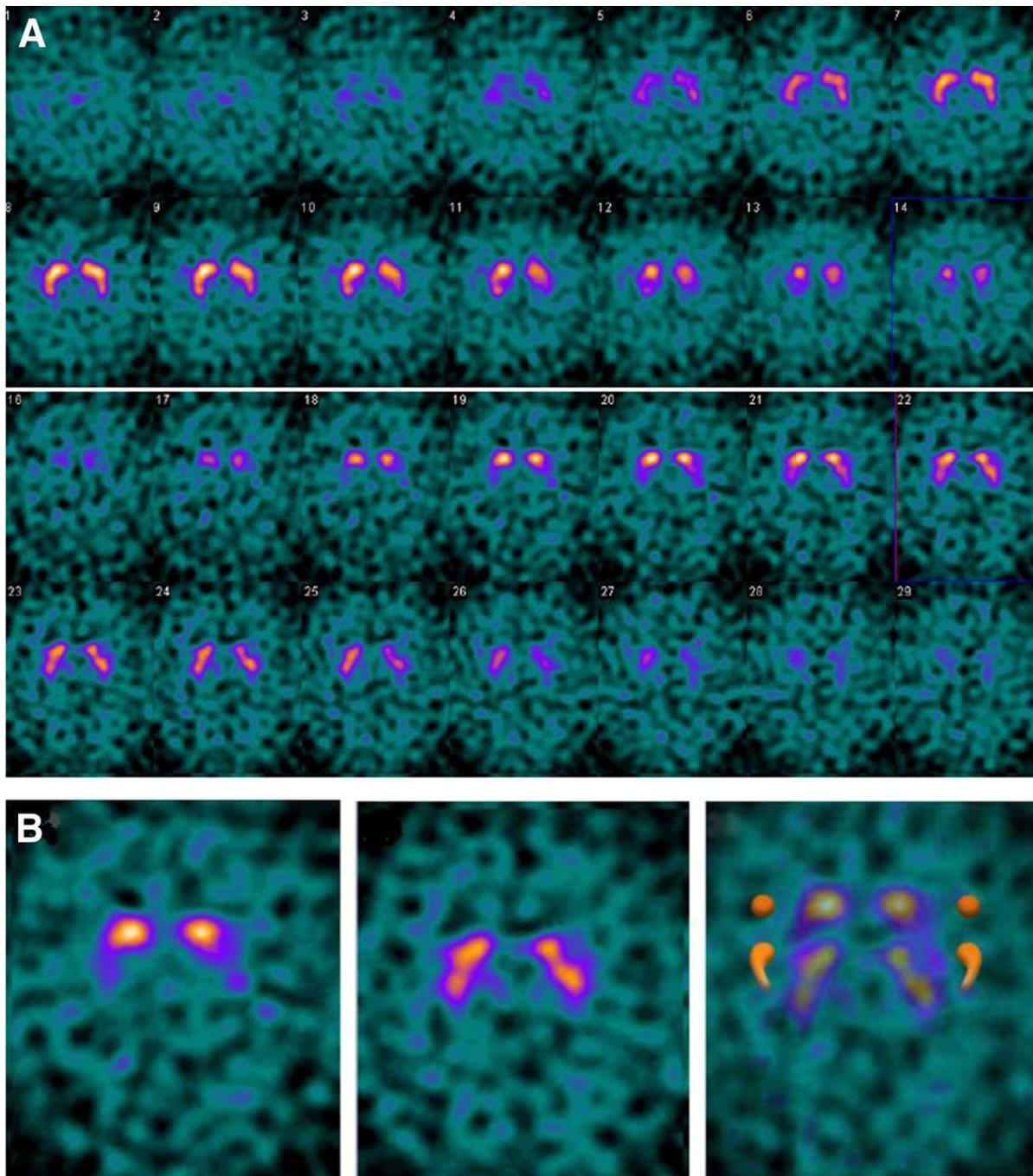


Figure 3: (A) DaT scan images visualizing the “semi-colon sign” (B) a forward head tilt artifact which falsely represents the caudate nuclei separate from the putamen. False positive artifact.

This image was originally published in JNMT. Covington The Semicolon Sign: Dopamine Transporter Imaging Artifact from Head Tilt. J Nucl Med Technol. 2013;41:106. © SNMMI. (<http://tech.snmjournals.org/content/41/2/105.full.pdf+html>)

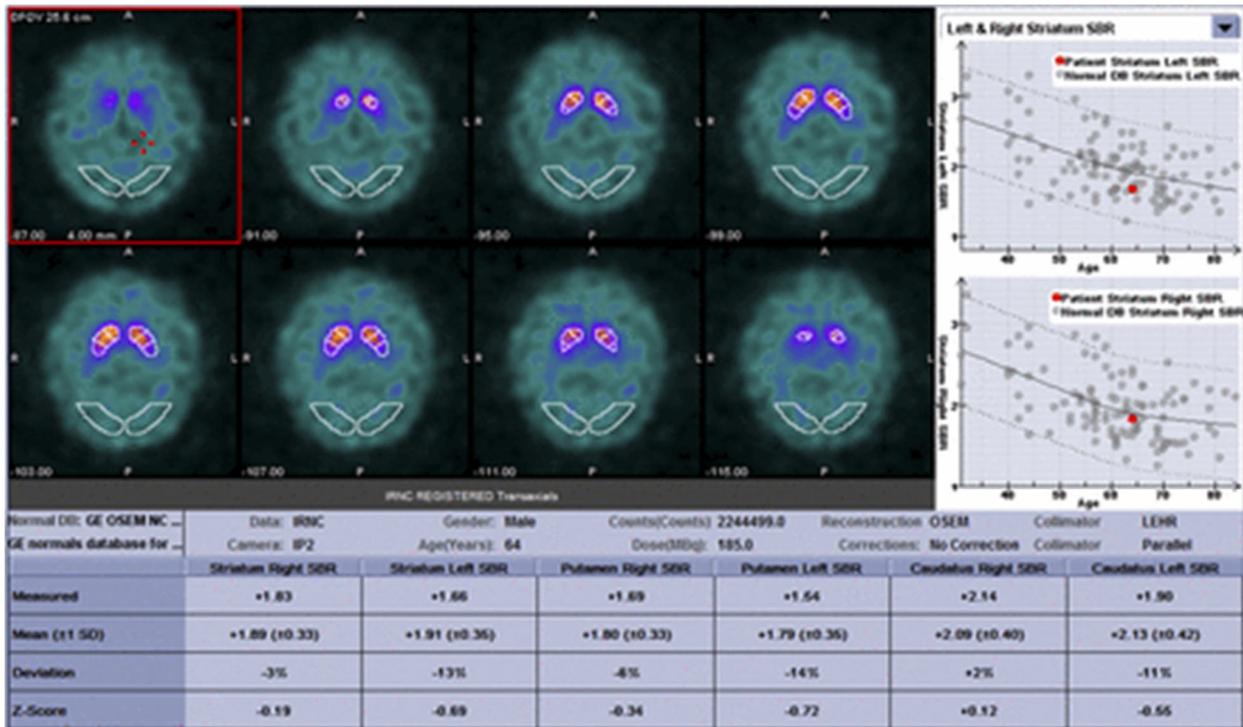


Figure 4: Sample save screen of the DaTQUANT (GE 2018) processing: white VOI placement in slices of images; the normals database on the top right, with “red dots” representing individual case results against range of normal database cases. Other calculated data at bottom of image.

This image was originally published in JNM. Booij. Diagnostic Performance of the Visual Reading of 123I-Ioflupane SPECT Images With or Without Quantification in Patients With Movement Disorders or Dementia. J Nucl Med. 2017;58:1822. © SNMMI (<http://jnm.snmjournals.org/content/58/11/1821.full.pdf+html>)