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Neuroradiology and Its Role in Neurodegenerative Diseases

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Abstract

A variety of radiological imaging techniques are used singly or in combination to diagnose and treat neurodegenerative diseases. Their respective roles are reviewed and discussed within the contexts of Alzheimer's disease and Parkinson's disease. In Alzheimer's, MRI and PET scans are usually employed to rule out confounding symptoms from other disorders/ diseases and to assess the extent of brain atrophy as the disease progresses. In Parkinson's, CT and MRI are not very informative but can rule out secondary causes of Parkinsonism; 3T-MRI is still under evaluation notwithstanding its high sensitivity and specificity; and PET and SPECT can rule out drug-induced Parkinsonism but are not reliable in distinguishing Parkinson's from other neurodegenerative causes of Parkinsonism. Functional SPECT/ DaTscan is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian syndromes in order to help differentiate essential tremor, multiple system atrophy, and progressive supranuclear palsy from Parkinson's but is unable to discriminate between them. However, DaTscan can help differentiate dementia with Lewy bodies from other forms of dementia. Because of its importance in Parkinson's, the complementary technology of magnetic resonance-guided high-intensity focused ultrasound is also reviewed and compared to electromagnetic brain stimulation and radiosurgery.

Abbreviations

AAD: Alzheimer's Disease; ALS: Amyotrophic Lateral Sclerosis; APP: Amyloid Precursor Protein; CNS: Central Nervous System; CT: Computed Tomography; DBS: Deep-Brain Stimulation; EMBS: Electromagnetic Brain Stimulation; ET: Essential Tremor; fGCA: Frontal Cortical Atrophy; fMRI: functional MRI; HD: Huntington's Disease; HIFUS: High-Intensity Focused Ultra-Sound; MRI: Magnetic Resonance Imaging; MRT:Magnetic Resonance Thermometry; MSA: Multiple System Atrophy; MTA: Medial Temporal lobe Atrophy; NDD: Neurodegenerative Disorder; PA: Posterior Atrophy; PD: Parkinson's Disease; PET: Positron Emission Tomography; PS: Parkinson's Syndrome; PSP: Progressive Supranuclear Palsy; RS: Radiosurgery; SPECT: Single Photon Computed Tomography; US: Ultrasound; VIN: Ventral Intermediate Nucleus.

Disorders mentioned

Alzheimer's disease; Amyotrophic lateral sclerosis; Dementia; Huntington's disease; Lewy body dementia; Multiple system atrophy; Parkinson's disease; Progressive supranuclear atrophy.

Introduction

To diagnose and treat neurodegenerative diseases, a variety of imaging techniques are used singly or in combination. These include computed tomography (CT), magnetic resonance imaging (MRI)

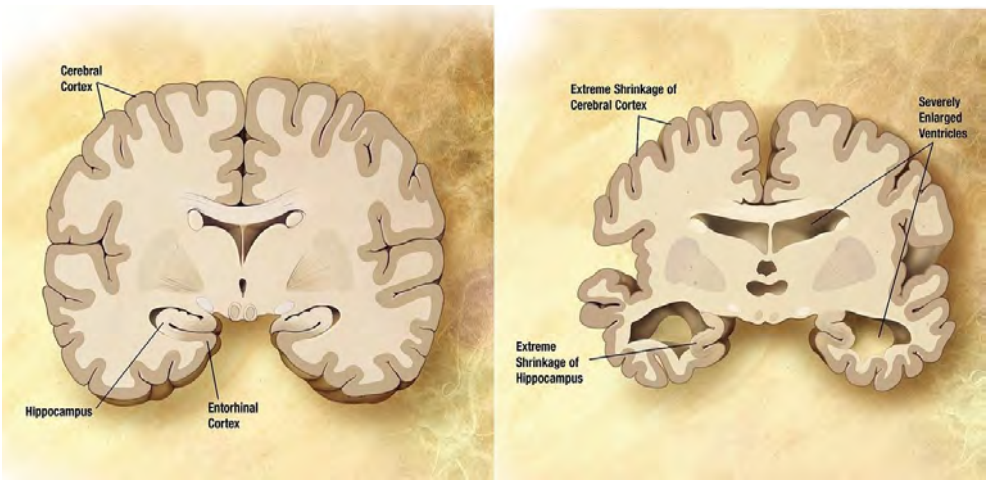


Figure 1: Contrasting a healthy brain with an Alzheimer's diseased brain

including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional SPECT/DaTscan. The applications of the above techniques (together with the corresponding procedures and processes) to the diagnosis and potential treatment of neurological and neurodegenerative diseases constitute the domain of neuroradiology. They are systematically reviewed below. Important complementary techniques that are also reviewed are MRI-guided high-intensity focused ultrasound (HIFUS), electromagnetic brain stimulation (EMBS), and radiosurgery. I am interested here in the applications of the above techniques and procedures for the diagnosis and treatment of Alzheimer's disease (AD) and Parkinson's disease (PD).

What Is Neurodegeneration?

Neurodegeneration is the progressive loss of structure or function or ultimately death of neuronal cells. Many neurodegenerative diseases, including AD, PD, amyotrophic lateral sclerosis (ALS), also known as Lou Gehring disease, and Huntington's disease (HD), occur as a result of neurodegenerative processes. Such diseases are presently incurable as we have been so far unable to trace their root cause(s). Interestingly, on a sub-cellular level, as research progresses, many similarities appear to relate these diseases to one another. Discovering these similarities and mapping them may lead to a biologically deeper and, therefore, better understanding of these diseases and hopefully suggest novel and improved therapies. Indeed, neurodegeneration was found at different neuronal circuit levels. In turn, this has allowed identifications between different neurodegenerative disorders[25,27,29,31,32,36,37,55,58]. The following sections will concentrate on AD and PD, more specifically on the use of radiological imaging techniques for their diagnosis and EMBS as one of their non-pharmacological (surgical) treatments.

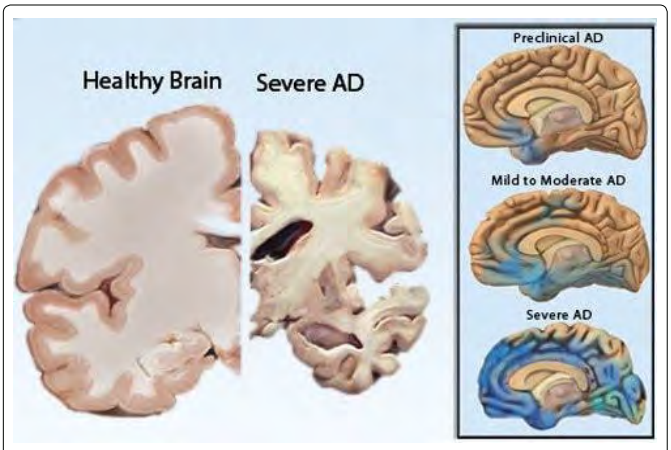


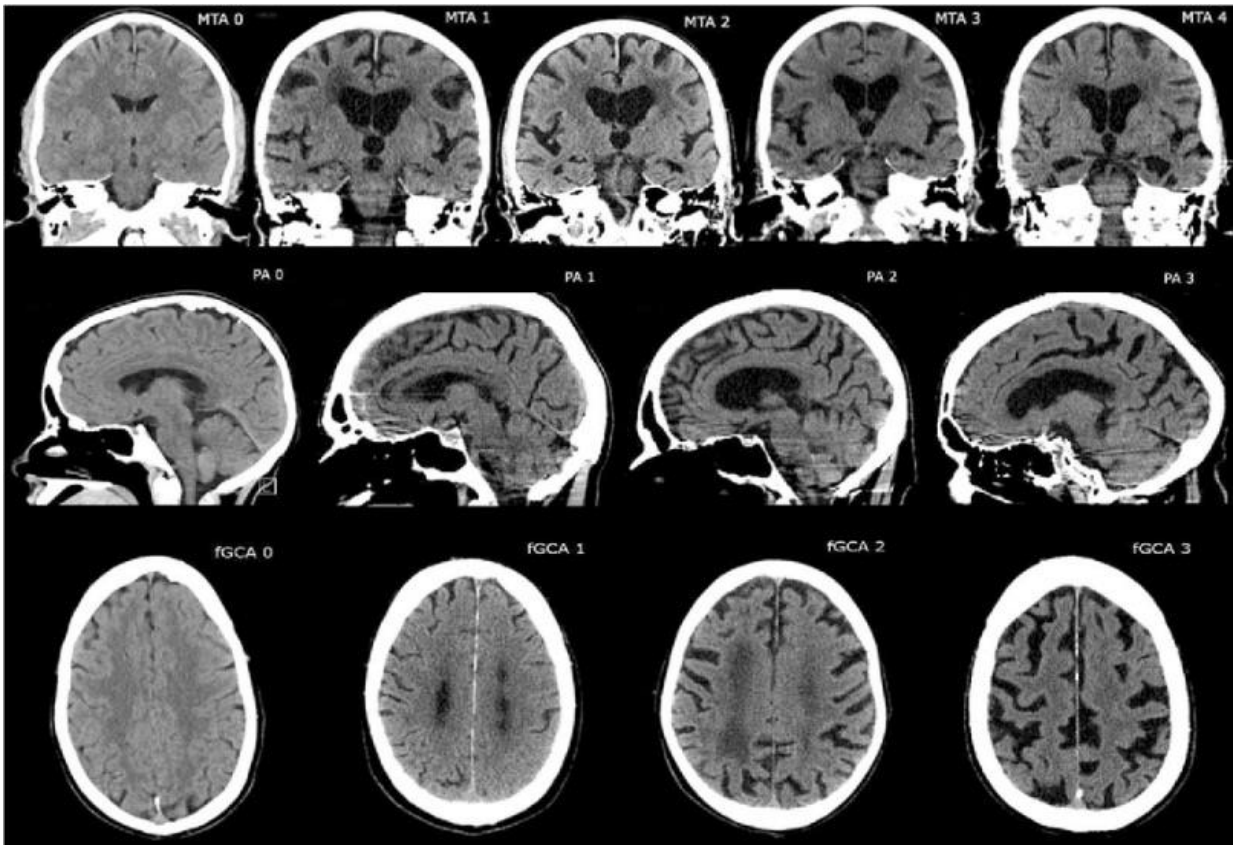
Figure 2: Brain shrinkage from preclinical AD to mild-to-moderate AD to severe AD

Case of Alzheimer's Disease

Brain degeneration and atrophy

Alzheimer's disease (AD) is characterized by the loss of neurons and synapses in the cerebral cortex and certain subcortical regions, resulting in gross atrophy of the affected regions (temporal lobe, parietal lobe, and parts of the frontal cortex and cingulate gyrus)[1,2,6-24,26,28,34,35,38,39,42,49,51-53,56,57,59,60]. I will illustrate this process with CT, MR, and PET images, and with fused (co-registered) PET/CT and PET/MRI images.

Figure 1 contrasts a healthy brain with an Alzheimer's diseased brain. It is readily seen that the brain structure and convolutions are distorted with extreme shrinkage of the cerebral cortex and the hippocampus and severely enlarged ventricles. The extent of brain shrinkage may be used as a rough gauge for assessing the severity of the disease. The brain ravages are further accentuated in Figure 2 where the shrinkage is highlighted (in blue color) for different clinical stages from preclinical AD to mild-to-moderate AD to severe AD.



(MTA=Medial temporal lobe atrophy; PA=Posterior atrophy; fGCA=Frontal cortical atrophy)

Figure 3: Head CT images of various grades of cerebral atrophy

Radiological imaging

The anatomical pictures in Figures 1 and 2 can be better seen with different radiological imaging apparatuses. Figure 3 is an example of actual CT images showing cerebral atrophy with different grading systems (observe the decreased size of the gyri and the secondary increased size of the sulci). The axial slices (first row) evidence the medial temporal lobe atrophy (MTLA) from grades 0 to 4. The posterior atrophy (PLA), grades 0 to 3, are shown in the sagittal slices (second row). The frontal cortical atrophy (fGCA), grades 0-3, are lastly seen in the coronal slices (third row).

Considering the crucial importance of PET in the imaging of AD, I provide several illustrations of it. Figure 4 is a sample brain PET image of a 56-year old patient (male). The blue areas are regions where low to no tracer have been accumulated. By contrast, the red areas delineate the regions of more accumulation of the active tracer substance (the biologically active molecule fludeoxyglucose, an analog of glucose). Such areas correspond to regional glucose uptake. They indicate metabolic activity whose extent and intensity are reflected by the areas covered and the depth of the red color. In the diagnosis of AD and its follow-up dementia, the similar technique is used as that illustrated in Figure 4. Other tracers such as fluorine-18 have been infrequently employed.

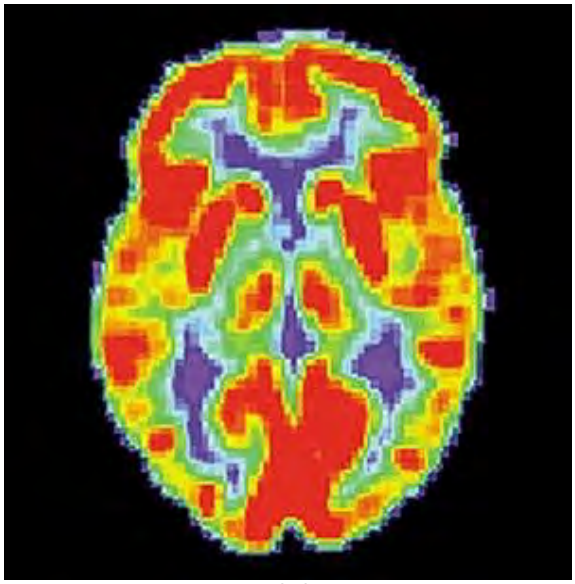


Figure 4: A sample brain PET image

The series of axial brain images of Figure 8 was obtained from the United Kingdom Biobank, which holds genetic, physical, and clinical data from a large cohort of individuals (by 2010, ~ 500,000 individuals aged 40-69 at recruitment, and scheduled to increase to 5 million

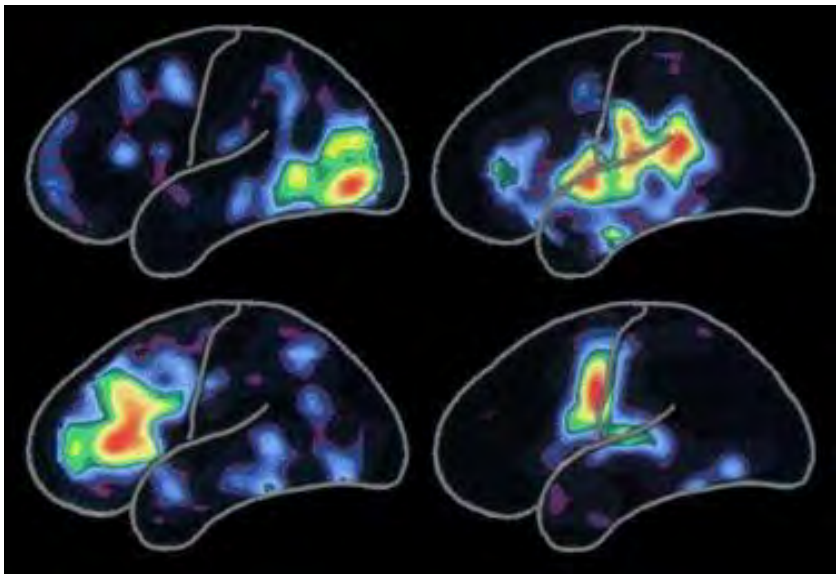


Figure 5: PET images illustrating AD effects in several brain areas

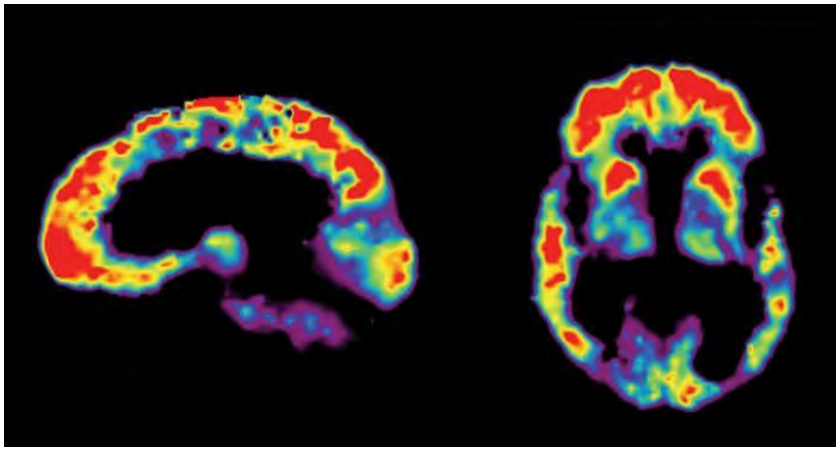


Figure 6: PET image of an Alzheimer-diseased brain

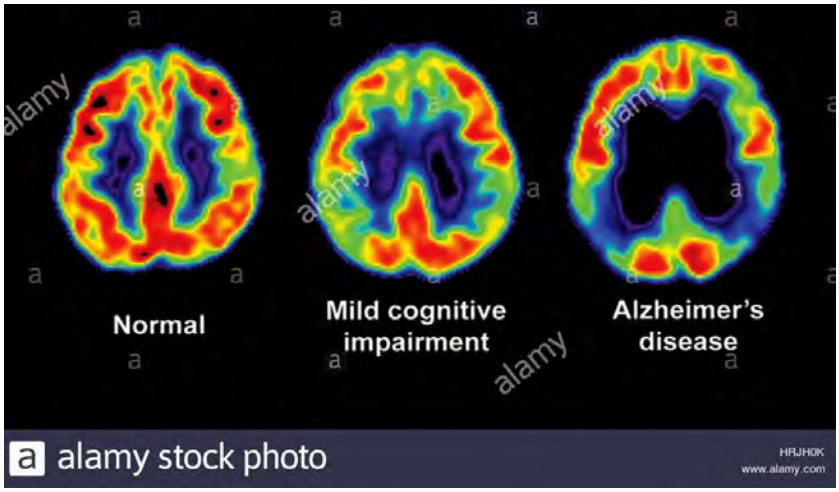


Figure 7: PET images contrasting a normal brain (left) to a brain with mild cognitive impairment (center) and an Alzheimer-diseased brain (right)

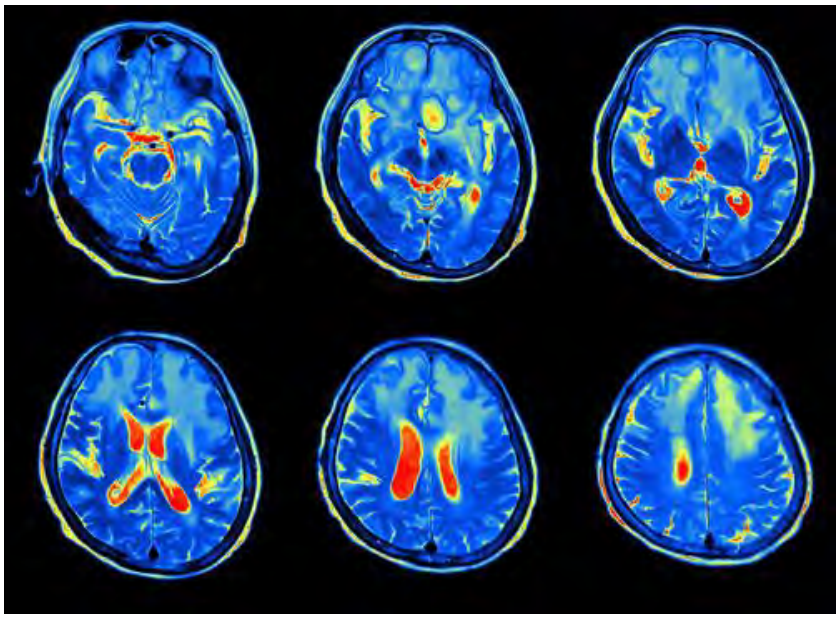


Figure 8: A cohort of axial brain MRI images
Source: United Kingdom Biobank

individuals). Following this age group has enabled researchers to focus on diseases of middle age and later including genetic influences on neurodegenerative diseases such as AD. In 2018, they reported a study of brain images of 10,000 individuals, which revealed genetic influences on brain structure and function, and showed correlations with neurodegenerative, psychiatric, and personality traits. This trove of data is available free of charge to scientific researchers for the pursuit of a variety of research projects aimed at better understanding AD and other neurological diseases and, hopefully, developing diagnostic and therapeutic procedures for such diseases.

Fused (also called co-registered) CT-MRI or PET-MRI images are also read together to provide concurrent anatomic and metabolic information. Examples of the images thus obtained are illustrated in Figure 9. However, for brain imaging, because of the absence of motions, such integrated registration may be more simply obtained with a device known as the N-localizer.

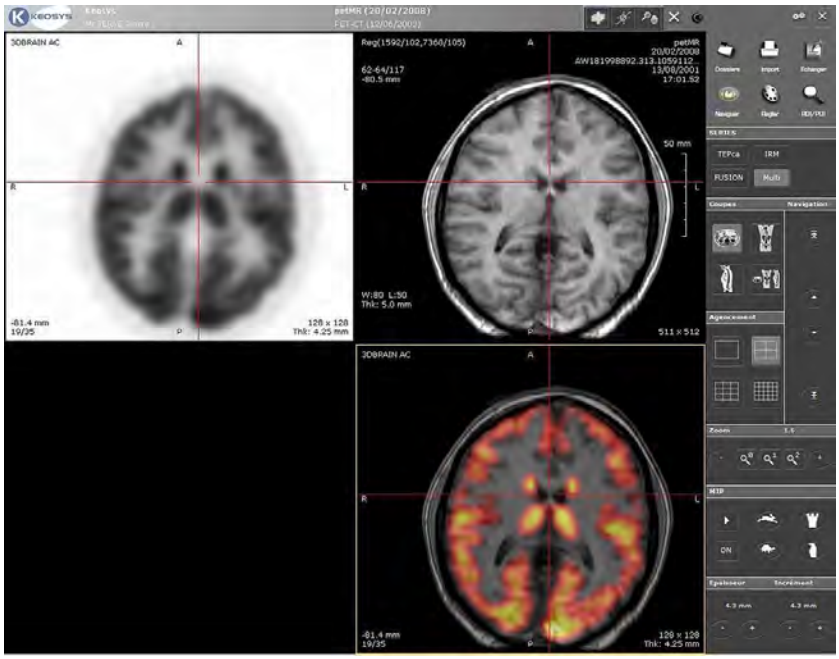


Figure 9: Fused PET/CT and PET/MRI technologies for brain imaging

With all these advanced technologies, whether singly or in combination, it is possible to accurately diagnose AD and monitor its ineluctable progression. When treatments and, hopefully, even a cure will be available, the same technologies will also enable us to follow their efficacy and personalize them to the patient.

Radiological imaging in the diagnosis of Alzheimer's disease

At this juncture in our understanding of the disease, the gold standard for AD's diagnosis is developed from the systematic testing of the various identified risk factors. However, having assessed these several risks, managing them may have benefits but will not yield a cure. The test results can provide a baseline against which one could gauge the benefits of any treatment followed. Although this set represents an ideal set, not all tests will be ordered by the treating physician for various reasons (not deemed necessary in particular situations; too costly, etc.). For the reader's convenience, I have charted these tests in Table 1, which could also serve as a reference.

Items 1 and 13 of Table 1 emphasize that radiological imaging plays important roles in respectively ruling out other diseases/disorders than AD and quantifying the extent of brain atrophy (an assessment of the state of the disease and its progressive advancement). The test results can provide a baseline against which one could gauge the benefits of any treatment followed.

Case of Parkinson's Disease

Dopamine-producing regions in the brain

Parkinson's disease (PD) is a long-term, slowly progressive degenerative disorder of the central nervous system (CNS) that belongs to a group of conditions called motor system (or movement) disorders. It results from either the insufficient production of a brain chemical called dopamine or/and the loss of dopamine-producing ("dopaminergic") brain cells. It predominately affects nerve cells (neurons) in a specific area of the brain called substantia nigra (see Figures 10-12)[30,33,50,54]. As neurons in parts of the brain become impaired or die, people may experience four primary symptoms (our acronym "TRBG").:

(1) *Tremor*, or trembling in the hands, arms, legs, jaw, and face;

(2) *Rigidity*, or stiffness of the limbs or trunk of the body;

(3) *Bradykinesia*, or slowness of movement; and

(4) *Gait* and *postural instability*, or impaired balance and coordination

However, these symptoms appear in other diseases as well so that not everyone with one or more of these symptoms has PD. By the time people have been diagnosed with PD, a significant amount of the substantia nigra neurons have already been lost or impaired, as illustrated in Figure 11.

Table 1: The gold standard evaluation for a diagnosis of Alzheimer's disease

Risk	Reason(s) for the test
0. Ruling out of other diseases/disorders brain tumor, Parkinson's disease, sleep disturbance, side effects of medication, or a non-Alzheimer's dementia.	To rule out confounding symptoms from other disorders or diseases. Usually with an MRI or PET scan
1. Genetics	o For early-onset and familial early-onset (FAD): inherited change in chromosomes 1, 14, 21 o For late-onset AD: ApoE ε4 and 23 other genes, particularly TREM2 that raise risk for AD. ApoE ε4 is associated with a higher risk of developing AD. (Note: The ApoE gene produces a protein that transports cholesterol into brain cells)
2. Inflammation	A key player
3. Infections	Pathogens including viruses (Herpes simplex, HIV), bacteria (*P.gingivalis*), molds, *Borrelia*, Lyme diseases, various fungi, and other pathogens
4. Homocysteine	An amino-acid causally associated with AD and brain atrophy
5. Fasting insulin level	Inflammatory response caused by sugar toxicity
6. Hormonal status	Estradiol, testosterone, thyroid-stimulating hormone, etc.
7. Toxic exposure	Mercury, mycotoxins, etc.
8. Immune system (particularly, the innate part)	Responds first to infections
9. Microbiome	Bacteria and other microbes living in the gut, mouth, nose, and sinuses
10. Blood brain barrier	Impaired integrity allows access to the brain by microbes, viruses, fungi, etc.
11. Body mass index	Measure of overweight condition
12. Diabetes or pre-diabetes status	Drivers of AD
13. Volumetrics	Extent of brain atrophy. Usually with MRI and PET scans: o Subtypes # 1 and # 2: hippocampal atrophy o Subtype # 3: generalized brain atrophy

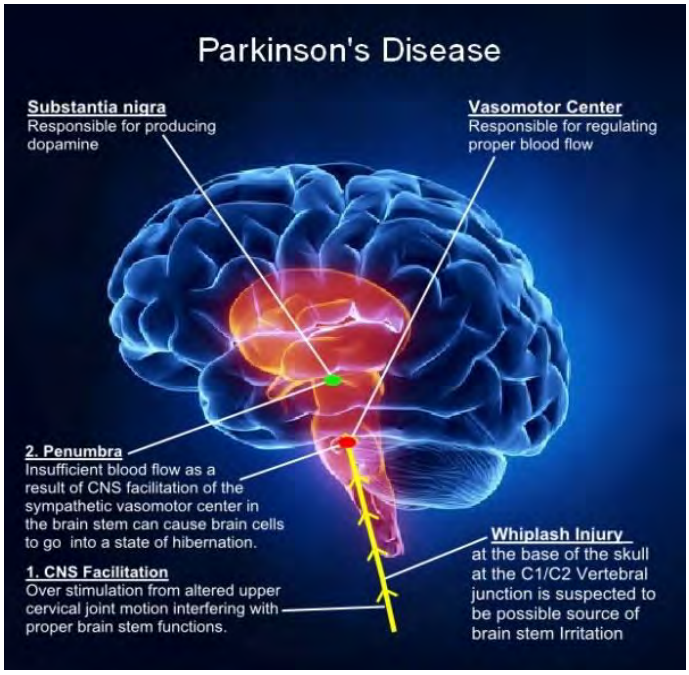


Figure 10: Pictorial illustrating Parkinson's disease

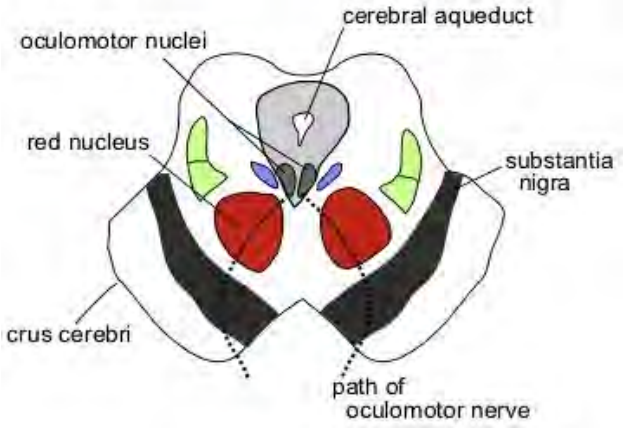


Figure 11: Pictorial showing the substantia nigra

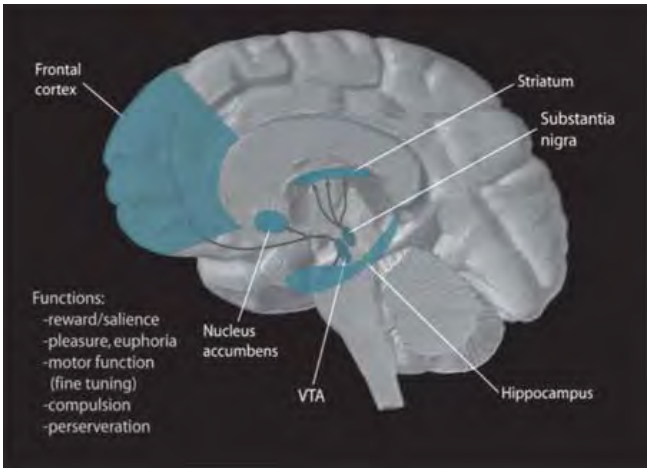


Figure 12: Showing the dopamine pathways in the brain

Many brain cells of people with PD contain Lewy bodies, which are unusual clumps of the protein alpha-synuclein. We do not yet fully understand that protein's function in either its normal or pathologic state. Likewise, we have not fathomed its relation (if any) to the genetic mutations that are known to impact PD and Lewy body dementia (LBD). Notwithstanding the above, and like for many other neurodegenerative diseases (NDDs), the cause remains largely unknown and there is presently no cure. The disease can be difficult to diagnose accurately as there are presently no blood or laboratory tests that have been proven to help. Nonetheless, there are treatment options that include medications and surgery. A variety of medicines sometimes help symptoms dramatically. Surgery and deep brain stimulation (DBS) can help regulate certain regions of the brain and improve symptoms.

It is not possible to predict the course the disease will take but many risk factors and corresponding protective factors have been proposed sometimes with theories (rather hypotheses) concerning possible mechanisms of the disease. However, none of these factors have been conclusively related to PD by empirical evidence.

The Parkinson-diseased brain

While we continue to unravel the complex brain, changes involved in the onset and progression of PD, it seems likely that damage to the brain started perhaps decades earlier or more, beginning gradually and getting worse over time. The brain regions affected by PD are illustrated in Figure 13.

Functional brain imaging with SPECT

In contrast with X-ray machines (including CT) which use X-rays to produce an image, SPECT employs gamma photons emitted from nuclear material. The SPECT imaging camera is a gamma camera. It requires delivery of a gamma-emitting radioisotope (a radionuclide) into the patient, normally through injection into the bloodstream. The marker radioisotope is Technicium-99m attached to a specific ligand to create a radioligand that binds to certain types of tissues where the ligand concentration is seen by the gamma camera.

Emissions from the radionuclide indicate the amounts of blood flow in the brain capillaries. In the same way that a plain X-ray is a two-dimensional (2-D) view of a 3-D structure, the image obtained by the gamma camera is also a 2-D view of the 3-D distribution of the radionuclide. Multiple 2-D images from multiple angles (also called "projections") are then fed into a specially-programmed computer to yield 3-D images in a manner similar to that employed in MRI, CT, and PET imaging.

The pictorial of Figure 14 illustrates the disappearance of the *substantia nigra* in a Parkinson-diseased brain whereas Figures 15-18 show transcranial DaTscan images for different patients under different conditions, namely a healthy 62-year old volunteer, a newly diagnosed 80-year old patient, and a 76-year old patient with a 7-year history of Parkinson's disease, respectively.

SPECT imaging of dopamine transporter with Iodine-123 Ioflupane - DaTscan

DaTscan is SPECT imaging of dopamine transporter with the radiopharmaceutical drug Iodine-123 Iofluopane (a radioiodinated cocaine analog). It is used for diagnosing PD as well as differentiating PD from other disorders that may present similar symptoms. The imaged brain region of interest is the striatum (a subcortical region of the basal

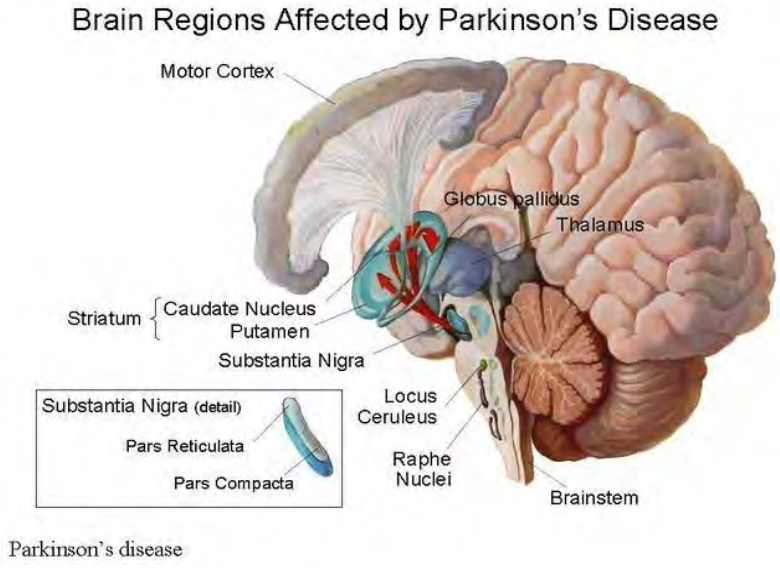


Figure 13: Brain regions affected by Parkinson's disease

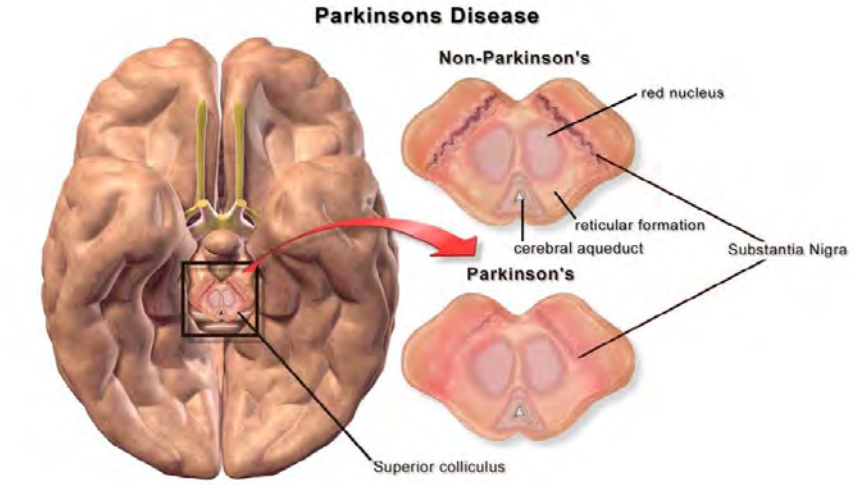


Figure 14: Disappearance of the substantia nigra in a Parkinson-diseased brain

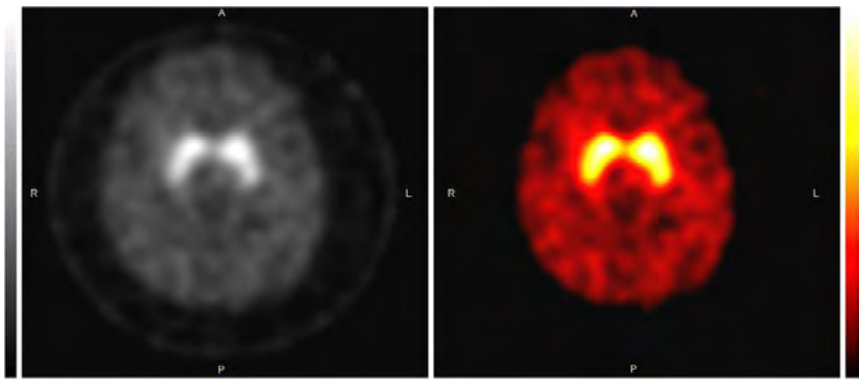


Figure 15: Transcranial DaTscan image of a healthy 62-year old volunteer

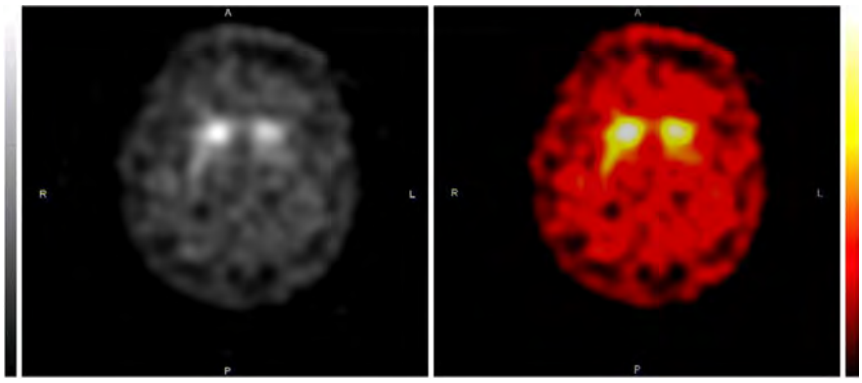


Figure 16: Transcranial DaTscan image of a newly diagnosed 80-year old patient

ganglia), particularly its nerve endings (axon terminals). Ioflupane binds to them thus acting as a biomarker. The efficacy of this biomarker has been demonstrated in the differentiation of essential tremor (ET) from PD, multiple system atrophy (MSA) and progressive supranuclear palsy (PSA). The current indication is as follows:

"*DaTscan is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes (PS) in order to help differentiate Essential Tremor from PS related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTscan is unable to discriminate between PD, MSA, and PSP.*"

DaTscan is an adjunct to other diagnostic evaluations.

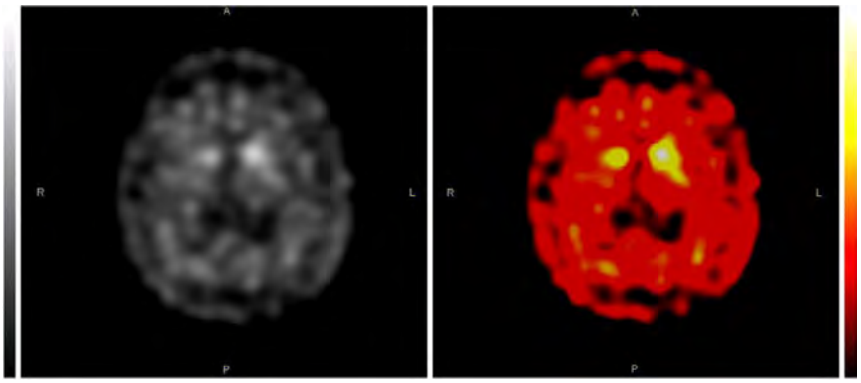


Figure 17: Transcranial DaTscan image of a 79-year old patient with a 7-year history of Parkinson's disease

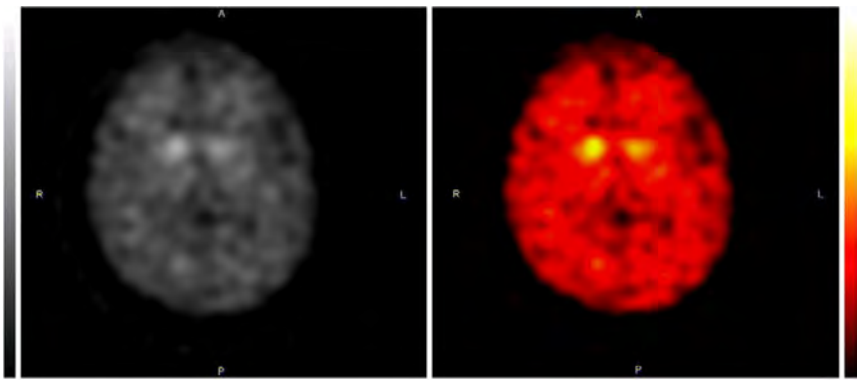


Figure 18: Transcranial DaTscan image of a 76-year old patient having a 12-year history of Parkinson's disease

However, its effectiveness has not been established either as a screening test, or a confirmatory test, or else for monitoring the progression of disease or response to therapy. It has also been proposed as an adjunct to the clinical diagnosis of dementia with Lewy bodies (DLB) as follows:

"*to help differentiate dementia with Lewy bodies from other forms of dementia*".

Method of administration: The DaTscan solution may contain up to 6% of free iodide (iodine 123 or I-123). It is supplied ready to inject with a nominal injection activity is 185 [Mbq] (MegaBecquerel). It is recommended that the scan not be performed with less than 111 [Mbq]. At least one hour before the administration of DaTscan, the thyroid gland must be blocked with 120 [mg] of potassium iodide to decrease thyroid accumulation of I-123 and prevent the long-term risk for thyroid neoplasia.The scan is conducted 3-6 hours post-injection.

Risks: DaTscan is contraindicated under the following conditions: hypersensitivity to the active substance, any of the excipients, or iodine, which may cause skin erythema and pruritus where side effects have been reported following the administration of the drug. In clinical trials, common side effects are headache, nausea, vertigo, dry mouth, or dizziness of mild to moderate severity, increased appetite, and formication. Less than 1% of patients experience pain at the injection site. The radiation risks are low with a committed effective dose for a single investigation on a 70 kg individual of 4.35 milliSievert [mSv].

It may be noted that other drugs that bind to the dopamine transporter with high affinity may interfere with the DaTscan image.

Pregnant patients should not undergo the test and breast-feeding patients must cease since I-123 is secreted in breast milk. It is unknown whether DaTscan can cause fetal harm or increase the risk of pregnancy loss in pregnant women. DaTscan should be given to pregnant women only if needed.

The effect of renal or hepatic impairment on DaTscan imaging has not been established. The kidney excretes DaTscan so patients with severe renal impairment may have increased radiation exposure and altered DaTscan images. It is unknown whether or not Ioflupane is dialyzable.

The major risks of overdose relate to increased

radiation exposure and long-term risk for neoplasia, which are reportedly low. Nonetheless, DaTscan emits radiation and radiation exposure to clinical personnel and patients must be minimized.

Radiological imaging in the diagnosis of PD

Many disorders can cause symptoms similar to those of PD. People with Parkinson's-like symptoms that result from other causes are sometimes said to have Parkinsonism. While these disorders initially may be misdiagnosed as Parkinson's, certain medical tests, as well as responses to drug treatments, may help to distinguish them from PD. Since many other diseases have similar features but require different treatments, it is important to make an exact diagnosis as soon as possible.

There are currently no blood or laboratory tests that diagnose sporadic PD. Therefore, the diagnosis is based on medical history and a neurological examination. Making a precise diagnosis is important so that people can receive the proper treatment.

In some cases, PD can be difficult to diagnose accurately early on in the course of the disease because early signs and symptoms may sometimes be dismissed as the effects of normal aging. Brain scans or laboratory tests can be helpful to rule out other disorders. Table 2 summarizes the known diagnostic features of several radiological imaging technologies[50].

Magnetic resonance-guided high-intensity focused ultrasound

Principle of operation under image-guidance: Similar to light waves, ultrasound waves can be focused using either single-element concave transducers or electronically-controlled phased-arrays of many smaller piezoelectric transducers. Through this focusing, the energy can be concentrated up to 3 orders of magnitude into a small and elongated ellipsoid volume (typical focus area ~ 2 × 7 mm). As a result, the rates of energy deposition generally used clinically are capable of raising the temperature of the tissues within seconds to 60°C or greater. They can induce denaturation of cell proteins and ultimately coagulative necrosis. In the intervening tissues of the pre- and post-focal regions, lower intensities of sonic energy are found, energy absorption is also lower, and the deleterious effects of the exposures (i.e. thermal damage) do not occur.

The above-mentioned devices employ multi-element, phased-array transducers for fast, accurate electronic beam steering. With current technology, more precise correction of aberrations in the sonic beam path are achieved. A targeted thermal lesion created within the brain through the intact skull allows for the application of HIFUS to a variety of neurologic conditions, including PD and other movement disorders.

Application to movement disorders treatment: The current standard for image-guided HIFUS for minimally invasive, non-incisional treatments in the brain employs MRI as the imaging modality. MRI-guided HIFUS enables high-resolution soft tissue imaging for treatment planning whereas magnetic resonance thermometry (MRT) also allows for quasi-real-time brain temperature monitoring. This validates the treatment region as having received the designated thermal dose, while also ensuring that regions outside of the treatment zone are not adversely affected.

Essential tremor (ET) was the first neurological disorder evaluated for treatment with MRg-HIFUS for several reasons:

- It is a common disorder where medical therapy is frequently inadequate for patients with severe disability tremor;
- The VIM of the thalamus is a well-established target for both lesioning and DBS for reduction in tremor in medically refractory patients with either ET or PD;
- The anatomical target—the VIM—is centrally located within the brain. It reduces the distortion effects of the skull on focusing the ultrasound energy;
- Treatment of the VIM in ET not only results in tremor reduction but also substantially reduces disability in selected patients with only unilateral treatment, such as patients with severe tremor in the dominant hand.

Several published clinical studies have validated the above approach, showing significant improvement after treatment. MRg-HIFUS has also targeted the VIM for relief of tremor associated with PD and other PD symptoms. A few years ago, the Rambam Hospital, Israel, was one of the first hospitals to perform this painless procedure using MRg-HIFUS. The technology was developed by the Insightec company at the Technion-Israel Institute of Technology. Dozens of the procedure have already been carried out at Rambam, which was a beta-site for Insightec's technology. The technique, which uses heat ablation on deep-seated brain tissue through an intact skull, was made possible with Israeli technology originally developed to remove myomas and benign fibroid growths in the uterus, but was later applied to ET. It was introduced in the US only in 2017

Comparison with deep brain stimulation: Essential tremor, and especially PD, are progressive conditions where motor symptoms worsen over time. Patients treated with DBS are seen at regular intervals where the parameters of stimulation are adjusted to compensate for worsening symptoms[47,48]. Unfortunately, disease progression may eventually result in worsening symptoms in many patients in spite of reprogramming. When significant worsening occurs after lesional surgery, repeat surgery may be performed, which has usually been successful in regaining

the original clinical response. The potential efficacy and safety of re-treatment of any aspect of a movement disorder with MRg-HIFUS remain to be determined.

Although effective, lesioning for movement disorders has been largely replaced by DBS surgery, which is similar in strategy to stereotactic lesioning. However, DBS has two significant advantages:

1. Unlike lesional surgery, DBS does not create any intentional brain injury; and
2. Suppression of motor abnormalities such as tremor is accomplished through continuous high-frequency (130–180 Hz) stimulation, although the mechanism of its lesion-like inhibitory effect is still debated. Unlike stereotactic lesions, bilateral DBS can be safely performed to improve the larger number of patients with bilateral motor symptoms. Adjustability of these devices is a major advantage of this approach over lesional surgery. When side effects of bilateral stimulation such as dysarthria occur, these can usually be mitigated by lowering the intensity of stimulation.

DBS is not, however, without its complications, including

1. Surgical complications such as intracerebral hemorrhage (0.5%–2.0%) and infection (1%–3%), as well as DBS-specific issues such as lead migration and fracture (1%–3%) and device malfunction (1%–3%); and
2. It also introduces added procedures and costs over surgical lesioning, including surgical implantation and periodic replacement of the programmable pulse generator, as well as device programming visits.

Comparison with radiosurgery: The goal of all forms of surgery for movement disorders is maximal relief of motor symptoms (tremor, bradykinesia, rigidity, and dystonia) without intrusion of symptoms associated with damage or stimulation of adjacent (off-target) brain regions such as diplopia, dysarthria, paresthesia, weakness, or visual field defects. The limitations of DBS, cited previously, provided a rationale for investigating less invasive surgical methods such as radiosurgery (RS). RS uses contemporary stereotactic methods to localize the brain target and a focused array of emitters that have been extensively used to treat brain tumors (Gamma Knife). This less invasive method has also been applied to relieve symptoms of both ET and PD, with the best results seen in lesioning of ventral intermediate nucleus (VIN) for ET.

A major issue preventing widespread acceptance of this method for functional neurosurgery is the delayed effect of ionizing radiation–based lesioning. The extent of the treatment is determined solely by a calculation of dose because the effects of radiation occur with a variable delay. Although the rate of off-target effects for RS is relatively low, these effects can occur with a delay of days to months. These previous studies of RS along with the real-time effects of sonic energy have added to the rationale for the study of MRg-HIFUS as a treatment of movement disorders.

Summary and Conclusions

Radiological imaging plays an important role in the diagnosis and treatment of neurodegenerative disorders. This has been abundantly demonstrated in the cases of Alzheimer's and Parkinson's disease. In the case of Alzheimer's disease, CT images and more particularly PET images with the biologically active tracer molecule fludeoxyglucose (an analog of glucose) can highlight the brain regions of tissue metabolic activity. The same tracer may also be used for PET investigation and diagnosis of types of dementia (the follow-up stage after AD). Less often, other radioactive tracers, usually but not always labelled with fluorine-18, can be employed to image the tissue concentration of other types of molecules of interest. PET scans are increasingly read alongside CT or MRI scans, with the combination (called co-registration" or "fusion") giving both anatomic and metabolic information. Table 1 emphasizes that radiological imaging plays important roles in ruling out other diseases/disorders than Alzheimer's disease and quantifying the extent of brain atrophy (an assessment of the state of the disease and its progressive advancement)[3-5,40,41,43-46]. With all these advanced technologies, whether singly or in combination, it is possible to accurately diagnose Alzheimer's disease and monitor its ineluctable progression. When treatments and hopefully a cure will be available, the same technologies will also enable us to follow their efficacy and personalize them to the patient.

Parkinson's disease can be difficult to diagnose accurately as there are presently no blood or laboratory tests that have been proven to help. SPECT imaging utilizing the marker radioisotope Technicium-99m can indicate the amounts of blood flow in the brain capillaries. Transcranial DaTscan imaging of dopamine transporter with Iodine-123 Ioflupane (a radioiodinated cocaine analog used as a neuro-imaging radiopharmaceutical drug) is used for the diagnosis of Parkinson's and its differential diagnosis over other disorders presenting similar symptoms. It can evidence the loss of functional dopaminergic neuron terminals in patients with Parkinsonian syndromes (PS). DaTscan is contraindicated in patients with known hypersensitivity to the active substance, any of its excipients, or iodine. The radiation risks are reportedly low. Table 2 shows the role of radiological imaging in the diagnosis and follow-up of Parkinson's disease.

Magnetic resonance-guided high-intensity focused ultrasound is also used for the diagnosis and treatment of movement disorders including Parkinson's disease. It enables high-resolution soft tissue imaging for treatment

planning whereas magnetic resonance thermometry also allows for quasi-real-time brain temperature monitoring. This validates the treatment region as having received the designated thermal dose, while also ensuring that regions outside of the treatment zone are not adversely affected. Essential tremor was the first neurological disorder so evaluated and validated in several published clinical studies.

While lying outside of radiological imaging, the complementary techniques of deep brain stimulation and radiosurgery have been described as they are also used to treat patients with Parkinson's and other movement disorders. Deep brain stimulation is similar in strategy to stereotactic lesioning but with significant advantages. Studies of radiosurgery along with the real-time effects of sonic energy have added to the rationale for the study of magnetic resonance-guided high-intensity ultrasound energy as a treatment of movement disorders.

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