Review Article

Changing Landscapes in the Neuroimaging of Dementia

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Abstract

Neuroimaging in dementia has advanced several folds in the past decade. It has evolved from diagnosing secondary causes of dementia to the current use in identifying primary dementia and aid in clinically perplexing situations. There has been a leap in the imaging technology that can virtually dissect the brain with a high degree of radiopathological correlation. The neuroimaging in dementia is classified into structural, functional, and molecular imaging. Structural imaging includes voxel-based morphometry and diffusion tensor imaging. Functional imaging includes 18F-fluorodeoxy glucose positron emission tomography imaging, ^{99m}Tc hexamethylpropyleneamineoxime single photon emission computed tomography imaging, and functional magnetic resonance imaging studies. Molecular imaging includes amyloid imaging, tau imaging, and translocated protein imaging. These advancements have led to using neuroimaging as a biomarker in assessing the progression and also in deciphering prognosis of the disease. In this article, we discuss the current clinical relevance of these neurological advancements.

Keywords: Biomarker, dementia, functional imaging, molecular imaging, structural imaging

Introduction

Dementia is characterized by a decline in the cognitive function that affects and impairs activities of daily living. With increasing longevity, the prevalence of dementia is increasing, which is estimated to affect about 8% of the geriatric population and 30% of the octogenarian and nonagenarian.[1,2] History and clinical examination form the basis of the approach to the evaluation of cognitive decline. Neuroimaging and laboratory evaluation complement the clinical evaluation in the differentiation between primary and secondary causes of dementia. The field of neuroimaging has further evolved and broadened the analysis of signature patterns in primary dementia. It is envisaged to be an important biomarker in the evaluation of dementia.

Changing Landscapes in the Technological Era

Neuroimaging in dementia, historically, was used as an investigatory modality to diagnose secondary causes of dementia including but not limited to vascular causes, normal pressure hydrocephalus, tumor, and infectious etiologies. However, with the technological advancements in neuroimaging that has paralleled better understanding and emergence of disease-modifying therapies, it becomes relevant in the current era to diagnose various primary dementias in the early stages. The changing landscape in the field of neuroimaging in dementia has been dramatic when compared with the technology two decades ago. Several novel imaging metrics and sequences have emerged in the past decade that virtually dissects the brain with high degree of radiological and pathological correlation.[3]

In the current scenario, the neuroimaging in dementia is categorized into structural, functional, and molecular imaging. In structural neuroimaging, computed tomography (CT) and magnetic resonance imaging (MRI) are used to analyze the structural changes in the brain. However, imaging findings in the conventional techniques in structural imaging lag behind the clinical symptomatology. The use of voxel-based morphometry (VBM) in the analysis of gray matter and Diffusion Tensor Imaging in the analysis of white matter enhances the

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clinicoradiological correlation. Functional imaging utilizes positron emission tomography (PET), single photon emission CT (SPECT), and functional MRI (FMRI) imaging in the analysis of functional activity of the brain. PET imaging utilizes 18F-fluoro deoxyglucose as a tracer and SPECT imaging utilizes ^{99m}Tc hexamethylpropyleneamineoxime (HMPAO) in the functional imaging for the analysis of the cerebral activity. These techniques measure the cerebral activity through indirect correlates. Fluorodeoxyglucose (FDG)-PET analyses glucose metabolism, whereas ^{99m}Tc HMPAO SPECT measures cerebral perfusion, and hence, these assess cerebral activity indirectly. Dopamine imaging utilizes radioactive label to analyze the functioning and integrity of dopamine circuitry within the brain. FMRI utilizes blood oxygen level dependent sequence. This is based on the fact that increase in cerebral activity is associated with increase in oxyhemoglobin to deoxyhemoglobin ratio. FMRI is useful in assessing the networks involved in a particular function based on the activation of gray matter hubs during a particular function and therefore useful in network imaging. A detailed discussion on FMRI is beyond the scope of this chapter. Molecular imaging utilizes radioactive tracers in PET imaging that bind to the protein deposits considered pathological in the particular disease process. Molecular imaging includes amyloid imaging, tau imaging, and translocation protein imaging.[4] In the current article, we discuss the neuroimaging in dementia under the following headings as shown in Figure 1:

a. Structural imaging
b. Functional imaging
c. Molecular imaging.

Structural Imaging

Diffusion tensor imaging

Structural imaging modalities that appear promising in diagnosing dementias in preclinical stages are diffusion tensor imaging and VBM. Until recently, the gray matter was the major focus in the pathology of Alzheimer's disease and the white matter changes were considered secondary to the gray matter loss. Recent studies in Alzheimer's disease have shown evidence for microstructural changes in the white matter of the brain including axonal and myelin loss that antedates other pathological changes which in turn results in the altered diffusion properties of the water in the *milieu* of white matter changes. Tau is a transport protein present predominantly in the axons. Neurofibrillary tangles, a core pathological feature of Alzheimer's disease are aggregates of hyperphosphorylated tau. Hyperphosphorylated tau results in abnormal axonal transport function explaining the early white matter changes associated with Alzheimer's disease. Furthermore, diffusion tensor imaging studies in carriers of APOE4 allele have shown white matter loss in the fornix, out of proportion to the medial temporal lobe atrophy adding strength to the recent concept of early white matter changes in Alzheimer's disease well before gray matter loss.[5]

The four important parameters in any diffusion tensor imaging as shown in Figure 2 include:

1. Fractional anisotropy which is a fraction of the tensor that is assigned to a particular direction of diffusion
2. Mean diffusivity which is the mean diffusion of water molecules in a given voxel
3. Axial diffusivity which is a measure of diffusion of water molecules along the long axis of the fibers in the region of study
4. Radial diffusivity which is a measure of diffusion of water molecules in a direction perpendicular to the long axis of the fibers in the region of study.[6]

The value of these parameters varies in accordance with the underlying pathological process. For example, mere demyelination with normal axonal integrity results in increased radial diffusivity without changes in axial diffusivity, whereas in case of Wallerian degeneration, there will be a decrease in fractional anisotropy and axial diffusivity with an increase in radial diffusivity and insignificant change in mean diffusivity.[6]

These parameters may also help to differentiate between mild cognitive impairment (MCI) and Alzheimer's disease based on DTI imaging as MCI is associated with decrease in axial diffusivity without accompanying change in radial diffusivity, whereas in patients with Alzheimer's disease, the decrease in axial diffusivity is accompanied by increase in radial diffusivity.

In Alzheimer's disease, there will be increased mean diffusivity and decreased fractional anisotropy with a predilection for corpus callosum, superior longitudinal and uncinate fasciculus, posterior part of cingulum, frontal and temporal lobes in a gradient manner so that the posterior part of the above structures are more involved than the anterior. The changes in the above structures follow the corresponding cortical atrophy suggesting Wallerian degeneration as the cause for white matter changes.[7]

In patients with amnestic MCI and in individuals who are genetically predisposed to Alzheimer's disease the white matter changes are not associated with cortical changes and these microstructural changes in white matter will be concentrated in corpus callosum, frontal lobes, and cingulum.[7]

In dementia with Lewy bodies (DLB), there will be decreased fractional anisotropy and increased mean diffusivity in the inferior longitudinal fasciculus and in the parieto-occipital tracts with relative sparing of frontal and temporal lobes which is in contrast to the features in Alzheimer's disease. In the behavioral variant of frontotemporal lobar degeneration, there will be a severe decrease in fractional anisotropy in the frontal lobes when compared to Alzheimer's disease. The nonfluent variant of frontotemporal lobar degeneration is known to have marked changes in the superior longitudinal fasciculus on the left side, whereas the characteristic findings in the semantic variant are decreased fractional anisotropy in the left temporal lobe connections. Diffusion tensor imaging of various tracts is shown in Figures 3 and 4.

Voxel-based morphometry

VBM is a statistical method of measuring the changes in the volume of brain under study in comparison with the template data available. In contrast to the manual volume measurement studies which are time-consuming and liable for bias because of subjective assessment, VBM are easy to perform and produce more consistent results. Moreover, with visual analysis, only gross volume changes are detectable and an early disease may be missed. This can be overcome using VBM which analyze every voxel in the region of interest or the particular study. However, the disadvantages with VBM are processing errors and the varying results depending on the methods employed for processing. Figure 5 summarizes the steps involved in the processing of VBM.[8]

In Alzheimer's disease, there will be a significant gray matter volume loss in the medial temporal lobe structure in the early stages which progresses to involve other lobes as the disease advances.

In patients with semantic variant of frontotemporal lobar degeneration, the temporal lobe volume loss is generalized which is in contrast to the medial temporal predilection in the early stages of Alzheimer's disease. In the behavioral variant of frontotemporal lobar degeneration, the gray matter loss will be more in the orbitofrontal cortex, inferior frontal gyrus, and the anterior cingulate cortex.[9]

Functional Imaging

Fluorodeoxyglucose positron emission tomography imaging

FDG-PET uses 2-fluoro-2-deoxy-D-glucose (glucose analog) to assess the brain metabolism (glucose is the chief metabolic substrate). FDG glucose is taken in neuronal cells and helps in estimating the metabolic rate of various structures of brain. Normally, the glucose metabolism of both hemispheres is similar.[10] FDG-PET scan is analyzed for any focal reduction of metabolism (hypometabolism) and right-to-left asymmetry in the uptake of FDG tracer.

The importance of utilizing FDG-PET is also useful during treatment, as certain drugs used to treat Alzheimer's dementia (AD) may worsen other types as exemplified by cholinesterase inhibitors and donepezil may worsen the behavioral symptoms of frontotemporal dementia.[11]

Mild cognitive impairment

MCI is a state, in which there is cognitive impairment, but the patient will be able to do his activities of daily living. The risk of developing AD is higher in patients with MCI. FDG-PET reveals significant hypometabolism in posterior cingulate cortex and also there is reduced metabolism in parahippocampal gyrus and temporal lobe.[12]

Alzheimer's dementia

The most common degenerative dementia in elderly is AD. It is characterized by deposition of beta-amyloid plaques and neurofibrillary tangles (tau) inside the brain. FDG-PET shows hypometabolism in posterior cingulate cortex, precuneus cortex, and hippocampus, and parietal and posterior temporal lobes. As the diseases progress, frontal lobe tends to get involved. Occipital lobes are relatively spared in AD.[13]

Frontotemporal dementia

Frontotemporal dementia is one of the most common primary dementias occurring in patients with <65 years. It is classified into behavioral-variant FTD, semantic variant, and primary progressive aphasic variant. In FTD, the hypometabolism is significant in frontal lobes (frontal polar cortex in particular), anterior temporal cortex, and it may also involve anterior cingulate cortex. Asymmetric involvement of one hemisphere over the other is evident depending on the subtype of frontotemporal dementia.[14]

Dementia with Lewy body

DLB is characterized by cognitive decline; Parkinsonism features with visual hallucinations. FDG-PET shows hypometabolism in occipital cortex extending into parietal and temporal lobes. Posterior cingulate cortex is spared in DLB.[15]

Vascular dementia

Vascular dementia is only next to AD as a cause of dementia. Vascular dementia usually has an acute onset associated with focal weakness. It is classified in multi-infarct dementia, single strategic infarct dementia, and subcortical dementia. FDG-PET reveals hypometabolism with abrupt onset corresponding to a vascular territory involving cortical and subcortical structures such as deep gray nuclei and cerebellum.[10,16]

Precautions in patient preparation and FDG-PET imaging:

1. Hyperglycemia may affect glucose metabolism of the brain (preferred blood sugar level <140 mg/dl)[1]
2. As the imaging is done 30 min after tracer injections, activities of the patient may alter the glucose uptake. The patient is instructed to be in a quiet room without any activities, not even speaking[8]
3. But if the patient has his/her eyes closed, FDG uptake in occipital lobe is reduced which may simulate DLB[8]
4. Cortical atrophy may mimic decreased uptake and hypometabolism[1,8]
5. Head movements may create artifacts producing difficulty while interpretation
6. Drugs like benzodiazepines reduce cerebral metabolism (e.g., diazepam reduces the cerebral metabolism by 20%) resulting in hypometabolism leading to misdiagnosis. Drugs for sedation should be used with caution.[17]

Case 1

Mrs. H, a 61-year-old woman, known diabetic on oral antidiabetic drugs with no other comorbidities and no addiction, presented with a history of difficulty in recollecting recent events for 18 months. However, she was able to recollect her remote past events such as her marriage, childbirth, and graduation without any difficulty. She is having difficulties in carrying out her activities of daily living. She does not have any

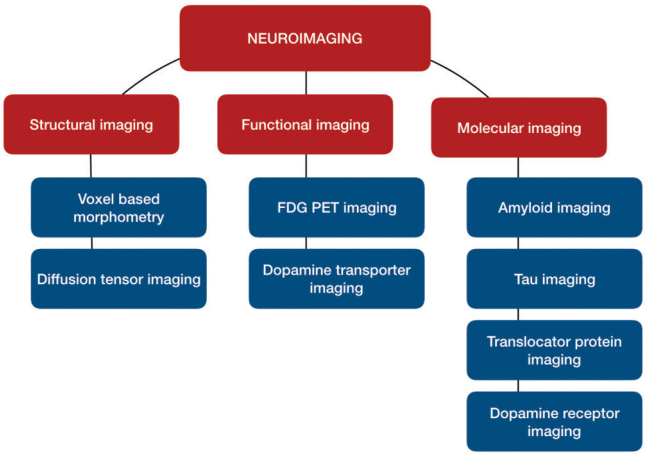

Figure 1: Neuroimaging armamentarium in dementia

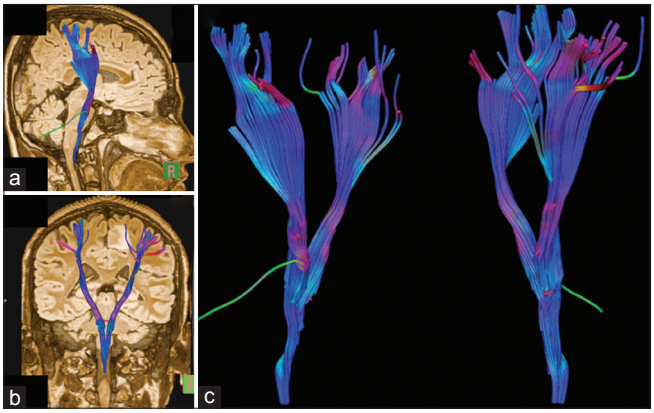

Figure 3: (a-c) Diffusion tensor imaging showing the pyramidal tract in a normal individual

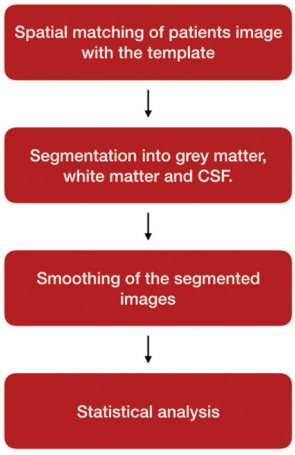

Figure 5: Schematic diagram showing the basic steps involved in voxel-based morphometry

difficulty in handling money or navigation. The relatives did not complain of any change in behavior, social interaction, sleep, difficulty in speaking, naming persons or objects. Neurological examination revealed episodic memory impairment. She also had a positive family history for Alzheimer's disease. MRI

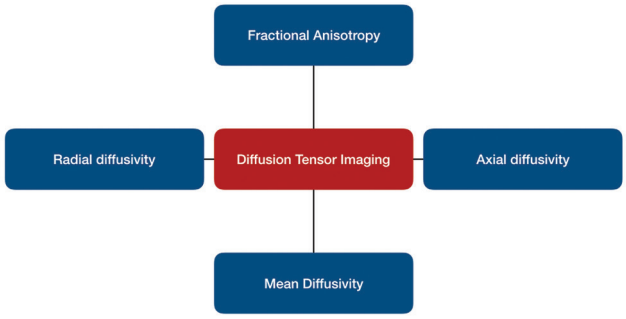

Figure 2: Various imaging metrics used in diffusion tensor imaging

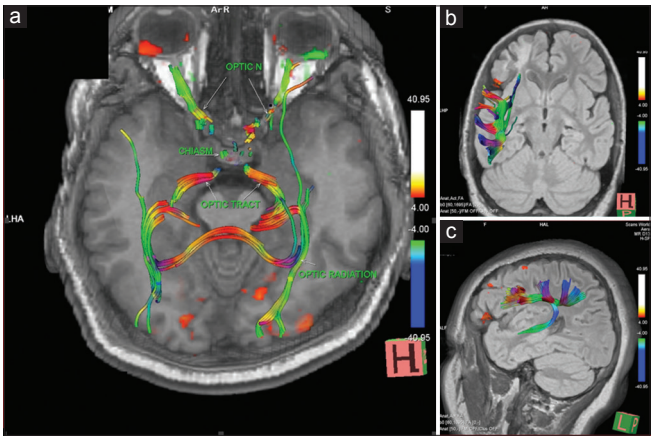

Figure 4: Diffusion tensor imaging showing the (a) optic pathway (b and c) arcuate fasciculus

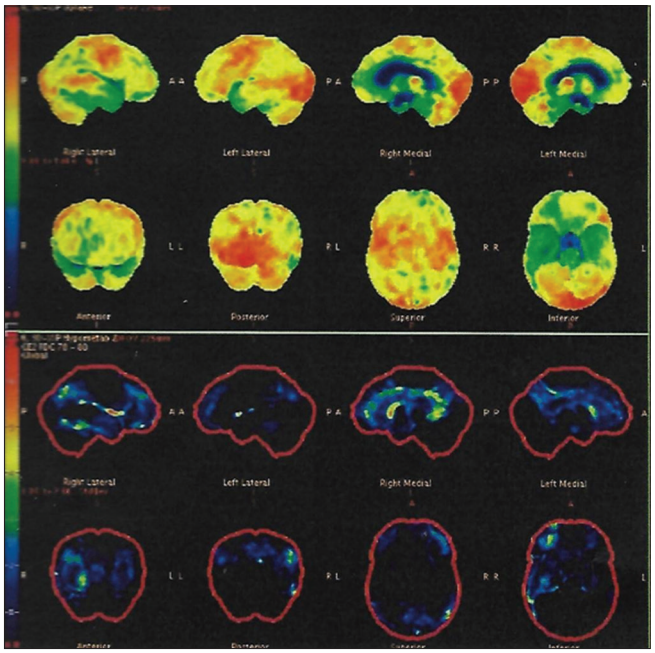

Figure 6: Moderate-to-severe asymmetric hypo metabolism noted in bilateral frontal and posterior parietal lobes suggestive of Alzheimer's disease

brain with hippocampal volumetric analysis was done which was normal. FDG-PET imaging revealed moderate-to-severe

hypometabolism in bilateral posterior parietal lobes and bilateral frontal lobes as shown in Figure 6. The clinical and radiological pattern was suggestive of Alzheimer's disease. The patient was treated with cholinesterase inhibitor and is on follow-up.

Dopamine imaging

Imaging the dopaminergic pathway is helpful in differentiating diffuse Lewy body dementia and Parkinson disease dementia from AD. Dopaminergic pathway can be imaged with specific isotope labeled PET or SPECT. Dopaminergic pathway extends from substantia nigra pars compacta of midbrain to the caudate nucleus and putamen. In the basal ganglia, dopamine is released from the presynaptic terminals and binds with the postsynaptic D1 or D2 receptors resulting in excitation and inhibition, respectively. The remaining dopamine in the synapse is again taken back into the presynaptic terminal by dopaminergic transporter located in the presynaptic neurons.[18] The dopaminergic imaging can be classified into two types.

1. Dopamine transporter (DAT) imaging (presynaptic)
2. Dopamine receptor imaging (postsynaptic).[19]

Lewy body disease spectrum includes Parkinson disease, Parkinson disease dementia, and Lewy body dementia. In this spectrum of diseases, there is deposition of Lewy body and Lewy neurites, both contain synuclein. Lewy body deposition occurs in the olfactory bulb, substantia nigra, thalamus, cerebellum, and neocortex. Neocortex involvement occurs early in Lewy body dementia, whereas the involvement of neocortex occurs late in Parkinson disease.[20] This explains the reason for the diseases with same pathology having various clinical manifestations.

In Lewy body diseases, due to the involvement of nigrostriatal pathway, the amount of dopamine released from the presynaptic terminal is reduced. This results in the upregulation of postsynaptic dopamine (D1/D2) receptors. Since the amount of dopamine in the synapse is reduced, there will be downregulation of the DAT located in the presynaptic neurons.

Dopamine transporter imaging

DAT imaging involves utilization of ligands that specifically bind to the DAT located presynaptically. Although it is a tool classified under molecular imaging, it is considered under dopaminergic imaging for ease of discussion. The ligands utilized in DAT imaging are listed in Table 1.

In Lewy body diseases, there is a reduced uptake of the ligands in presynaptic region due to degeneration of nigrostriate pathway. The reduced uptake is more prominent in putamen than caudate nucleus. The patterns of reduced uptake have been categorized into:[18]

1. Reduced uptake in putamen on one side
2. Reduced uptake in putamen on both sides
3. Absent uptake of tracers on bilateral striatum.

The overall sensitivity of DAT scan in differentiating Lewy body dementia from AD is around 90% when compared to the clinical criteria which are around 50%.[19]

Dopamine receptor imaging

Dopamine receptor imaging involves imaging of the postsynaptic D1/D2 receptors. In synucleopathies including Lewy body dementia, there is an upregulation of the postsynaptic dopamine receptors as a result of reduced levels of dopamine in the synaptic terminals. The ligands utilized for imaging D1 and D2 receptors are different as shown in Table 2.

Dopamine receptor ligands

Imaging of postsynaptic D1 receptors is still under development as the above ligands for D1 receptor do not compete with endogenous dopamine and various clinical trials have shown that there was no significant difference on D1 receptor imaging between controls and Parkinson disease patients.[21,22]

Table 1: Radioligands used in imaging of dopamine transporter

Ligands for DAT imaging	
Abbreviated Form	**Expanded Form**
^{11}C-CFT	[^{11}C] 2β-carbomethoxy-3β-ltropane
^{123}I-β-CIT	[^{123}I] (1R) 2 β-carbomethoxy-3β-(4-iodophenyl) tropane
^{11}C-altropane	2β-carbomethoxy-3β-(4-fluorophenyl)-N-((E)-3-iodo-prop-2-enyl) tropane
^{99m}Tc-TRODAT-1	[^{99m}Tc] technetium [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo [3.2.1]oct-2-yl]-methyl](2-mercaptoethyl) amino]-ethyl] amino]ethane-thiolato (3-)-N2, N2′, S2, S2′]oxo-[1R-(exo-exo)]

DAT=Dopamine transporter

Table 2: Radioligands used in the imaging of dopamine receptors

Ligands for DAT imaging		
Dopamine Receptor	**Abbreviated Form**	**Expanded Form**
Dopamine D_1 receptor	^{11}C-NNC 112	(+)-5-(7-benzofuranyl)-8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine
	^{11}C-SCH 23390	(R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1H-3-benzazepin-7-ol
Dopamine D_2 receptor	^{11}C-Raclopride	3,5-dichloro-N-{[(2S)-1-ethylpyrrolidin-2-yl]methyl}-2-hydroxy-6-[^{11}C]methoxybenzamide
	^{123}I-IBZM	(S)-(-)-3-[^{123}I]iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl] benzamide

DAT=Dopamine transporter

Imaging for D2 receptors is widely used clinically to diagnose synucleinopathies. Imaging reveals increased uptake of ligands in patients who have not received L dopa, but there is reduced uptake in patients who are receiving L-dopa treatment. The reasons for reduced uptake include downregulation of receptors, competition between exogenous dopamine, and ligand in binding the receptor or internalization of the receptors due to dopamine binding.[19,22]

Both DAT and dopamine receptor imaging differentiate Lewy body pathology from other spectrum of diseases but cannot differentiate the types of Lewy body spectrum disorders. The various tracers used in dopamine imaging are summarized in Figure 7.

Case 2

A 57-year-old male presented with the complaints of tremor of upper limbs and stiffness of limbs. Examination revealed cogwheel rigidity, resting tremor, and reemergent tremor. MRI brain revealed cortical atrophy. The patient underwent DAT scan which revealed severely decreased tracer uptake in the putamen with normal uptake in the caudate nucleus [Figure 8]. The patient was diagnosed of having Parkinson disease. He was started on levodopa and improved. DAT scan is useful to assess the function of nigrostrial pathway. In Parkinson disease, there will reduced uptake in the putamen. DAT scan is useful in differentiating Lewy body dementia from AD.

Molecular Imaging

While the structural imaging images the architectural consequences of the disease process and functional imaging measures the correlates of cerebral hypometabolism that results from the pathological process, the molecular imaging is able to measure the pathological protein that plays a role in the disease process causing the above consequences. In molecular imaging, the radioactive tracer ligand with specific affinity to the target protein being imaged is performed using PET. Since it samples the pathological protein, it is able to detect at an earlier stage before the structural change.

The target proteins that are widely imaged using radioactive tracers are amyloid and tau deposits. Recently, translocator protein (TSPO) ligands have also been imaged. The radioactive tracer ligand utilizes either 11-Carbon isotope or 18-Fluorine isotope. The 11-Carbon isotope has limited clinical utility owing to its short half-life (20 min) and hence requires an onsite cyclotron, thereby limiting its use to the research field. The difficulty is overcome using 18-Fluorine labeled isotope which has a longer half-life (110 min). An ideal PET ligand should have high-affinity binding to the target of interest and low affinity to nontarget binding proteins, high blood–brain barrier permeability.[23]

Amyloid imaging

Amyloid imaging is useful for the detection of beta-amyloid deposits in the brain. The radiotracers bind to amyloid plaques in varied protein configuration (fibrillary and oligomers). The oldest known compound, ^{11}C-Pittsburgh compound, was limited in utility due to short half-life. The recent tracers that have extended its utility from bench to bedside include 18F-Florbetaben, 18F-Florbetapir, and 18F-Flutemetamol. The diagnostic capabilities of the fluorinated tracers are equivalent. The Alzheimer's association recommends imaging for patients with unexplained progressive mild cognitive impairment, patients with core clinical features suggestive of possible Alzheimers disease, and young onset atypical dementia. Amyloid imaging has a high negative predictive value. The absence of amyloid deposit negates the diagnosis of Alzheimer's disease. The presence of high density of amyloid favors the diagnosis of Alzheimer's disease. However, the mere presence of amyloid deposits is insufficient.[24,25]

Tau imaging

Tau imaging using radioactive tracers help to detect tau protein *in vivo*, which plays a role in various diseases including Alzheimers disease and other tauopathies. The tau protein exists in six isoforms and are categoried either 3R or 4R based on the number of repeats in the microtubule-binding domain where

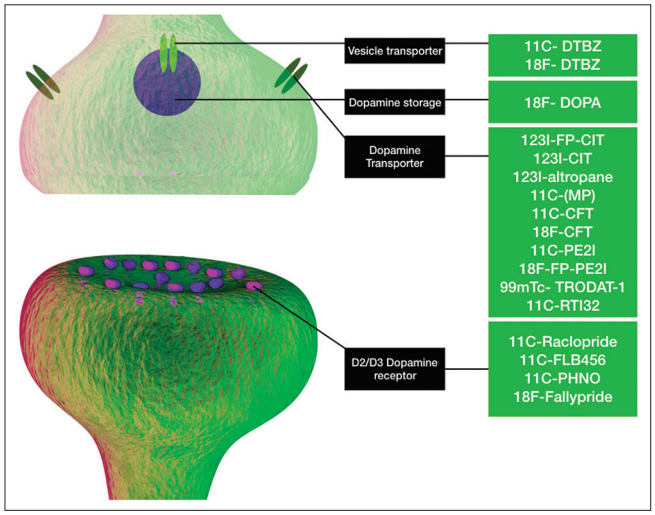

Figure 7: The radioligands and their corresponding tracers used in the dopamine imaging

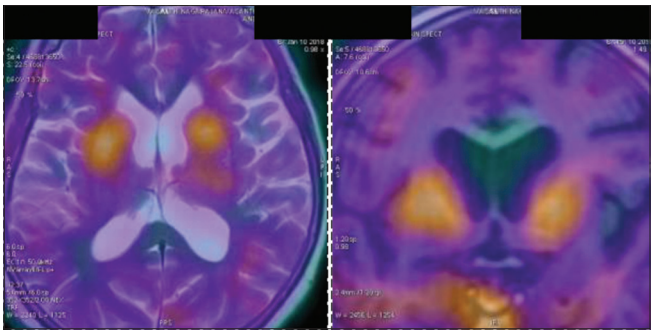

Figure 8: ^{99m}Tc-trodat brain single photon emission computed tomography/magnetic resonance imaging hybrid fusion study assessing the presynaptic nigrostriatal pathway. The scan reveals severely decreased uptake in bilateral putamen and normal uptake in caudate nucleus

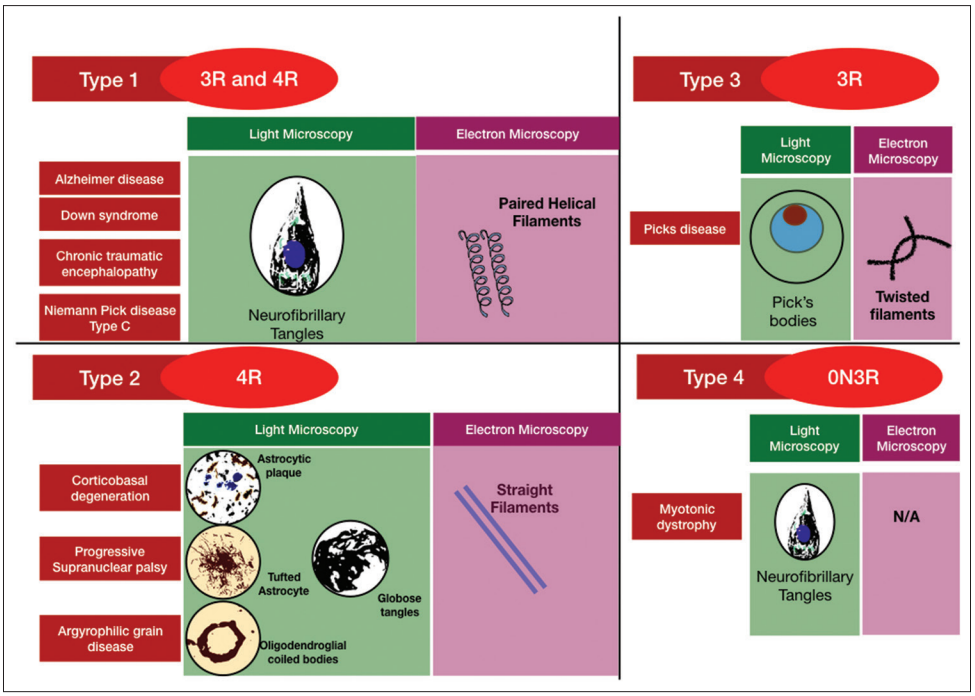

Figure 9: Four types of tauopathy, light microscopy, and electron microscopy findings. There are six isoforms of tau classified as either 3R or 4R based on the number of microtubule binding domains. The classification of tauopathy is based on the occurrence of either 3R/4R alone or in combination

it functions to stabilize the microtubules. The tau filaments in the deposit can exist in paired helical filaments (PHF), straight filaments, or twisted filaments. Based on the accumulation of isoforms, the tauopathies are divided into four types. Type 1, 2, and 3 is characterized by the accumulation of PHF, straight filaments, and twisted filaments, respectively, [Figure 9].[26]

The complexities and challenges faced in tau imaging include,[27]

a. Presence of six isoforms of tau with several conformational changes due to various posttranslational modification
b. The presence of tau aggregates in the white matter affects the visual inspection
c. The tau deposit in Alzheimer's disease is accompanied by beta-amyloid deposits
d. The concentration of beta-amyloid far exceeds the tau deposits
e. The presence of tau deposit in the intracellular location earlier in the disease requires the tau tracer to traverse the blood–brain barrier and the cell membrane.

Tau burden has a better correlation with clinical disease burden, disease progression, and hence, delineation of tau using PET imaging has better clinical correlation. The PET tau tracers are classified as follows: nonselective tau tracer and selective tau tracer. Nonselective tau tracer, 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl} ethylidene) malononitrile (18F-FDDNP), binds to both tau protein located intracellularly and beta-amyloid protein located extracellularly. This is due to the ability of the PET tracer to identify the misfiled beta-pleated sheet structure but not the pathological misfiled protein that underlies the

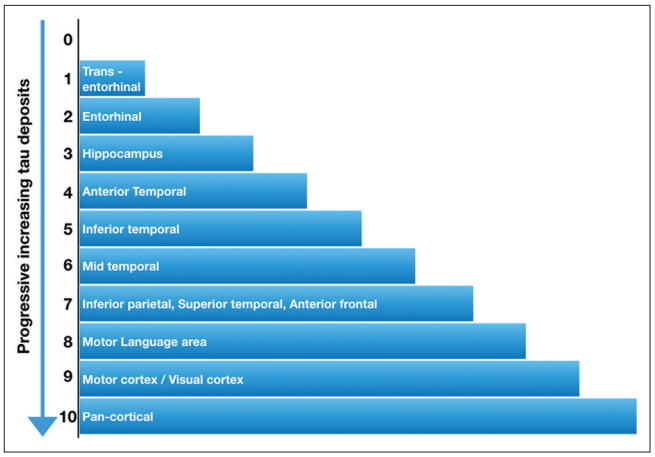

Figure 10: Stepwise progression of tau deposits in the brain in sequential order in parallel with disease progression

disease and hence limits its use clinically. The selective tracers are fast emerging with various kinetics and dynamics which requires extensive *in vitro* testing to quantify and pathological correlation studies to specificity analysis. The quinolone derivative, 2-(4-aminophenyl)-6-(2-[^{18}F] fluoroethoxy) quinoline (18F-THK523) has high specificity for tau protein over beta-amyloid protein. The significant binding of the tracers in the white matter hinders visual inspection. The 2-arylquinolone derivatives, 6-[(3-[^{18}F] fluoro-2-hydroxy) propoxy]-2-(4-dimethyl-aminophenyl) quinolone (18F-THK5105), 6-[(3-[^{18}F] fluoro-2-hydroxy) propoxy]-2-(4-methylaminophenyl) quinolone (18F-THK5117), and 6-[(3-^{18}F-2-hydroxy) propoxy]-2-(4-methylaminopyridyl) quinoline

(18F-THK5351) have lower signal-to-noise ratio and lower white matter binding that enables better visual inspection. The benzimidazole-pyrimidine derivatives, (*E*)-4-(2-(6-(2-(2-(2-[18F]fluoroethoxy)ethoxy)ethoxy) pyridin-3-yl)vinyl)-*N*-methyl benzenamine (18F-T807) and 2-(4-(2-[^{18}F] fluoroethyl)piperidin-1-yl)benzo[4,5] imidazo(1,2-a) pyrimidine (18F-T808), have improved kinetics. The use of 18F-Lansoprazole is limited by the sparsity of the data.[28]

The use of the above-mentioned specific tracers has high degree of pathological correlation in autopsy studies and parallels the Braak stages of tau accumulation in Alzheimers disease where it binds to the PHF-tau. The progression of the tau deposit is shown in Figure 10. The tau deposit may be seen in the transentorhinal cortex and entorhinal cortex in normal elderly population and may not be associated with cognitive decline. In the absence of amyloid deposits, the tau deposits are limited to the entorhinal cortex. The complex interaction between beta-amyloid and PHF-tau in Alzheimer's disease causes spread of the tau filaments to the subsequent areas. However, the above-mentioned tracers binds to PHF-tau, and hence, their use is limited in the assessment of non-Alzheimers tauopathies. The use of phenyl/pyridinyl-butadienyl-benzothiazole/benzothiazolium derivative (11C-PBBB) binds selectively to tau. It also shows binding to non-Alzheimer's tau protein and hence further data and studies are required to validate the tracer.[28]

The use of tau are in the early days and requires newer and improved PET tracers with desired kinetics. The tau protein load serving as a surrogate marker helps to assess the treatment response to newer anti-tau agents in clinical trials.

Translocator protein-ligand imaging

TSPO is a peripheral benzodiazepine receptor with five transmembrane components. It is undetectable in normal brain parenchyma and shows increased expression in microglia during the process of neuroinflammation.[29] PET tracer ligand that detects TSPO serves as a marker of neuroinflammation. The use of 11C-(R)-PK11195 is limited to research field due to its short half-life. The use of fluorinated tracers 18F-FEPPA, 18F-FEDAA1106, 18F-PBR111, has improved signal-to-noise ratio and increased sensitivity. However, the polymorphism in TSPO gene that influences TSPO binding affects quantification and visualization. The newer tracer 18F-GE180, owing to its insensitive binding may help overcome and is being evaluated. In Alzheimer's disease, the TSPO PET tracer shows a biphasic distribution. The first phase of TSPO uptake occurs in mild cognitive impairment followed by decline in uptake by 18%. The second phase of TSPO uptake occurs as the Alzheimers disease progresses. The first phase of neuroinflammation is considered protective against the amyloid deposition and the second phase is considered a part of neuropathological disease process. In frontotemporal dementia, the uptake of TSPO is increased in frontal and temporal regions that reflect the inflammatory component in the progressive neuronal degeneration. The future studies on PET tracers and role in other dementia appear promising.[25,30]

Neuroimaging as a Biomarker

Imaging modalities of the brain can be used as potential biomarkers in diagnosing dementia and other degenerative diseases. It also serves as a useful biomarker in assessing the progression of disease. Studies have revealed that baseline structural MRI is a better prognosticator in assessing the progression of the disease than CSF biomarkers.[31] Neuroimaging can also be useful for prediction of progression of minimally cognitive impairment (MCI) patients landing up in Alzheimer's diseases. Longitudinal follow-up studies using MRI VBM and FDG-PET in patients with MCI have shown that early volume loss and hypometabolism, respectively, in medial temporal lobe (hippocampus and entorhinal cortex) predicts progression to AD than in patients without these patterns of volume loss.[32] Amyloid imaging can be utilized in assessing the response to drug. Gantenerumab and bapineuzumab are humanized monoclonal antibodies against beta-amyloid plaques. Amyloid imaging before and after the administration of the above drugs revealed that there is a significant reduction in amyloid deposition. However, these patients had minimal or no cognitive improvement after treatment.[33]

Conclusion

The neuroimaging field has grown several folds in the past decade. Its advancement in the current changing landscape fast approaches the precision and accuracy of pathological examination. Moreover, its ability to administer *in vivo* increases the usefulness as opposed to the pathological examination. Further, detecting it at an early stage helps administer disease-modifying therapies producing significant impact in the quality of life of the patient.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dormont D, Seidenwurm DJ; Expert Panel on Neurologic Imaging, American College of Radiology. Dementia and movement disorders. AJNR Am J Neuroradiol 2008;29:204-6.
2. Spaan PE. Cognitive decline in normal aging and early Alzheimer's disease: A continuous or discontinuous transition? A historical review and future research proposal. Cogent Psychol 2016;3:1185226.
3. Martin-Macintosh EL, Broski SM, Johnson GB, Hunt CH, Cullen EL, Peller PJ. Multimodality Imaging of Neurodegenerative Processes: Part 1, The Basics and Common Dementias. AJR Am J Roentgenol 2016;207:871-82.
4. Rayment D, Biju M, Zheng R, Kuruvilla T. Neuroimaging in dementia: An update for the general clinician. Prog Neurol Psychiatry 2016;20:16-20.
5. Sachdev PS, Zhuang L, Braidy N, Wen W. Is Alzheimer's a disease of the white matter? Curr Opin Psychiatry 2013;26:244-51.
6. Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW,

et al. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. Biochim Biophys Acta 2012;1822:386-400.
7. Medina DA, Gaviria M. Diffusion tensor imaging investigations in Alzheimer's disease: The resurgence of white matter compromise in the cortical dysfunction of the aging brain. Neuropsychiatr Dis Treat 2008;4:737-42.
8. Whitwell JL. Voxel-based morphometry: An automated technique for assessing structural changes in the brain. J Neurosci 2009;29:9661-4.
9. Scarpazza C, De Simone MS. Voxel based morphometry: Current perspectives. Neuroscience and Neuroeconomics 2016;5:19-35.
10. Shivamurthy VK, Tahari AK, Marcus C, Subramaniam RM. Brain FDG PET and the diagnosis of dementia. AJR Am J Roentgenol 2015;204:W76-85.
11. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. Arch Neurol 2007;64:830-5.
12. Berti V, Pupi A, Mosconi L. PET/CT in diagnosis of dementia. Ann N Y Acad Sci 2011;1228:81-92.
13. Marcus C, Mena E, Subramaniam RM. Brain PET in the diagnosis of Alzheimer's disease. Clin Nucl Med 2014;39:e413-22.
14. Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, *et al.* FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 2007;130:2616-35.
15. Ishii K. PET approaches for diagnosis of dementia. AJNR Am J Neuroradiol 2014;35:2030-8.
16. Kerrouche N, Herholz K, Mielke R, Holthoff V, Baron JC. 18FDG PET in vascular dementia: Differentiation from Alzheimer's disease using voxel-based multivariate analysis. J Cereb Blood Flow Metab 2006;26:1213-21.
17. Brown RK, Bohnen NI, Wong KK, Minoshima S, Frey KA. Brain PET in suspected dementia: Patterns of altered FDG metabolism. Radiographics 2014;34:684-701.
18. Booth TC, Nathan M, Waldman AD, Quigley AM, Schapira AH, Buscombe J, *et al.* The role of functional dopamine-transporter SPECT imaging in Parkinsonian syndromes, part 1. AJNR Am J Neuroradiol 2015;36:229-35.
19. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: A review. Nucl Med Commun 2007;28:511-9.
20. Donaghy PC, McKeith IG. The clinical characteristics of dementia with lewy bodies and a consideration of prodromal diagnosis. Alzheimers Res Ther 2014;6:46.
21. Shen LH, Liao MH, Tseng YC. Recent advances in imaging of dopaminergic neurons for evaluation of neuropsychiatric disorders. J Biomed Biotechnol 2012;2012:259349.
22. Niccolini F, Su P, Politis M. Dopamine receptor mapping with PET imaging in Parkinson's disease. J Neurol 2014;261:2251-63.
23. Eberling JL, Dave KD, Frasier MA. A-synuclein imaging: A critical need for Parkinson's disease research. J Parkinsons Dis 2013;3:565-7.
24. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, *et al.* Appropriate use criteria for amyloid PET: A report of the amyloid imaging task force, the society of nuclear medicine and molecular imaging, and the Alzheimer's association. Alzheimers Dement 2013;9:e-1-16.
25. Payoux P, Salabert AS. New PET markers for the diagnosis of dementia. Curr Opin Neurol 2017;30:608-16.
26. Buée L, Bussière T, Buée-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev 2000;33:95-130.
27. James OG, Doraiswamy PM, Borges-Neto S. PET imaging of tau pathology in Alzheimer's disease and tauopathies. Front Neurol 2015;6:38.
28. Villemagne VL, Fodero-Tavoletti MT, Masters CL, Rowe CC. Tau imaging: Early progress and future directions. Lancet Neurol 2015;14:114-24.
29. Wilms H, Claasen J, Röhl C, Sievers J, Deuschl G, Lucius R, *et al.* Involvement of benzodiazepine receptors in neuroinflammatory and neurodegenerative diseases: Evidence from activated microglial cells *in vitro*. Neurobiol Dis 2003;14:417-24.
30. Fan Z, Brooks DJ, Okello A, Edison P. An early and late peak in microglial activation in Alzheimer's disease trajectory. Brain 2017;140:792-803.
31. Ruan Q, D'Onofrio G, Sancarlo D, Bao Z, Greco A, Yu Z, *et al.* Potential neuroimaging biomarkers of pathologic brain changes in mild cognitive impairment and Alzheimer's disease: A systematic review. BMC Geriatr 2016;16:104.
32. Varghese T, Sheelakumari R, James JS, Mathuranath P. A review of neuroimaging biomarkers of Alzheimer's disease. Neurol Asia 2013;18:239-48.
33. Pich EM, Jeromin A, Frisoni GB, Hill D, Lockhart A, Schmidt ME, *et al*. Imaging as a biomarker in drug discovery for Alzheimer's disease: is MRI a suitable technology?. Alzheimers Res Ther 2014;6:51.