

## REVIEW ARTICLE

# Functional Neuroimaging: Single Photon Emission Computed Tomography (SPECT) In Neurological Disorders

RAHMAN A<sup>1</sup>, SALAM F<sup>2</sup>, BEGUM R<sup>3</sup>, AKHTER A<sup>4</sup>, NABI S<sup>5</sup>, RAHMAN MK<sup>6</sup>,  
ISLAM MT<sup>7</sup>, ALI Z<sup>8</sup>, SAHA UK<sup>9</sup>, QURAIISHI FA<sup>10</sup>

### Abstract:

*A single photon emission computed tomography (SPECT) scan is a functional nuclear imaging technique performed to evaluate regional cerebral perfusion. Because cerebral blood flow is closely linked to neuronal activity, the activity distribution is presumed to reflect neuronal activity levels in several areas of the brain. Although structural magnetic resonance imaging (MRI) and computed tomography (CT) provide exquisite anatomical detail, SPECT provide complementary functional information. Frequently, brain pathology will manifest as functional changes before anatomical changes are detectable. SPECT has clinical value in the diagnosis, therapeutic management, and follow-up of patients. A general consideration of the clinical value of this technique is followed by relevant information on cerebral physiology and pathology for proper understanding of brain SPECT images. The diversity of central nervous system diseases and therefore the still incomplete knowledge of the mechanisms that underlie them have contributed to the success of brain perfusion SPECT as a research tool in neurosciences. Finally, step-by-step recommendations for interpreting and reporting brain perfusion SPECT images are provided to get the utmost clinical benefit from this technique.*

**Key Words:** SPECT; Regional cerebral blood flow; Functional Neuroimaging

### Introduction:

Neuroimaging is an emergent method of investigation that deals with the in vivo depiction of anatomy and function of the central nervous system (CNS) in health and disease<sup>1</sup>. It classifies into two broad categories: structural imaging and functional imaging. Structural imaging such as CT or MRI, which deals with the structure of the brain and the diagnosis of large-scale intracranial diseases (such as a tumor, infection etc.), as well as injury. Functional imaging such as SPECT or PET, which

is used to diagnose metabolic diseases and lesions on a finer scale (such as dementia, PD etc), and also for neurological and cognitive-psychology research.<sup>2</sup> Functional imaging allows the brain's information processing to be visualized directly, because activity in the involved area of the brain increases metabolism and "lights up" on the scan.

Brain SPECT provides tridimensional information on the perfusion and metabolic status of brain tissue. This information is often complementary to the anatomic detail provided by structural

1. Dr. Aminur Rahman, Assistant Professor, Dept. of Neurology, SSMC& Mitford Hospital, Dhaka, Bangladesh.
2. Dr. Farhana Salam, Resident Surgeon, Dept. of Surgery, Kurmitola General Hospital, Dhaka, Bangladesh.
3. Dr. Rubina Begum, Chief Medical Officer, Institute of Nuclear Medicine and Allied Science, DMCH, Dhaka, Bangladesh.
4. Dr. Afroza Akhter, Senior Medical Officer, Institute of Nuclear Medicine and Allied Science, DMCH, Dhaka, Bangladesh.
5. Dr. Shahryar Nabi, Associate Professor, Dept. of Radiology, DMCH, Dhaka, Bangladesh.
6. Prof. (Dr.) Md. Khalilur Rahman, Professor, Dept. of Radiology, Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh.
7. Dr. Md Tariqul Islam, Assistant Professor, Dept. of Neuroradiology and Imaging, NINS&H, Dhaka, Bangladesh.
8. Prof. (Dr.) Zahed Ali, Professor, Dept. of Neurology, SSMC& Mitford Hospital, Dhaka, Bangladesh.
9. Prof. (Dr.) Uttam Kumar Saha, Professor (Retd.), Dept. of Neurology, NINS&H, Dhaka, Bangladesh.
10. Prof. (Dr.) Firoz Ahmed Quraishi, Professor, Dept. of Neurology, Anwar Khan Modern Medical College, Dhaka, Bangladesh.

neuroimaging techniques. This tomographic imaging technique is using gamma ray which is very similar to conventional nuclear medicine planar imaging employing a gamma camera but is in a position to supply true 3D information. It evaluates regional cerebral perfusion because cerebral blood flow is closely linked to neuronal activity, the activity distribution is presumed to reflect neuronal activity levels in different areas of the brain. A 3-dimensional representation of cerebral blood flow can be iterated using gamma detectors, allowing for interpretation.

#### **Radioisotopes in SPECT:**

The radioisotopes typically utilized in SPECT to label tracers are iodine-123, technetium-99m, xenon-133, thallium-201, and fluorine-18. Among them lipophilic, PH-neutral three radioisotopes have approved by the U.S. Food and Drug Administration (FDA) for clinical use in brain perfusion<sup>3,4</sup>. The oldest one, iodine 123 isopropylidoamphetamine (IMP), distributes proportionally to rCBF over a range of flows but may be decreased with low plasma pH as in cerebral ischemia or acidosis. Brain activity remains relatively constant from 20 to at least 60 minutes after injection which is widely used in Japan, not commercially available in the United States. Technetium-99m hexamethyl propyleneamine oxime (HMPAO), a lipid-soluble macrocyclic amine, is available for routine clinical use [6]. Brain uptake is rapid and reaches its maximum within 10 minutes. Radiotracer distribution remains constant for many hours after injection. A third radiopharmaceutical, 99mTc ethyl cysteinyl dimer (ECD) has a rapid blood clearance, resulting in high brain-to-soft tissue activity ratios early and with less exposure to radiation<sup>5</sup>. The Tc-radiolabeled compounds are stable for about 6 hours, facilitating their use for the study of episodic phenomena, such as seizures. The inert gas xenon-133(<sup>133</sup>Xe) has also been used to study rCBF. <sup>133</sup>Xe SPECT is performed after inhalation of the gas and is based on clearance techniques that relate the change in radiotracer activity over time to blood flow<sup>5</sup>. The principal advantage over other tracers that remain in the brain is that rCBF can be measured

quantitatively and repeatedly without arterial sampling. <sup>133</sup>Xe does have major limitations, including poor spatial resolution and the need for specialized instrumentation. Various drugs and other chemicals can be labeled with these isotopes too that enhance regional cerebral blood flow, such as acetazolamide. Acetazolamide increases local pCO<sub>2</sub> and causes arteriolar dilation, allowing for assessment of cerebrovascular reserve in transient ischemic attack (TIA), stroke and vascular anomalies and distinguishing vascular from neuronal causes of dementia<sup>6</sup>.

#### **Principles of SPECT:**

SPECT integrates computed tomography (CT) and a radioactive tracer. The radioisotopes usually used in SPECT to label tracers are iodine-123, technetium-99m, xenon-133, thallium-201, and fluorine-18. These radioactive forms of natural elements will pass through the body and be detected by the scanner. Various drugs and other chemicals can be labeled with these isotopes too. Before the SPECT scan, a tracer is injected into bloodstream. The tracer is radiolabeled, meaning it emits gamma rays that can be detected by the CT scanner. The computer collects the information emitted by the gamma rays and displays it on the CT cross-sections. SPECT imaging is performed by using a gamma camera to acquire multiple 2-D images (also called projections), from multiple angles. A computer is then used to apply a tomographic reconstruction algorithm to the multiple projections, yielding a 3-D data set and form a 3D image of brain.

The type of tracer used depends on the physicians according to the expected pathological lesions. For example, in case of suspected tumor, the radiolabeled glucose (FDG) can be used to detect the metabolism of the tumor. Depending on the type of imaging system and tracer used, the resolution ranges from 14–17 mm full width at half maximum (FWHM) for single-head gamma cameras, now seldom used for brain imaging, to 8–10 mm FWHM for three- and four head camera systems and to 7–8 mm FWHM for special purpose ring-type imaging systems. In general, system cost is directly proportional to the number and

complexity of camera heads or crystals. To acquire SPECT images, the gamma camera is rotated around the patient. Projections are acquired at defined points during the rotation, typically every 3–6 degrees. In most cases, a full 360-degree rotation is used to obtain an optimal reconstruction. The time taken to obtain each projection is also variable, but 15–20 seconds is typical. This gives a total scan time of 15–20 minutes. Multi-headed gamma cameras can accelerate acquisition. For example, a dual-headed camera can be used with heads spaced 180 degrees apart, allowing two projections to be acquired simultaneously, with each head requiring 180 degrees of rotation. Triple-head cameras with 120-degree spacing are also used.

#### **Clinical applications of SPECT:**

A SPECT scan is primarily used to view how blood flows through arteries and veins in the brain. Tests have shown that it might be more sensitive to brain injury than either MRI or CT scanning because it can detect reduced blood flow to injured sites. SPECT scanning is useful for blood deprived (ischemic) areas of brain following a stroke, aid in the diagnosis and differential diagnoses of suspected dementia, assessment of brain death, mood disorders and evaluating & sub typing attention-deficit disorder. SPECT scanning is also useful for presurgical evaluation of medically uncontrolled seizures (Fig.1)<sup>6,7</sup>. The test can be performed between seizures (interictal) or during a seizure (ictal) to determine blood flow to areas where the seizures originate<sup>8</sup>. This type of scanning is also important in diagnosing stress fractures in the spine (spondylolysis), tumors and substance abuse. More recent studies have shown the accuracy of SPECT in Alzheimer's diagnosis may be as high as 88%<sup>9</sup>. In meta analysis, SPECT was superior to clinical exam and clinical criteria (91% vs. 70%) in being able to differentiate Alzheimer's disease from vascular dementias<sup>10</sup>. This latter ability relates to SPECT's imaging of local metabolism of the brain, in which the patchy loss of cortical metabolism seen in multiple strokes differs clearly from the more even

or "smooths" loss of non-occipital cortical brain function typical of Alzheimer's disease (Fig. 2). Another recent review article showed that multi-headed SPECT cameras with quantitative analysis result in an overall sensitivity of 84-89% and an overall specificity of 83-89% in cross sectional studies and sensitivity of 82-96% and specificity of 83-89% for longitudinal studies of dementia<sup>11</sup>.

#### **Limitations of SPECT:**

The major limitation of brain SPECT study is the attenuation by the skull. The commonly used Chang method of attenuation correction is based on a simple mathematical formula, which is susceptible to technical variation. In diagnosis of dementia with SPECT, it can be difficult to separate the real defect from the attenuation artifact.<sup>9</sup> Variation between images owing to the Chang attenuation correction may generate artifact when ictal-interictal subtraction SPECT scans are used for seizure localization. SPECT/CT will provide more accurate attenuation correction and diagnostic results. SPECT is technically less sophisticated and demanding when compared with positron emission tomography (PET), but provides lower-resolution images. It can be used to evaluate regional variations in blood flow, but its role in everyday clinical practice is, like that of PET, a small one.

#### **Comparison SPECT with PET scan:**

SPECT is similar to PET in its use of radioactive tracer material and detection of gamma rays. In contrast with PET, the tracers used in SPECT emit gamma radiation that is measured directly, whereas PET tracers emit positrons that annihilate with electrons up to a few millimeters away, causing two gamma photons to be emitted in opposite directions. A PET scanner detects these emissions "coincident" in time, which provides more radiation event localization information and, thus, higher spatial resolution images than SPECT (which has about 1 cm resolution). SPECT scans are significantly less expensive than PET scans, in part because they are able to use longer-lived and more easily obtained radioisotopes than PET. The test differs from a PET scan in that the tracer stays in

the blood stream rather than being absorbed by surrounding tissues, thereby limiting the images to areas where blood flows. SPECT scans are cheaper and more readily available than higher resolution PET scans.

**Interpreting and Reporting Images of SPECT:**

Perfusion patterns may differ from one subject to another, because the normal brain is not always completely symmetric, and small structural differences are frequent within normal subjects. This result is partly caused by variations in functional activity and therefore by a varying vascular supply to cerebral regions at the time of injection. In a normal brain perfusion SPECT image <sup>12</sup> regions with higher perfusion, such as cortical and subcortical gray matter structures, have the highest tracer uptake. Subcortical white matter shows low tracer uptake, and no tracer uptake is seen in areas containing cerebrospinal fluid (i.e., cerebral ventricles, fissures and sulcus) or bone (i.e., scalp or petrous part of temporal bones). The cerebral region showing the maximum tracer

uptake varies with the radiopharmaceutical used (i.e., most probably the cerebellum with HMPAO, but the calcarine cortex with ECD), the patient's condition at the time of injection (e.g., influence of visual activity on calcarine cortex uptake), and image manipulation during reconstruction (i.e., influence of attenuation correction on basal ganglia activity). The common causes of different tracer uptake patterns in brain perfusion SPECT images shown in Table: 1.

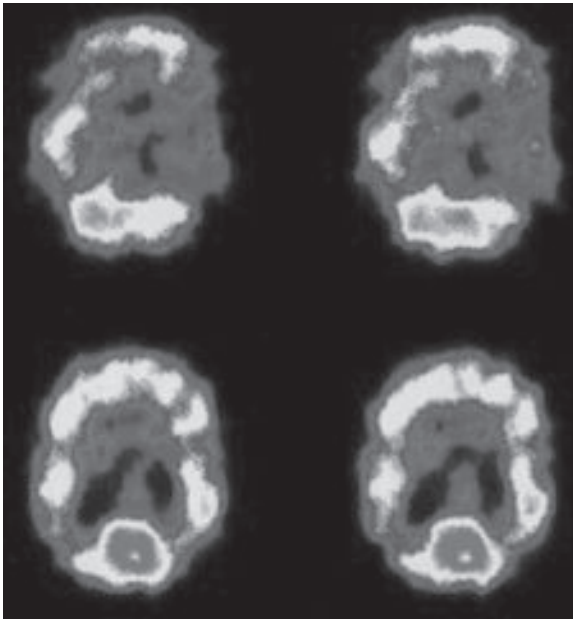
**SPECT in Epilepsy:**

Patients with refractory focal epilepsy, who are candidates for surgical resection of the epileptogenic focus, frequently benefit from SPECT<sup>12,13</sup>. MRI is also essential in the management of these patients, although not all epileptogenic foci can be accurately localised using this modality and, conversely, not all anatomical foci are the cause of a patient's seizures. So SPECT can localize the epileptogenic focus accurately which will help for neurosurgical procedure (Fig: 1 & 2).

**Table-I**  
*Common Causes of Different Tracer Uptake Patterns in Brain Perfusion SPECT Images*

Tracer uptake pattern	Causes
Cold (no uptake)	Cerebrospinal fluid Edema Necrosis Space-occupying lesions (e.g., hemorrhage, tumors,* cysts, arteriovenous malformation, postsurgery)
Hypoactive (decreased uptake)	Ischemia Hypometabolism (hypofunction): degeneration, deafferentation Atrophy
Hyperactive (increased uptake)	Luxury perfusion Encephalitis Acetazolamide-induced vasodilation Hyperfunction (epilepsy [ictal], neuroactivation, other causes of increased neuronal activity) Tumors*

\* Tumors can produce a variety of patterns in SPECT perfusion images. The most frequent tumors with increased tracer uptake are meningiomas.



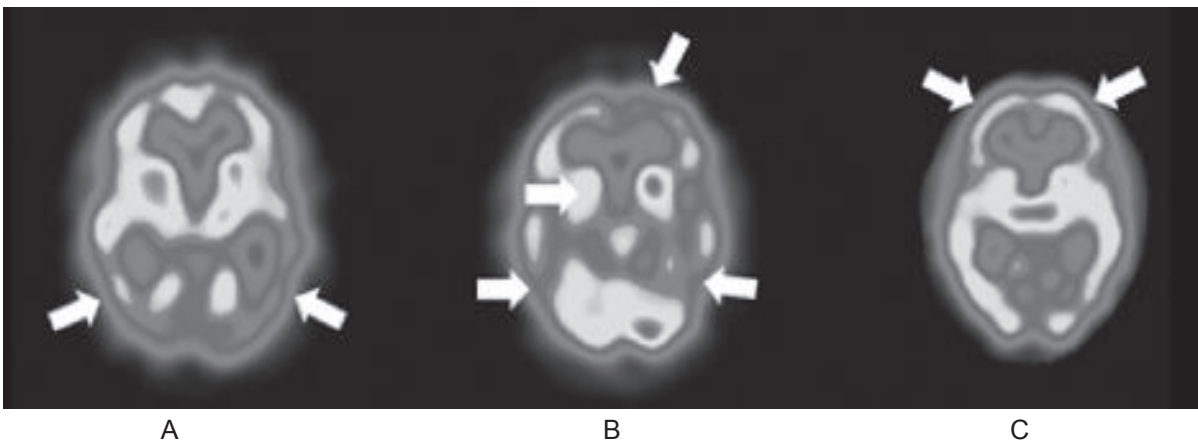
**Fig.1:** A SPECT scan of a patient with uncontrolled complex partial seizures. The temporal lobe on the left side of the brain shows less blood flow than the right, confirming for the surgeon the nonfunctioning area of the brain causing seizures. Dinesh, E. et al. "Instinctive classification of Alzheimer's disease using FMRI, pet and SPECT images." 2013 7th International Conference on Intelligent Systems and Control (ISCO): 405-409.

#### SPECT in Dementias:

In patients with dementia, anatomical imaging frequently shows little or no change. Characteristic patterns of functional involvement using SPECT scan, however, enable more accurate differentiation of these forms of dementia (Fig.2)<sup>14</sup>. In AD, reduction in regional cerebral blood flow is seen, especially in the bilateral, temporal lobes hypoperfusion (Fig.2.A). There may be also hypometabolism in the posterior parietal lobes. These changes can occur early in the disease process and may help to distinguish AD from other forms of dementia. In vascular dementia with multiple asymmetrical lesions affecting the anterior and posterior cortex and right striatum (Fig.2.B) and in fronto-temporal dementia with frontal hypoperfusion (Fig.2.C).

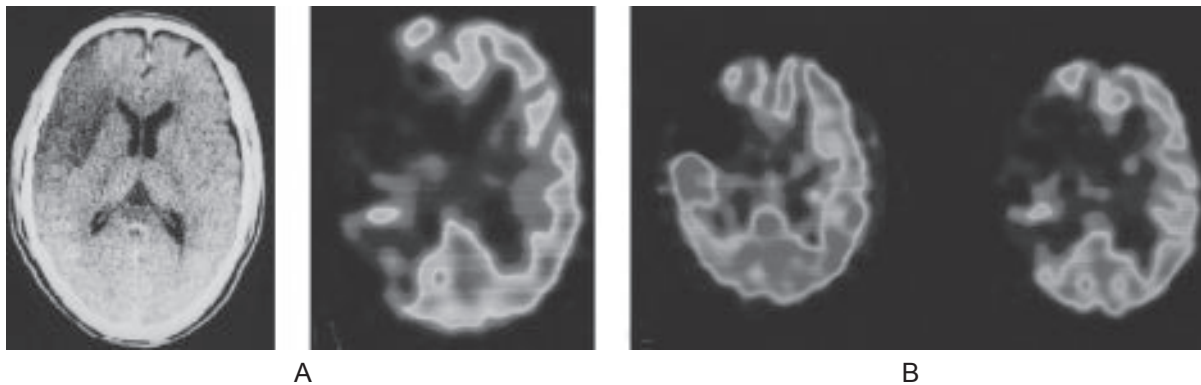
#### SPECT in Stroke:

The localization and extent of lesions as a result of defects in blood supply can be assessed by SPECT studies. This techniques are more sensitive than CT for detecting both the presence and the extent of infarction<sup>13,15</sup> (Fig: 3&4). In the first 8 hr after stroke, SPECT was shown to be positive in 90%, and sensitivities of 61%–74% and specificities of 88%–98% were reported<sup>13</sup>. Transient ischemic attacks can be differentiated from ischemic strokes

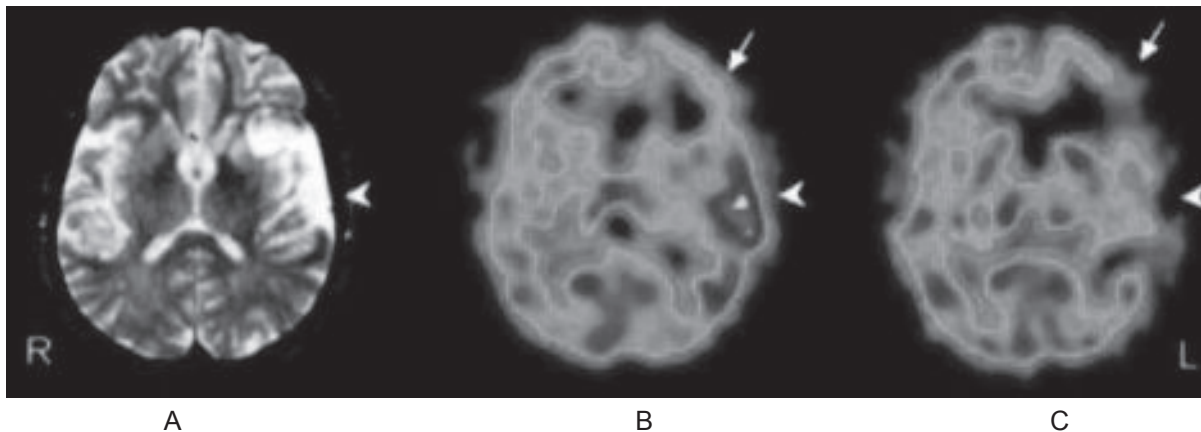


**Fig.-2:** Tc-99m HMPAO SPECT scans in 3 patients with dementia showing perfusion patterns suggestive of Alzheimer's disease, with bilateral temporo-parietal hypoperfusion (A), vascular dementia with multiple asymmetrical lesions affecting the anterior and posterior cortex and right striatum (B) and fronto-temporal dementia with frontal hypoperfusion (C). Warwick, J. "Brain imaging with SPECT and PET." Continuing Medical Education "2013; 31.8: 307-309.





**Fig: 3:** 54-year-old man with atrial fibrillation and sudden onset of left-sided hemiparesis. (A) CT scan of brain and 99mTc-HMPAO SPECT image 4.5 hours after the onset of stroke shows hypoactivity in the right frontal and temporal lobes. (B) 99mTc-HMPAO SPECT image (left) obtained 12 hours after the initial study shows hyperactivity in the right temporal lobe; a 99mTcECD SPECT image (right) shows hypoactivity in the same area. Ogasawara, K., Mizoi, K., Fujiwara, S., & Yoshimoto, T. (1999). 99mTc-bicisate and 99mTc-HMPAO SPECT imaging in early spontaneous reperfusion of cerebral embolism. *AJNR.*, 20 4, 626-8.



**Fig.-4:** (A) MRI (T2-weighted) at admission shows hyperintensity at site of infarction (arrowhead). (B) 99mTc-HMPAO SPECT image obtained 1 wk after stroke shows increased tracer uptake (hyperperfusion) in left temporal lobe caused by luxury perfusion (arrowhead). Hypoperfusion is also seen in left frontal cortex (arrow), interpreted as ischemia in anatomically preserved region. (C) 99mTc-HMPAO SPECT image obtained 1 mo after stroke shows left temporal lobe hypoperfusion (arrowhead) corresponding to initial MR image of ischemia. Perfusion changes in left frontal lobe are also seen: improvement in anterior and mesial aspects caused by recovery of ischemia, as well as perfusion impairment in lateral aspect caused by extension of the infarction (arrow). Ana M. Catafau "Brain SPECT in Clinical Practice. Part I: Perfusion" *J Nucl Med* 2001; 42:259–271

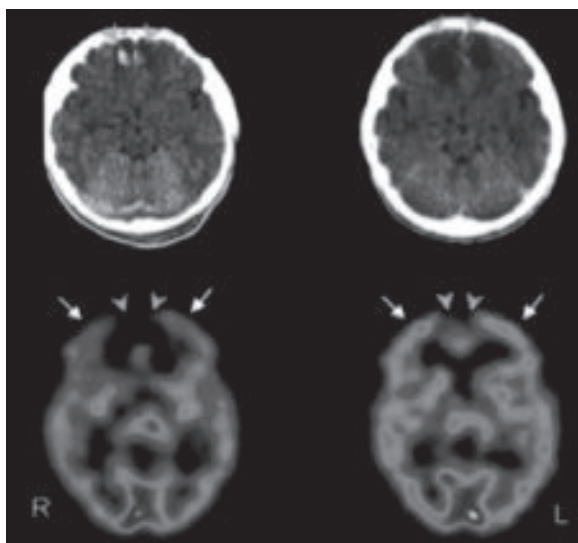
within 6 hr of symptom onset by, in SPECT, counting rate densities of 70% compared with the contralateral side (perfusion in stroke tissue 35%–60% of contralateral values) <sup>16</sup>.

#### **SPECT in Traumatic Brain Injury:**

Abnormalities are more frequently found in traumatic brain injury (TBI) patients when SPECT

is performed than with MRI and CT scans<sup>17</sup>. Hypoperfusion in the frontal and parietal lobes is common (Fig. 5), although the basal ganglia, as well as the occipital, parietal and cerebellar areas, can also be affected. SPECT has a high sensitivity and negative predictive value for TBI, and a normal study is predictive of good

recovery.<sup>18</sup> However, given its limited specificity, SPECT alone is not enough to diagnose TBI.



**Fig.-5:** CT (top) and 99mTc-HMPAO SPECT (bottom) images from 16-y-old patient with traumatic brain injury after traffic accident. (A) CT at time of admission shows subarachnoid hemorrhage with small contusional hemorrhagic foci in both frontal lobes (orange arrowheads). SPECT was subsequently performed and shows absence of tracer uptake (cold areas) in anteromedial aspect of both frontal lobes corresponding to hemorrhagic lesions, in addition to global hypoperfusion, more marked in both frontal cortices (white arrows). (B) CT and SPECT images obtained 1 mo later at time of discharge after clinical recovery. Hypodense images in both frontal lobes can be seen on CT as consequence of hematoma's resolution. Corresponding cold areas persist on SPECT image (orange arrowheads) but show improvement in global cerebral perfusion, particularly in both frontal lobes (white arrows). Ana M. Catafau "Brain SPECT in Clinical Practice. Part I: Perfusion" *J Nucl Med* 2001; 42:259–271

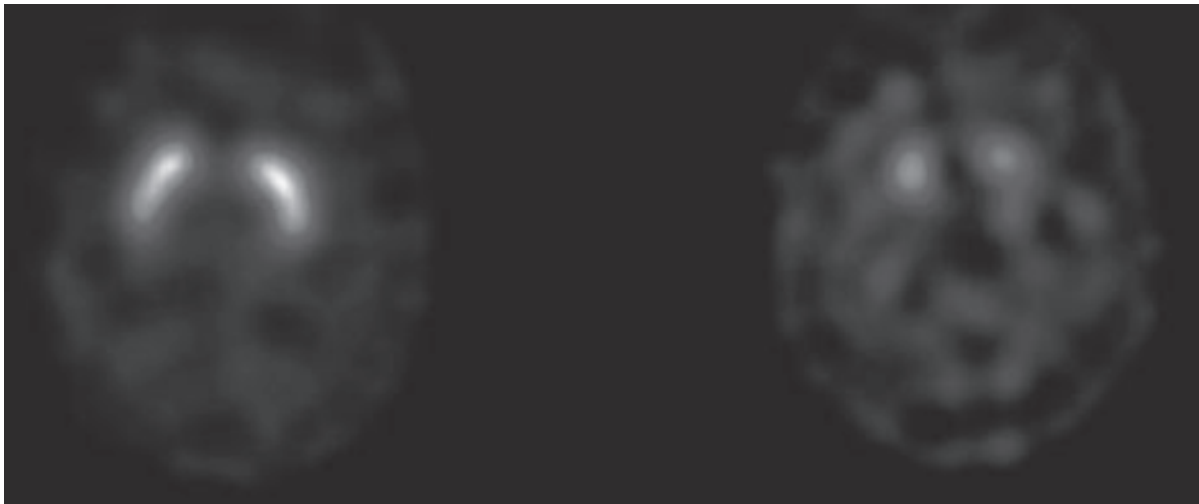
#### SPECT in Parkinsonism:

SPECT is commonly used for PD diagnosis<sup>19</sup>. SPECT imaging using <sup>123</sup>I-loflupane (<sup>123</sup>I-loflupane-SPECT) provides information based on local binding of presynaptic dopamine transporters (DaTs) with <sup>123</sup>I-loflupane, which has been shown to be highly correlated with PD progression<sup>19, 20</sup>. This binding measure is quantitative and assesses

the spatial distribution of dopamine transporters. Furthermore, <sup>123</sup>I-loflupane-SPECT is an imaging modality that is capable of differentiating between PD and essential tremor<sup>21</sup>. SPECT imaging can also distinguish between PD and drug-induced Parkinsonism<sup>22, 23</sup>. However, any disease that causes loss of the presynaptic dopamine neurons will appear as abnormal compared with normal controls (NCs)<sup>24</sup>. Thus, SPECT is not able to differentiate among PD, progressive supranuclear palsy, multiple system atrophy, and other neurodegenerative disorders that affect the dopamine neurons<sup>25</sup>. Most studies that use <sup>123</sup>I-loflupane-SPECT have focused on the striatum (i.e., putamen and caudate)<sup>26-29</sup>. Researchers have reported that PD has markedly reduced DaT levels in the striatum, which are correlated with disease progression and clinical scores<sup>28,29</sup>. DaT imaging reveals reduced presynaptic neuronal degeneration in PD and other parkinsonian syndromes, even when clinical features are subtle, while conditions such as essential tremor have normal striatal DaT density<sup>29</sup> (Fig. 6).

#### SPECT in Brain tumour:

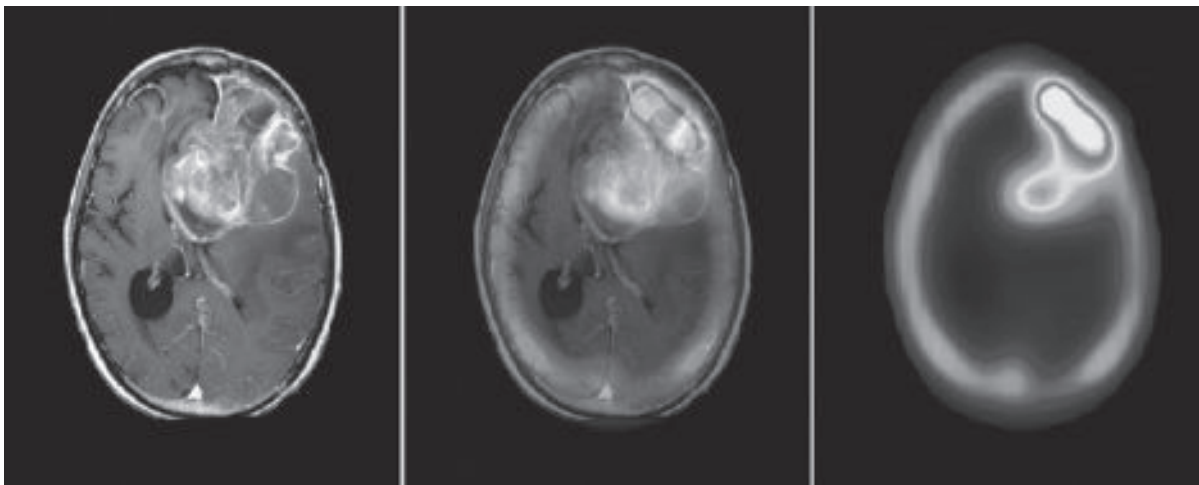
The primary role of SPECT in brain tumor patients lies on the noninvasive assessment of tumor aggressiveness, differentiation of treatment-induced necrosis from tumor recurrence, assessment of response to treatment, and estimation of overall prognosis. It also suggests that it has a high sensitivity and specificity in localizing ICSOLs and can be used in patients who cannot undergo CECT/CEMR due to contraindications or if the waiting lists for such a test is long. The common radiopharmaceuticals of SPECT are Tc-99m diethylenetriaminepentaacetic acid (DTPA), and Tc-99m glucoheptonate (Tc-99m GHA), which are well-known renal radiopharmaceuticals, devoid of the shortcomings of Tc-99m pertechnetate. Tc-99m GHA SPECT is capable of distinguishing high-grade gliomas from low-grade gliomas as well as metastases.<sup>30</sup> Similarly, thallium-201, Tc-99m tetrofosmin, and Tc-99m sestamibi were found to delineate brain tumors which involved multiple mechanisms of uptake besides blood-brain barrier (BBB) disruption; however, their overwhelming cost and availability of morphological imaging techniques send these modalities to a back burner<sup>31</sup>(Fig.7) . SPECT has also been used with the radioactive



A

B

**Fig.-6:** Scans of two patients with parkinsonism. In one case, DaT SPECT shows normal striatal DaT density, virtually ruling out Parkinson's disease or other causes of presynaptic dopaminergic neuron degeneration (A). The second scan shows a patient with Parkinson's disease with marked loss of striatal uptake, particularly in the putamen, and a high level of background activity (B). Warwick, J. "Brain imaging with SPECT and PET." *Continuing Medical Education*, 2013; 31.8:307-309.



**Fig.-7:** Tc-99m GHA SPECT (Tc-99m glucoheptonate ) shows anaplastic oligodendroglioma of the left prefrontal region. Alam S.S, Junaid S., Ahmed S.M" *Evaluation of Technetium-99m glucoheptonate single photon emission computed tomography for brain tumor grading*" *Asian J Neurosurg*. 2016 Apr-Jun; 11(2): 118–128.

labeled amino acid 3-(<sup>123</sup>I) iodo-α-methyl-L-tyrosine for the diagnosis of brain tumors and evaluation of tumor response to radiation therapy.

**Conclusion:**

SPECT is rapidly emerging as an important clinical imaging method which is well-recognized clinical

applications mainly in dementia, stroke, parkinsonism and epilepsy. This technique generally adds valuable information to the clinical management of patients with neurological disorders of a broad variety, helping in diagnosis, therapeutic management and follow-up. Accurate



knowledge of the physiologic and pathophysiologic basis of brain perfusion SPECT, together with the appropriate technique and careful interpretation of images and reporting, will enhance the clinical use of brain SPECT. At present, the long-term clinical and economic effects of the technology, although promising, are still to be determined.

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