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GUIDELINES

EANM procedure guidelines for brain neurotransmission SPECT using ^{123}I-labelled dopamine transporter ligands, version 2

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Abstract These guidelines summarize the current views of the European Association of Nuclear Medicine Neuroimaging Committee (ENC). The aim of the guidelines is to assist nuclear medicine practitioners when making recommendations, performing, interpreting, and reporting the results of clinical dopamine transporter (DAT) single photon emission computed tomography (SPECT) studies using ^{123}I-labelled radiopharmaceuticals. The aim is to achieve a high-quality standard of DAT SPECT imaging, which will increase the diagnostic impact of this technique in neurological practice. The present document is an update of the 2002 guidelines [1] and has been guided by the views of various national societies: the Task Group Neuro-Nuclear-Medicine of the German Society of Nuclear Medicine [2], a consensus statement of the imaging centres included in the "Kompetenznetz-Parkinson" sponsored by the German Federal

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Ministry of Education, and the Task Group of Neuro-Nuclear-Medicine of the French Society of Nuclear Medicine [3]. The guidelines reflect the individual experience of experts in European countries. The guidelines are intended to present information specifically adapted to European practice. The information provided should be taken in the context of local conditions and regulations.

Keywords Brain · DAT · SPECT · Parkinson

Background and definitions

From animal studies, clinical investigations and post-mortem evaluations it is well known that the dopaminergic neurotransmitter system plays a major role in movement disorders and particularly in parkinsonism as well as in dementia with Lewy bodies. The nigrostriatal dopaminergic pathway is best analysed at the striatal level where the nigrostriatal neurons end and connect to the postsynaptic nerve terminals using dopamine as neurotransmitter which binds to the postsynaptic (D1 and) D2 receptors. Both pre- and postsynaptic levels can be targeted by PET or SPECT tracers. Imaging of D2 receptors is addressed in another guideline; here we deal with the evaluation of the presynaptic dopaminergic system.

Presynaptic events can be summarized as follows. Dopamine is stored in vesicles before being released into the synaptic cleft. VMAT-2 transports cytosolic and newly synthesized dopamine into vesicles. The DAT, which is located in the membrane of the presynaptic nigrostriatal nerve terminals, is responsible for the reuptake of dopamine from the synaptic cleft. L-DOPA is taken up by the presynaptic neurons via an amino acid transporter, decarboxylated to dopamine by an L-aromatic acid decarboxylase.

Various PET tracers have been used to study these presynaptic targets such as ^{18}F-DOPA for the aromatic acid decarboxylase, ^{11}C-DTBZ for VMAT-2 and ^{11}C-PE2I for the DAT. Various cocaine analogues labelled with ^{123}I suitable for SPECT have shown to bind with high affinity to DAT [4–6]. Currently β-CIT (DOPASCAN) and FP-CIT (DaTSCAN) are commercially available in Europe via MAP Medical Technologies Oy (Finland) and GE Healthcare (United Kingdom), respectively, and are widely used in the clinical evaluation of patients.

These guidelines deal with the indications, assessment, processing, interpretation and reporting of DAT SPECT investigations using the commercially available radiopharmaceuticals [^{123}I]β-CIT and [^{123}I]FP-CIT.

Indications

A. Legal registration

For [^{123}I]FP-CIT [7]:

A.1. [^{123}I]FP-CIT imaging is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndromes. It helps differentiate essential tremor from parkinsonian syndromes related to Parkinson's disease (PD), multiple system atrophy and progressive supranuclear palsy. On its own, [^{123}I]FP-CIT imaging is unable to discriminate between PD, multiple system atrophy and supranuclear palsy [8–11].

A.2. [^{123}I]FP-CIT imaging is indicated for the differentiation of dementia with Lewy bodies from other dementias [12–14].

B. Other potential indications

B.1. Establishment of early diagnosis of neurodegenerative parkinsonism. DAT SPECT imaging is suitable for assessing the presynaptic deficit in early PD [15, 16].

B.2. Assessment of disease severity. DAT binding is related to the clinical stage and severity of PD [17, 18].

B.3. Differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism, e.g. between PD and neuroleptic-induced parkinsonism.

C. Contraindications

C.1. Pregnancy.

C.2. Breast feeding: mothers should interrupt breast feeding for 24 h if SPECT is indicated.

C.3. Inability to cooperate with the procedure.

Procedure

A. Patient preparation

A.1. Prearrival

Prior to the investigation patients should avoid taking any medications or drugs of abuse which could significantly influence the visual and quantitative analysis of DAT binding ligands [19] (Table 1) (except if the specific aim of the study is to assess the effect of such medication on

Table 1 Medication and drugs of abuse which may significantly influence the visual and quantitative analysis of [^{123}I]FP-CIT SPECT studies (reproduced from reference [19], with permission from Springer)

Drug class	Drug name	Comments
Cocaine		May decrease striatal [^{123}I]FP-CIT binding
Amphetamines	d-Amphetamine, methamphetamine, methylphenidate	May decrease striatal [^{123}I]FP-CIT binding
CNS stimulants	Phentermine or ephedrines	May decrease striatal [^{123}I]FP-CIT binding; influences are likely when used as tablets
Modafinil		May decrease striatal [^{123}I]FP-CIT binding
Antidepressants	Mazindol, bupropion, radafaxine	May decrease striatal [^{123}I]FP-CIT binding
Adrenergic agonists	Phenylephrine or norepinephrine	May increase striatal [^{123}I]FP-CIT binding; influences are likely when infused at high doses
Anticholinergic drugs		Benztropine may decrease striatal binding ratios; other anticholinergics may increase these ratios which will likely not affect visual assessments
Opioids	Fentanyl	May decrease striatal [^{123}I]FP-CIT binding
Anesthetics	Ketamine, PCP, isoflurane	May decrease striatal [^{123}I]FP-CIT binding; of interest particularly for animal SPECT studies, although ketamine and PCP are sometimes used illicitly

DAT binding). A withdrawal period of at least five times the drug's biological half-life is suggested. It should be noted that smoking may interfere with DAT availability [20]; however, such an effect would be too small to lead to misinterpretation of an individual scan. Antiparkinsonian medications (e.g. L-DOPA, dopamine agonists, NMDA receptor blockers, MAO-B inhibitors and COMT inhibitors taken in standard dosages) do not markedly affect DAT binding and therefore do not need to be withdrawn prior to DAT SPECT [21]. However, caution is advised in intra-individual follow-up studies, since the possibility that L-DOPA downregulates DAT expression cannot be excluded [22].

A.2. Preinjection

A.2.1. Check and ensure that the patient is able to cooperate during the investigation.

A.2.2. Block the thyroid gland by an adequate regimen (e.g. at least 200 mg of sodium perchlorate given at least 5 min prior to injection) to prevent free radioactive iodine accumulating in the thyroid.

B. Information pertinent to performing DAT SPECT studies

- Patient's history with particular focus on neurological and psychiatric disorders, and current neurological and psychiatric status.
- Patients ability to lie still for approximately 40 to 60 min. If sedation is necessary, it should be given at the earliest 1 h prior to the SPECT acquisition.
- Information about (recent) morphological imaging studies (CT, MRI).
- Current medication, and when last taken.

C. Precautions

Continuous supervision of the patients during the whole scanning procedure is necessary.

D. Radiopharmaceutical

D.1. Radiopharmaceuticals

- [^{123}I]β-CIT: [^{123}I]2β-carboxymethoxy-3β-(4-iodophenyl)tropane.
- [^{123}I]FP-CIT: [^{123}I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane.

D.2. Preparation of the radiopharmaceutical

Radiopharmaceuticals will be delivered ready to use.

D.3. Quality control check

Check for radiochemical purity and other parameters of quality given in the package inserts and follow the instructions of the manufacturer.

D.4. Injection

Inject the radiopharmaceutical intravenously as a slow bolus over approximately 20 s followed by saline to flush the intravenous line.

D.5. Time interval for injection

Inject the radiopharmaceuticals within the time frame given by the manufacturer (generally on the day of delivery).

D.6. Activity

- *Adults*: 150–250 MBq (typically 185 MBq) of either radiopharmaceutical.
- *Children*: currently no established clinical indications; if indicated, activity according to the recommendations of the EANM Paediatric Task Group.

D.7. Radiation dosimetry

The doses of the radiopharmaceuticals in adults and children are shown in Table 2.

E. Data acquisition

E.1. Time from injection to start of data acquisition

- [^{123}I]β-CIT: 18 to 24 h after injection.
- [^{123}I]FP-CIT: 3 to 6 h after injection.

It is recommended that a fixed time delay is used between injection and the beginning of data acquisition to ensure that data are comparable between subjects and intraindividual follow-up studies.

E.2. Set-up for data acquisition

E.2.1. Positioning of the patient

- The patient should be encouraged to void prior to the start of acquisition to ensure maximum comfort during the study. The patient should be advised to void after the scan session to minimize radiation exposure.
- The patient should be informed about the total acquisition time and positioned for maximum comfort. Since postprocessing routines allow correction for some obliquities of head orientation, the patient's comfort (which reduces the likelihood of motion during acquisition) is more important than perfect alignment of the head. The patient should be told of the importance of avoiding (voluntary) movements of the head and should be asked for her/his active cooperation. If a patient is uncooperative, sedation can be used. The patient's head should be only lightly restrained. It is not recommended to fix the head firmly in place.

E.2.2. Imaging device

- Multiple detector (triple or dual head) or other dedicated SPECT cameras for brain imaging should be used for data acquisition [23].
- Single detector units cannot generally be recommended. They may only be used if the scan time is prolonged appropriately (>3 million total counts), an activity in the upper permissible range is applied, and meticulous care is taken to produce high-quality images.
- LEHR or LEUHR parallel-hole collimators are the most frequently available collimator sets for brain imaging. However, fan-beam collimators are preferred over parallel-hole collimators due to the advantageous trade-off between resolution and count rate capability. All-purpose collimators are not suitable. The use of medium energy collimators could be advantageous regarding septal penetration; however, usually they are hampered by a lower spatial resolution [24]. If available, collimator sets specifically adapted to the characteristics of ^{123}I may be used.
- Acquisition parameters:
  - *Rotational radius*: smallest possible with appropriate patient safeguards.
  - *Matrix*: 128×128.

Table 2 Radiation dosimetry (adapted from [31–33])

	Organ receiving the largest radiation dose		Effective dose equivalent (mSv/MBq)
	Organ	Dose equivalent (mGy/MBq)	
Adults			
[^{123}I]β-CIT	Lung, liver	0.10	0.031–0.035
	Basal ganglia	0.27	
[^{123}I]FP-CIT	Urinary bladder wall	0.054	0.024
	Lung, large intestine	0.042	
Children			
[^{123}I]β-CIT	No data available		
[^{123}I]FP-CIT	No data available		

  - *Angular sampling*: 3° is recommended (360° rotation).
  - *Zoom*: acquisition pixel size should be one-third to one-half of the expected resolution; therefore it may be necessary to use a hardware zoom to achieve an appropriate pixel size.
  - *Acquisition mode*: step and shoot mode is used predominantly. Continuous mode acquisition may provide shorter total scan times and reduce mechanical wear to the system.
  - *Total detected events*:

    >3 million (FP-CIT);
    >1 million (β-CIT).
    When scatter correction is applied, lower numbers may be acceptable.
  - *Total scan time*: depending on the imaging device used, typical scan time for a triple head camera is around 30 min (e.g. 120 projections; 40 projections per head; 45 s/projection)
- Segmentation of data acquisition into multiple sequential acquisitions may permit exclusion of data with artefacts, e.g. remove segments of projection data with patient motion.

F. Interventions

Usually no intervention is performed.

G. Image processing

G.1. Review of projection data

Unprocessed projection data should be reviewed in cinematic display prior to reconstruction to assess the presence and degree of motion, target-to-background ratios and other potential artefacts. Inspection of projection data in sinogram form may also be useful.

G.2. Reconstruction

- Methods:
  - Filtered back-projection
  - Iterative reconstruction [25]
- Ensure that the entire brain volume is reconstructed.
- Reconstruct data at the highest pixel resolution, i.e. one pixel slice thickness.

G.3. Filtering

- Data should be filtered in all three dimension (x,y,z). This can be achieved either by two-dimensional prefiltering of the projection data or by applying a three-dimensional postfilter to the reconstructed data.
- Low-pass (e.g. Butterworth) filters should generally be used. Resolution recovery or spatially varying filters should be used with caution, as they may produce artefacts. Therefore the latter cannot be recommended for general use.

G.4. Corrections

Values from semiquantitative analysis are strongly dependent on the corrections performed (attenuation, scatter and partial volume effect) [26]. Attenuation correction is recommended using either:

- A calculated homogeneous correction matrix according to Chang (linear correction coefficient for ^{123}I: μ=0.10–0.12 cm^{-1}). Shape contouring should be used if available. Contours should include scalp and not just grey matter. Contours should be defined for each individual transaxial slice. Correct shape and position of the contours should be reviewed prior to calculation of the corrected slices.
- The measured attenuation map, e.g. from a simultaneously or sequentially acquired transmission scan or from a CT scan.

G.5. Reformatting

- Transaxial slices should be reformatted into at least three orthogonal planes. Generate transverse sections parallel to a given anatomic orientation (e.g. AC-PC line) ensuring a high degree of standardization in plane orientation. Create coronal and sagittal sections orthogonal to the transverse sections.

G.6. Semiquantitative evaluation

- Region of interest (ROI) techniques should be used to assess specific DAT binding in the striatum and striatal subregions (caudate nucleus, putamen). Reference regions with absent (or low) DAT density (e.g. occipital cortex, cerebellum) are used to assess nonspecific binding.
- It is helpful if ROI size (should be at least twice FWHM) and shape are standardized (e.g. use of templates) [27]. If available, ROI definition may be based on individual morphology as obtained by image fusion with MRI, which is particularly important when low specific binding is expected (e.g. in case of a severe loss or blockade of the DAT). Standardized ROIs can be obtained using atlas templates [28–30].

- Specific binding [(mean counts of the striatal ROI − mean counts of background ROI)/(mean counts of the background ROI)] values obtained from a patient are compared with those in normal (preferably age-matched) controls obtained with the same technique. The use of control values from a central database may reduce the need for each centre to establish its own control groups, but only if currently performed phantom studies turn out to allow comparative calculations for the different imaging set-ups used.
- If intraindividual comparison is performed (i.e. baseline vs. follow-up for therapy control or assessment of disease progression) standardized evaluation using approaches based on, for example, stereotactic normalization are most useful. They allow a more reliable verification of even subtle changes.

H. Interpretation criteria

H.1. Visual interpretation

- Visual assessment allows the normality of DAT binding to be evaluated, and, if it is abnormal, to evaluate the magnitude of compromised DAT binding. In particular visual assessment provides information regarding right to left asymmetry and about the structures (i.e. striatal subregions) most affected.
- Images should be read on the computer screen rather than from hard copy, because this allows variation in colour table and adjustments of background subtraction or contrast.
- Data evaluation should take into account age and relevant morphological information (CT, MRI). Specific attention should be paid to known structural lesions in the basal ganglia and to the structures selected as reference region for semiquantitative evaluation.
- Pitfalls/sources of error:
  - Age dependency. The known reduction of DAT binding with age has to be appreciated to avoid overinterpretation.
  - Level of contrast and background subtraction. Inappropriate thresholding may result in artefacts. Thresholding, if used, must be based upon knowledge of a normal database for specific radiopharmaceuticals and set-up.
  - Technical artefacts. The images should be critically examined during interpretation for the presence of head motion, or attenuation artefacts or other technical artefacts due to gamma camera problems (centre of rotation, lack of homogeneity).
  - Medication. Possible interaction of concomitant medication has to be taken into account.

H.2. Quantification

- In addition to visual interpretation, semiquantitative analysis is recommended to objectively assess striatal DAT binding.
- Usually transverse/oblique slices are selected for ROI definition. For semiquantitative evaluation, either only the slices with the highest striatal binding are chosen or the entire striatal volume is taken into account.
- Quantification can be performed with standardized or anatomically adjusted ROIs (using templates or MRI overlay techniques).
- Interpretation of quantitative results must take into account the performed corrections (see above) and is based on comparison of specific DAT binding values obtained by ROI techniques with those of age-matched normal controls. In general DAT binding is assessed for the entire striatum, the head of the caudate, and the putamen. Determination of putamen to caudate ratios may also be helpful.

I. Reporting

I.1.General

Reports should include all pertinent information, including the name of the patient and other identifiers, such as date of birth, name of the referring physician(s), type and date of examination, patient history including the reason for requesting the study.

I.2. Body of the report

I.2.1. Procedures and materials:

- Include a brief description of the imaging procedure: radiopharmaceutical including administered activity, scan acquisition delay and assessment of scan quality (if compromised give the reason, e.g. motion artefacts, etc.).
- If sedation is performed, briefly describe the procedure including type and time of medication given in relation to the radiotracer injection.

I.2.2. Findings: Describe if the SPECT pattern is normal or not. If it is not normal, describe the location and intensity of abnormal DAT binding. State what criteria were used for interpretation (visual assessment, quantitative or semiquantitative measures, comparison with normal database, etc.).

I.2.3. Limitations: Where appropriate, identify factors that could have limited the sensitivity and specificity of the result of the examination (i.e. movement, concomitant medication).

I.2.4. Clinical issues: The report should address or answer any pertinent clinical issues raised in the request for the imaging examination.

I.2.5. Comparative data: Comparisons with previous examinations and reports, if available, should be part of the report. In particular, information about the postsynaptic D2 receptor status or FDG pattern (and structural lesions) may be helpful in specific situations.

I.3. Interpretation and conclusions

I.3.1. A precise diagnosis should be given whenever possible. It should be based on generally accepted disease-specific patterns. Any interpretation not based on such criteria has to be explicitly stated as subjective and considered as hypothetical.

I.3.2. Interpretation should be based on the results of the visual and quantitative evaluation and in conclusion the report should state:

- Whether a presynaptic dopaminergic deficit has been confirmed or excluded by the study.
- The extent and characteristics (e.g. asymmetry, predominantly affected structures) of an observed presynaptic dopaminergic deficit.

I.3.3. When appropriate, follow-up or additional studies (e.g. dopamine D2 receptor or FDG metabolism studies) should be recommended to clarify or confirm the suspected diagnosis.

J. Sources of error

- Artefacts (patient movement, camera-related, induced by inappropriate processing).
- Interference from drugs possibly acting on the DAT.
- Physical biases for quantification.

Issues requiring further clarification

- Physical corrections to be applied for routine use.
- Assessment of disease progression and effects of putative neuroprotective or neurorestorative treatments.
- Other methods for operator-independent definition of ROIs, e.g. histogram analysis.

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Disclaimer These guidelines summarize the views of the Neuroimaging Committee of the EANM and reflects recommendation for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

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