European Association of Nuclear Medicine Procedure Guidelines
For Brain Neurotransmission SPET using $^{123}$I-labelled Dopamine Transporter Ligands

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I. Purpose

These guidelines summarize the views of the European Association of Nuclear Medicine Neuroimaging Committee (ENC). The purpose of the guidelines is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of dopamine transporter SPET studies using $^{123}$I-labelled radiopharmaceuticals. Aim is to achieve a high quality standard of dopamine transporter SPET imaging, which allows to increase the diagnostic impact of this technique in neurological practice.

The present document has been inspired by the sights of the Task group Neuro-Nuclear-Medicine of the German Society of Nuclear Medicine [1], by a consensus statement of the imaging centers included in the „Kompetenznetz-Parkinson“ sponsored by the German Federal Ministry of Education and Research, by the Society of Nuclear Medicine Procedure Guideline for Brain Perfusion SPECT [2], by the views of the Society of Nuclear Medicine Brain Imaging Council [3], and the individual experience of experts in European countries. The guidelines intend to present information specifically adapted to the European practice. The information provided should be taken in the context of local conditions and regulations.

II. Background information 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. Today by the use of PET and SPET various functional aspects of the dopaminergic neurotransmission can be visualized in vivo. Even though the number of PET devices is rapidly increasing, due to the limited availability of radiotracers (e.g. fluorodopa or raclopride) PET is still a research tool rather than suitable for routine application. On the other hand in the past SPET investigations of the dopaminergic system have proven to deliver comparable results to PET in clinical settings.

Currently SPET investigations predominantly assess two aspects of the dopaminergic system: the presynaptic dopamine transporter binding and the postsynaptic dopamine D2 receptor status [4-6]. Whereas imaging of D2 receptors is addressed in another guideline, this one deals with the evaluation of the presynaptic dopaminergic system.

During the past decade several cocaine analogues have shown to bind with high affinity to the dopamine transporter (DAT) located in the membrane of the presynaptic nigrostriatal nerve terminals. The DAT is responsible for the reuptake of dopamine from the synaptic cleft. DAT SPET imaging, therefore, offers the unique opportunity to study in vivo via striatal uptake measures the structural and biochemical integrity of the presynaptic dopaminergic nerve terminals. In the past various cocaine analogues labelled with $^{123}$I such as β-CIT, FP-CIT (or more precisely β-CIT-FP) and others, and more recently also $^{99m}$Tc-labelled cocaine analogues such as TRODAT-1 have been introduced for SPET imaging of the DAT [7]. The affinity and selectivity to the DAT and pharmacokinetic properties have shown to vary considerably among the mentioned...
radiotracers resulting in major differences with respect to specific binding ratios and time point of acquisition. Many of the radiotracers introduced in the past are not generally available and therefore cannot be used for routine investigations. Exceptions are ß-CIT (DOPASCAN) and FP-CIT (DaTSCAN) which are commercially available in Europe via MAP Medical Technologies Oy (Finland) and Nycomed Amersham (United Kingdom).

This guideline deals with the indications, assessment, processing, interpretation and reporting of dopamine transporter SPET investigations using the commercially available radiopharmaceuticals $^{123}$Iß-CIT and $^{123}$IFP-CIT.

III. Common indications

**Indications**

A. **Confirmation or exclusion of dopamine nerve cell loss in parkinsonian syndromes.** DAT SPET is valuable to discriminate essential tremor [8, 9] and dopa-responsive dystonia [10] from parkinsonian syndromes (e.g. Parkinson's disease (PD), multiple system atrophy, or progressive supranuclear palsy). Further indications include the evaluation of inconclusive cases to confirm or exclude presynaptic dopaminergic nerve cell loss [11].

B. **Establishment of early diagnosis.** DAT SPET imaging is suitable to assess the presynaptic deficit in early PD [12, 13].

C. **Assessment of severity of disease.** DAT binding is related to the clinical stage and severity of PD [14-17].

D. **Measuring disease progression.** In PD and non-PD patients the progressive loss of DAT binding can be monitored over time with DAT SPET [18, 19].

Besides the common indications mentioned here DAT SPET appears to be promising in some additional indications (e.g. monitoring neuroprotection/neurorescue, establishment of preclinical diagnosis e.g. in high risk populations, assessment of Lewy body dementia) which are currently under further evaluation and which have also been suggested by PET investigations of the presynaptic dopaminergic system.

**Contraindications**

A. Pregnancy (mothers should interrupt breast feeding for 24hrs if SPET is indicated)

B. Evident lack/unability of cooperation

IV. Procedure

A. **Patient preparation**

A.1. **Pre-arrival**

Prior to the investigation patients should avoid any drugs known to affect DAT binding (e.g. methylphenidate, modafenil, SSRI), except if the specific aim of the study is to assess the effect of this medication on DAT binding.
A.2. Pre-injection

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. perchlorate 1000 mg given at least 30 min prior to injection) to prevent free radioactive iodine to accumulate in the thyroid.

B. Information pertinent to performing DAT SPET studies

- Patient history with particular focus on neurological and psychiatric disorders, current neurological and psychiatric status.

- Patients ability to lie still for approx. 40 to max. 60 min. If sedation is necessary, it should be given earliest one hour prior to the SPET acquisition.

- Information about (recent) morphologic imaging studies (CT, MRI).

- Current medication, and when last taken. Note that based on current knowledge typical anti-parkinsonian medication (e.g. dopamine and dopamine agonists taken in standard dosages) does not markedly affect DAT binding and therefore not necessarily has to be withdrawn prior to a first (diagnostic) DAT SPET [20, 21]. Caution, however, may be advised in intraindividual follow-up studies, since subtle changes due to drug treatment currently may not be completely ruled out.

C. Precautions

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

D. Radiopharmaceutical

D.1. Radiopharmaceutical

- $^{[123}I\beta$-CIT:
  - $^{[123}I2\beta$-carboxymethoxy-3$\beta$-(4-iodophenyl)tropane

- $^{[123}I$FP-CIT:
  - $^{[123}IN$-$\omega$-fluoropropyl-$2\beta$-carbomethoxy-$3\beta$-(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 assessment given in the package inserts and follow the instructions of the manufacturer.

D.4. Injection

Inject the radiopharmaceutical intravenously as a slow bolus over approx. 20 sec followed by saline to flush the i.v. line.

D.5. Time interval for injection

Inject the radiopharmaceuticals within the time frame given by the manufacturer (generally on day of delivery).
D.6. Dose
   Adults: 150 – 250 MBq (typically 185 MBq) of either radiopharmaceutical
   Children: currently no established clinical indications, if indicated dosage according
to the recommendations of the EANM Pediatric Task Group

D.7. Radiation dosimetry

<table>
<thead>
<tr>
<th></th>
<th>Organ receiving the largest radiation dose mGy/MBq</th>
<th>Effective dose equivalent mSv/MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$[^{123}I] \beta$-CIT</td>
<td>0.10; lung, liver 0.27; basal ganglia 0.054; urinary bladder wall 0.042; lung, large intestine</td>
<td>0.031-0.035 0.024</td>
</tr>
<tr>
<td>$[^{123}I]$FP-CIT</td>
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<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$[^{123}I] \beta$-CIT</td>
<td>no data available</td>
<td>no data available</td>
</tr>
<tr>
<td>$[^{123}I]$FP-CIT</td>
<td>no data available</td>
<td>no data available</td>
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</table>

Data are taken from the literature [22-24].

E. Data acquisition

E.1. Time delay from injection to begin of data acquisition
   - $[^{123}I] \beta$-CIT: 18 to 24 hrs p.i.
   - $[^{123}I]$FP-CIT: 3 to 6 hrs p.i.
   - It is recommended to use a fixed time delay between injection and begin of data
     acquisition to ensure that data are comparable between subjects and in
     intraindividual follow-up studies.

E.2. Set up for data acquisition

E.2.1. Positioning of the patient
   - Patients should void prior to acquisition for maximum comfort during the study.
     Advice patients to void after the scan session to minimize radiation exposure.

   - Patients should be informed about the total acquisition time and positioned for
     maximum comfort. Since postprocessing routines allow to correct for minor
     obliquities of head orientation, patients’ comfort (which reduces the probability
     of motion during acquisition) is more important than perfect alignment of the
     head. The patient has to be informed about the necessity to avoid (voluntary)
     movements of the head and has to be asked for her/his active cooperation. If
     cooperation is poor sedation may be used. The patient’s head should be only
     lightly restrained. It is not recommended to rigidly fix the head in place.

E.2.2. Imaging device
   - Multiple detector (triple or dual head) or other dedicated SPET cameras for brain
     imaging should be used for acquisition.
- Single detector units cannot generally be recommended. They may only be used if scan time is prolonged appropriately (e.g. > 3 million total cts using FP-CIT), a dose in the upper suggested range is applied, and meticulous care is taken to produce high-quality images.

- LEHR or LEUHR parallel-hole collimators are the mostly available collimator sets for brain imaging. All purpose collimators are not suitable. The use of medium energy collimators could be advantageous, however, usually they are hampered by a low sensitivity. They may only be used if acceptable count rates are obtained. If available, collimator sets specifically adapted to the characteristics of $^{123}$I may be used. Fan-beam collimators may be generally preferred over parallel-hole collimators due to the advantageous trade-off between resolution and count rate capability.

- Acquisition parameters
  - Rotational radius: smallest possible with appropriate patient safeguard
  - Matrix: 128 x 128
  - Angular sampling: $\leq 3^\circ$ (360° rotation)
  - Zoom: acquisition pixel size should be 1/3–1/2 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 predominantly used. Continuous mode acquisition may provide shorter total scan times and reduce mechanical wear to the system
  - Total counts: > 3 million (FP-CIT) > 1 million (β-CIT)
  - Total scan time: depending on the imaging device, typical scan time for a triple head camera is about 40 to 50 min (e.g. 120 projections; 40 projections per head; 50-60 sec/projection)
  - Segmentation of data acquisition into multiple sequential acquisitions may permit to exclude bad data, e.g. remove segments of projection data with patient motion

F. Interventions

Usually no interventions are performed.

G. Image processing

G.1. Review of projection data
Unprocessed projection data should be reviewed in cinematic display prior to filtering to assess presence and degree of motion artifacts, target-to-background ratios and other potential artifacts. Inspection of projection data in sinogram form may also be useful.

G.2. Reconstruction
  - methods: filtered backprojection iterative reconstruction
  - make sure to reconstruct the entire brain volume
  - reconstruct data at highest pixel resolution, i.e. one pixel thick

G.3. Filtering
Data should be filtered in all 3 dimensions (x,y,z). This can be achieved either by two-dimensional prefiltering the projection data or by applying a 3-dimensional postfilter to the reconstructed data.

Low-Pass (e.g. Butterworth) filters should generally be used. Resolution recovery or spatially varying filters have to be used with caution, as they may produce artifacts. Therefore the latter cannot be recommended for general use.

G.4. Attenuation correction
- Attenuation correction has to be performed mandatory.
- Methods
  - Use of a calculated homogenous correction matrix according to Chang (linear correction coefficient for $^{123}$I: $\mu = 0.10 - 0.12 \text{ cm}^{-1}$).
    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.
  - Use of a measured correction matrix e.g. from a simultaneously assessed transmission scan or from a CT scan

G.5. Reformating
- Transaxial slices have to be reformatted into 2 orthogonal planes. Generate transverse sections parallel to a given anatomic orientation (e.g. AC-PC line) assuring a high degree of standardization in plane orientation. In addition create coronal sections orthogonal to the transverse sections and correct for obliquities.

G.6. Comparative evaluation
- ROI techniques have to be used to assess specific DAT binding in the striatum and striatal subregions (head of caudate, putamen). Reference regions with absent (or low) DAT density (e.g. occipital cortex, cerebellum) are used to assess unspecific binding.
- It is helpful when ROI size (should be at least twice FWHM) and shape is standardized (e.g. use of templates) [25]. 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).
- Specific binding ([mean cts of the striatal ROI - mean cts of background ROI] / mean counts of the background ROI) values obtained in the patients are compared with those in normal (preferably age matched) controls obtained with the same technique. Use of control values from a central database may prevent to establish own control groups in each center, if currently performed phantom studies turn out to allow comparative calculations for the different imaging setups 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 e.g. stereotactic normalisation are most useful. They allow to more reliably verify even subtle changes.
- If data from age matched normal controls are available for comparison it is recommendable to use analytical approaches based on stereotactic normalisation in order to determine abnormalities of DAT binding in an observer independent way.

H. Interpretation criteria

H.1. Visual interpretation

- Visual assessment assists quantitative evaluation and gives an idea whether DAT binding is (probably) normal or reduced, and, if abnormal, about the magnitude of compromised DAT binding. In particular visual assessment informs about right to left asymmetries and about the structures (i.e. striatal subregions) most affected.

- Images should be read on the computer screen rather than from hard copies, because this allows variation in colour table and adjustments of background subtraction or contrast.

- For comparison it is desirable to have a normal (preferably age matched) database available, studied with the same type of camera and processed in the same way as patient studies (reconstruction, filtering, attenuation correction).

- Data evaluation must consider relevant morphologic information (CT, MRI). Specific attention should be paid to known structural lesions in the basal ganglia and the structures picked as reference region for semiquantitative evaluation.

- Pitfalls/sources of error
  - Age dependency
    The known age dependency of DAT binding has to be appreciated to avoid overinterpretation.
  - Level of contrast and background subtraction
    Inappropriate thresholding may result in artifacts. Thresholding, if used, must be based upon knowledge of a normal data base for specific radiopharmaceuticals and set-up.
  - Color table
    Use of non-continuous color tables may overestimate findings due to abrupt color changes.
  - Technical artifacts
    The images should be critically examined during interpretation for presence of head motion- or attenuation-artifacts or other technical artifacts due to gamma camera problems (center of rotation, inhomogenity).
  - Medication
    Possible interaction of concomitant medication has to be taken into account.

H.2. Quantification

- Semiquantification is mandatory to objectively assess striatal DAT binding.

- Usually transverse/oblique slices are picked for ROI definition. For evaluation either only the slices with the highest striatal binding are picked or the entire striatal volume is taken into account.
- Quantification can be performed with anatomically adjusted ROIs (using templates or MRI overlay techniques) or on a pixelwise basis (see above).

- Interpretation of quantitative results is based on
  - the 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 caudate, and the putamen. Additionally assessment of putamen to caudate ratios may be helpful.
  - pixelwise comparisons of a patient study with a normal data base.

I. Reporting

I.1. General
Reports should include all pertinent information, including name of patient and other identifiers, such as birthdate; name of the referring physician(s); type and date of examination; radiopharmaceutical including the administered activity; patient history, including the reason for requesting the study.

I.2. Body of the report

I.2.1. Procedures and materials
- Include in the report a brief description of the imaging procedure, and assessment of scan quality (if compromised give the reason, e.g. motion artifacts 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 SPET 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 to normal data base etc.).

I.2.3. Limitations
Where appropriate, identify factors that can limit 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, have to be part of the report. In particular information about the postsynaptic D2 receptor status (and structural lesions) may be helpful in specific situations.

I.3. Interpretation and conclusions

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

I.3.2. Interpretation should be based on the results of the visual and more important quantitative evaluation and conclude on
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
studies) should be recommended to clarify or confirm the suspected diagnosis.

J. Quality control

See procedure guidelines of the TG QA&St of the EANM

K. Sources of error

Artifacts (patient movement, camera related, induced by inappropriate processing)

Interference with drugs possibly acting on the dopamine transporter

V. Issues requiring further clarification

Value of iterative reconstruction

Measured transmission scans for attenuation correction

VI. Concise bibliography

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VII. Disclaimer

The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be different than a spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition resources available to care for patients may vary greatly from one European country or one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

VIII. Acknowledgments

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