External Radioactive Reference Markers in SPECT Imaging of the Dopamine System

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Objective: External radioactive reference markers have been used to localize the canthomeatal (CM) line and correct for head rotation in perfusion brain SPECT. This ensures that regardless of the subject's head position or rotation under the SPECT camera, reconstructed transaxial slices are reoriented parallel to the CM line. This study was undertaken to demonstrate the value of external radioactive reference markers in dopamine SPECT imaging.

Methods: We compared visual and marker methods of reorienting the transaxial slices between dopamine and perfusion brain SPECT studies, respectively. These consisted of imaging normal controls and patients with Alzheimer's or Parkinson's disease using a triple-head camera. Intra- and interoperator variability of the visual and marker methods of reorientation was determined for both perfusion and dopamine studies.

Results: In both intra- and interoperator studies, the variability of image reorientation was significantly reduced (P = 0.0066 and 0.014, respectively) by using the marker method on dopamine images. The variability of reorientation using the marker method for a single operator with dopamine images was 3.0% coefficient of variation (CV), and for the interoperator study (5 different operators) this was 7.0% CV.

Conclusion: This study demonstrated that SPECT imaging of the dopamine system with external radioactive reference markers significantly reduced the variability of determining the angle of reorientation. This resulted in a standardized and consistent method of reorienting transaxial slices, allowing comparison within and between subjects of pre- and postsynaptic dopamine SPECT studies.

Key Words: dopamine; neuroreceptors; SPECT; reorientation; markers

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SPECT imaging of the dopamine neurotransmitter system is becoming widely used and has several potential clinical applications (*1–3*). Currently, two important components of this neurotransmitter system can be imaged: presynaptic transporters with ^{123}I-β-CIT, and postsynaptic D_2 receptors with ^{123}I-IBF (Fig. 1). Measurements of dopamine transporter/receptor parameters within the same anatomical regions for a subject can be made on these two images. For the same subject, a standardized method of reorientation of the reconstructed transaxial slices is necessary so that the two different image sets are oriented the same way. To quantitatively compare patients with age-matched normal subjects (*4,5*), the same standardized method of image reorientation should be used.

External radioactive reference markers have been used to localize the canthomeatal (CM) line and correct for head rotation in perfusion brain SPECT (*6–8*). This ensures that regardless of the subject's head position or rotation under the SPECT camera, reconstructed transaxial slices are reoriented parallel to the CM line (*7,8*). Alternatively, reorientation can be performed visually, without using markers, by using internal anatomical landmarks to estimate the anterior commissure and posterior commissure (ACPC) line and subsequently reorient parallel to it. In dopamine SPECT imaging, the radiopharmaceutical is visualized primarily in the striatum with minimal activity elsewhere in the brain (Fig. 1). Consequently visual reorientation of dopamine SPECT images is more difficult than perfusion brain SPECT due to limited visualization of internal landmarks on the former. The purpose of this study was to demonstrate that the use of external radioactive reference markers is valuable in dopamine SPECT imaging.

MATERIALS AND METHODS

Radioactive Markers

Four radioactive markers were prepared by cutting Whatman No. 1 chromatography paper into 2-mm square pieces and placing them on separate strips of transparent tape. A microdrop of ^{99m}Tc containing 37–92.5 kBq (1–2.5 μCi) then was placed on each square marker and the tape was folded over. These were placed and taped so that one radioactive marker was on the outer canthus of the eye (OC) and another over the external auditory meatus (EAM) bilaterally on all subjects.

SPECT Imaging

To show the value of reference markers, we compared visual and marker methods of image orientation between dopamine and perfusion SPECT studies, respectively. These experiments

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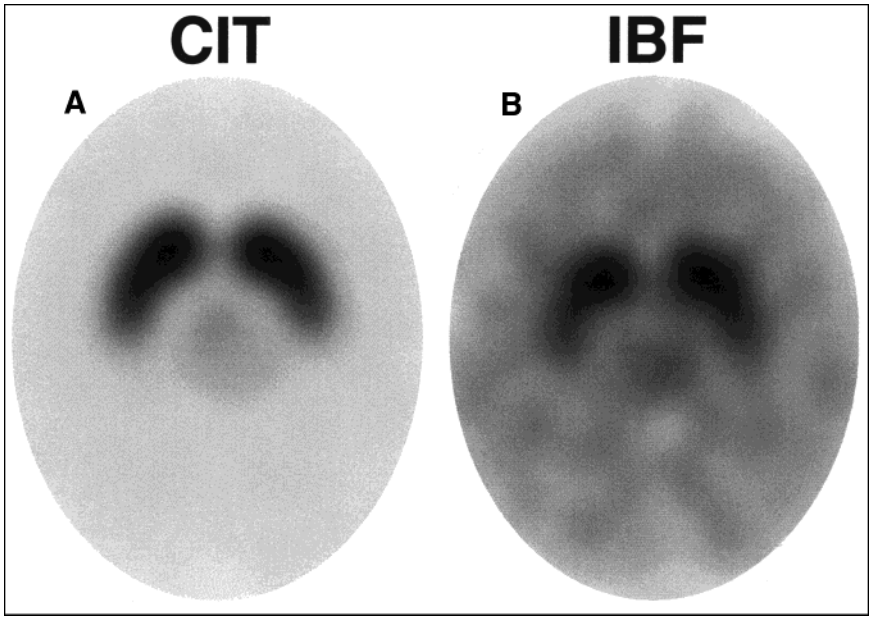

FIGURE 1. Transaxial images of a 56-y-old female normal control subject. (A) Dopamine presynaptic transporters with ^{123}I-β-CIT at 21.5 h postinjection and (B) postsynaptic D_2 receptors with ^{123}I-IBF 60 min postinjection.

consisted of SPECT imaging of normal controls (NCs) and patients with Alzheimer's (AD) or Parkinson's (PD) disease, performed using a triple-head camera (Prism 3000XP; Picker International, Inc., Cleveland, OH). The data were acquired using a continuous scan mode of 3° intervals on a 128 × 128 matrix for 360°, each head rotating 120°, at a radius of rotation fixed at 13.5 cm. One experiment consisted of imaging 5 subjects (3 NCs and 2 ADs) injected with 740 MBq (20 mCi) ^{99m}Tc-ECD. Scans were acquired 30 min postinjection for 15 min each. The other experiment included imaging 5 subjects (3 NCs and 2 PDs) with ^{123}I-β-CIT for dopamine presynaptic transporters (2 subjects) and ^{123}I-IBF for dopamine D_2 postsynaptic receptors (3 subjects), respectively. Iodine-123-β-CIT scans were acquired 18–22 h postinjection of 260–330 MBq (7–9 mCi), for 30 min each. Iodine-123-IBF scans were acquired according to our previously published method (*9*). All SPECT images were reconstructed using a three-dimensional Butterworth postreconstruction filter after applying a ramp backprojection filter.

Transaxial Reorientation

To perform the visual method of reorientation and not have the markers present, they were eliminated by masking anything outside of the skull ellipse to zero during the Chang method of attenuation correction (*10*). The ECD and dopamine transaxial slices were visually reoriented parallel to the ACPC line by the following modifications to the method of Minoshima et al. (*11*): (a) on the sagittal ECD slices, 3 instead of 4 internal anatomical landmarks (Fig. 2A) were aligned to estimate the ACPC line; and (b) on dopamine slices, only 2 landmarks (Fig. 2B) were used as there is no uptake in the thalamus. The angles, determined when visually aligning the landmarks, were subsequently used to reorient the transaxial slices.

The marker method of reorientation of transaxial slices parallel to the CM line consisted of alignment through the center of the OC and EAM markers on both transaxial and sagittal planes. This angle was determined on both right and left sides for each subject, averaged and subsequently used in reorientation of the transaxial slices. This method was used for both ECD and dopamine images and is illustrated on dopamine images in Figure 3.

Data Analysis

Intra- and interoperator variability of the visual and marker methods of reorientation was determined for both ECD and

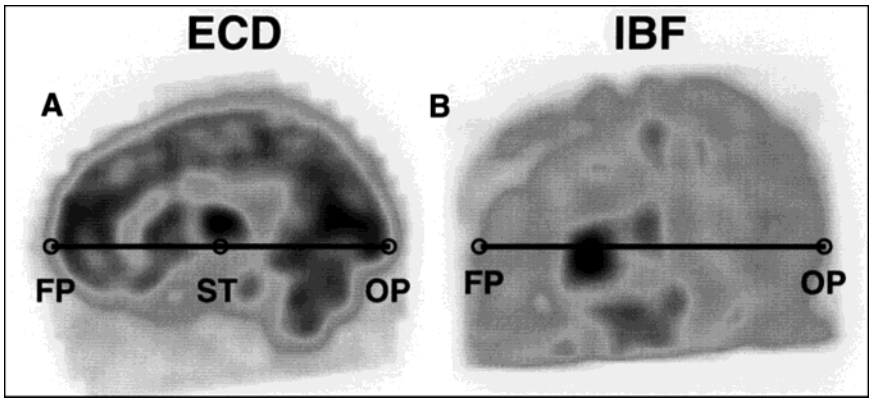

FIGURE 2. (A) Visual reorientation of an ECD sagittal slice through the middle of the thalamus showing the 3 landmarks of anatomy used to estimate the ACPC line: the frontal pole of the brain (FP); the subthalamic point (ST); and the occipital point (OP). (B) A dopamine (IBF) image of a sagittal slice through the putamen showing the 2 landmarks (FP and OP) used to estimate the ACPC line.

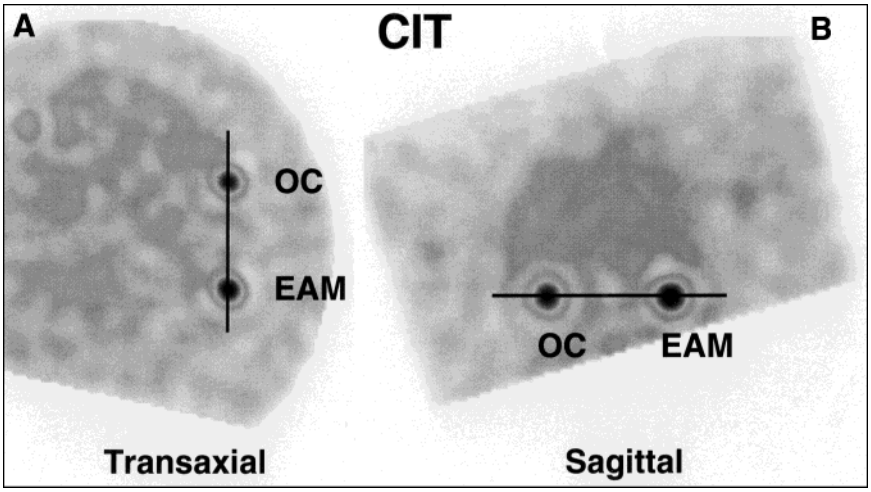

FIGURE 3. Marker reorientation of a dopamine (CIT) (A) transaxial image and (B) a sagittal image showing alignment on 2 orthogonal planes of the outer canthus (OC) of the eye and the external auditory meatus (EAM) to measure the CM line. Note that at the level of the markers no dopamine uptake is visualized. On the transaxial image, the striatum would appear at a higher level. On the sagittal image, the striatum would appear more medially.

dopamine experiments. Intraoperator variability was determined by 1 operator performing the reorientation 5 different times. Interoperator variability was determined by 5 different trained operators performing the reorientation once each. For both intra- and interoperators, a mean coefficient of variation (CV) was calculated for each subject's reorientation angle. The % CV was computed by expressing the SD as a percentage of the mean value. A paired *t* test was performed to compare CVs of the visual method to that of the marker method for each ECD and dopamine experiment. An unpaired *t* test was performed to allow comparison between ECD and dopamine experiments. In addition, another unpaired *t* test was performed to determine if the variability produced by interoperators was significantly different from the variability produced by the intraoperator.

RESULTS

The mean CV of each subject's reorientation angle, using visual and marker methods for both dopamine and ECD in the intraoperator study, is illustrated in Figure 4. Also shown in Figure 4 are the paired *t* test results of the comparison between visual and marker methods. The interoperator results of the same data are illustrated in Figure 5. For both dopamine and ECD experiments, the marker method produced a significant reduction in the variability of determining the reorientation angle. In the intraoperator study, dopamine reorientation variability was reduced 10-fold using the marker method from a mean of 32.4% CV to 3.0% CV ($P = 0.0066$), for ECD the reduction was almost 4-fold ($P = 0.02$). The interoperator study showed that dopamine variability was reduced more than 13-fold using markers, from 97.1% CV to 7.0% CV ($P = 0.014$) and for ECD almost a 4-fold reduction ($P = 0.041$) was obtained.

The results of the unpaired *t* test comparing dopamine and ECD reorientation methods for both intra- and interoperator studies are summarized in Table 1. In both intra- and interoperator studies, there was a significant increase in variability, 2.5 ($P = 0.021$) and 3.6 ($P = 0.013$) times greater, respectively, between the visual method of reorientation for dopamine compared to ECD. There were no differences between the marker methods for dopamine and ECD.

The results of the unpaired *t* test comparing interoperators to intraoperator variability are summarized in Table 2. The data demonstrate that there was a significant increase in variability

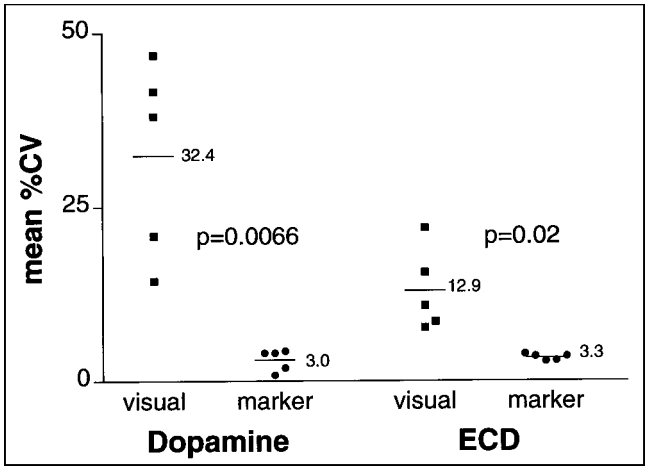

FIGURE 4. Intraoperator scatter diagram of the mean (% CV) reorientation angle for each subject using visual and marker methods for both dopamine and ECD brain SPECT.

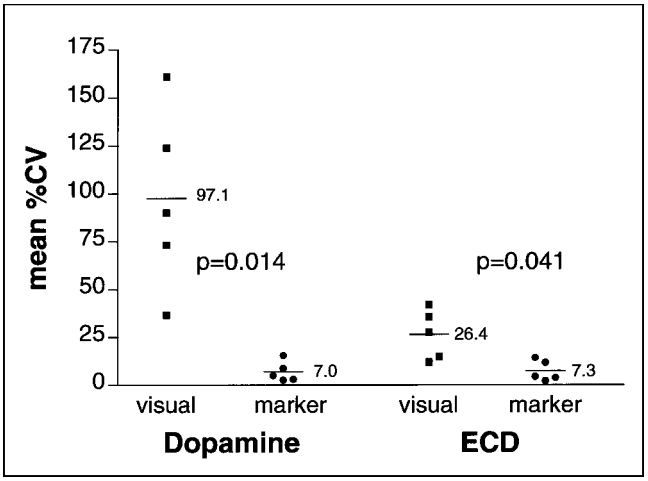

FIGURE 5. Interoperator scatter diagram of the mean (% CV) reorientation angle for each subject using visual and marker methods for both dopamine and ECD brain SPECT.

TABLE 1
P Values for Unpaired *t* Test Between Intra- and Interoperator Variability

	Intraoperator	Interoperator
Visual	0.021	0.013
Markers	0.68	0.94

of 3-fold (from 32.4% CV to 97.1% CV; $P = 0.019$) between operators for the visual method of dopamine compared to a single operator. There were no differences in variability between interoperators and the intraoperator for either the visual method of ECD, or the marker methods for dopamine and ECD.

DISCUSSION

Accurate evaluation of the dopamine system requires a reproducible method of orienting pre- and postsynaptic image sets the same way to allow for comparison within and between subjects. This has been accomplished by various methods in the past. One method requires that the subject be reproducibly positioned under the SPECT camera for the two different scans (*3,12,13*). This can be difficult and time consuming (*13*), especially with the types of patients who require these scans (i.e., patients with movement disorders). Quantitatively comparing subjects requires that they all be reproducibly positioned. This is highly unlikely to be achieved.

Another method that has been used for perfusion brain SPECT requires the additional use of morphological imaging such as MRI or x-ray CT to coregister with the functional SPECT images (*13,14*). Alignment of SPECT with morphological images is often difficult, however, because of the difference in spatial resolution and lack of easily defined outer contours (*8,13*).

Yet another approach has been to orient to a standardized stereotactic coordinate system such as the Talairach method (*15*). An advantage of this approach is that morphological imaging is not required (*6,14,16*). This is the approach that we have used with visual and marker methods to estimate the stereotactic baseline, the ACPC or CM lines, respectively.

Our results demonstrate that visual methods for reorienting dopamine transaxial slices both intra- and interoperatively are not consistent. The variability is too large to be used. In fact, the variability produced by multiple operators is significantly worse (3 times) than that of a single operator, further supporting the need for a more reproducible method of dopamine image reorientation. The significantly better visual reorientation with ECD than that of dopamine appears to be due to visualization of more anatomical landmarks on the ECD images.

TABLE 2
P Values for Unpaired *t* Test Between Dopamine and ECD Variability of Reorientation Methods

	Dopamine	ECD
Visual	0.019	0.066
Markers	0.14	0.14

The marker methods significantly reduced the variability of reorientation with both ECD and dopamine. These marker methods were very reproducible and there were no significant differences in variability between ECD and dopamine, or between interoperators and that of a single operator. The reduction in variability by using markers was most evident in the dopamine studies. A mean reduction of 29.4% CV and 90.1% CV for single and multiple operators, respectively. The variability of reorientation using the marker method for a single operator with dopamine images was 3.0% CV. For the multioperator study (5 different operators) the variability was 7.0% CV. These results suggest that the use of reference markers is valuable in dopamine SPECT imaging.

In addition, the use of reference markers was valuable during attenuation correction of the dopamine images. In some cases, the edges of the skull were not easily discernible and, therefore, the ellipse placement was difficult. The reference markers were helpful in delineating the edges of the skull (*9*).

There are some limitations to this study. The visual method estimates the ACPC line, while the marker method measures the CM line. These may not be identical. The CM line is parallel to the ACPC line, but is separated by known constant distances (*6,17*). This is not a problem so long as the lines are parallel. If they are not parallel, this will increase the intersubject variability. A limitation of the marker method is the variability between the external and true brain orientations (*13,14,16*), this again may increase the intersubject variability. Another limitation is that this study evaluated precision (or variability) only, but not accuracy. No actual measurements of how accurate the estimation of the ACPC lines were made. This would have required a method of coregistration with morphological imaging which in itself has some limitations that have been previously discussed. Precision, however, is particularly important in comparing dopamine images within and between subjects.

CONCLUSION

The use of external radioactive reference markers significantly improved the reproducibility of reorienting transaxial slices of pre- and postsynaptic dopamine SPECT images. This practical and simple method allows comparisons within and between subjects of function of the dopamine neurotransmitter system.

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