Eur J Nucl Med Mol Imaging (2008) 35:1330–1333
DOI 10.1007/s00259-008-0842-x

EDITORIAL COMMENTARY

Is absolute quantification of dopaminergic neurotransmission studies with ^{123}I SPECT ready for clinical use?

Habib Zaidi · Georges El Fakhri

Published online: 4 June 2008

^{123}I neuroligands allow SPECT imaging of dopaminergic and benzodiazepine systems in various movement disorders including Parkinson's disease, Huntington's disease, progressive supranuclear palsy, multiple system atrophy, and Wilson's disease. Cocaine analogs with high affinity and selectivity for dopamine transporter (DAT) sites in the putamen and the caudate nucleus such as ^{123}I-CIT [1], ^{123}I-altropane [2], and ^{123}I-FPCIT [3] allow SPECT imaging of the DAT system. Likewise, dopamine transporters can be imaged with SPECT using ^{123}I neuroligands such as ^{123}IBZM [4], ^{123}IBF [5], etc. Significant progress has been made in the design of high-resolution SPECT cameras dedicated for brain imaging. Also, improved physical compensation and reconstruction algorithms have been proposed, and some have been incorporated into commercial software supplied by vendors to end-users. However, in spite of the advances in algorithmic designs allowing improved quantitative accuracy, absolute quantitation of DAT or D2 has been and is still very challenging with SPECT, unlike PET, due to the difficulty to accurately and simply compensate for image-degrading factors such as attenuation, scatter, limited spatial resolution, and low sensitivity [6]. Sensitivity is an important impediment against dynamic brain SPECT imaging which is required to achieve absolute quantitation of the distributions of many of these neuroligands. Photon attenuation and contributions from scattered photons reduce the accuracy of measured activities and activity concentrations. In addition, limited spatial resolution causes a "hot" object that is less than two to three times the system's resolution in a "colder" background to appear blurred with reduced activity concentration (partial volume effect). While the total reconstructed counts within the object are conserved, the count density is decreased from the true value because the data are distributed over a larger area than the object's true activity distribution.

Advances in the quantification of dopaminergic neurotransmission studies using SPECT, especially for small structures such as the putamen and caudate nucleus rely on two improvements: (1) hardware improvements to enhance spatial resolution and sensitivity and addition of components or other imaging modalities (e.g., SPECT/MR [7]) to allow anatomolecular fusion imaging and to enable correction for physical degrading factors and (2) software improvements to achieve better image quality and achieve more accurate quantification of physiological parameters. In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Crespo et al. [8] assess what level of accuracy can be achieved when quantifying dopaminergic ^{123}I radioligands in Monte Carlo simulations of two gamma cameras using different combinations of correction techniques including system response function, scatter, attenuation, and partial volume effect. This editorial gives a summary of recent advances in brain SPECT instrumentation, compensation methods available for scatter, attenuation, system response, partial volume effect, and motion. It also explores the role and limitations of Monte Carlo simulation in the development and performance assessment of quantitative

This Editorial Commentary refers to the article doi:10.1007/s00259-007-0711-z.

H. Zaidi (✉)
Division of Nuclear Medicine, Geneva University Hospital,
CH-1211 Geneva 4, Switzerland
e-mail: habib.zaidi@hcuge.ch

G. El Fakhri
Nuclear Medicine and Molecular Imaging Division,
Department of Radiology, Harvard Medical School
and Massachusetts General Hospital,
Boston, MA 02114, USA

protocols for brain SPECT and a critical appraisal of the future of quantitative DAT imaging using brain SPECT in clinical setting.

Due to the location of the striata deep within the brain, the attenuation of photons emitted from DAT binding sites is very substantial compared to cortical perfusion studies, for example, and accounts for a reduction in signal of approximately 75%. Attenuation correction, on the other hand, is usually considered to be easy to achieve in the brain except when accurate quantification is desired in all regions [9]. It has been reported that modified uniform attenuation maps that account for bone tissue yield accurate attenuation compensation that is not significantly different from nonuniform attenuation compensation [10]. Likewise, scatter compensation can be achieved using spectral approaches that rely on the estimation of scatter contribution in one or several energy windows or more sophisticated scatter compensation approaches such as those using neural networks, spectral factor analyses, or statistical iterative reconstruction techniques [11]. The absence of internal organ motion in brain imaging simplifies greatly the motion problem which can be tackled using head restraint and rigid registration [12]. One of the major physical factors affecting quantitation in DAT SPECT is partial volume effect due to the combination of limited spatial resolution of the gamma cameras available today (approximately 8 mm) and small size of the caudate nucleus and putamen (similar size to spatial resolution). This yields major underestimation of striatal activity (e.g., [13, 14]) that requires to be compensated for using some knowledge about the striatal volume from another modality such as MRI. Under these conditions, Crespo et al. [8] show that accurate quantitation of activity concentration is feasible. However, quantitation of activity concentration in the striatal volume is not synonymous to the absolute quantitation of DAT population and the latter requires kinetic modeling of the neuroligand density within the nigrostriatal cellular space. While kinetic modeling is feasible for many neuroligands used along with ^{123}I (e.g., altropane [2]), the major difficulty resides in the collection of short dynamic frames of the neurotransmitter study due to the limited statistics associated with such studies. Furthermore, even in the presence of high-count statistics, the mechanical motions involved and the bulk of the detector heads limit the shortest time in which a complete set of projections can be recorded to several minutes [15]. To address this problem, several attempts have been made to dramatically increase brain SPECT sensitivity using many heads or ring-like geometry detectors that allow very fast acquisition of a full set of projections. Although the use of such systems is not widespread in clinical routine in brain SPECT, they are of interest because they illustrate possible future avenues of research. A good example of such systems is the FASTSPECT developed at the University of Arizona which consists of 24 position-sensitive NaI(Tl) detectors that are completely stationary, along with a stationary set of 2-mm pinhole collimators hence achieving high sensitivity (fast dynamic brain scans) and high spatial resolution [16]. Another dedicated brain scanner with stationary annular NaI (Tl) detector is the CERASPECT system developed by Digital Scintigraphics Inc. [17], which is equipped with a rotating collimator. A modified version of this collimator is the SensOgrade, a variable focusing collimator which samples the projections unequally with central regions more heavily represented to compensate for attenuation from central brain structures thus yielding a fourfold to ninefold increase in sensitivity compared to conventional dual-head cameras [18]. A third example is the SPRINT II system developed at the University of Michigan which consists of 11 detectors arranged in a polygonal fashion and a rotating collimator which allows the acquisition of a complete set of fan-beam projection data within 1/12 of a rotation [19]. Another example of unconventional systems is the NeuroFocus™ multi-conebeam imager (Neurophysics Corporation, Shirley, MA, USA), which produces tomographic SPECT images with an intrinsic spatial resolution of approximately 3 mm. The operation of the NeuroFocus™ scanner follows the same principles as scanning optical microscopes to obtain high-resolution, three-dimensional images of biological tissue. A highly focused point of light is scanned mechanically in three dimensions to uniformly sample the volume under observation. As an alternative to dynamic SPECT imaging using multiple, fast rotations, strategies involving the use of only a single, slow camera rotation have been proposed [20]. Further advances in electronics are permitting new counting strategies, and advances in electronic component capability are allowing for enhanced sensitivity [21].

Within the context of functional brain imaging, the aim of quantification is to provide a reliable numerical measure of brain function. It is always hypothesized that the availability of accurate quantitative information about the dopaminergic system would provide a higher diagnostic accuracy than visual interpretation alone. Therefore, the aim of the study by Crespo et al. [8] is to assess the performance of various collimation geometries and image correction strategies on the accuracy of semiquantitative indices (specific uptake ratio) obtained from dopaminergic neurotransmission SPECT studies with ^{123}I-labeled radioligands which might enable reliable standardization in multicentric studies and the transfer of normal functional brain databases.

Modeling and simulation of the SPECT image formation process play a significant role in the development and assessment of algorithms for quantitative brain imaging. In particular, Monte Carlo techniques were extensively used to analyze the performance of new collimators design for planar imaging and SPECT [22]. Practical guidance could

be offered for understanding trade-offs that must be considered for clinical imaging. Selective comparisons among different collimators could also be presented and assessed quantitatively. Approaches to the collimator optimization problem and more sophisticated 'task-dependent' treatments and important considerations for collimators design have been performed [22]. Well-established imaging performance parameters of parallel-hole collimators could be compared with those of fan- and cone-beam collimators which have enjoyed considerable success in recent years, particularly for brain SPECT. Monte Carlo simulations have been shown to be very useful for the development, validation, and comparative evaluation of image correction and reconstruction techniques because it is possible to obtain a reference image to which corrected/reconstructed images should be compared [23]. Monte Carlo modeling thus allows a detailed investigation of the spatial and energy distribution of Compton scatter which would be difficult to perform using the present experimental techniques, even with very good energy resolution semiconductor detectors [11]. Monte Carlo simulations are also powerful tools to investigate the limits of algorithms developed for the correction of partial volume effect by allowing to replicate realistic conditions in emission tomography for a wide range of practical situations and to study the effect of object shape and size on recovery performance [24]. In addition, the assessment of the impact of inherent assumptions such as accurate characterization of system response function, perfect registration between MRI and SPECT, anatomical image segmentation, and other hypotheses regarding tracer distribution on quantification bias is more straightforward compared to experimental approaches [14].

Inverse Monte Carlo approaches with simultaneous compensation for attenuation, scatter, and distance-dependent collimator response have been advocated as a promising alternative for SPECT reconstruction in the 1980s [25]. The interest in fully 3-D Monte Carlo-based statistical reconstruction approaches spurred the development of computationally efficient algorithms capable of obtaining highly accurate quantitative data in clinically acceptable computation times [26, 27] On the other hand, the capability to theoretically model the propagation of photon noise through SPECT reconstruction algorithms is fundamental in evaluating both the quality and quantitative accuracy of reconstructed images as a function of the parameters of the algorithm. Monte Carlo methods can be used to check the validity of the predictions of the theoretical formulations through the computation of the sample statistical properties of the algorithms under evaluation [28].

The combination of realistic computational anthropomorphic models of the human anatomy and accurate models of the imaging process allows the simulation of SPECT data that are ever closer to actual patient data [29]. Monte Carlo simulation techniques will find an increasingly important role in the future of quantitative SPECT in the light of the further development of realistic computational models, the accurate modeling of projection data, and computer hardware. However, caution must be taken to avoid errors in the simulation process, and verification via comparison with experimental and clinical data is crucial.

Advances in dedicated SPECT instrumentation stimulated the clinical use of high-resolution imaging of the brain [6]. Recent studies seem to suggest that the time of clinical application of quantitative brain SPECT imaging has come. The technique was shown to provide a higher diagnostic accuracy in differential diagnosis [30] and to improve consistency in quantitative measurements between facilities using different cameras and analysis software [31]. Quantitative brain SPECT incorporating advanced corrections for attenuation, scatter, system response, and partial volume will continue to play an important role both in clinical and research settings [27, 32–34]. It is expected that the development of more specific tracers in combination with advances in neuroscience will expand the understanding of the pathophysiology of neurological clinical diseases in the coming years, hopefully leading to improved diagnosis and treatment, and eventually to the implementation of preventive techniques.

It is highly likely that automated operator-independent analysis of high-resolution DAT SPECT images will lead to largely reduced analysis variability, improved availability, and increased diagnostic sensitivity, independent of observer performance [35]. However, it should be emphasized that the process of clinical diagnosis cannot be automated in a straightforward manner. Despite the fact that automated image analysis methods are essential, they should be considered as complementary instruments to clinical diagnosis and decision-making process. Interpretation of functional and molecular alterations observed in a SPECT scan requires an enormous collection of understanding, involving physiology, pathophysiology, and clinical science, which is difficult to integrate in an easy to implement decision-making algorithm or computer-aided diagnostic system.

References

1. Laruelle M, Baldwin RM, Malison RT, Zea-Ponce Y, Zoghbi SS, al-Tikriti MS, et al. SPECT imaging of dopamine and serotonin transporters with [123I]beta-CIT: pharmacological characterization of brain uptake in nonhuman primates. Synapse 1993;13:295–309.
2. Fischman AJ, Bonab AA, Babich JW, Palmer EP, Alpert NM, Elmaleh DR, et al. Rapid detection of Parkinson's disease by SPECT with altropane: a selective ligand for dopamine transporters. Synapse 1998;29:128–41.
3. Abi-Dargham A, Gandelman MS, DeErausquin GA, Zea-Ponce Y, Zoghbi SS, Baldwin RM, et al. SPECT imaging of dopamine

transporters in human brain with iodine-123-fluoroalkyl analogs of beta-CIT. J Nucl Med 1996;37:1129–33.
4. Schwarz J, Antonini A, Tatsch K, Kirsch CM, Oertel WH, Leenders KL. Comparison of 123I-IBZM SPECT and 11C-raclopride PET findings in patients with parkinsonism. Nucl Med Commun 1994;15:806–13.
5. Ichise M, Ballinger JR, Golan H, Vines D, Luong A, Tsai S, et al. Noninvasive quantification of dopamine D2 receptors with iodine-123-IBF SPECT. J Nucl Med 1996;37:513–20.
6. Madsen MT. Recent advances in SPECT imaging. J Nucl Med 2007;48:661–73.
7. Wagenaar DJ, Kapusta M, Li J, Patt BE. Rationale for the combination of nuclear medicine with magnetic resonance for pre-clinical imaging. Technol Cancer Res Treat 2006;5:343–50.
8. Crespo C, Gallego J, Cot A, Falcón C, Bullich S, Pareto D, et al. Quantification of dopaminergic neurotransmission SPECT studies with (123)I-labelled radioligands. A comparison between different imaging systems and data acquisition protocols using Monte Carlo simulation. Eur J Nucl Med Mol Imaging. 2008;in press. DOI 10.1007/s00259-007-0711-z.
9. Zaidi H, Montandon M-L, Meikle S. Strategies for attenuation compensation in neurological PET studies. Neuroimage 2007;34:518–41.
10. El Fakhri G, Kijewski MF, Albert MS, Johnson KA, Moore SC. Quantitative SPECT leads to improved performance in discrimination tasks related to prodromal Alzheimer's disease. J Nucl Med 2004;45:2026–31.
11. Zaidi H, Koral KF. Scatter modelling and compensation in emission tomography. Eur J Nucl Med Mol Imaging 2004;31:761–82.
12. Koch W, Mustafa M, Zach C, Tatsch K. Influence of movement on FP-CIT SPECT quantification: a Monte Carlo based simulation. Nucl Med Commun 2007;28:603–14.
13. Shao L, Billings J, Pfeiffer N, Kung HF. Concentration recovery for SPECT CNS dopamine-receptor studies for monkeys. Med Phys 1994;21:675–81.
14. Soret M, Koulibaly PM, Darcourt J, Hapdey S, Buvat I. Quantitative accuracy of dopaminergic neurotransmission imaging with ^{123}I SPECT. J Nucl Med 2003;44:1184–93.
15. Cherry S, Sorenson JA, Phelps ME. Physics in nuclear medicine. 3rd ed. Philadelphia: Saunders; 2004.
16. Rowe RK, Aarsvold JN, Barrett HH, Chen JC, Klein WP, Moore BA, et al. A stationary hemispherical SPECT imager for three-dimensional brain imaging. J Nucl Med 1993;34:474–80.
17. Genna S, Smith AP. The development of ASPECT, an annular single crystal brain camera for high efficiency SPECT. IEEE Trans Nucl Sci 1988;35:654–8.
18. El Fakhri G, Ouyang J, Zimmerman RE, Fischman AJ, Kijewski MF. Performance of a novel collimator for high-sensitivity brain SPECT. Med Phys 2006;33:209–15.
19. Rogers WL, Clinthorne NH, Shao L, Chiao P, Ding Y, Stamos JA, et al. SPRINT II: a second generation single photon ring tomograph. IEEE Trans Med Imaging 1988;7:291–7.
20. Farncombe T, Celler A, Noll D, Maight J, Harrop R. Dynamic SPECT imaging using a single camera rotation (dSPECT). IEEE Trans Nucl Sci 1999;46:1055–61.
21. Wong WH, Li H, Uribe J, Baghaei H, Wang Y, Yokoyama S. Feasibility of a high-speed gamma-camera design using the high-yield-pileup-event-recovery method. J Nucl Med 2001;42:624–32.
22. Ljungberg M, Strand S-E, King MA. Monte Carlo calculations in nuclear medicine: applications in diagnostic imaging. Bristol: IOP Publishing; 1998.
23. Zaidi H. Relevance of accurate Monte Carlo modeling in nuclear medical imaging. Med Phys 1999;26:574–608.
24. Dewaraja YK, Ljungberg M, Koral KF. Monte Carlo evaluation of object shape effects in iodine-131 SPET tumor activity quantification. Eur J Nucl Med 2001;28:900–6.
25. Floyd CE, Jaszczak RJ, Greer KL, Coleman RE. Inverse Monte Carlo as a unified reconstruction algorithm for ECT. J Nucl Med 1986;27:1577–85.
26. Beekman FJ, de Jong HW, van Geloven S. Efficient fully 3-D iterative SPECT reconstruction with Monte Carlo-based scatter compensation. IEEE Trans Med Imag 2002;21:867–77.
27. Ouyang J, Fakhri GE, Moore SC. Fast Monte Carlo based joint iterative reconstruction for simultaneous [sup 99m]Tc/[sup 123]I SPECT imaging. Med Phys 2007;34:3263–72.
28. Wilson DW, Tsui BMW, Barrett HH. Noise properties of the EM algorithm. II. Monte Carlo simulations. Phys Med Biol 1994;39:847–71.
29. Zaidi H, Xu XG. Computational anthropomorphic models of the human anatomy: the path to realistic Monte Carlo modeling in medical imaging. Annu Rev Biomed Eng 2007;9:471–500.
30. Koch W, Hamann C, Radau PE, Tatsch K. Does combined imaging of the pre- and postsynaptic dopaminergic system increase the diagnostic accuracy in the differential diagnosis of parkinsonism? Eur J Nucl Med Mol Imaging 2007;34:1265–73.
31. Tossici-Bolt L, Hoffmann SMA, Kemp PM, Mehta RL, Fleming JS. Quantification of [123I]FP-CIT SPECT brain images: an accurate technique for measurement of the specific binding ratio. Eur J Nuc Med Mol Imaging 2006;33:1491–9.
32. El Fakhri G, Moore SC, Maksud P, Aurengo A, Kijewski MF. Absolute activity quantitation in simultaneous 123I/99mTc brain SPECT. J Nucl Med 2001;42:300–8.
33. Du Y, Tsui BMW, Frey EC. Model-based compensation for quantitative 123I brain SPECT imaging. Phys Med Biol 2006;51:1269–82.
34. Vanzi E, De Cristofaro M, Ramat S, Sotgia B, Mascalchi M, Formiconi A. A direct ROI quantification method for inherent PVE correction: accuracy assessment in striatal SPECT measurements. Eur J Nuc Med Mol Imaging 2007;34:1480–9.
35. Koch W, Radau PE, Hamann C, Tatsch K. Clinical testing of an optimized software solution for an automated, observer-independent evaluation of dopamine transporter SPECT studies. J Nucl Med 2005;46:1109–18.