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Original article

Dopamine Transporter Scan: Determining the Diagnostic Performance of Hermes Brain Registration and Analysis Software Suite with Parkinson Disease and Essential Tremor Disease Patients

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Abstract

Parkinson Disease is the most baffling and complex of all neurological disorders because its causes barely remain a mystery. The hallmark of Parkinson Disease (PD) is the loss of brain cells that transport dopamine in the basal ganglia of the brain. The study devised a robust semi-quantitative brain analysis technique to accurately differentiate patients with PD from patients with Essential Tremor (ET). The mode of data collection was retrospective since the brain scans, consisting PD and ET patients, were previously carried out using a Toshiba SPECT scanner. The sample size was made up of 15 brain scans of ET and PD patients. Five Hermes BRASS techniques were used to determine the specific bindings and binding ratios in the putamen and caudate regions of the brain while the mean binding ratios were calculated using MS Excel. Hermes BRASS techniques numbers; 2, 3 and 4 (Table 8) misdiagnosed one patient out of the 15 patients. However, notable was the fact that diagnostic technique number 3 had no instance of coincidence diagnosis. The graphical and numerical outcomes obtained with Hermes BRASS and MS Excel showed that a population of PD patients was separable from a population of ET disease patients. T-test confirmed that value of the derived t-statistics (0.19) was less than value of the t-statistics (2.18). Hence the alternate hypothesis was accepted since the difference between the two populations was significant. The quest to identify a robust Hermes diagnostic technique that differentiates patients with PD from patients with ET was successfully realized where the Hermes New BRASS had remarkable improvement over the Hermes Old BRASS. Most essentially the incidence of misdiagnosis, in the differentiation of patients with PD from patients with ET, was minimized to one patient out of the 15 patients. This translated to patients deriving maximum benefit from the pool of medical drugs available for the treatment of PD and ET patients.

Keywords: ***Parkinson Disease, Essential Tremor, Brain Registration, Iterative Reconstruction, Filter Back Projection, Attenuation Correction, Binding Ratio and Cut-off line, coincidence diagnosis.***

Introduction

Parkinson Disease is a major concern among members of the global medical care communities [1;2]. It is the most baffling and complex of all neurological disorders yet up to present date its causes remain a mystery [1;3]. Parkinson disease (PD) is a clinical syndrome comprising hypokinesia, rigidity and tremor [4]. Its characteristic pathological feature is the destruction of dopamine-containing nerve cells in substantia nigra of the basal ganglia [5]. PD occurs worldwide affecting all ethnic age groups. Its peak age of onset is between 35 and 65 years, the progression of illness ranges from 10 to 25 years and approximately 0.3% of the general population and 3% of the population above 65 years have PD [5]. Community-based prevalence studies in India shows a prevalence rate of 7 to 328 per 100,000 people over 50 years of age and it is found to be common in females in India [6]. In 1817, James Parkinson differentiated Essential Tremor from other tremors, including Parkinson disease. Surprisingly little is known about the etiology and pathophysiology of essential tremor, which is characterized by pathologic tremor affecting mainly the upper extremities followed by the head and voice [7;8]. While functional and psychosocial disability range from minimal to severe among ET disease patients, mortality remains unaffected [9]. This is because the tremor is a less debilitating neurological disorder and

patients with the disease have higher prognosis if only they received early treatment with the appropriate medication [10]. In fact, in the UK, more than 120,000 people suffer from these diseases and up to 25% of them are misdiagnosed every year [2;3]. Dopamine transporter scan with Single Photon Emission Computer Tomography (SPECT) using the tracer ^{123}I-FP-CIT) or DatScan has proven to be an effective procedure in the diagnosis of neurodegenerative disorders linked to disturbances of the nigrostriatal dopaminergic system [11;12]. Clinical indications with ^{123}I-FP-CIT SPECT imaging include images for the differentiation of Parkinson disease from essential tremor [13;14]. The outcomes of medical ^{123}I-FP-CIT SPECT scans are mostly obtained using visual assessment of tracer binding [15]. Although visual interpretation is usually sufficient for dopaminergic degeneration accurate diagnosis [7], this type of assessment is subjective in nature, with the reporter's judgment relying heavily on experience and knowledge within the field [8;16]. For a more objective approach, quantitative evaluation of tracer binding can be a useful aid with a variety of methods available for quantification [9] such as the semi quantitative techniques. In this case, the caudate nucleus and putamen regions of the basal ganglia are well defined to assess tracer binding. The relative accuracy of diagnosis between visual analysis and a semi quantitative approach was studied [10] and the outcome was that semi quantification which is objective, according to scientific methodology, gives diagnostic accuracy comparable to visual analysis because it is subjective. The consistency between visual and semi quantitative assessments has also been investigated, with reassuring outcomes [17,18]. According to highlights of a study, a general problem with semi quantitative approach for ^{123}I-FPCIT SPECT imaging is that normal reference values have not been easily available due to inter-scanner differences in parameters such as sensitivity, collimator design and lack of standardization in imaging and reconstruction protocols [19]. In fact, center-specific reference values have historically been needed. Many brain analysis softwares have been in use for the differentiation of patients with PD patients with ET and the results have been a high rate of misdiagnosis, which makes it difficult for physician specialists to effectively treat the patients. The research seeks to develop a robust semi quantitative tracer binding technique in order to, efficiently, differentiate patients with PD from patients with ET in dopamine transporter scan of the brain. Hence, it ascertained the diagnostic efficacy of the following brain analysis techniques: (a) Hermes Old (HO) Brain Registration and Analysis Software Suit (BRASS); applied to Iterative Reconstruction and Each Image Attenuation Correction (IR & EIAC), (b) Hermes New (HN) BRASS; applied to Iterative Reconstruction and Each Image Attenuation Correction (IR & EIAC), (c) HOBRASS; applied to Iterative Reconstruction and Global Image Attenuation Correction (IR & GIAC), (d) HNBRASS; applied to Iterative Reconstruction and Global Image Attenuation Correction (IR & GIAC) and (e) HNBRASS; applied to Filter Back Projection (FBP). As reproducibility is a determining factor as to whether or not the techniques were fit and optimal for clinical diagnoses, further investigations were therefore made into how data variability among different operators and by the same operator affected the diagnoses. Achieving a reduction in the incidence of clinical misdiagnosis translates to patients deriving the maximum benefit from the pool of choices of medical treatment drugs, which are currently available for the treatment of PD and ET patients.

Materials and Methods

Imaging modality: SPECT (double Head), energy source: emission, energy peak: 159 keV, matrix size: 128 x128, typo of collimation: LEHR collimator, step angle: 3 degrees, acquisition time: 40 sec/step and the total rotation angle: 180 degrees. Radioisotopes and labelled chemical: ^{99}Technetium (metastable) and ioflupane (N-*w*-fluoropropyl-*B*-CIT) or ^{99}Tc-FP-CIT. The retrospective study collected brain scan data of 15 patients who had been diagnosed and confirmed at post mortem as patients with PD or ET. Patients numbered one to eight were all patients with ET and patients numbered nine to 15 were all patients with PD. The scan data of all patients were retrieved from a Pictures and Archives Communication System (PACS) into a workstation of the Department of Nuclear Medicine purposely for the research. The Toshiba SPECT with double head and 180 degrees rotation was deployed for data sampling in nuclear diagnostics in the Department of Nuclear Medicine. The target anatomical areas of the scan included the caudate and the putamen of the basal ganglia of the brain. All scan data were, generally subjected to Hermes Old BRASS (HOBRASS) and Hermes New BRASS (HNBRASS) both of which are Hermes dedicated brain analysis diagnostic software. Iterative reconstruction and Filter Back Projection were applied on each brain scan data alongside with the choice of an attenuation correction to correct for problems with the salivary glands and photon scattering. Qualitatively, a patient whose scan appeared as a comma was diagnosed an ET patient and the patient scan with full stop was diagnosed a PD patient. Quantitatively, the specific bindings and binding ratios in selected regions of interests (ROIs) in the basal ganglia of the brain namely; putamen and caudate were obtained and recorded for each patient. The mean value of binding ratio that marked the boundary between patients with PD and patients with ET denoted, hereafter, as cut-off line was determined. Patients with PD were found below the cut-off line while patients with ET were found above the cut of line. MS Excel version 16 was used to enter values of binding ratios and analysed for presentation.

Results

Fifteen patients were selected for the study with the first eight (8) being patients with ET and the last seven (7) being patients with PD. The SPECT acquired data of each patient was reconstructed and analysed using five different brain analysis techniques comprising the combinations of IR, FBP, EIAC and GIAC from HOBRASS and HNBRASS as listed in continuation.

(a) **Technique # 1:** HOBRASS applied to Iterative Reconstruction and Each Image Attenuation Correction (IR & EIAC).
(b) **Technique # 2:** HNBRASS applied to Iterative Reconstruction and Each Image Attenuation Correction (IR & EIAC).
(c) **Technique # 3:** HOBRASS applied to Iterative Reconstruction and Global Image Attenuation Correction (IR & GIAC).
(d) **Technique # 4:** HNBRASS applied to Iterative Reconstruction and Global Image Attenuation Correction (IR & GIAC) and
(e) **Technique # 5:** HNBRASS applied to Filter Back Projection (FBP).

Since reproducibility among operators is a determining factor as to whether or not a technique is fit and optimum for clinical diagnoses, further investigation was made into how data variability, among operators and for the same operator, affected the

diagnosis. Hence, the technique HNBRASS applied to IR and GIAC was used.

Technique #1: Analysis with HOBRASS applying IR & EIAC

Figure 1 represents the analysis results for HOBRASS applying IR & EIAC where the cut off binding ratio was calculated to be 2.3. The technique misdiagnosed two patients out of 15 the patients. Patient number eight was misdiagnosed with PD on binding ratios of 2.17 in the right putamen-caudate and 2.22 in the left putamen-caudate. Patient number nine was misdiagnosed with ET on binding ratios of 3.39 in the right putamen-caudate and 3.40 in left putamen-caudate.

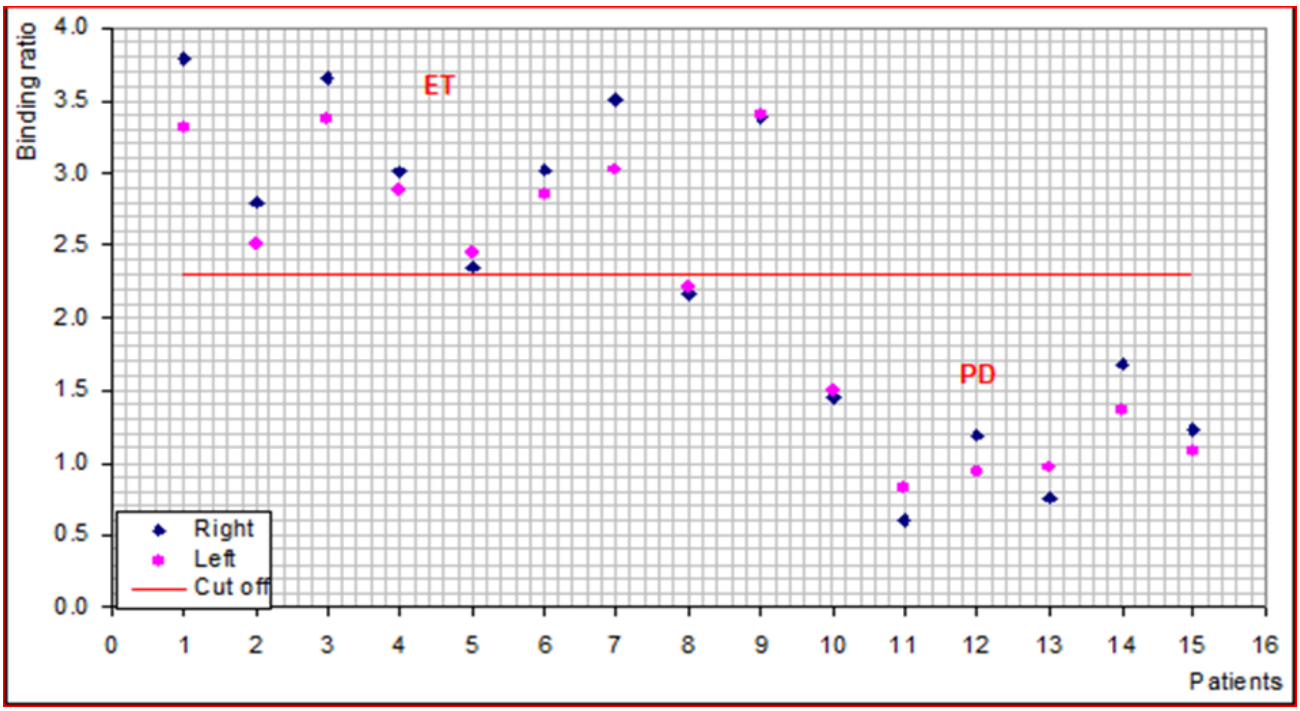

Figure 1: Technique # 1: Analysis with HOBRASS applying IR & EIAC

Table 1 gives a detailed numerical outcome of brain scan with technique number 1, which involves the application of HOBRASS applied to IR & EIAC. The anatomical regions of interest, all in the corpus striatum, were Caudate and Putamen in both hemispheres. Simulation and optimization of visual brain scans gave numerical values of the radio isotope binding in the caudate, putamen and background regions and as well as the binding ratios. Patients with ET have binding ratios above the cut-off point (2.3) while those with PD have binding ratios below the cut-off point (2.3). The yellow cells indicate patients who were misdiagnosed according to the technique.

Table 1: Technique # 1: HOBRASS applied to IR & EIAC

Patients Number	Caudate and Putamen Regions					
	Right	Left	Back Ground.	Binding ratios		
				Right	Left	Cut off
1	67	60.5	14	3.79	3.32	
2	77.4	71.5	20.4	2.79	2.50	
3	74.4	69.9	16	3.65	3.37	
4	92.1	89.3	23	3.00	2.88	
5	70.8	72.6	21.1	2.36	2.44	
6	47.8	45.9	11.9	3.02	2.86	
7	60.5	53.9	13.4	3.51	3.02	
8	49.8	50.5	15.7	2.17	2.22	
9	50	50.2	11.4	3.39	3.40	2.3
10	70.4	71.8	28.7	1.45	1.50	
11	75.2	85.5	46.9	0.60	0.82	
12	54.2	48	24.7	1.19	0.94	
13	85.7	95.4	48.7	0.76	0.96	
14	72.7	63.8	27.1	1.68	1.35	
15	56.5	52.6	25.3	1.23	1.08	

Technique # 2: Analysis with HNBRASS applying IR & EIAC

Figure 2 represents the analysis results for HNBRASS applying IR & EIAC where the cut off binding ratio was determined as 2.8. The technique misdiagnosed one patient out of the 15 in total. Patient number 14 was misdiagnosed with ET in the right caudate on a binding ratio of 3.02.

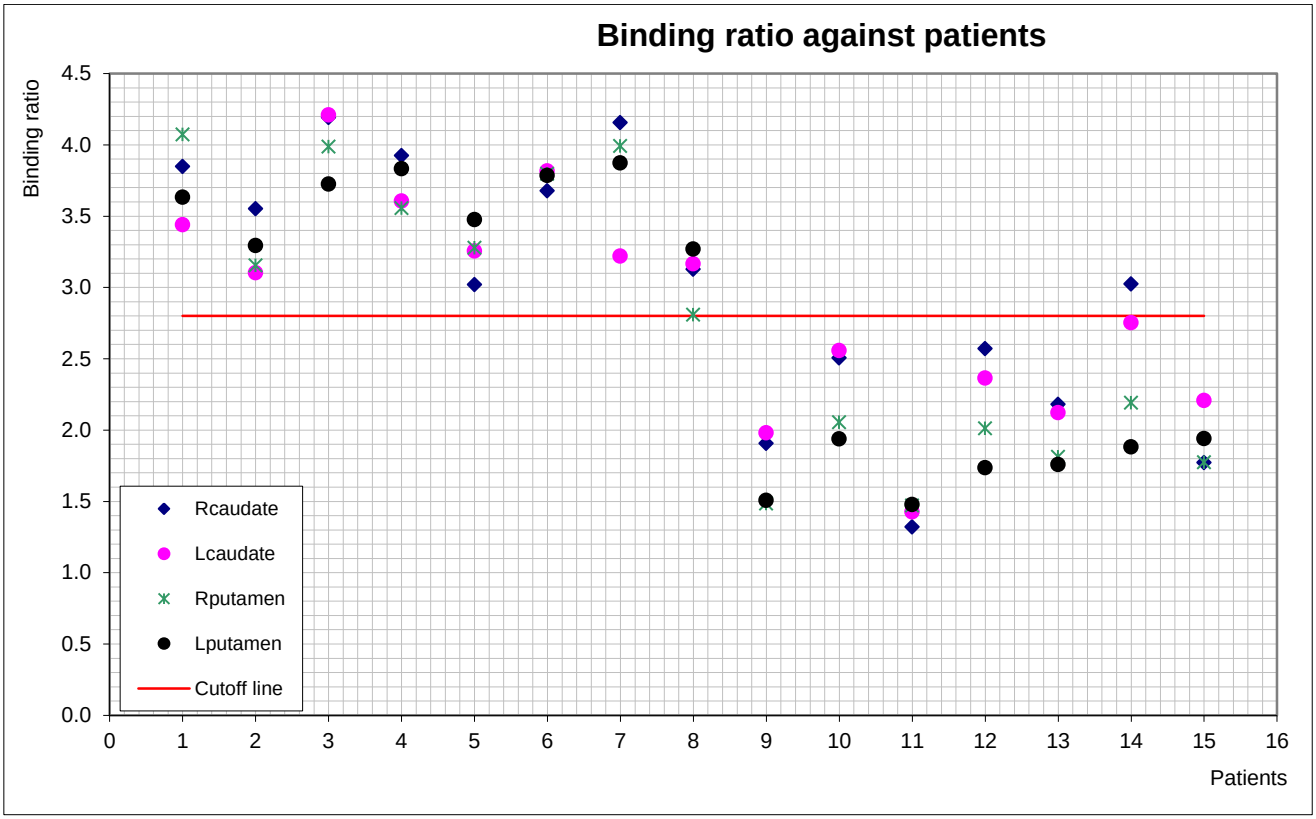

Figure 2: Technique # 2: Analysis with HNBRASS applying IR & EIAC

Table 2 gives a detailed numerical outcome of brain scan with technique number 2, which involves the application of HNBRASS applied to IR & EIAC. Similarly, the anatomical regions of interest, all in the corpus striatum, were caudate and putamen in both hemispheres of the brain. Simulation and optimization of visual brain scans for each patient gave numerical values of the radio isotope binding in the caudate, putamen and background regions and as well as the binding ratios. Patients with ET have binding ratios above the cut-off point (2.8) while those with PD have binding ratios below the cut-off point (2.8).

Table 2: Technique # 2: Analysis with HNBRASS applying IR & EIAC

Caudate and Putamen Regions										Cutoff
Patients	Posterior	Right (RC) Caudate	Left (LC) Caudate	Right (RP) Putamen	Left (LP) Putamen	Binding Ratios				
						RC	LC	RP	LP	
1	27.7	106.6	95.3	112.8	100.6	3.85	3.44	4.07	3.63	
2	36.4	129.3	112.9	114.8	119.9	3.55	3.10	3.15	3.29	
3	31.5	132	132.6	125.6	117.3	4.19	4.21	3.99	3.72	
4	44.1	173.1	159	156.8	169	3.93	3.61	3.56	3.83	
5	34.5	104.2	112.3	113.1	119.9	3.02	3.26	3.28	3.48	
6	20.1	73.9	76.7	76.3	76.1	3.68	3.82	3.80	3.79	
7	25	103.9	80.5	99.8	96.8	4.16	3.22	3.99	3.87	
8	26.7	83.5	84.5	75	87.3	3.13	3.16	2.81	3.27	
9	39.3	74.9	77.8	58.3	59.2	1.91	1.98	1.48	1.51	2.8
10	42.1	105.5	107.7	86.5	81.6	2.51	2.56	2.05	1.94	
11	72.9	96.3	103.9	107.2	107.7	1.32	1.43	1.47	1.48	
12	32.6	83.8	77.1	65.6	56.6	2.57	2.37	2.01	1.74	
13	59.4	129.5	126.1	107.7	104.5	2.18	2.12	1.81	1.76	
14	38.5	116.4	106	84.4	72.4	3.02	2.75	2.19	1.88	
15	41.4	73.3	91.4	73.4	80.3	1.77	2.21	1.77	1.94	

Technique # 3: Analysis with HOBRASS applying IR & GAC

According to Figure 3, out of 15 patients, HOBRASS applying IR & GIAC at a cut off binding ratio of 2.3 misdiagnosed patient number 9 as ET patient at a binding ratio of 4.25 in both right and left putamen-caudate.

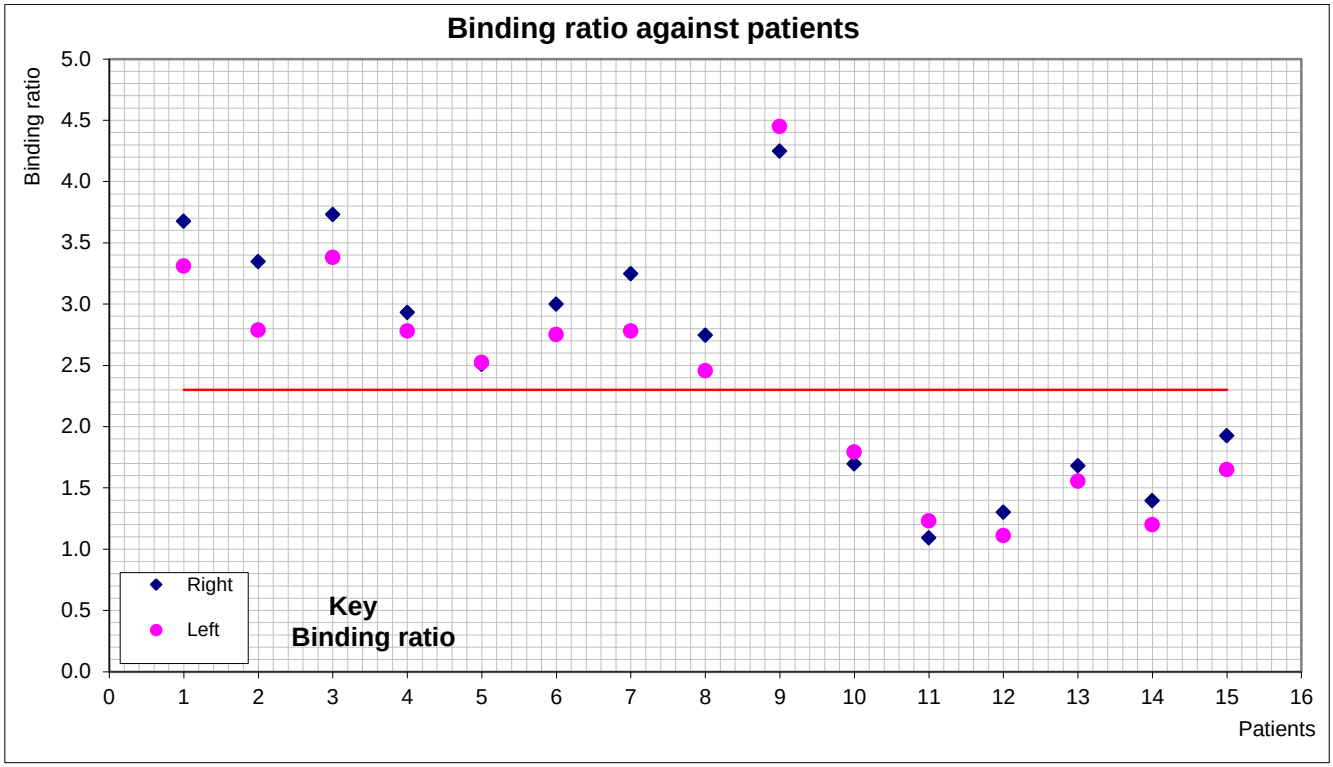

Figure 3: Technique # 3: Analysis with HOBRASS applying IR & GAC

Table 3 gives a detailed numerical outcome of brain scan with technique number 3, which involves the application of HOBRASS applied to IR & GIAC. Similarly, the anatomical regions of interest, all in the corpus striatum, were caudate and putamen in both hemispheres of the brain. Simulation and optimization of visual brain scans for each patient gave numerical values of the radio isotope binding in the caudate, putamen and background regions and as well as the binding ratios. Patients with ET have binding ratios above the cut-off point (2.3) while those with PD have binding ratios below the cut-off point (2.3).

Table 3: Technique # 3: Analysis with HOBRASS applying IR & GIAC

	Caudate and Putamen Regions of Interest					
	Right	**Left**	**Back ground**	**Binding ratio**		**Cut off**
Number				**Right**	**Left**	
1	67.8	62.5	14.5	3.68	3.31	
2	67.8	59.1	15.6	3.35	2.79	
3	75.7	70.1	16	3.73	3.38	
4	98.3	94.5	25	2.93	2.78	
5	69.8	70.1	19.9	2.51	2.52	
6	48.4	45.4	12.1	3.00	2.75	2.3
7	61.6	54.8	14.5	3.25	2.78	
8	50.2	46.3	13.4	2.75	2.46	
9	46.7	48.5	8.9	4.25	4.45	
10	64.7	67	24	1.70	1.79	
11	47.3	50.4	22.6	1.09	1.23	
12	50.6	46.4	22	1.30	1.11	
13	87.1	83	32.5	1.68	1.55	
14	75.9	69.7	31.7	1.39	1.20	
15	51.5	46.6	17.6	1.93	1.65	

Technique # 4: Analysis with HNBRASS applying IR & GIAC

Figure 4 shows that technique # 4 (HNBRASS applying IR&GIAC) at a cut off binding ratio of 2.94 misdiagnosed two patients. Patient number 8 was misdiagnosed as a PD patient in the right putamen on a binding ratio of 2.90. Patient number 2 was neither PD nor ET, since the corresponding binding ratio on the left caudate (2.94) was the same as that of the cut off binding ratio (2.94).

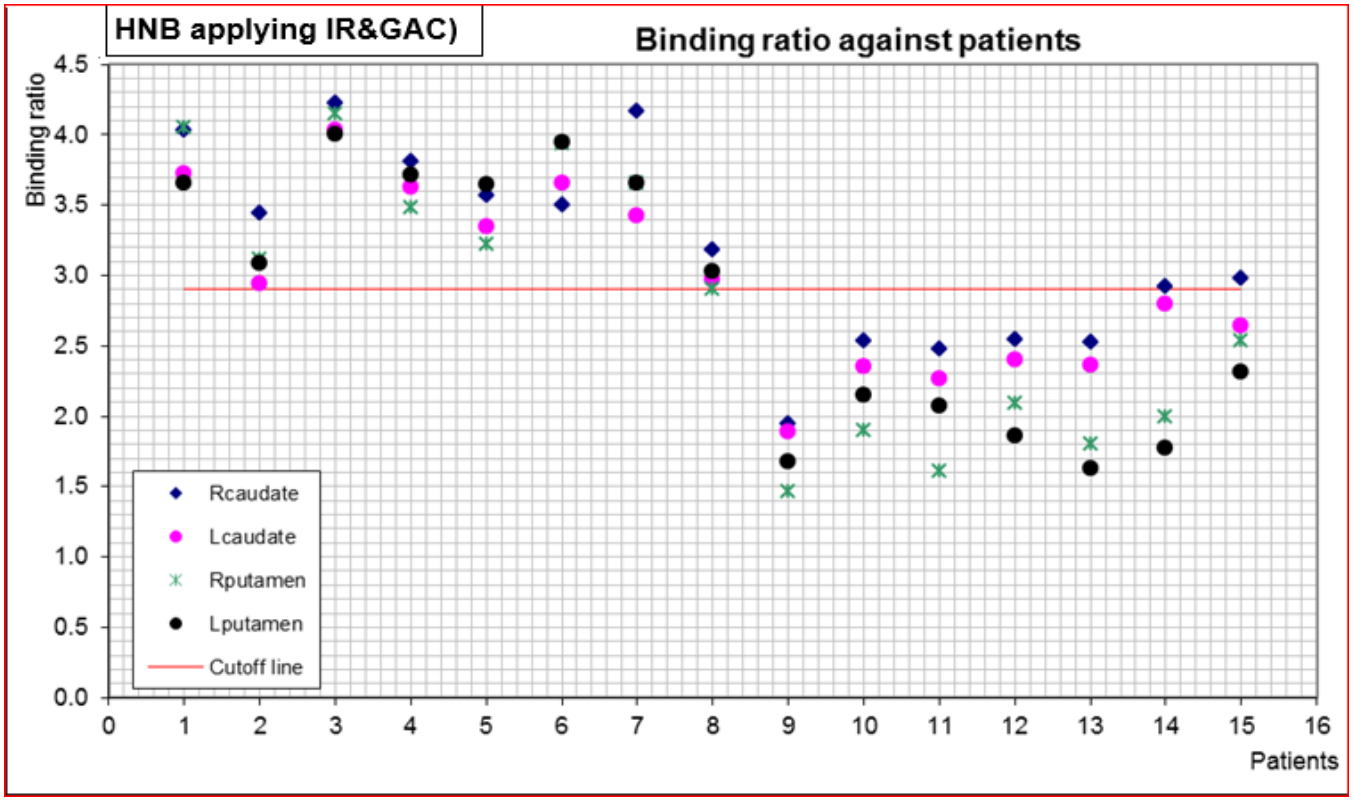

Figure 4: Technique # 4: Analysis with HNBRASS applying IR & GIAC

Table 4 gives a detailed numerical outcome of brain scan with technique number 4, which involves the application of HNBRASS applied to IR & GIAC. Similarly, the anatomical regions of interest, all in the corpus striatum, were caudate and putamen in both hemispheres of the brain. Simulation and optimization of visual brain scans for each patient gave numerical values of the radio isotope binding in the caudate, putamen and background regions and as well as the binding ratios. Patients with ET have binding ratios above the cut-off point (2.94) while those with PD have binding ratios below the cut-off point (2.94).

Table 4 Technique # 4: Analysis with HNBRASS applying IR and GIAC

Number	Posterior	Right (RC) Caudate	Left (LC) Caudate	Right (RP) Putamen	Lift (LP) Putamen	RC	LC	RP	LP	Cut off
1	27.4	110.5	102.1	111.1	100.1	4.03	3.73	4.05	3.65	
2	31.5	108.6	92.6	98.1	97.1	3.45	2.94	3.11	3.08	
3	32.4	137	130.6	134.5	129.8	4.23	4.03	4.15	4.01	
4	41.9	159.8	152.1	146.1	155.5	3.81	3.63	3.49	3.71	
5	32.2	114.9	107.9	103.7	117.3	3.57	3.35	3.22	3.64	
6	20	70	73.1	78.8	79	3.50	3.66	3.94	3.95	
7	24.8	103.3	85	90.6	90.7	4.17	3.43	3.65	3.66	2.94
8	25	79.5	74.3	72.6	75.8	3.18	2.97	2.90	3.03	
9	38.4	74.6	72.6	56.3	64.3	1.94	1.89	1.47	1.67	
10	39.5	100.2	92.9	75.2	84.9	2.54	2.35	1.90	2.15	
11	30.3	75.2	68.6	48.9	62.8	2.48	2.26	1.61	2.07	
12	28.7	73.2	68.9	60	53.4	2.55	2.40	2.09	1.86	
13	52.6	132.7	124.1	95	85.7	2.52	2.36	1.81	1.63	
14	40.9	119.7	114.4	81.5	72.5	2.93	2.80	1.99	1.77	
15	26	77.5	68.8	65.9	60.2	2.98	2.65	2.53	2.32	

Technique # 5: Analysis with HNBRASS applying FBP

Figure 5 shows that technique # 5 (HNBRASS applying FBP) has a cut off binding ratio of 2.15 that separates patients with ET from those with PD. A total of 4 patients were misdiagnosed with details as presented in continuation. Patient number 3 was misdiagnosed as a PD patient at a binding ratio of 1.8. Patient number 8 was misdiagnosed with PD on binding ratios of 1.52 and 1.72 in the right and left caudates respectively. Again, patient number 8 was misdiagnosed on a binding ratio of 1.72 in the right putamen. Patient number 13 was misdiagnosed with ET on a binding ratio of 2.16 in the right putamen. Patient number 14 was misdiagnosed with ET in the right caudate on a binding ratio of 2.29. Patient number 15 was misdiagnosed with ET in the right caudate on binding ratios of 2.31.

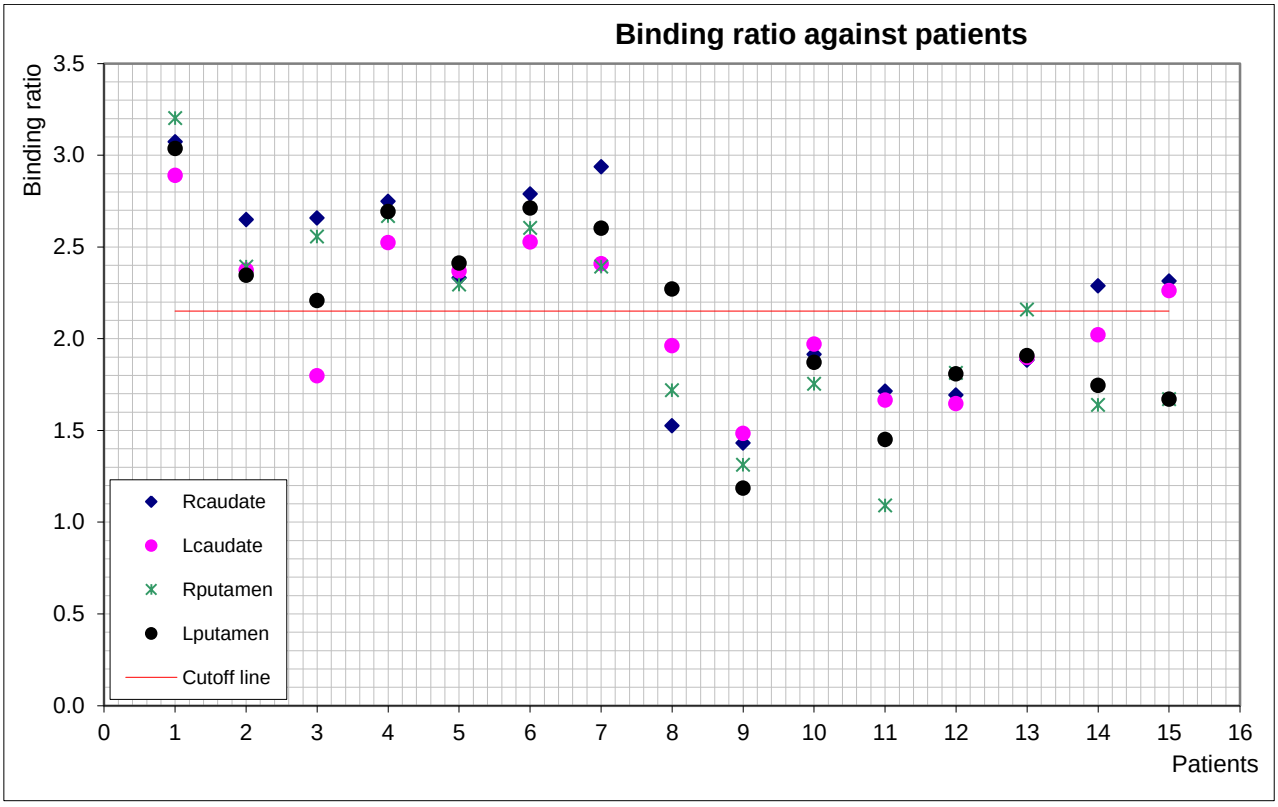

Figure 5: Technique # 5: Analysis with HNBRASS applying FBP

Table 5 gives a detailed numerical outcome of brain scan with technique number 5, which involves the application of HNBRASS applying FBP. Similarly, the anatomical regions of interest, all in the corpus striatum, were caudate and putamen in both hemispheres of the brain. Simulation and optimization of visual brain scans for each patient gave numerical values of the radio isotope binding in the caudate, putamen and background regions and as well as the binding ratios. Patients with ET have binding ratios above the cut-off point (2.15) while those with PD have binding ratios below the cut-off point (2.15).

Table 5 Technique # 5: Analysis with HNBRASS applying FBP

Patients	Posterior	Right (RC) Caudate	Left (LC) Caudate	Right (RP) Putamen	Left (LP) Putamen	Binding ratio				
						RC	LC	RP	LP	Cut off
1	10.9	33.5	31.5	34.9	33.1	3.07	3.20	3.20	3.04	
2	14.5	38.4	34.4	34.7	34	2.65	2.39	2.39	2.34	
3	23.7	63	42.6	60.6	52.3	2.66	2.56	2.56	2.21	
4	31.3	86	79	83.5	84.3	2.75	2.67	2.67	2.69	
5	13.6	31.7	32.2	31.2	32.8	2.33	2.29	2.29	2.41	
6	14.6	40.7	36.9	38	39.6	2.79	2.60	2.60	2.71	
7	19.1	56.1	46	45.7	49.7	2.94	2.39	2.39	2.60	
8	18.5	28.2	36.3	31.8	42	1.52	1.72	1.72	2.27	2.15
9	30.4	43.5	45.1	39.9	36	1.43	1.31	1.31	1.18	
10	26.9	51.5	53	47.2	50.3	1.91	1.75	1.75	1.87	
11	12.2	20.9	20.3	13.3	17.7	1.71	1.09	1.09	1.45	
12	17.2	29.1	28.3	31.2	31.1	1.69	1.81	1.81	1.81	
13	19.5	36.7	37	42.1	37.2	1.88	2.16	2.16	1.91	
14	28.2	64.5	57	46.2	49.2	2.29	1.64	1.64	1.74	
15	11.5	26.6	26	19.2	19.2	2.31	1.67	1.67	1.67	

Intra-operator and Inter-operator data variability with Hermes

Further investigation was made into how data variability, by the same operator and among different operators, affected the diagnosis. The combination of Iterative Reconstruction and Global Attenuation Correction methods (IR and GIAC) with the Hermes New Brain Registration and Analysis Software Students (HNBRASS); technique # 4 was employed. Results were obtained, as presented in Table 6 for intra-operator data variability where results of the binding ratios for the same operator in two runs were the same.

Table 6: Intra-operator data variability with (HNBRASS applied to IR and GIAC)

Patients	1st Run Binding ratio operator A				2nd Run Binding ratio: Operator A			
	Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen
1	4.03	3.73	4.05	3.65	4.03	3.73	4.05	3.65
2	3.48	2.97	3.14	3.11	3.45	2.94	3.11	3.08
3	4.40	4.20	4.28	3.95	4.23	4.03	4.15	4.01
4	3.81	3.63	3.49	3.71	3.81	3.63	3.49	3.71
5	3.57	3.35	3.22	3.64	3.57	3.35	3.22	3.64
6	3.50	3.66	3.94	3.95	3.50	3.66	3.94	3.95
7	4.17	3.43	3.65	3.66	4.17	3.43	3.65	3.66
8	3.18	2.97	2.90	3.03	3.18	2.97	2.90	3.03
9	1.94	1.89	1.47	1.67	1.94	1.89	1.47	1.67
10	2.54	2.35	1.90	2.15	2.54	2.35	1.90	2.15
11	2.48	2.17	1.61	2.07	2.48	2.26	1.61	2.07
12	2.32	2.21	2.16	1.92	2.55	2.40	2.09	1.86
13	2.52	2.36	1.81	1.63	2.52	2.36	1.81	1.63
14	2.93	2.80	1.99	1.78	2.93	2.80	1.99	1.77
15	2.98	2.65	2.53	2.32	2.98	2.65	2.53	2.32

In the case of inter-operator data variability, Table 7 and Figure 6 showed that HNBRASS applied to IR and GIAC (technique # 4) gave reproducible results since the values of binding ratios for both operators were the same. Previous diagnostic works with HOBRASS had shown that Each Image Attenuation Correction technique was operator dependent although with promising results most of the time especially from qualified and experienced operators.

Table 7: Inter-operator data variability with (HNBRASS applied to IR and GIAC)

Patients	Binding ratio operator A				Binding ratio operator B			
	Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen
1	4.03	3.73	4.05	3.65	4.03	3.73	4.05	3.65
2	3.48	2.97	3.14	3.11	3.45	2.94	3.11	3.08
3	4.40	4.20	4.28	3.95	4.23	4.03	4.15	4.01
4	3.81	3.63	3.49	3.71	3.81	3.63	3.49	3.71
5	3.57	3.35	3.22	3.64	3.57	3.35	3.22	3.64
6	3.50	3.66	3.94	3.95	3.50	3.66	3.94	3.95
7	4.17	3.43	3.65	3.66	4.17	3.43	3.65	3.66
8	3.18	2.97	2.90	3.03	3.18	2.97	2.90	3.03
9	1.94	1.89	1.47	1.67	1.94	1.89	1.47	1.67
10	2.54	2.35	1.90	2.15	2.54	2.35	1.90	2.15
11	2.48	2.17	1.61	2.07	2.48	2.26	1.61	2.07
12	2.32	2.21	2.16	1.92	2.55	2.40	2.09	1.86
13	2.52	2.36	1.81	1.63	2.52	2.36	1.81	1.63
14	2.93	2.80	1.99	1.78	2.93	2.80	1.99	1.77
15	2.98	2.65	2.53	2.32	2.98	2.65	2.53	2.32

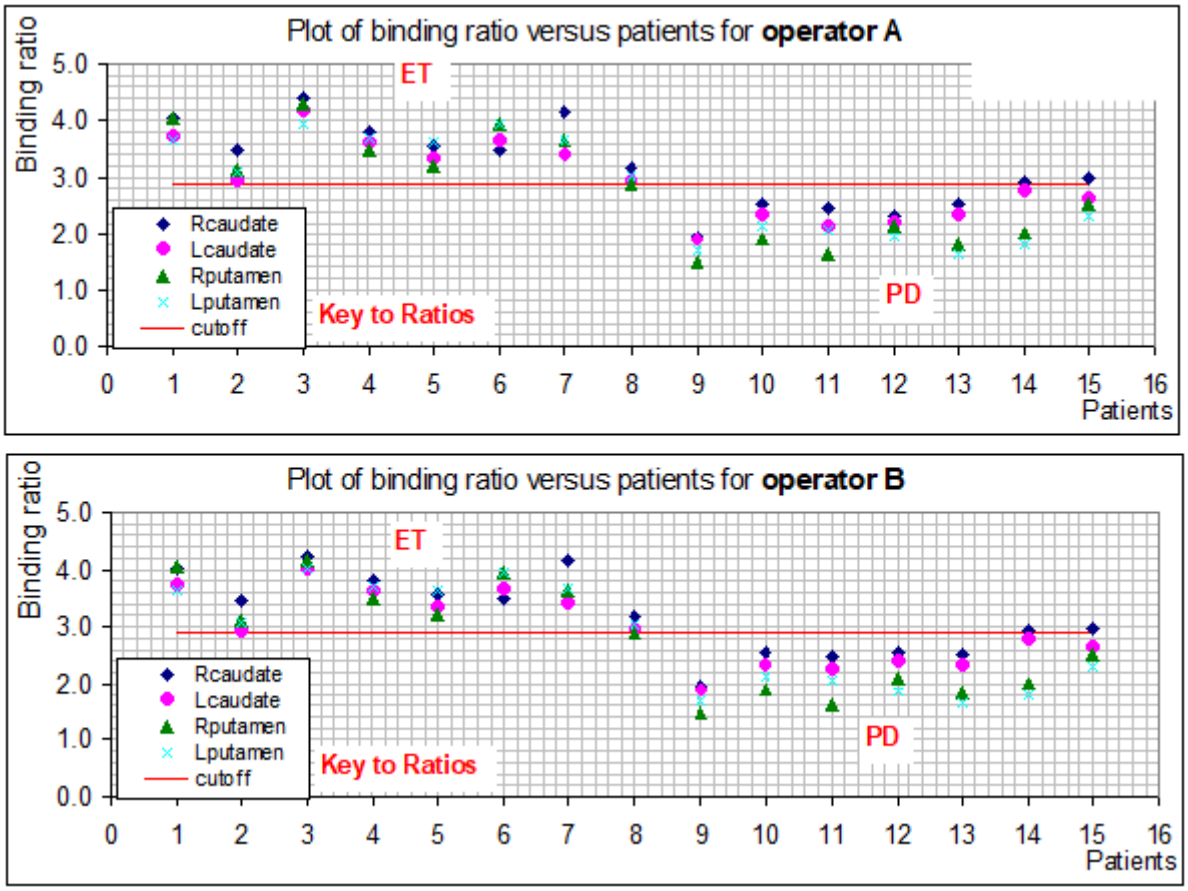

Figure 6: Inter-operator data variability with HNBRASS applied to IR and GIAC

Selection of a robust Hermes diagnostic technique

In the quest to select a robust Hermes brain analysis diagnostic technique (Table 8), it was revealed that diagnostic techniques; number 2, number 3 and number 4 misdiagnosed only one patient. However, most notable was the fact that the diagnostic technique number 3 had no instance of coincidence in the diagnosis of ET and PD as shown in the last column of Table 8.

Table 8: Selection of the robust diagnostic technique that efficiently differentiated PD patients from ET patients

Diagnostic Technique	Image Reconstruction Technique	Type of Attenuation Correction	Number of Misdiagnoses	ET and PD Diagnosis Same time
HOB (Technique #1)	**IR**	**EIAC**	**2**	**None**
HNB (Technique #2)	**IR**	**EIAC**	**1**	**Two**
HOB (Technique #3)	**IR**	**GIAC**	**1**	**None**
HNB (Technique #4)	**IR**	**GIAC**	**1**	**Two**
HNB (Technique #5)	**FBP**	**-**	**3**	**None**

Descriptively, the graphical and numerical outcomes obtained with Hermes BRASS showed that a population of ET disease patients and a population of PD disease patients are separable. However, in order to confirm for stronger conclusions, statistical inference approach was adopted using the T-test to confirm acceptance or rejection of the hypothesis (Table 9). The derived t-statistics was less than the t-statistics (0.19 < 2.18), hence the alternate hypothesis was accepted since the difference between the two populations was significant.

Table 9: T-test analysis of PD and ET patients with Hermes using the binding ratio of the radioisotope

A group of ET patients is separable from a group of PD patients			
Probability level	**Degree of freedom**	**Derived t-statistics**	**t-statistics**
Two tailed test 0.05 (5%)	13	0.19	2.18
Derived t- statistics is less than t- statistics			
0.19<2.18			
Hence the hypothesis was accepted			

Discussions

It was observed that all reconstructed images with the Hermes BRASS showed the salivary glands confirming a considerable uptake of DATScan in the glands. The blockage of these glands from considerable uptake is imperative, not only to prevent the advent of an induced cancer to patients in the region in the light of radiation stochastic effects but also is it important to avoid

misdiagnosis among ET and PD patients. It must be emphasize here that the regions of interests in the striatum (caudate and putamen) should always remain as the sole regions with the highest uptake as a well identified hot spot. This in effect favours the brain data computer analysis algorithm of the striatum for optimum results.

It is imperative that the automated attenuation correction algorithm (GIAC) for Hermes brain scans analysis is clinically adopted in order to obtain objective results on patients' analysis. In this case the influence of operators on the outcome of brain scan analysis becomes a thing of the past. It also provides a workable platform from which both experienced and non-experienced operators con perform brain scan analysis with the complete avenue for reproducible results.

The advent of semi quantitative DATscan analysis has opened a whole new charter in the differentiation of PD and ET patients with efficency. Hence, quantitative measurements based on ratio analysis of the concentration of radioactivity in the striatum to that in a non-specific brain region is feasible in visual quantification of radioactivity.

Hermes New BRASS, unlike the Old BRASS was able to identify the caudate and putamen as separate regions which in effect gave more specificity in the description of which parts of the region of a patent were affected. In fact the New BRASS gave best results with the SPECT transverse image data which were reconstructed and analysed by employing the combination of Iterative reconstruction, Global image attenuation correction and Butterworth filter; the operational technique is completely operator independent.

Although the Hermes New BRASS gave marvellous results on the SPECT transverse image data which were reconstructed and analysed with the combination of Iterative reconstruction, Each Image attenuation correction and Butterworth filter, the disadvantage was discovered in its operation dependence. Finally the appropriate statistics, T-test, was employed and remarkable results were obtained confirming that the two groups of patient populations were separable.

Hermes Old BRASS was the first semi quantitative diagnostic brain analysis software that saw application in the differentiation of patients with ET from patients with PD. Unfortunately, the number of misdiagnosis was unacceptable especially with FBP, which led to the implementation of the Hermes New BRASS. This measure broad about an improvement in the quality of diagnosis taking into consideration the drop in the number of misdiagnosis.

The application of Filter Back Projection to Hermes New BRASS (Technique number 5) recorded the highest incidence of misdiagnosis with patients' numbers 3, 8, 13, 14 and 15 being misdiagnosed. This is because the image reconstruction technique; Filter Back Projection omits a tiny percentage of patient image details which is considered the finest touch during image reconstruction.

The calculated cutoff lines obtained for each diagnostic technique (Tables 1 to 5) varied although the diagnosis was performed on the same set of patients. The phenomenon was due to machine deterioration with age which turns to vary reference diagnostic values of imaging modalities even if the machines were built by the same manufacturer. According to Tondeur et al, (2003) the general problem with semi quantitative approach for 123I-FPCIT SPECT imaging is the absence of standard reference values which are yet to be identified for intra scanner differences based on age.

Conclusion

Parkinson Disease is a major concern among members of the global medical communities (Williams 2010; Hughes, 1992). Hence the decision that strived for a robust semi quantitative tracer binding technique to, efficiently, differentiate patients with PD from patients with ET in dopamine transporter scan of the brain. Five brain analysis diagnostic techniques were tested where diagnostic techniques; number 2, number 3 and number 4 misdiagnosed one patient. Notable was the fact that diagnostic technique number 3 had no instance of coincidence diagnosis of ET and PD. Reproducibility using one operator and among operators is a determining factor as to whether or not a diagnostic technique is fit and optimum for clinical diagnoses. Further investigations were therefore made into how intra-operator and inter operator data variability affected the diagnosis. HNBRASS applied to IR and GIAC (Technique # 4) was employed where the obtained results showed that for intra-operator data variability the values of binding ratios for the same operator in two runs were the same. In the case of inter-operator data variability, HNBRASS applied to IR and GIAC (Technique # 4) also gave reproducible results since the values of binding ratios for both operators were the same. Previous diagnostic works with HOBRASS technique had shown that Each Image Attenuation Correction was operator dependent which required only qualified and experienced operators for the diagnosis.

Ethics approval and consent to participate

The dissertation, in fulfilment for Master of Science degree in Medical Physics, was conducted as part of an ongoing Dopamine Transporter Scan research project collaborated between the University of Surrey, UK and the Royal Surrey County Radiation Oncology, UK. Ethical clearance was therefore waived for the retrospective data collection from the PACS of the Radiation Oncology.

List of abbreviations

Parkinson disease (PD)
Essential Tremor (ET)
Brain Registration and Analysis Software Suite (BRASS)
Single Photon Emission Computer Tomography (SPECT)
Hermes Old (HO)
Iterative Reconstruction and Each Image Attenuation Correction (IR & EIAC)
Hermes New (HN)
Iterative Reconstruction and Global Image Attenuation Correction (IR & GIAC)
Filter Back Projection (FBP)
^{99}Tc-ioflupane (N-*w*-fluoropropyl-*B*-CIT) or ^{99}Tc-FP-CIT
Pictures and Archives Communication System (PACS)
Interests (ROIs)
Picture Achieving and Communication System (PACS)

Data Availability

The mixed qualitative and quantitative data used to formulate the conclusions of this study are all included in the manuscript.

Conflicts of Interest

We the authors of the research have no form of conflict of interest to declare.

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