

symptoms in their left or right side, and the authors attempt to find associations between the SAI and these symptoms.

It is conventional in the art to compare the patient image with age-matched controls, since it is known that the striatal uptake of a dopamine transporter radiopharmaceutical declines with age. Such comparison requires the use of normal image databases. Such databases are, however, only really meaningful for a coherent set of data, which may well mean the same camera, same software, same imaging protocol etc.

There is therefore still a need for dopamine transporter imaging methodology which is robust enough to give comparable results across a range of camera types, and avoids the large spread of data seen in multi-site studies, which is statistically sound, and is suitable for any age of patient.

The Present Invention Disclosure.

In dopamine transporter radiopharmaceutical imaging, when uptake of the radiopharmaceutical in the brain is quantified, the values obtained vary significantly depending on the camera configuration and set-up, image acquisition parameters, and many other factors. It has therefore so far proved impossible to establish a meaningful normal database that is built on data from more than one camera type, without considerable effort to apply 'correction factors'.

In the current GE Healthcare product 'DaTQUANTTM', normal data from non-GE cameras is removed from the data set before calculating. In the Hermes BRASS product, correction factors are applied but this significantly compromises the utility and applicability of the 'normal' average values reported.

In an aspect, there is provided a method of imaging useful in the diagnosis of neurological disease, which comprises:

- (i) provision of a subject previously administered with a radiopharmaceutical suitable for imaging dopamine function;
- (ii) assessing the uptake of said radiopharmaceutical in an equivalent region of:
 - (A) the left; and

(B) the right;

of the striatum of the brain of said subject;

(iii) calculating the ratio of the uptake in the equivalent left and right striatum region from step (ii);

(iv) comparing the ratio for said subject from step (iii) with a normal range of such ratios for normal subjects.

In another aspect, there is provided a method of diagnosis which comprises the method of imaging as defined above, where the comparing of step (iv) is with a database of such ratios, wherein said database contains such ratios for normal subjects; and which further comprises:

(v) when the ratio from step (iv) is within the normal range, said subject is classified as having a normal presentation;

(vi) when the ratio from step (iv) is outside the normal range, the patient is classified as suffering from a neurological disease.

In a further aspect, there is provided a method of selecting or excluding a subject for a particular therapy of a neurological disease, which comprises the method of imaging as defined above, or the method of diagnosis as defined above.

In another aspect, there is provided a method of monitoring the efficacy of a course of therapy of a neurological disease of a subject, which comprises the method of imaging as defined above, or the method of diagnosis as defined above.

In another aspect, there is provided a software tool suitable for carrying out:

(a) steps (ii) and (iii) of the method of imaging as defined above; or

(b) steps (ii) to (v) of the method of diagnosis as defined above; or

(c) the method of selection as defined above; or

(d) the method of monitoring as defined above; or

(e) combinations of one or more of (a) to (d).

In another aspect, there is provided the use of the radiopharmaceutical suitable for imaging dopamine function as defined above in one or more of:

(i) the method of imaging as defined above;

- (ii) the method of diagnosis as defined above;
- (iii) the method of selection as defined above; or
- (iv) the method of monitoring as defined above.

5 In another aspect, there is provided the use of the software tool as defined above in one or more of:

- (i) the method of imaging as defined above;
- (ii) the method of diagnosis as defined above;
- (iii) the method of selection as defined above;
- (iv) the method of monitoring as defined above.

10

In another aspect, there is provided the use of a tomographic imaging device in one or more of:

- (i) the method of imaging as defined above;
- (ii) the method of diagnosis as defined above;
- (iii) the method of selection as defined above; or
- (iv) the method of monitoring as defined above.

15

20 The present invention-disclosure is based on the observation that left : right symmetry of striatum uptake in the normal patient population is maintained independent of the age and gender of the patient. This symmetrical left/right striatum uptake is shown to be independent of camera type and image acquisition parameters, and is proposed as a more robust way to generate both a normal database and patient comparator data –

wherein imaging data can be compared without the need for complex correction factors.

Visual assessment of dopamine transporter radiopharmaceutical images is generally used to determine whether brain uptake patterns are normal or abnormal. Quantification of DaTSCANTM uptake in the striatum (putamen and caudate separately and in sum) and comparison with average values obtained from a normal population has been proposed as a more sensitive and more reproducible method of detecting abnormal (reduced) uptake suggestive of Parkinson's disease (PD) and Parkinsonian Syndromes.

A problem with this method is that average striatum binding ratio (SBR) and related values vary significantly between camera types, and even between the same camera type at different clinical sites – even when the same radiopharmaceutical is used. The reason for such a wide variation is not yet fully understood, but factors such as collimator type and image reconstruction methodology have been suggested. The consequence is that the 'average' value of SBR cannot easily be transferred from one site to another as a comparator for the subject. A normal database that is constructed with data from more than one site shows a very wide spread of values for average SBR and associated regions of interest, such as entire striatum, putamen or caudate.

Furthermore the standard deviation of 'normal' SBR even from a single site and camera is large – due to the natural variation within the normal human population. If the data set includes data from multiple cameras/sites, then the statistical variation becomes wider still. The effect is that a subject with e.g. early PD and a relatively low level of reduced striatal uptake may lie within the apparently 'normal' population of such a data set (i.e. within 1 to 2 standard deviations of the mean value), when a more statistically robust, coherent normal data set would have flagged the deviation from normal uptake.

30

The present ~~invention~~-disclosure is based on an analysis of left-right symmetry of striatal uptake. Surprisingly, the left-right symmetry of such uptake has been found to be maintained in healthy subjects irrespective of subject age and gender. Thus, for a normal population, the ratio left striatum: right striatum (absolute or SBR) is close to 1.0 with

35

low standard deviation. This has been found to hold true even when patient image data from different clinical sites and/or different camera systems are used.

Furthermore, it is not necessary to apply any correction factors for different cameras employed in multi-centre datasets, as the symmetry is 'self-calibrating' for each image.

In neurological disorders where there is loss of dopaminergic function, one side is usually more affected than the other and the left:right ratio drifts away from 1.0.

Comparison of the left:right ratio with that of the normal population therefore gives a way to assess whether a subject has abnormal uptake compared to a normal population that is independent of camera set up and site. This is expected to be especially valuable in earlier stages of such disease, when a deviation in the left:ratio for the patient compared to the normal population may be detected while the SBR and similar ratios remain within the normal range (due to the much larger standard deviation of SBR as described above). This is expected to improve accuracy and sensitivity and also to facilitate earlier diagnosis of disease. It will also permit earlier differentiation of PD/PS and Lewy Body Dementia diseases from other disorders with similar clinical symptoms e.g. ET, AD, vascular and drug-induced PS.

A further advantage is that when comparing left:right uptake values, absolute values can be used rather than comparing target:background ratios. That eliminates the need for more complex calculations, and reduces statistical variation due to subtraction of two numbers, each having an associated error bar. This is particularly important with respect to the counts in the background/reference region. Those counts will be intrinsically low – hence the error bar or “noise” is relatively large. Furthermore, the conventional SBR calculates two ratios, so the error bar is compounded by the calculation. Subtraction of such a figure therefore introduces a statistical variation. Differences introduced through variations in background in left and right hemispheres are thereby avoided, and an even narrower distribution of the normal data can be expected.

Furthermore, the method of the present ~~invention~~ disclosure does not require analysis to carry out comparison with age-matched and gender-matched patients/controls.

That is because the striatum L/R ratio is close to 1.0 in normal subjects regardless of age and

(iv) the method of monitoring of claim 13.

19. The use of a tomographic imaging device in one or more of:

(i) the method of imaging of any one of claims 1 to 10;

5 (ii) the method of diagnosis of claim 11;

(iii) the method of selection of claim 12; or

(iv) the method of monitoring of claim 13.

10 | ~~20. A database as defined in claim 11.~~