CLAIMS

1. An *in vivo* method of determining the progression of Parkinson's disease over time in a subject, said method comprising:

(i) obtaining a first Neuromelanin-Magnetic Resonance Imaging (NM-MRI) scan at a first time point;

(ii) after step (i), obtaining a second NM-MRI scan at a second time point;

(iii) comparing the first neuromelanin magnetic resonance image to said second neuromelanin magnetic resonance image thereby determining whether a change in the level, signal and/or concentration of neuromelanin occurred between said first time point and said second time point.

2. The method according to claim 1, wherein if the change in the level, signal and/or concentration of neuromelanin at the second time point is more than about 1%, more than about 2%, more than about 3%, more than about 4%, more than about 5%, more than about 6%, more than about 7%, more than about 8%, more than about 9%, more than about 10%, more than about 11%, more than about 12%, more than about 13%, more than about 14%, more than about 15%, more than about 20%, or more than about 25% less than the level, signal and/or concentration of neuromelanin at the first time point, Parkinson's disease is progressing.

3. An *in vivo* method of diagnosing Parkinson's disease, said method comprising:

(i) obtaining a first neuromelanin magnetic resonance image at a first time point;

(ii) after step (i), obtaining a second neuromelanin magnetic resonance image at a second time point;

(iii) comparing the first neuromelanin magnetic resonance image to said second neuromelanin magnetic resonance image thereby determining whether a change in the level, signal and/or concentration of neuromelanin occurred between said first time point and said second time point.

4. The method according to any preceding claim, wherein if the change in the level, signal and/or concentration of neuromelanin at the second time point is more than about 1%, more than about 2%, more than about 3%, more than about 4%, more than about 5%, more than about 6%, more than about 7%, more than about 8%, more than about 9%, more than about 10%, more than about 11%, more than about 12%, more than about 13%, more than about 14%, more than about 15%, more than about 20%, or more than about 25% less than the

level, signal and/or concentration of neuromelanin at the first time point,, a diagnosis of Parkinson's disease is provided.

5. A method of diagnosing a patient with Parkinson's disease, said method comprising:

(i) measuring a level of neuromelanin

(ii) comparing the level of neuromelanin to a standard control,

(iii) optionally providing a diagnosis of Parkinson's disease if the measured level of neuromelanin is lower relative to the standard control.

6. The method according to any preceding claim, further comprising determining a first signal intensity from said first neuromelanin magnetic resonance image and determining a second signal intensity from said second neuromelanin magnetic resonance image, wherein said comparing the first magnetic resonance image to said second magnetic resonance image comprises comparing the first signal intensity to the second signal intensity.

7. The method of any of the preceding claims, wherein a standard control is a level of neuromelanin present at approximately the same levels in a population of subjects, or said standard control is approximately the average level of neuromelanin present in a population of subjects.

8. The method according to any preceding claim, wherein a neuromelanin gradient phantom is used to measure the level, signal and/or concentration of neuromelanin.

9. The method according to any preceding claim, wherein a neuromelanin phantom concentration gradient is scanned about once per patient, about once an hour, about once a day, about once a week, or about once a month.

10. The method of any of the preceding claims, wherein a neuromelanin phantom gradient is scanned daily.

11. The method according to any preceding claim, wherein a neuromelanin phantom gradient is scanned with each patient.

12. The method according to claims 5-11, wherein if the change in the level, signal and/or concentration of neuromelanin at the second time point is more than about 5% less or more than about 10% less than the level, signal and/or concentration of neuromelanin at the first time point, wherein the first time point and the second time point are about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years apart, a diagnosis of Parkinson's disease is provided.

13. The method according to any preceding claim, wherein if the change in the level, signal and/or concentration of neuromelanin at the second time point is more than about 35% less, more than about 40% less, more than about 45% less, or more than about 50% less signal and/or concentration of neuromelanin at the first time point, wherein the first time point and the second time point are about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years apart, a diagnosis of Parkinson's disease is provided.

14. The method according to any preceding claim, wherein the second time point is about 3 months, about 6 months, about 9 months, about 12 months, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, about 10 years, about 15 years, about 20 years, about 25 years, or about 30 years after the first time point.

15. A method of assessing the neuromelanin concentration in a region of interest of the brain of a subject comprising:

performing a Neuromelanin-Magnetic Resonance Imaging (NM-MRI) scan on the subject;

acquiring a neuromelanin dataset from the NM-MRI scan;

optionally encrypting the neuromelanin dataset;

uploading the neuromelanin dataset to a remote server;

optionally decrypting the dataset;

performing an analysis of the neuromelanin dataset, wherein the analysis comprises one or more of:

(i) comparing the neuromelanin dataset with one or more previously acquired neuromelanin datasets from the said subject;

(ii) comparing the neuromelanin dataset with a control dataset;

(iii) comparing the neuromelanin dataset with one or more previously acquired neuromelanin datasets from different subjects;

generating a report comprising the neuromelanin analysis;

optionally encrypting the report;

uploading the report to remote server; and

optionally decrypting the report.

16. A method of determining if a subject has or is at risk of developing Parkinson's disease, the method comprising analyzing one or more Neuromelanin-Magnetic Resonance Imaging (NM-MRI) scans of the subject's brain region of interest, wherein the analyzing comprises:

receiving imaging information of the brain region of interest; and

determining a NM concentration in the brain region of interest using voxelwise analysis based on the imaging information;

wherein the determining if a subject has or is at risk of developing Parkinson's disease comprises:

(1) if the one or more NM-MRI scans has a decreased NM signal compared to a one or more control scans without Parkinson's disease then the subject has or is at risk of developing Parkinson's disease; or

(2) if the one or more NM-MRI scans has a NM signal comparable to the signal of a one or more control scans without Parkinson's disease then the subject does not have or is not at risk of developing Parkinson's disease.

17. Use of one or more of levodopa and carbidopa in the manufacture of a medicament for ~~A~~a method of treating a subject with Parkinson's disease, the one or more of levodopa is to be administered after ~~the method comprising~~ analyzing Neuromelanin-Magnetic Resonance Imaging (NM-MRI) scans of the subject's brain region of interest, wherein the analyzing comprises:

(i) receiving imaging information of the brain region of interest at a first time point;

(ii) receiving imaging information of the brain region of interest at a second time point;

(iii) determining a NM concentration at the first and second time points in the brain region of interest using voxelwise analysis based on the imaging information; and

(iv) comparing the NM concentration at the first time point to the second time point,

~~wherein the treatment method further comprises:~~ wherein the one or more of levodopa and carbidopa is to be administered

~~(1)~~ if ~~the~~ NM-MRI scan at the second time point has a decreased NM signal compared to the NM signal at the first time point, ~~the method comprises administering one or more of levodopa and carbidopa~~; or the administration of the one or more of levodopa and carbidopa is to be withhold and the steps (i) through (iv) are to be repeated

~~(2)~~ if the NM-MRI scan at the second time point has an increased NM signal compared to the NM signal at the first time point.~~, the method comprises:~~

~~(a) withholding adinistering one or more of levodopa and carbidopa; and~~

~~(b) repeating steps (i) through (iv).~~

18. The method and the use according to any preceding claim, wherein the MRI scan is neuromelanin sensitive.

19. A method of providing a treatment regimen to a patient comprising performing the NM-MRI scan, acquiring NM signal from the NM-MRI scan in a region of interest, comparing the NM signal from the NM-MRI scan in a region of interest data to age matched database numbers, if the NM signal is less than a pre-determined value, administering a corresponding treatment regimen.

~~21~~20. The method and the use according to any preceding claim, wherein the patient displays symptoms of Alzheimer's disease.

~~22~~21. The method and the use according to any preceding claim, wherein the NM-MRI scan distinguishes between Alzheimer's disease and Parkinson's disease.

~~23~~22. The method and the use according to any preceding claim, wherein the subject or patient exhibits one or more symptom of Parkinson's disease.

~~24~~23. The method and the use according to any preceding claim, wherein a patient is diagnosed with Parkinson's disease without displaying symptoms.

~~25. The method according to any preceding claim, wherein the NM-MRI distinguishes between Alzheimer's disease and Parkinson's disease.~~

~~25~~24. The method according to any preceding claim, further comprising diagnosing the patient as having Parkinson's disease or as not having Parkinson's disease; and indicating the diagnosis to a user via a user interface.

~~26~~25. The method and the use according to any preceding claim, wherein the analysis is a voxelwise analysis.

~~27~~26. The method and the use according to any preceding claim, wherein the voxelwise analysis comprises determining at least one topographical pattern within the brain region of interest.

~~28~~27. The method according to any preceding claim, wherein the method further comprises a calculation using a value that represents a volume of a neuromelanin voxel.

~~29~~28. The method and the use according to any preceding claim, wherein the voxelwise analysis region of interest is the substantia nigra.

~~30~~29. The method and the use according to any preceding claim, wherein the voxelwise analysis region of interest the ventral substantia nigra subregion.

~~31~~30. A diagnostic system for providing diagnostic information for Parkinson's disease, the diagnostic system comprising:

an MRI system configured to generate and acquire a neuromelanin sensitive MRI scan along with a neuromelanin data series for a voxel located within a region of interest in a subject's brain;

a signal processor configured to process the series of neuromelanin data to produce a processed neuromelanin MRI spectrum; and

a diagnostic processor configured to process the processed neuromelanin MRI spectrum to:

extract a measurement from the region of interest corresponding with neuromelanin at a time point,

compare the measurement to one or more control measurements acquired prior to the time point;

provide a diagnosis of Parkinson's disease if the measurement is more than about 25% less than the control measurement.

~~32~~31. Use of L-dopa in the manufacture of a medicament ~~A method~~ for treating a patient with Parkinson's disease, wherein an initial amount of L-dopa is to be administered to a patient before ~~comprising:~~

~~a) administering to a patient an initial amount of L-dopa;~~

~~b)~~ performing serial NM-MRI scans of the patient monitoring the neuromelanin concentration in a region of interest in the patient's brain and assessing treatment-related adverse events over an initial treatment period;

~~c)~~ if, during the initial treatment period, the patient exhibits

i) decreased neuromelanin concentration in the region of interest in the patient's brain;

ii) no L-dopa associated adverse or side effects;

then ~~increasing the dose~~ an increased dose of L-dopa is to be administered to the patient in a subsequent treatment period;

wherein the L-dopa treatment results in an improvement in Parkinson's disease symptoms in the patient.

~~33~~32. The ~~method~~use of claim ~~32~~31, ~~including the following step:~~wherein the administration of the initial amount of L-dopa followed by the increased dose of L-dopa in the subsequent treatment period is repeated

~~d) repeating steps a) c)~~ until the patient fails to exhibit one or more of ~~i) ii) in step c).~~ the following symptoms:-

(i) decreased neuromelanin concentration in the region of interest in the patient's brain;

(ii) no L-dopa associated adverse or side effects;

~~34~~33. The method according to any preceding claim, wherein the method is used with a second imaging method, wherein the second imaging method is selected from the group consisting of positron emission tomography (PET), structural MRI, comprises functional MRI (fMRI), blood oxygen level dependent (BOLD) fMRI, iron sensitive MRI, quantitative susceptibility mapping (QSM), diffusion tensor imaging DTI, and single photon emission computed tomography (SPECT), DaTscan and DaTquant.

~~35~~34. The method according to any preceding claim, wherein the second imaging method comprises Positron Emission Tomography (PET).

~~36~~35. The method according to any preceding claim, wherein the second imaging method comprises structural MRI.

~~37~~36. The method according to any preceding claim, wherein the second imaging method comprises functional MRI (fMRI).

~~38~~37. The method according to any preceding claim, wherein the second imaging method comprises blood oxygen level dependent (BOLD) fMRI.

~~39~~38. The method and the use according to any preceding claim, wherein the voxelwise analysis comprises determining at least one topographical pattern within the brain region of interest, wherein the brain region of interest is one or more Parkinson's disease symptom-associated voxels.

~~40~~39. The method and the use according to any preceding claim, wherein the voxelwise analysis comprises determining at least one topographical pattern within the brain region of interest, wherein the brain region of interest is one or more patient specific Parkinson's disease symptom-associated voxels.

~~41~~40. The method and the use to according to any preceding claim, wherein the brain region of interest is the substantia nigra or the locus coeruleus.

~~42~~41. The method and the use according to any preceding claim ~~claims 1-41~~, wherein the brain region of interest is the ventral substantia nigra.

~~43~~42. The method and the use according to ~~claims 1-41~~ any preceding claim, wherein the brain region of interest is the lateral substantia nigra.

~~44~~43. The method and the use according to ~~claims 1-41~~ any preceding claim, wherein the brain region of interest is the ventrolateral substantia nigra.

~~45~~44. The method and the use according to ~~claims 1-41~~any preceding claim, wherein the brain region of interest is the substantia nigra pars compacta (SNpc).

~~46~~45. The method and the use according to ~~claims 1-41~~ any preceding claim, wherein the brain region of interest is the substantia nigra pars reticulata (SNpr).

~~47~~46. The method and the use according to ~~claims 1-41~~ any preceding claim, wherein the brain region of interest is the ventral tegmental area (VTA).

~~48~~47. The method and the use according to ~~claims 1-41~~any preceding claim, wherein the brain region of interest is the locus coeruleus.