

NINDS PD CDEs – Imaging Recommendations

Imaging Guidance for CDE Use

Introduction

Imaging data is widely used in Parkinson's disease (PD) clinical research studies both to understand normal brain function and to detect and monitor brain disease in living patients. Imaging is a non-invasive technique that is widely available, very safe, and well tolerated. Molecular imaging tools can be used to inform disease diagnosis and to longitudinally monitor disease progression and the effects of a PD therapy on progression. Importantly, it is also possible to use imaging to identify individuals at risk for PD, because imaging changes can be detected in the brain several years in advance of clinical symptoms. This provides an opportunity to examine a population who might benefit from future PD therapies that could prevent the onset of PD. Currently imaging targeting the dopamine system is widely used in clinical practice and research. The availability of molecular and MR imaging tools continues to rapidly grow, enabling a more comprehensive imaging strategy that could inform PD at all stages of disease and target disease subsets defined by disease pathology, molecular biomarkers, and clinical symptoms.

During the past decade, advances in the science and technology underlying neuroimaging studies and in the clinical study design and data analytics enabling implementation of these studies has created an enormous opportunity to deploy brain imaging in PD therapeutic studies.

There have been four areas of growth and development supporting neuroimaging:

- Molecular neurobiology - has uncovered key molecular targets for PD imaging probes. Highly specific and selective PET and SPECT imaging probes focused on specific brain proteins known to cause neurodegeneration (amyloid, tau), neuroinflammation, synaptic function, and several other neuroreceptors are in development and may be utilized in clinical studies. While developing an imaging tracer for synuclein remains a key goal, imaging tracers across a spectrum of targets may provide biomarkers at all stages of disease may target PD genetic, biomarker or clinical subsets that might benefit from precision therapies.
- Imaging technology - advances in PET and MRI camera technology have dramatically improved the sensitivity to detect imaging signals. Several MRI sequences including resting state, iron-sensitive and neuro-melanin sequences may enable early detection and monitoring of disease progression.
- Clinical study design - development of standardized processes to acquire and analyze imaging data at clinical sites worldwide has enabled imaging to be used widely in clinical

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therapeutic and observational studies. Quality control measures such as motion correction should be a standard for all imaging studies.

- **Data analytics** – advanced analytic techniques using machine learning have been successfully implemented to assess complex imaging outcomes. Novel imaging analysis tools have optimized imaging signals to further improve the reliability and sensitivity of imaging outcomes.

We have focused the imaging CDEs on those imaging tools with sufficient data to support their use in clinical studies. We recognize that imaging technology and analysis is rapidly evolving, and that additional imaging tools and outcomes will require CDEs in the future. For example, other MRI sequences or optical imaging may be added in the future.

We have developed CDEs that would provide the data to enable investigators to assess the methods of acquisition of the imaging data for each imaging tool and modality. Our goal is to allow investigators to utilize these CDEs to customize their analyses based on their expertise and the study question and the study cohort. A more imaging tool specific approach suggesting analysis methods for some imaging modalities is also included as a guide for use of these technologies.

It is recommended that, if possible, raw imaging data using standardized image transfer formats be made available for independent analysis of imaging data.

DAT SPECT Imaging

Scan acquisition

- **Camera:** Double or triple headed SPECT
Specific scan parameters including collimation and acquisition mode may be camera dependent.
- **Time of Scan:** Typically, 30 minutes (timing tracer specific) timing p.i. (timing tracer specific)
- **Pre-treatment:** Subjects should be pre-treated with saturated iodine solution (10 drops in water) or perchlorate (1000 mg)
- **Tracer Delivery:** Injection of approx. 185 MBq (5.0 mCi) depending on tracer as bolus
- **Attenuation Correction:** Homogeneous attenuation correction (Change 0)
- **Reconstruction:** Either filtered back-projection or an iterative reconstruction algorithm using standardized approaches.

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- **Image Matrix Size:** Raw projection data acquired into a 128 x 128 matrix. One strategy is stepping each 3 degrees for a total of 120 (or 4 degrees for a total of 90) projections into two 20% symmetric photopeak windows centered on 159 KeV.

Analysis (example)

Following attenuation correction and reorientation of the axial slice along the canthomeatal line, striatal slices may be summed and then operationalized striatal and occipital regions of interest are placed, and count densities are extracted using a standard method. Brain regions can be analyzed as target region: reference region uptake ratios, the cerebellum or occipital cortex providing a reference for non-specific brain tissue binding, or as a total or specific volume of distribution (Vd). The specific volume of distribution is often termed a binding potential BP.

Dataset

- Primary outcome - Specific regional binding
- Target regions - Bilateral caudate, anterior/posterior putamen
- Reference region - Occipital region, Cerebellum
- Key demographic data
 - Age at imaging
 - Sex
 - Symmetry of motor symptoms

MIBG Myocardial Scintigraphy

Scan acquisition

SPECT camera characteristics should be described. Dual or triple head cameras can be used, though the latter is preferred. 100-200 MBq of ¹²³I-MIBG is injected intravenously and myocardial SPECT images should be obtained 4 hours after injection. Subjects with the following conditions should be excluded because these conditions can affect MIBG myocardial uptake: ischemic heart disease, chronic heart failure, and diabetes. Medications that can be safely stopped should be held for 12 hours prior to scanning. The following medications may affect MIBG uptake and consideration should be given to excluding subjects on these medications: antipsychotics, sympathomimetics, dopamine depleting drugs (e.g., tetrabenazine, reserpine), and antidepressants.

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Analysis

Regions of interest (ROI) are drawn around the heart and mediastinum, and tracer uptake is measured in each region. ROI characteristics may vary (size and location), but the characteristics and methods for drawing the ROIs should be described. The heart to mediastinum (H/M) ratio is calculated. H/M ratios can then be compared between subject groups (e.g., controls, PD, atypical parkinsonism, etc.) or correlated with clinical (or other) measures utilizing standard statistical methods. Myocardial MIBG washout rates can also be calculated as an additional measure.

Amyloid PET Imaging

Scan acquisition

- **Camera:** PET camera with data collected in 3D
- **Time of Scan:** Typically, 20 minutes (timing tracer specific) starting 50-90 minutes p.i.
- **Tracer Delivery:** Injection of approx. 180-300 MBq depending on tracer as bolus MR - T1-weighted, 3D sequence (e.g., MPRAGE or SPGR)
- **Attenuation Correction:** Based on camera vendor and type
- **Reconstruction Algorithm:** Iterative (i.e., OSEM, >4 iterations, 16 subsets)
Transmission scan acquired or if PET –CT acquired with CT.
- **Image Matrix Size:** 128 x128
- **Zoom:** 2
- **Slice Thickness:** 5 mm (match slices to CT slices)
- **Post Reconstruction Filter:** i.e., Gaussian FWHM 5.0 mm
- **Subject Information:** Body weight

Analysis

PET 3D data-sets are generally co-registered to the MR for the same subject. First step is to align all the dynamic PiB images. Once all the PET data sets are adequately co-registered to the T1-MR, a transformation matrix from the MR normalization is applied to the PET files. As a result of this step, the PET data sets are normalized to something like MNI space and are in the same orientation as the MR for each subject. The co-registration of PET and MRI may require a non-affine warping approach if substantial atrophy is present. Similarly, atrophy correction methods can be used to correct for volume averaging that consider brain-nonbrain and may also incorporate white and gray matter differences.

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Images are regionally analyzed by applying volumes of interest (VOIs) to multiple brain regions, such as bilateral frontal, orbitofrontal, mesial temporal, lateral temporal, occipital, and parietal cortices, caudate, putamen, thalamus, anterior and posterior cingulate, and cerebellar gray. The pons, subcortical white (centrum semi-ovale) and cerebellar white may also be analyzed using ROIs. Images are regionally analyzed by applying volumes of interest (VOIs) to the brain regions listed above on MR images normalized to MNI space using a standardized template. Standard uptake values (SUVs) can be calculated for the areas of interest by using the established methods for normalizing to subject weight and injected dose. Alternatively, BP or V_T can be calculated on a regional basis.

Quantitative analysis may be performed on software systems such as PMOD system which allows co-registration of images and includes tools for applying standardized regional brain VOIs to the MRI, transfer of the adjusted VOIs to the PET study, and extraction of the g/ml brain tissue for calculation of standard uptake values (SUVs) on averaged PET frames.

In PET studies without MR – VOIs can be placed based on standard MR templates.

Dataset

- SUV for brain regions above
- Calculated SUVR for brain regions above

DTBZ PET Scanning

Scan acquisition

A current generation PET camera is recommended, and resolution should ideally be 6 mm or better after image reconstruction. Data is ideally collected in 3D mode to improve signal to noise. Subjects are best positioned with the image plane parallel to the orbito-meatal line. Head movement can be restrained using either a thermo-plastic moulded head rest or face mask. Tissue attenuation should be measured for later use in attenuation correction. Depending on the nature of the camera either a 5-10-minute transmission scan can be performed using an external ^{68}Ge / ^{137}Cs ring point rotating source or, if the camera is CT-PET, a transmission scan can be performed with the CT.

The active form of ^{11}C -DTBZ is the (+) enantiomer and this should ideally be used. The (-) enantiomer appears to show no specific binding to vesicular monoamine transporters (VMAT2) so use of a racemic mixture will result in 50% lower specific binding. Subjects should receive an

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intravenous injection of at least 5 mCi / 185 mBq and ideally 10 mCi /370 mBq or higher of ^{11}C -DTBZ as a bolus. The cold amount of (+) DTBZ injected should not exceed 5 mcg to avoid significant blockade of VMAT2 sites. Medications directly binding to VMAT2, such as tetrabenazine, should be stopped at least 24 hours before PET. The effect of other dopaminergic agents on VMAT2 availability is still unclear. Anti-parkinsonian agents should be withdrawn for at least 8 hours before PET and long acting dopamine agonists at least 24 hours before PET. Recently, AVID have developed (+) ^{18}F -FP-DTBZ (AV-133) as a commercial VMAT2 imaging biomarker. This agent provides a higher specific signal than ^{11}C -DTBZ. In trials 10mCi of ^{18}F -AV-133 have been administered as an intravenous bolus and imaging performed for 5-10 minutes starting 60 minutes post injection.

^{11}C -DTBZ uptake into brain regions can be analyzed as target region: reference region uptake ratios, the cerebellum or occipital cortex providing a reference for non-specific brain tissue binding, or as a total or specific volume of distribution (Vd). The specific volume of distribution is often termed a binding potential BP. If a plasma arterial input function is used, corrected for metabolite formation from the tracer, then the blood-brain transport rate constant K1 for ^{11}C -DTBZ can also be computed providing a measure of tracer delivery. For uptake ratios and VD measurements, it is recommended that at least 60 minutes of scan data are collected. Time frame protocols vary across units, epochs increasing from 1-10 minutes over 60 minutes. List mode acquisition allows the option for data to be binned post collection however the investigator wishes. If region: reference uptake ratios are required at least a 15-minute acquisition 45 - 60 minutes after tracer administration is recommended though this has not been formally validated. In trials of (+) ^{18}F -FP-DTBZ (AV-133) imaging has been performed for 5-10 minutes starting 60 minutes post injection and region: cerebellar uptake ratios computed.

Analysis of PET

Activity collected from 0 to 60 minutes after ^{11}C -DTBZ administration can be summed to produce an integral image allowing coalignment with patient MRIs and definition of regions of interest (ROIs). The transformation matrices are then applied either to the dynamic images and/or corresponding parametric maps of tracer binding. Transformation of images into standard stereotaxic space with software such as SPM (www.fil.ion.ucl.ac.uk/spm/) allows the use of standard templates of ROIs or probabilistic atlases though this is not essential. An example of standard ROIs previously used to sample dorsal striatal activity are a circular ROI (diameter 8 mm) for each head of caudate nucleus and three circular ROIs (diameter 8 mm) to

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define each putamen. Reference ROIs sampling non-specific tracer signal include parieto-occipital or cerebellar cortex. These can be traced, or circular ROIs (diameter 18-20 mm) placed contiguously along the cortex. For parieto-occipital cortex ROIs are placed on the slices where the caudate and putamen are most clearly seen.

For BP computation the graphical method described by Logan can be used either with a metabolite corrected arterial plasma or a non-specific tissue reference input function. VD is computed from the gradient of the linear section of the transformed time activity curve. BP values can be computed as $VD_t/VD_r - 1$ for ROIs or generated at a voxel level, the latter resulting in parametric images. To reduce the noise in parametric images, basis functions may be used to determine the gradients of the linear portion of the transformed time activity curves. Alternatively, VDs can be fitted with formal compartmental modelling of brain region time activity curves (TACs). ^{11}C -DTBZ uptake reaches a secular equilibrium by 60' post injection and so the total VD is given by $K_1/k_2/(1+k_3/k_4)$. The cerebellar VD reflects K_1/k_2 . Where k_2 is required for Logan analyses as value of 0.073min^{-1} has been used. (Logan J, Wolf AP, Shiue CY, Fowler JS. Kinetic modeling of receptor-ligand binding applied to positron emission tomographic studies with neuroleptic tracers. J Neurochem. 1987 Jan;48(1):73-83.)

Optionally, ^{11}C -DTBZ dynamic images can be corrected for between-frame head movements during PET scans by applying a frame-by-frame realignment paradigm. The non-attenuation corrected dynamic images are first denoised (e.g., using a level-2, order-64 Battle-Lemarie wavelet). Dynamic scan frames are then co-registered to say time frame 3 (the first frame with high signal-to-noise ratio) and the transformation matrices are applied to the corresponding frames of the attenuation corrected dynamic images.

FDG PET Scanning

Scan acquisition

A current generation PET camera is recommended, and resolution should ideally be 6 mm or better after image reconstruction. Data is ideally collected in 3D mode to improve signal to noise. Subjects are best positioned with the image plane parallel to the orbito-meatal line. Head movement can be restrained using either a thermo-plastic moulded head rest or face mask. Tissue attenuation should be measured for later use in attenuation correction. Depending on the nature of the camera either a 5-10-minute transmission scan can be performed using an external $^{68}\text{Ge} / ^{137}\text{Cs}$ ring point rotating source or, if the camera is CT-PET, a transmission scan

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can be performed with the CT. For quantitative studies for which rate constants for each subject are required, a dynamic 45-60-minute scan must be performed; a single venous blood sample can be taken between 20-30 minutes after FDG injection to measure plasma levels of ¹⁸FDG and glucose.

Subjects should receive an intravenous injection of at least 0.035 mCi / Kg and ideally 0.071 mCi / Kg (5 mCi for a 70 Kg subject). Subjects should be scanned in a restful state in a dimly lit room with minimal auditory stimulation. Subjects should be NPO for 4 hours prior to scanning, and medications that can be safely stopped should be held for 12 hours prior to scanning. Absolute quantification is not required for most FDG PET studies. For quantitative studies, images must be converted from raw radioactivity count units to cerebral metabolic rate units (CMRGlc: ml/min/100g.). This is achieved by using a published method (e.g., Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol.* 1979 Nov;6(5):371-88.; Rhodes CG, Wise RJ, Gibbs JM, Frackowiak RS, Hatazawa J, Palmer AJ, Thomas DG, Jones T. In vivo disturbance of the oxidative metabolism of glucose in human cerebral gliomas. *Ann Neurol.* 1983 Dec;14(6):614-26.).

Analysis of PET

The method of data analysis should be specified. FDG PET data can be analyzed on a voxel or region of interest basis. Scans can be co-registered to the subject's own MRI or to a standardized MRI template (e.g., using SPM). Statistical packages for data analysis may utilize univariate or multivariate approaches. SPM is commonly used for FDG PET image analysis, but other methods may be used.

F-dopa PET Scanning

Scan acquisition

A current generation PET camera is recommended, and resolution should ideally be 6 mm or better after image reconstruction. Data is ideally collected in 3D mode to improve signal to noise. Subjects are best positioned with the image plane parallel to the orbito-meatal line. Head movement can be restrained using either a thermo-plastic moulded head rest or face mask. Tissue attenuation should be measured for later use in attenuation correction. Depending on the nature of the camera either a 5-10-minute transmission scan can be performed using an external ⁶⁸Ge / ¹³⁷Cs ring / point rotating source or, if the camera is CT-PET, a transmission

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scan can be performed with the CT.

Subjects should receive an intravenous injection of at least 3 mCi / 111 mBq of 18F-dopa and ideally 5 mCi /185 mBq of FD 1 h after premedication with 150-200 mg of oral carbidopa to block peripheral tracer decarboxylation. Optionally, 200 mg - 400 mg oral entacapone can also be administered to reduce peripheral methylation of 18F-dopa. It is conventional to stop PD medication for at least 4 hours before PET though this is probably not necessary. As a high protein meal can block 18F-dopa uptake into the brain the patient should avoid eating a meal for four hours prior to PET.

18F-dopa uptake into brain regions can be analyzed as either an influx constant K_i or a striatal uptake ratio relative to a region where only non-specific tracer signal occurs. For K_i measurements it is recommended that 90-120 minutes of scan data are collected. Time frame protocols vary across units, some choosing to collect 28-time frames, epochs increasing from 30 seconds to 10 minutes across 90-120 minutes. Other units simply collect serial 5 minute or 10-minute scans over 90-120 minutes. List mode acquisition allows the option for data to be binned post collection however the investigator wishes. Some units also measure striatal 18F washout after 18F-dopa administration. For this purpose, scan data are collected for 4 hours after administration. If striatal: reference uptake ratios are required a 15-minute acquisition 75-90 minutes after tracer administration is recommended.

Analysis of PET

Activity collected from 0 to 90/120 min after 18F-dopa administration can be summed to produce an integral image allowing coalignment with patient MRIs and definition of regions of interest (ROIs). The transformation matrices are then applied to the dynamic images and/or corresponding parametric maps of tracer binding. Transformation of images into standard stereotaxic space with software such as SPM allows the use of standard templates of ROIs or probabilistic atlases though this is not essential. Examples of standard ROIs previously used to sample dorsal striatum include a small circular ROI (diameter 8-10 mm) for each head of caudate nucleus and three circular ROIs (diameter 8 mm) or an ellipse (8x18 - 10x24 mm) to define each putamen. The ROIs were adjusted on the integral image to maximize the average ROI activity. Reference ROIs sampling non-specific tracer signal include parieto-occipital or cerebellar cortex. These can be traced, or circular ROIs (diameter 18-20 mm) placed contiguously along the cortex. For parieto-occipital cortex ROIs are placed on the slices where

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the caudate and putamen are most clearly seen.

For K_i computation the graphical method described by Patlak and Blasberg (Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab. 1985 Dec;5(4):584-90.) is conventionally used either with a metabolite corrected arterial plasma or non-specific tissue reference input function. Conventionally, K_i is computed from the gradient of the linear section of the transformed time activity curve from 30 to 90/120 min. K_i values can be computed for ROIs or generated at a voxel level, the latter resulting in parametric images. In order to reduce the noise in parametric images basis functions are conventionally used to determine the gradients of the linear portion of the transformed time activity curves.

If 18F-dopa effective distribution volume (EDV) reflecting dopamine turnover is required, then extended 4-hour scan data is required to fit a loss constant in addition to K_i . The ratio of loss: K_i represents the EDV. A higher dose of 18F-dopa, typically 7 mCi / 259MBq, needs to be administered. Patients are scanned for 90 minutes starting at injection, taken out of the scanner for 60 minutes, carefully repositioned, and then scanned for another 90 minutes. Images from the first and second scanning sequences should be realigned using automated image registration software.

Optionally, 18F-dopa dynamic images can be corrected for between-frame head movements during PET scans by applying a frame-by-frame realignment paradigm. The non-attenuation corrected dynamic images are first denoised (e.g., using a level-2, order-64 Battle-Lemarie wavelet). Dynamic scan frames are then co-registered to, for example, time frame 3 (the first frame with high signal-to-noise ratio) and the transformation matrices are applied to the corresponding frames of the attenuation corrected dynamic images.

MR Imaging and Spectroscopy in PD

Current conventional MRI techniques are not sufficiently sensitive to detect reproducible changes in patients with PD. Abnormalities in other neurodegenerative parkinsonian syndromes have been reported, however, and conventional MRI can play a role in the diagnostic evaluation of these disorders, especially if done by an expert review of the scans. Advanced MRI methods can be used for quantitative studies of cortical and sub-cortical structures, understanding tissue composition alterations, and functional and metabolic changes. As with other movement

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disorders, attention is required in the setup, so reduce the motion and distortion artifacts that would contaminate acquisition.

Research utilizing MRI studies should provide sufficient information regarding image acquisition including the scanner and coil used, pulse sequences and acquisition parameters, to allow for the comparison of results across studies. Studies should also report the pre-processing, processing, and statistic methods used. New sequences and processing techniques are continuously being developed. As guidance, we include here some examples of acquisition and processing.

It is good practice to store the raw data, either as nifti files, or as DICOM. And it is recommended to follow the standards for removing identifiers, assigning subjects a pseudonymous code for the study to follow through on all modalities.

For all MRI modalities, record the information about

- Scanner maker, model, and field strength
- Scanner software and version
- Head Coil: include manufacturer and number of channels.

Include the sequence type, name, and parameters, and slice orientation, matrix resolution, orientation, and acquisition times. Indicate whether acceleration was used. More recommendations are provided in the following sections.

Structural MRI

Structural images are collected in most studies, and used for morphometric analyses, as ancillary for other modalities, or both. These images are T1-weighted. Most studies use a high-resolution 3D T1 sequence, mostly MPRAGE sequence, Fast SPGR based sequences are also commonly used, though they provide less contrast. Typical acquisition is of voxel size of 1 mm³ for a 3T scanner, and should cover all head, including full skull, brainstem including medulla oblongata, and cerebellum. Sagittal orientation is preferred since it is less prone to distortions, even though it is slower, if higher resolution is desired, acquisition at higher fields can be obtained. Another strategy is averaging over multiple acquisitions of the same sequence. Keep records of the acquisition parameter, including voxel size, matrix resolution, acquisition orientation, acceleration, repetition time (TR), flip angle, Echo time (TE), and inversion time (TI). Indicate whether multi-echo and/or multi-band was used in the acquisition and include the corresponding parameters.

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It is recommended to follow the minimum requirements of the software to be used for the planned analysis. Typical analyses include cortical thickness and segmentation generated in FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>), and Voxel Base Morphometry (VBM) comparisons using FSL or SPM. When results are reported from VBM, include whether a group's specific template (recommended) or a standard template was used.

Diffusion Weighted Images

Diffusion imaging is used to study the properties of the tissue and provide a unique way to evaluate the diffusivity of molecules in the different compartments. When used for clinical purposes, a typical acquisition will have 30 directions, one B value (typically around 1000), and one phase encoding. It is important to acquire isotropic voxels to avoid biasing the diffusion metrics. These images are typically combined to estimate apparent diffusion coefficient. Given that the gradients are applied in the scanner space, it is important to place the slices in axial orientation.

When used for research, these images are typically combined to estimate the diffusion tensor. Quality can be improved by adding more acquisition directions, if the scanner capabilities and available scan time permits, it is recommended to use a combination of phase encoding directions that will permit distortion corrections.

There is interest in computing the diffusion metrics considering the parenchymal volumes and CSF-like compartments, for this type of analysis, intermediate b values are recommended. It is important to keep records of acquisition parameters including echo time (TE), field of view, repetition time (TR), B values, acceleration factor, number of directions, and phase encoding direction. Recommended voxel size is 2 mm³, isotropic voxel size, at least 60 axial slices for full brain coverage. Indicate phase encoding for each sequence.

T2-weighted images might be required for registration and distortion correction. If needed for the desired analysis, please specify the parameters.

Fluid-Attenuated Inversion Recovery (FLAIR)

FLAIR sequences are T2-weighted and enhance parenchymal lesions. These lesions are common in the elderly population. These images can discover non-PD related lesions. These

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images have also been used to delineate the Nigrosome-1. The absence of this boundaries might be related to parkinsonism.

Nigrosome Measurements

Nigrosome 1 is a dopaminergic dense area of the substantia nigra, making it an area of interest in PD patients. Nigrosome 1 images can be obtained based on several contrast mechanism. The delineation of the substantia nigra can be achieved with diffusion data, neuromelanin sensitive sequences such as MT, and with iron sensitive sequences based on T2* contrast, including iron contrast from GRE based sequences. Based on different contrast mechanisms, the different sequences might identify different aspects of the substantia nigra. Since these methods and their application have significant differences, it is important for researchers to provide all relevant information regarding data acquisition, including number of echoes utilized, whether phase images were stored, and information about analysis.

Iron content (SWI and GRE): Several MRI methods have been reported for estimation of regional iron content, of importance in PD due to reports of increased nigral iron in this disorder. Increased spin–spin interactions due to iron-induced local field inhomogeneities are exploited to estimate iron content using iron-sensitive sequences based on a reduction in T2* relaxation time or an increase in R2* (1/T2*), phase changes and shifts in SWI, or increased susceptibility values on QSM. When using SWI images, a sub-millimeter in-plane resolution is desirable. Depending on the planned analysis, multi-echo acquisition and phase images are needed. Quantitative analyses such as QSM can be obtained with a 3D GRE similar to that used for routine SWI. To this end, multiple echoes should be used to allow for multi-exponential T2*-decay correction and for detection of weak susceptibility changes.

Keep records of the acquisition parameter, including voxel size, number of echoes, echo times, and acquisition orientation.

Neuromelanin-sensitive MR: Neuromelanin acts as a paramagnetic agent because of its iron-binding potential, and it has been associated with the paramagnetic T1-shortening and MT effects by the melanin-iron complex. Neuromelanin-sensitive T1-weighted sequences are advanced T1 sequences developed to improve detection of neuromelanin containing brainstem nuclei such as SN and LC through a combination of T1 effects and direct or indirect MT effects using gradient-echo sequences with a MT pulse or more commonly TSE sequences with or

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without a MT pulse, with most of the studies having used an off-resonance MT pulse to increase contrast. Besides 2D sequences, more recently 3D MRI pulse sequences have been introduced.

Keep records of the acquisition parameter such as TE/TR, slice thickness, in-plane resolution, MT pulse duration and MT frequency offset. Include details of the landmarks for the partial acquisition, voxel location and orientation. For analysis, include definitions on how region of interest and reference region are defined.

fMRI

fMRI is gaining interest due to the information provided.

The acquisition should include parameters for the acquisition sequence, slice orientation and acquisition order, matrix and FOV, echo time(s), and echo numbers. It is important to note the medication status for this sequence. Indicate if multi-band is used.

If a task, a descriptor needs to be included, and possible link to repository of the experiment. If resting state, it is important to note whether subjects were with eyes open or closed. For resting state, a minimum of 5 minutes usable data after data cleaning is recommended, and 8 minutes or more is preferred.

If results for analysis are included, criteria for data cleaning, such as motion correction and censoring/scrubbing, needs to be added. Documentation of quality assurance measures include whether frame displacement exclusion, and if so, what value was used as cut-off, and whether or not DVARS and if so, what value was used as cut-off. The minimum frames acceptable per subject and any other quality controls were used should be specified. Both the number/percent of healthy control participants rejected for quality control and the number/percent disease participants rejected for quality control should also be documented.

MR spectroscopy

MRS is an important research tool allowing the quantitation of certain metabolites, most often within a single voxel of brain tissue. A reduced concentration of N-acetyl aspartate in patients versus controls is generally considered to be a surrogate marker of neuronal loss. Reports involving spectroscopy should include all relevant details regarding data acquisition and

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analysis, including information regarding voxel location and size, metabolites modelled, units of measurement (e.g., metabolite ratios, “machine units”, or absolute quantitative units). MR spectroscopic imaging (MRSI) allows the simultaneous acquisition of spectra from multiple voxels. When spectroscopy data are collected this way, add parameters related to matrix and voxel size, and grid localization.

Detail pulse sequence utilized, spectral width, echo time (TE), and repetitions. Include whether saturation pulses were used.