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Play a Part in Parkinson's Research

MRI
Technical Operations Manual

Final Version 7.0
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1   FUNCTIONAL MAGNETIC RESONANCE IMAGING

A non-contrast enhanced, T2 weighted brain MRI using at least a 1.5 Tesla scanner and a non-contrast enhanced 3D volumetric T1-weighted brain MRI will be performed at baseline for all PPMI subjects. Therefore, it is required that the radiology center (or person identified as responsible) transmit the MRIs to the imaging core lab. All MRI sequences should be transmitted to the imaging core lab.

1.1   **MRI Acquisition Procedures**

A 3D T1-weighted sequence (e.g. MPRAGE or SPGR) is required. The total scan time is expected to be in the range from between 20 – 30 min. The field of view (FOV) must include the vertex, cerebellum and pons. **The T1-weighted image must be acquired as a 3D sequence and have a slice thickness of 1.5 mm or less with no interslice gap.** All other parameters including repetition (TR) and echo (TE) time should follow your manufacturer recommendations for a T1-weighted, 3D sequence.

Type of sequence	**T1-3D e.g. MPRAGE, SPGR**
Slice thickness (mm)	1.2
Interslice gap (mm)	0
Voxel size (mm)	1*1*1.2
Matrix	256 x 256 x 170-200
Plane	Sagittal

For detailed assessment of cerebrovascular disease, a T2-weighted double-echo and/or FLAIR + T2 sequence should also be performed. Starting with version 7.0 of this manual the 3D T1 sequence will be based on standardized ADNI sequences provide to all sites. The scan needs to be sent to the imaging core lab.

1.2   **MRI Local Read Requirement (Baseline Only)**

The MRI scan obtained at the Baseline visit will be read by the local site's radiologist to meet the standards for clinical practice and ensure there are no significant abnormalities. The radiologist should provide a read interpretation that the scan results are normal, abnormal (not clinically significant), or abnormal (clinically significant). This documentation will be maintained in the study source files at the clinical site. The radiologist's interpretation is captured on the MRI data form. The radiologist's clinical interpretation is not required as eligibility criteria to complete the enrollment process.

2 ELECTRONIC FILE INSTALLATION (NEW VERSION 7.0)

2.1 Overview

Electronic files are being distributed in order to standardize MRI acquisitions across the range of MR imaging platforms being used in the PPMI study. This was previously being done just for sites participating in the DTI and resting state substudies, but will now take place for all sites.

The electronic files are being supplied by the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The support of this study and in particular Clifford Jack, Michael Weiner and Bret Borowski is gratefully acknowledged.

The only sequences being used from the ADNI files will be the T1 and T2/FLAIR sequences. As noted below the files may contain several other sequences since the protocols were originally built for ADNI. However, these additional sequences **SHOULD NOT BE USED** when scanning PPMI subjects. Performing additional scans, beyond the ones approved for each site will unnecessarily prolong the subject's time in the scanner and the additional data will not be accepted by PPMI.

Please refer the site list (provided as a separate PDF) to determine which sequences you should use.

2.2 General Installation Instructions

Electronic files will be sent by e-mail. Please use standard PC tools to unzip the files and copy them to an empty virus free USB drive, then follow the directions below for your scanner type.

The files should be unzipped on a PC and not on an Apple computer. Note that for GE scanners, some protocol directories that start with a "."may not be visible in the file manager (Explorer). This may make it difficult to know if files were properly copied to a USB drive. To make these folders visible go to Control Panel > Folder Options > View > then click "Show hidden files, folders and drives > then click OK".

2.3 Installation for GE scanners

2.3.1 Software versions 14 and 15 (or lower)

Applicable to software revisions using Linux host computer

11.0 M4, 11.1   (1.5T EXCITE)
12.0 M4   (1.5T EXCITE)
12.0 M5 or M5a   (1.5T EXCITE)
14.0 M5, M5a   (1.5T EXCITE)
15.0 M3, M4, M4a   (1.5T EXCITE)

Do the following steps:

1) Contact your GE MR Field Service Engineer or Internal Service Engineer or physicist and have him/her execute the following steps.

2) Insert the CD into the CD drive of the scanner host computer.

3) Open up C shell from tools desktop.

4) Login in as root (su) with correct password.

5) Type the following commands carefully in a C-shell (on tools desktop)

6) After installation, keep the instructions and disk in case you need to re-load software

7) If you upgrade to new revision of software, you will be given a new disk if necessary

Command	Description
`mkdir /tmp/cdrom`	*creates temporary mount directory*
`mount –t iso9660 /dev/cdrom /tmp/cdrom`	*links CD to this mount directory*
`cd /tmp/cdrom`	*changes to CD mount directory*
`cp ADNI* /usr/g/protocols/site/head`	*copies protocols to scanner*
`cd /usr/g/protocols/site/head`	*changes to protocol directory*
`umount /dev/cdrom`	*disconnects CD from file system*
`eject`	*ejects CD*
`exit`	*logs out of root (su)*
`cd /usr/g/protocols/site/head`	*changes to protocol directory*
`/usr/g/bin/protocolup –f ADNI*`	*synchronizes protocol (e.g. M3 to M4)*
`setupProtocols`	*installs new protocol in SITE>HEAD*

2.3.2 Software versions > 16.x

2.3.2.1 Part A: USB preparation

- GE protocol files will be in the following 2 directories

  `.rawProtocols` (extracted from rawProtocols.zip)

  And

  `GE_ProtocolExchange` (extracted from GE_ProtocolExchange.zip)

- Transfer both of these directories to a standard USB memory stick (also called thumb drive, etc.):

- Insert the USB drive with the 2 directories into the scanner's computer tower.

2.3.2.2 Part B: Copy and install the protocols

1. With the USB drive in the computer, select the ProtocolExchange feature (see Figure 1, blue arrow.)
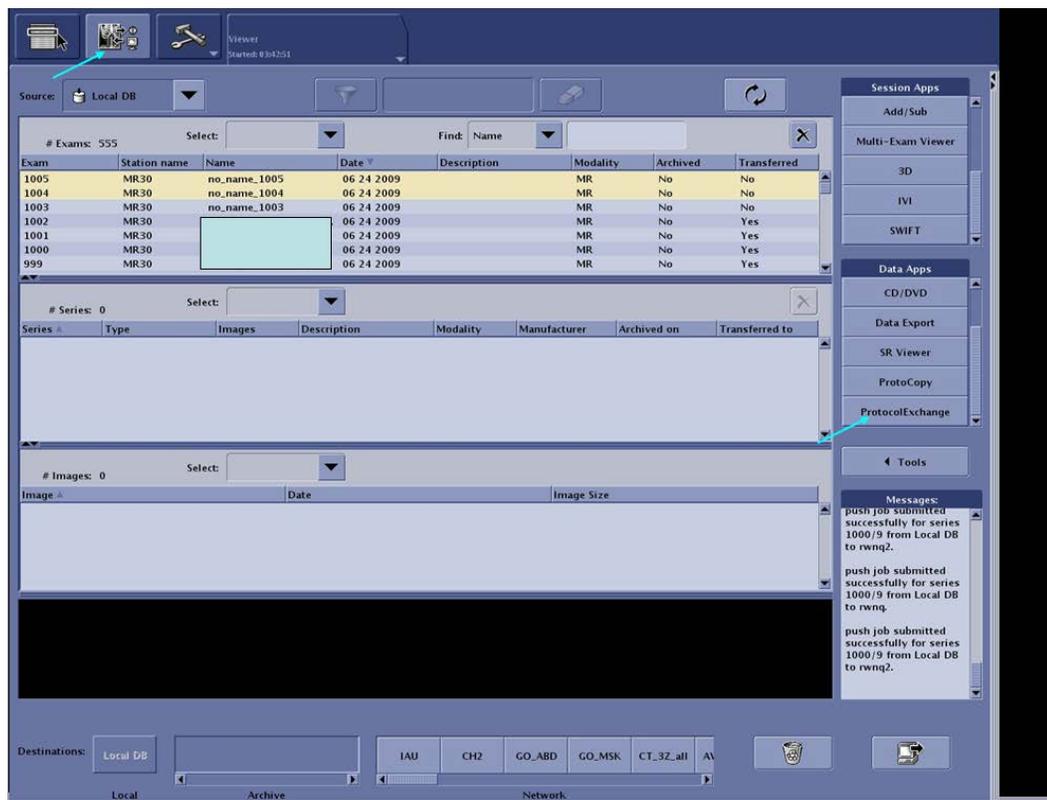
Figure 1: GE ProtocolExchange selection

2. Select Import mode, followed by OK, and then select USB

Figure 2: GE Import Mode Selection

3. Explore the USB to show the protocols. Drag only the human protocol to the right-hand window (Note, the protocol names could differ from the example shown in the Figure).
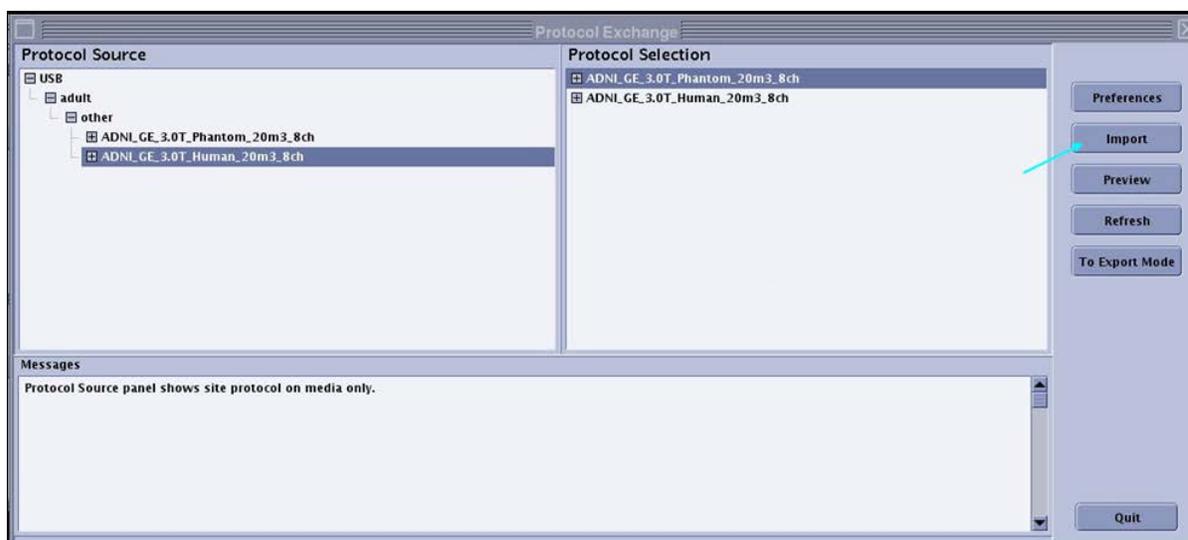
Figure 3: GE protocol selection

4. Select one protocol, and import it by clicking the Import button (blue arrow Figure 3).

5. Enter the scanner password, if prompted for it.

6. After successful importing, the USB drive may be removed.

7. The desired protocol can be found under the site protocol list, "other".

2.4 **Installation for Siemens scanners**

1. Save the EDX file to a USB drive.

2. While the scanner is not being used, insert your virus free USB drive.

3. Go to the protocol editing tool in the Exam card. It is the icon at the bottom right that has a pencil on it. See Figure 4 (blue arrow).
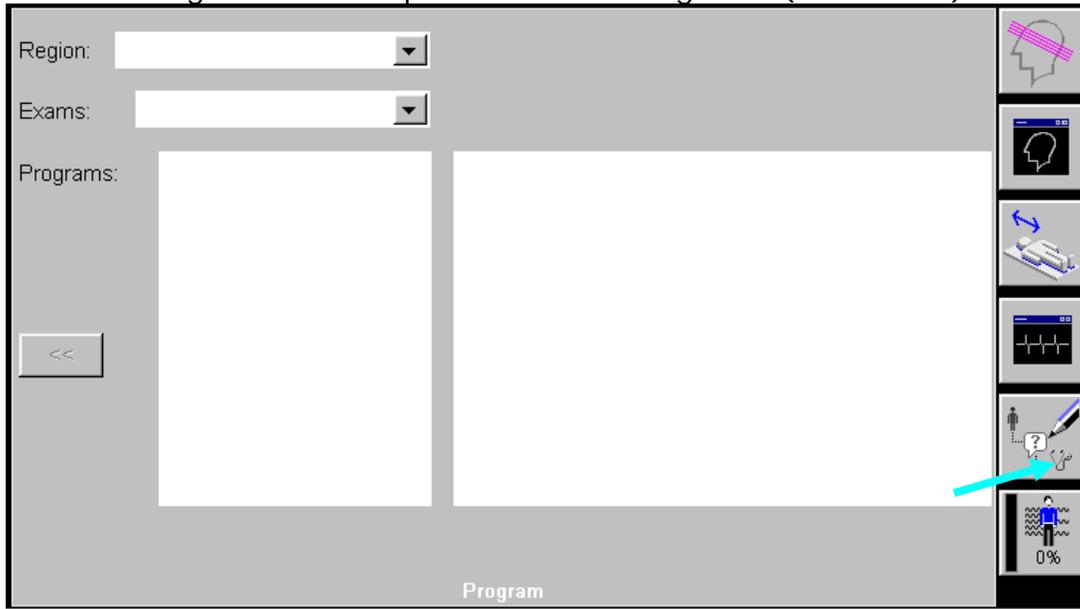
Figure 4: Siemens protocol editing tool.

4. In the protocol editing tool, highlight the USER tree with a single click, Figure 5.

   Make sure Siemens Exam Tree and User Exam Tree are closed. Leave USER tree highlighted in blue
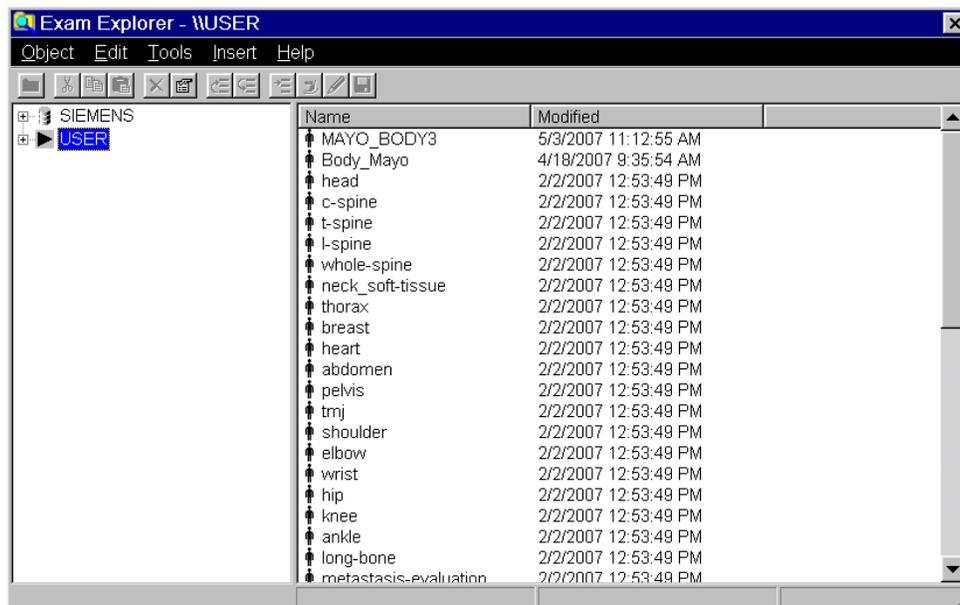
Figure 5: Siemens Exam Explorer

5. Go to the Object Menu and choose Import, Figure 6. You will be warned that this will take some time, Figure 7, but it is relatively quick.
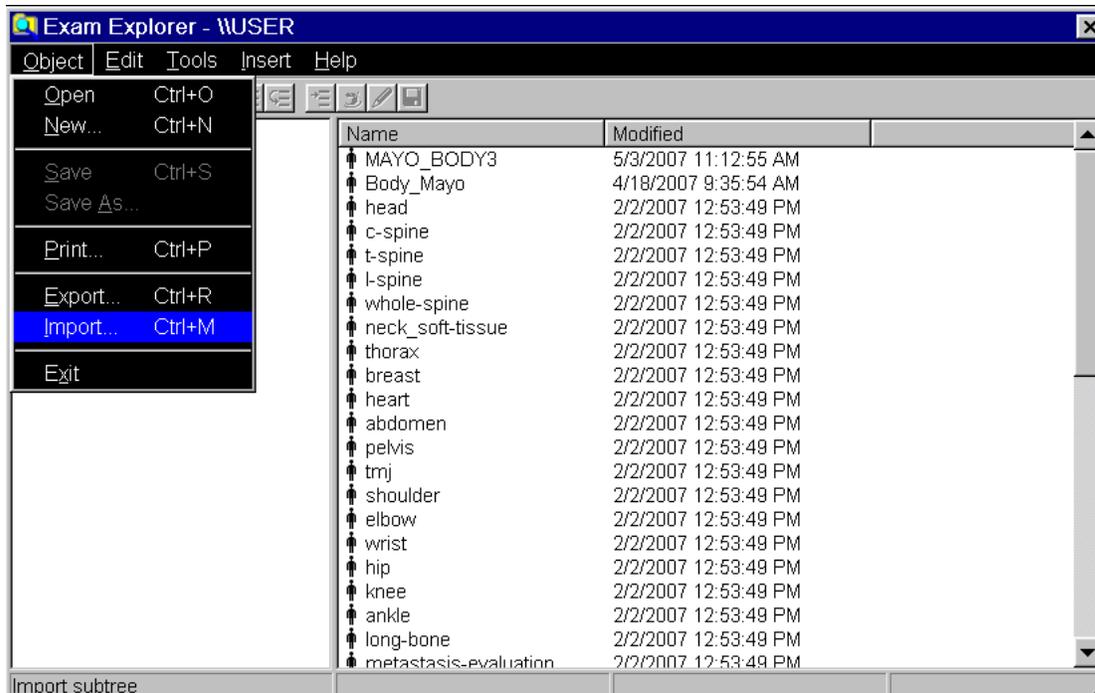
Figure 6: Siemens: Select Import.
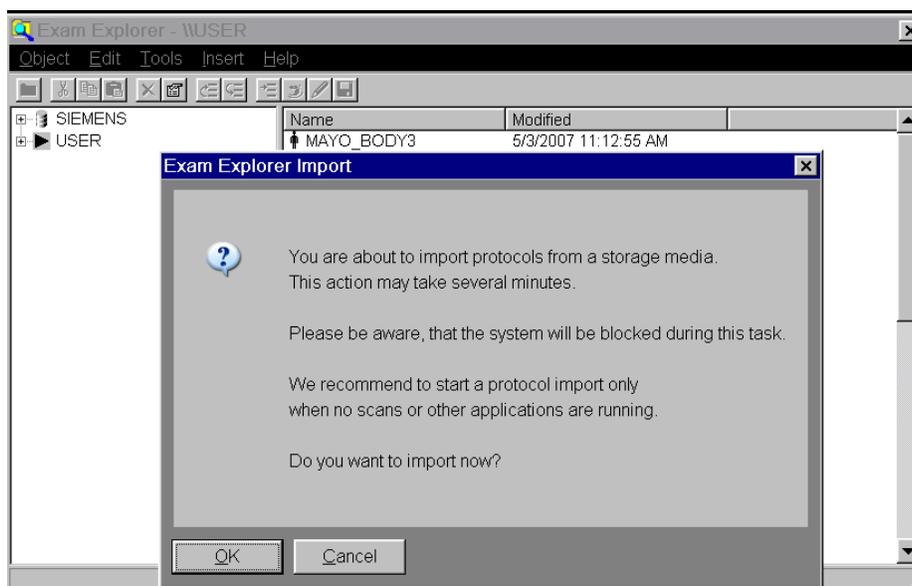
Figure 7: Siemens: Message on selecting import.

6. On the bottom right, select the USB drive (typically F:) and then navigate to the file saved on the USB drive, Figure 8.
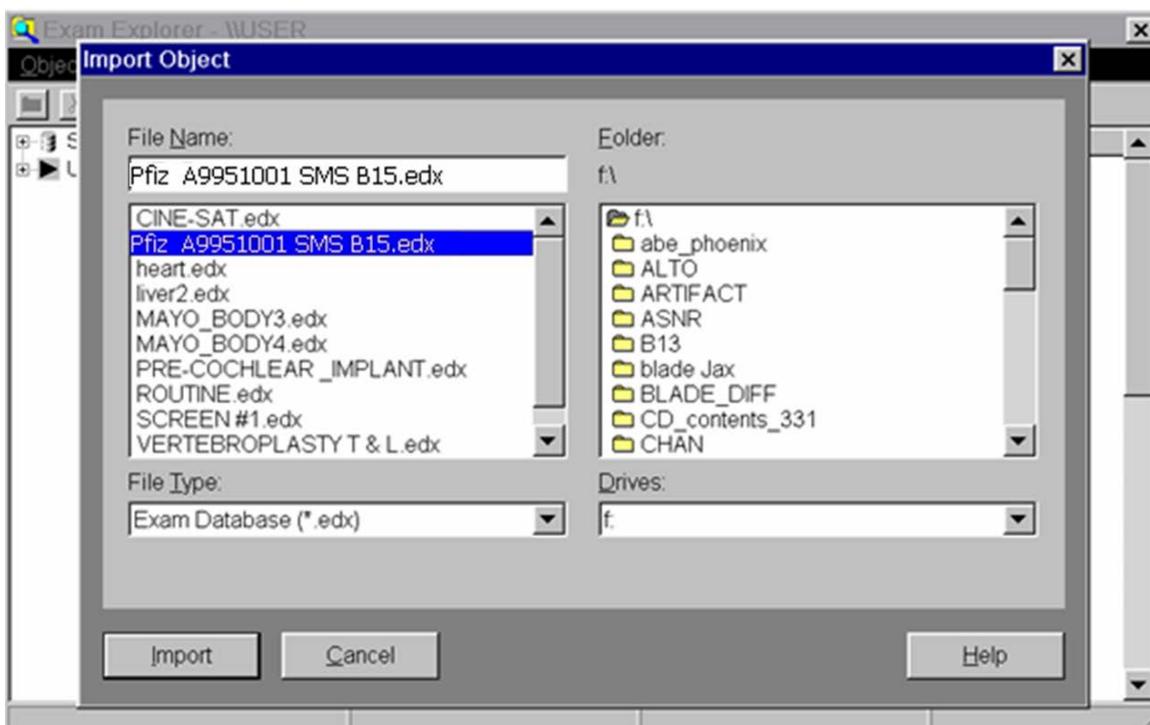
Figure 8: Siemens Import Window

7. Select the Import button. If a window pops up asking if you want to convert the protocol, then accept the conversion. This could happen, for example, if the gradients of your system differ from the gradients of the system where the protocol was built. Once it finishes, close the editing tool. The protocol will appear at the bottom the USER tree. Verify that it is there.

2.5 Installation for Philips scanners

1. Copy the .ExamCard file to your virus free flash drive.

2. Insert the flash drive into the scanning computer and import the file per the manufacturer's directions.

3 SITE SPECIFIC SEQUENCES

3.1 Non-DTI / Non-resting-state site Procedures

Non-DTI sites will use designated 3D-T1 and T2 sequences from the ADNI protocol. See the **PPMI Site and ADNI Protocol Spreadsheet** sent separately.

For any sites currently using a 1.5T scanner, we suggest upgrading to a 3T scanner if possible. If you switch scanners, you must first inform IND and the proper sequences will be sent to you.

It is imperative to review the **PPMI Site and ADNI Protocol Spreadsheet** that has been sent separately by e-mail. Make sure that PPMI has the correct Scanner and Software listed for your site. If there are any changes, please inform the core imaging lab as soon as possible. Also, review the sequences you will be using from the ADNI protocol.

Prior to running the first PPMI subject with the new ADNI sequences at a site, please use the specified ADNI sequences to scan a phantom (see section 5) and upload the images to the imaging core lab. The phantom will be reviewed to make sure you are using the correct sequences.

3.2 DTI / resting state site Procedures

DTI / Resting state sites will use PPMI provided sequences **AND** certain ADNI sequences. The old 3D-T1 sequence from the PPMI protocol will be run in order to maintain longitudinal continuity. The new ADNI 3D-T1 sequence will be run to allow future standardization The T2, DTI and resting state sequences will be from the PPMI protocol.

Prior to running the first PPMI subject with the new ADNI 3D-T1 sequence please scan a phantom with just the new ADNI sequence, and upload the images to the core imaging lab. The phantom will be reviewed to make sure you are using the correct sequence.

4 DTI MRI IMAGING

A subset of subjects will undergo DTI acquisitions. Site participation in this sub-study is dependent upon model and software version of each site's MRI scanner. The specific scanner model to be used in this sub-study is the Siemens 3T TIM Trio. Software versions must be VB15 or higher. Data will be collected using a 12 channel Matrix head coil.

DTI MRI's will be performed based on the subject's cohort (see clinical protocol).

Sites will be supplied with software version specific electronic protocol (EDX file) that will need to be imported into each scanner. Use only the imported PPMI sequences when scanning a subject.

4.1 Human Subject Data collection Protocol

4.1.1 Fiducial Marker Placement

A fiducial marker is to be used for each scanning session in order to accurately determine right to left subject orientation during image review. Prior to the start of each scanning session, tape a vitamin E capsule to the right temple of the subject. See Figure 9 for correct placement of the vitamin E capsule.

Images showing placement of the stereotactic marker (vitamin E capsule)
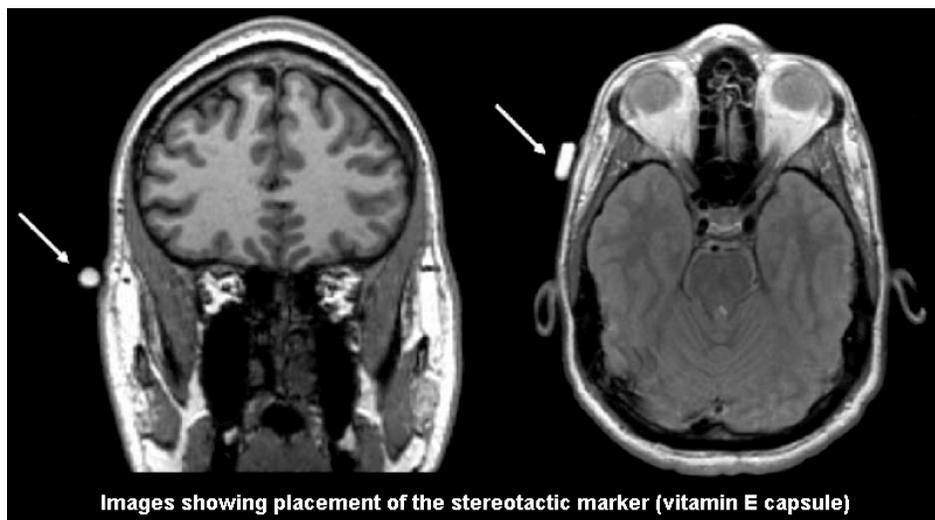
Figure 9: Fiducial marker placement using vitamin E capsule (image courtesy of ADNI).

4.1.2 Subject Positioning and Instructions

The subjects must be scanned head first in a supine position in the 12 channel Matrix head coil. The head should be placed in a comfortable position in the head coil. The laser crosshairs should line up with both the nasion and the marks on the coil. Padding and the calipers should be used to keep the head in a comfortable position and to constrain excessive movement. The use of a soft neck brace is encouraged as this keeps the subject in the same position during a single scanning session as well as across multiple sessions.

In patients that are particularly kyphotic or stiff, we have found that removing the spine coil from the table is helpful. The thin cushion can be placed on the table for comfort. Positioning the body lower reduces the angle on the neck.

It is critical that subjects are as comfortable as possible, and that their head is constrained to minimized head movements. Excess movements significantly degrade the quality of all MRI images, but particularly the DTI and resting state scans.

It is important to take the time to instruct subjects on the need to remain as still as possible while the scanner is running (making noise). In between scans, subjects can shift if necessary, but any shift of more than a

few mm will require repeating the localizer scan. Subjects should be instructed not to repetitively move their mouth or tongue, but they can swallow as necessary. They should also not deliberately shift or blink their eyes more than necessary. Subjects must try to avoid deliberately moving their limbs, hands and feet as any repetitive movements may cause a slight shift in the position of their head. Shifts of more than 1-2 mm, particularly if repetitive and not isolated, can make MRI scans unusable.

4.1.3 Finger Pulse Signal Setup

Use the standard Siemens finger pulse device. Place this on the middle or ring finger since they are less calloused. Remind the subject not to move this hand as it will disrupt the pulse signal. You may place a towel under their arm to make them more comfortable and to minimize movement. Select the physiologic monitoring button in the EXAM tab to view the pulse waveform; see figure 10 (green arrow). You will have to select **pulse/trigger** as the input signal. Verify that you have an appropriate looking waveform and that the subject is not moving their finger.
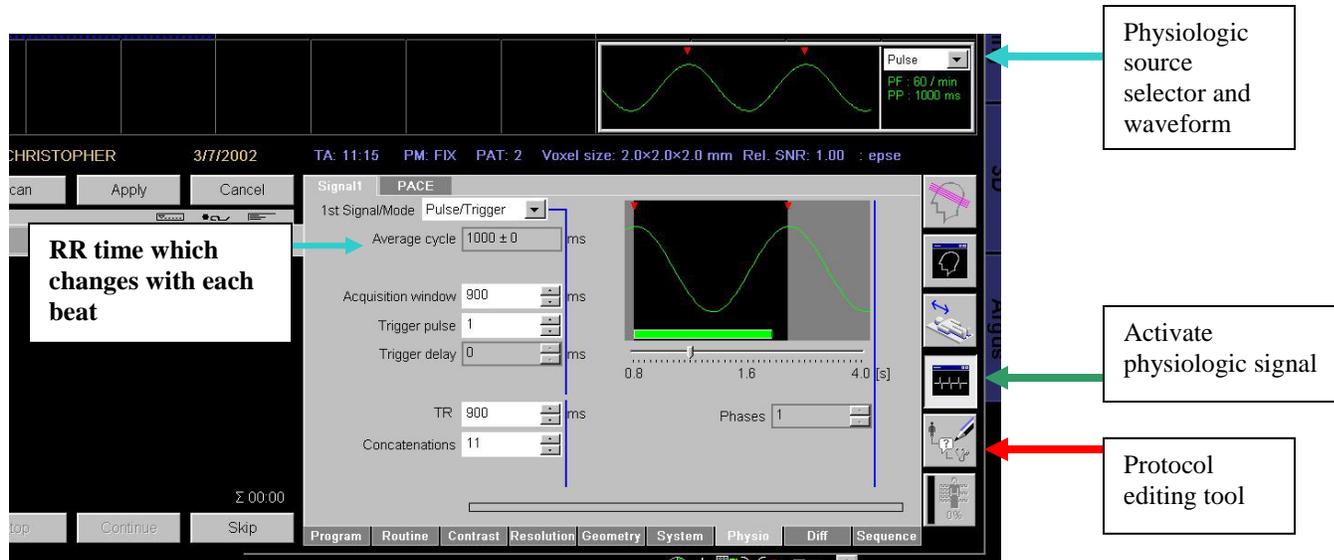
Figure 10: Physio tab with the physiological signal displayed above. The pulse waveform must be selected. The average cycle indicates the RR interval for that beat and gives a variance. The TR, Acquisition Window, and concatenations parameters are on this page.

4.1.4 Subject Registration

Follow the naming convention described in section 6 and register the subject. Enter the subject's date of birth so that the scanner can calculate the Specific Absorption Rate (SAR). Remember to use your site's anonymization procedures to remove the date of birth when preparing the data to be sent to the core lab.

4.1.5 MRI Acquisition Protocol (for sites participating in the DTI and/or fMRI substudies)

All scan parameters are described in the accompanying PDF document. The following scans will be performed in the exact order below:

    A. Localizer scan
    B. Cardiac triggered DTI
    C. MPRAGE with GRAPPA
    D. Resting State MRI ()
    E. T2 Weighted Acquisition
    F. Repeat DTI acquisition

A. Localizer scan (less than 1 min)

B. Cardiac Triggered DTI: 10-15 minutes depending on heart rate

    1. Positioning

        a) Position the axial DTI slices along the AC-PC plane with particular care that slices cover from the vertex through the cerebellum. The

slices should be centered in the axial plane to prevent aliasing in the Anterior/Posterior direction. The next step is to set the triggering parameters described below**.**

2. Cardiac triggering

a) Go to the PHYSIO tab on the EXAM card. Verify that the signal source is pulse.

b) Monitor the subject's RR value. The RR is the time between consecutive beats. This time varies slightly from beat to beat so watching the average value for a minute will give you an idea of the variability and range of the RR value. The variability will inform you on how much additional buffer to build into the parameters below.

c) SET THE TR AND ACQUISITION WINDOW PARAMTERS: The safe useable value for the TR (bottom of window) is 90% of the average RR displayed at the top. In the example in Figure 11, you would enter 900ms for the TR when the RR is 1000ms. Now enter the same value (90% of the RR) for the acquisition window value. The number of concatenations will change. Make sure that the number of concatenations is set to the minimum value after adjusting the TR and acquisition window times. The variability is 0 in this example so 90% is good but with some variability you would reduce the TR and acquisition window. These parameters can be adjusted in the physio window before the sequence is started. In the example in Figure 11, the number of concatenations is 11 so it will take 11 heart beats to collect a single direction.

d) Once the number of concatenations has been set to the minimum, reduce the TR and the acquisition window to the minimum values. This will provide additional time for the scanner to capture the next pulse wave. This small adjustment will make sure to minimize the missed heartbeats.

Figure 11: Physiological signal and the acquisition of data. The red triangles indicate each heart beat. The green bar is the acquisition window for each group of slices. Note the slight gap between beats. The use of only 90% of the RR allows for variations. If the subject has a large range in their heart rate then this setting may need to be reduced to 80%.
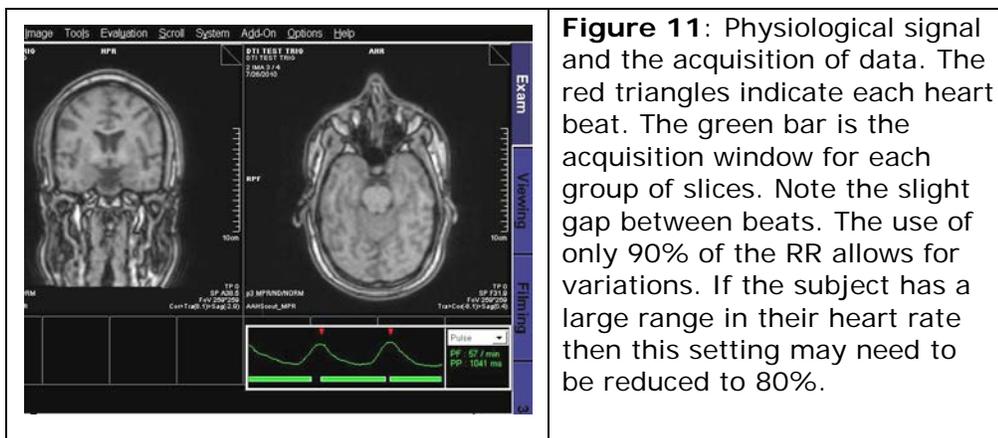
e. You can now start the scan. The automated shimming scan will be acquired for about a minute. Then the DTI scan will be ready to start. Make sure to monitor the study in case the subject's heart rate changes or they move their fingers. You should hear a rhythmic acquisition coming from the scanner and no missed beats in the physiological monitoring window, see Figure 11. A few missed heart beats is not a problem, but consistent missed triggering will make the scan time very long, see Figure 12. The RR should be re-evaluated and the scan restarted.
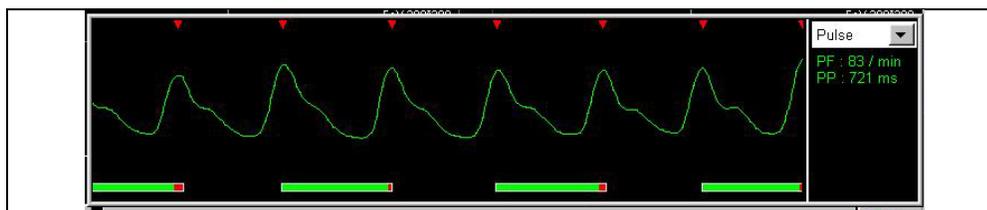
Figure 12:

The physiologic trace when the TR and acquisition window are not correctly set; the TR=750ms so it extends into the next pulse waveform and misses that beat. This setting doubles the scan time. To remedy this problem, the TR and acquisition window setting should be reduced to 650ms. The number of concatenations will increase but will trigger on every beat.

When issues arise during the gated sequences that cause a variable heart rate (e.g., tremor, increased anxiety or minor cardiac arrhythmias) this can interfere with the gated acquisition. In such cases you may notice a much longer scanning time during the DTI sequence (e.g. from the usual 12 to more than 15 min) or variable triggering of the scanner. This can be detected by noticing frequent pauses in the scanning sounds or gaps between scans as shown by the green bar below the pulse waveform in the physiologic window (see Figure 12 in the operations manual for an example of delayed triggering).

If a variable heart rate prevents an appropriate acquisition window from being set quickly and easily, or frequent pauses are noted during the DTI acquisition you should stop the gated DTI sequence and perform a non-gated DTI acquisition. Any remaining DTI sequences should also be non-gated. However, it is not necessary to repeat any gated sequences if they have already been completed. If some or all sequences are non-gated, or if a scan is interrupted please note this on the IND transfer document.

C. 3D-T1 Sequence: 5 minutes 12 seconds (Current DTI sites will collect 2 MPRAGE scans: one using the previous sequence for longitudinal continuity and the other using the new ADNI sequence.)

The brain must be centered in the field of view (FOV). **Do not use a tight rectangular field of view and make sure to avoid wrap around in the ANT/POST and the L/R directions**. **The slices should cover the entire brain from the bottom of the cerebellum to the vertex. Typically, 176 slices are sufficient to cover the entire head from ear to ear. In order to accommodate larger brains, the number of slices can be increased up to a maximum of 192 and any corresponding increase in TR timing that is calculated automatically should be accepted. No other parameters other than TR can be changed. In particular, changing image resolution to accommodate head size is NOT ALLOWED.**The MPRAGE scan will be acquired in a sagittal orientation using an IPAT factor of 2. The image plane should be aligned in the Sagittal plane along the hemispheric fissure and axially along the AC-PC plane.

D. Resting State fMRI (rsfMRI) (8 min, 4 sec)—For Sites Participating in Sub-study

Position the axial rsfMRI slices along the AC-PC plane with particular care that there is 1 slice above the vertex, and then cover the rest of the brain and as much of the cerebellum as possible with the remaining slices. Do not change the number of slices or the TR. The slices should be centered in the axial plane to prevent aliasing in the Anterior/Posterior direction.

Subjects should be instructed to rest quietly with their eyes open, to clear their mind, and to not fall asleep. They should also be reminded to minimize all movements during the scan.

E. T2 axial Acquisition Sequence: 5 minutes 8 seconds

This Turbo Spin echo scan is used to quickly screen for pathology or changes in the brain during the course of the study. The orientation is axial and should be copied from the DTI positioning automatically when the entire protocol is copied into the scanning window. Verify that the brain is centered in the field of view to avoid any aliasing in the Left/Right direction. Confirm that the phase encoding direction is L/R.

F. Repeat Cardiac Triggered DTI:

Follow steps outlined in item #2 above.

5   PHANTOM ACQUISITION

- **Non-DTI/Resting state sites:** The phantom scan only needs to be performed before the ADNI sequences are used for the first time at the site. It **does not** need to be performed for all subjects. Use whatever standard phantom is available at the site for the scan.

For **DTI and DTI + Resting state sites ONLY** an ADNI 3D-T1 phantom scan only needs to be performed before the ADNI sequences are used for the first time at the site. It **does not** need to be performed for all subjects. DTI and resting-state phantom scans (if applicable) DO need to be performed for all subjects at the site. If there are multiple human subjects being imaged on the same day, only one DTI / Resting-state phantom scan needs to be acquired.

The DTI phantom data will be acquired without cardiac triggering and will use the protocols at the bottom of the protocol tree labeled phantom scans.

- **DTI + Resting state sites:** Use the fBIRN agar phantom only.

- **DTI only sites:** Use whatever phantom you are currently using to scan: either the fBIRN agar phantom or the Siemens phantom (after waiting 10 minutes to allow the water to settle).

All Sites
1. Register the phantom as a subject according to the naming convention described in section 6.2.

2. The phantom should always be positioned in the center of the coil (physical marker on coil) at the isocenter of the magnet.

3. Run the localizer scan.

4. Run the phantom scan as indicated below.

Non-DTI sites
1. Run the phantom scan ONLY 1 TIME before the ADNI sequences are used for the first time at your site.

2. Make sure to check the separate **PPMI Site and ADNI Protocol Spreadsheet** for which sequences to run at your site. Typically this will be a 3D-T1 sequence (MPRAGE, IR-SPGR, etc) and either a double echo T2 or a FLAIR plus T2.

3. Acquire the phantom scans and upload the images to the core imaging lab..

DTI + Resting State sites
1. Run the DTI protocol designated for phantoms, which uses the same settings as the human subject scan but without triggering. The scans should be acquired in the axial plane centered on the phantom in all three orientations.

2. Run the Resting state protocol designated for phantoms, which uses the same settings as the human subject but with fewer slices. The scans should be acquired in the axial plane centered on the phantom in all three orientations.

3. Before the ADNI sequences are used for the first time at your site obtain a 3D-T1 phantom scan and upload the images to the core imaging lab.

DTI only sites
1. Run the DTI protocol designated for phantoms, which uses the same settings as the human subject scan but without triggering. The scans should be acquired in the axial plane centered on the phantom in all three orientations.

2. Before the ADNI sequences are used for the first time at your site obtain a T1 (MPRAGE, IR-SPGR, etc.) phantom scan and upload the images to the core imaging lab.

6   MRI SUBJECT AND PHANTOM ID NAMING CONVENTION

6.1. Subject Naming Convention

Each set of subject MRI data transferred to the imaging core lab will be identified by registering the human subject according to the following structure: SSS_NNNN_V

Where SSS is the 3 digit site code, NNNN is the 4 or 5 digit subject number, and V is the visit number according to the key below.
    1 = MRI 1 (Baseline)
    2 = MRI 2 (Month 12/Visit 4)
    3 = MRI 3 (Month 24/Visit 6)
    4 = MRI 4 (Month 48/Visit 10)
    5 = MRI 5 (Premature Withdrawal)

Example subject data collected at baseline for subject number 1455 acquired from site 023 will be indentified as "023_1455_1".

6.2. Phantom Naming Convention (DTI and RS Sites only)

A phantom scan needs to be acquired each subject imaging day. If more than one subject is scanned on the same day, only one phantom scan is to be acquired.

Each set of phantom MRI data transferred to the imaging core lab will be identified by registering the phantom scan according to the following structure: SSS_DDMONYR.

Where SSS is the 3 digit site code, DDMONYR represents the 7 digit date of acquisition, according to the key below.

Example phantom data collected acquired from site 023 on August 11, 2010 will be indentified as "023_11AUG10".

7   MRI TRANSMITTAL PROCEDURE TO IND

The following files are to be forwarded to the imaging core lab in DICOM 3.0 format. These can be sent either by sFTP transfer, direct DICOM transfer, or on CD. All data should be registered and labeled according to the file naming procedure specified in Section 3.0.

Files to be transferred:

Non-DTI / Non-Resting State sites:

Phantom Data (Only sent one time, before ADNI sequences are used for the first time at the site)
* ADNI 3D T1
* T2 weighted
* FLAIR (if listed for the site)

Subject Data
* ADNI 3D T1
* FLAIR (if listed for the site)
* T2 Weighted

DTI + Resting State Sites:

Phantom Data
* DTI Sequence (send each time a DTI sequence is acquired)
* Resting State Sequence (send each time a resting state sequence is acquired)
* ADNI 3D T1 (Only sent one time, before ADNI sequences are used for the first time at the site)

Subject Data
* DTI sequence
* Repeat DTI sequence
* MPRAGE with GRAPPA
* ADNI 3D T1
* T2 Weighted Acquisition
* Resting State Sequence

DTI only Sites:

Phantom Data
* DTI Sequence (send each time a DTI sequence is acquired)

- ADNI 3D T1 (Only sent one time, before ADNI sequences are used for the first time at the site)
-

Subject Data
- DTI sequence
- Repeat DTI sequence
- MPRAGE with GRAPPA
- ADNI 3D T1
- T2 Weighted Acquisition

An MRI Transmittal Source Document, Figure 13, should be sent to the imaging core lab with each MRI transmission.

Please note: MRI images should be sent de-identified (i.e. no patient names or dates of birth). Also, if CDs are sent, please make sure that both the CD case and the CD itself are labeled with Site ID#, Site Name and subject PID#.

Figure 13: MRI Imaging Data Transmittal Source

8   IMAGING CORE LAB CONTACT INFORMATION

For all questions relating to electronic file transfer and server issues, please contact

Jeremy Greenberg
Imaging Data Associate
Telephone: 203-508-1505
Fax: 203-401-4303
Email: jgreenberg@indd.org

For all technical questions (camera, image processing, file-naming, etc.):

Justin Albani
Imaging Technical Quality Control & Processing Specialist
Telephone: 203-401-4343
Fax :   203-401-4303
Email: jalbani@indd.org

For questions concerning completion of the forms, or if you need more supplies, please contact:

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