

# IDAE Users' Manual

The Integrative Data Analysis Environment for Brain PET

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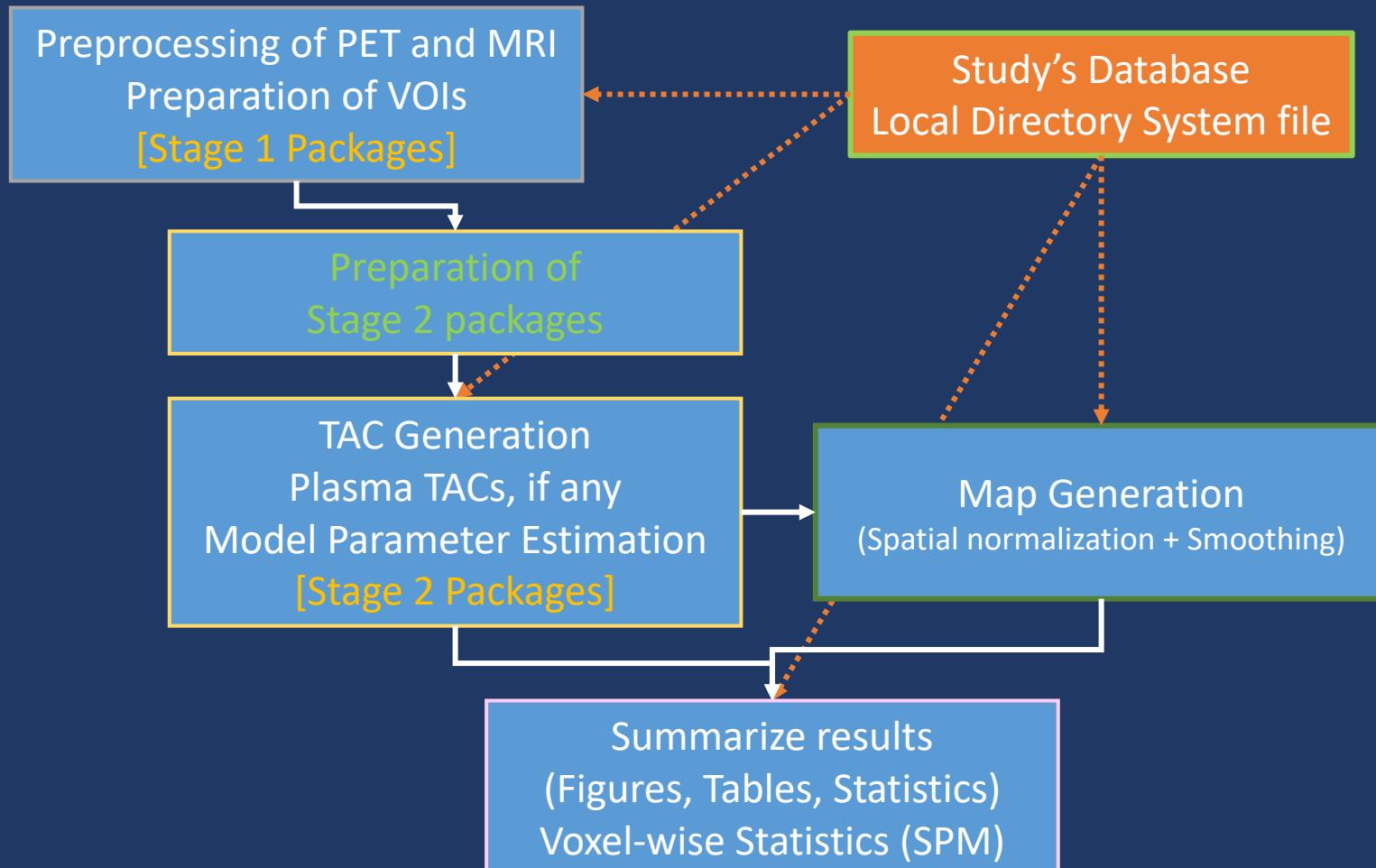
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# Introduction to IDAE

- The integrative data analysis environment (IDAE) is a comprehensive data analysis system for brain research using PET (and MRI):
  - Users can generate & manage (customize) analysis packages (a.k.a., pipelines), carry out the analyses, and summarize the results, all **via GUI and clickable, organized menus alone** (minimal editing).
    - ≈ IDAE is primarily intended to aid non-technical researchers such as neurologists, psychiatrists, and neuroscientists to perform PET data analyses, and thus presents the user with a step-wise procedure
  - IDAE is project oriented: Analysis packages interact with the study's database to perform analyses on groups of subjects, which made result-summary functions possible
    - ≈ A 'study' (a.k.a. 'project') refers to studying groups of subjects to address scientific hypotheses
    - ≈ Final products from IDAE for a study will be tables and figures for publications
  - IDAE's modular programming makes it easy to for technical scientists to incorporate free-ware or their own codes to analysis package bases
  - IDAE is built upon MATLAB (thus, independent to operating systems)
- Analyses are carried out as outlined in the Flowchart (next slide)
  - Users select / customize IDAE-supplied analysis package bases as needed for a study using GUIs alone
    - ≈ Stage 1 packages deal with preparation of PET, MRI, and VOIs (volumes of interest)
      - Each study typically has a few Stage 1 packages
    - ≈ Stage 2 packages deal with everything else. a few/several Stage-2 packages per Stage-1 package
  - Users prepare / update a database file (one per study) using GUI-based modules.
    - ≈ The database interacts with user-managed packages when carrying out the analyses.
  - Users can summarize the results (tables & figures) and perform statistics via GUIs alone
  - Local managers are required to local adaptor codes using a template to cope with site-specific data archive conventions (paths) and other settings.

# Analysis Flowchart



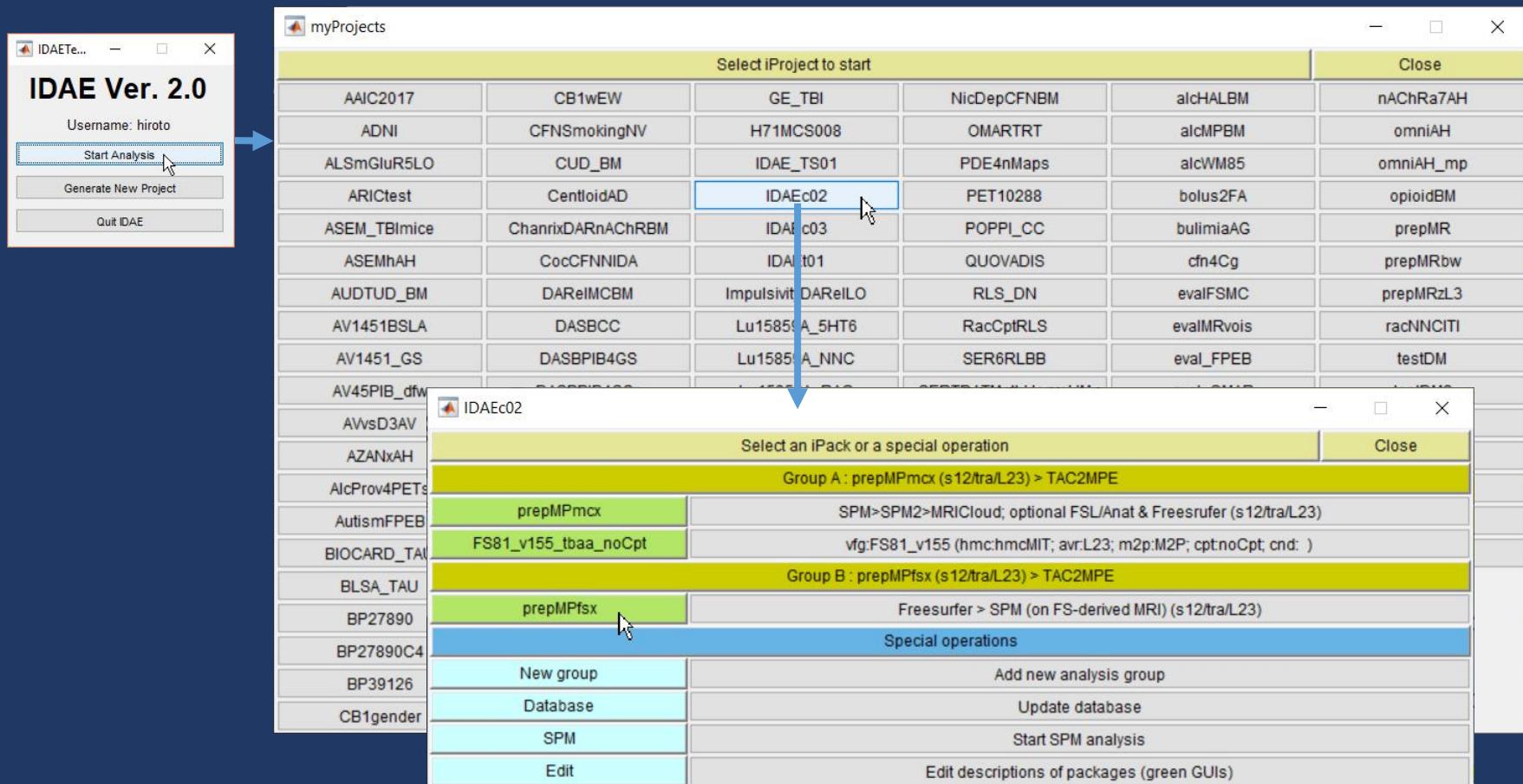
Flowchart showing major analysis components of brain PET studies. In IDAE, the **database** of the study interacts with a few **Stage 1 Packages** and several **Stage 2 packages** to carryout analyses on groups of subjects.

VOI: Volume of interest; TAC: Time-activity curve

# Performing Analyses with IDAE

- The next two slides outline the way analyses are performed using GUIs in IDAE
- To start a session of a desired package of a desired ‘project’:
  - Type as follows in Matlab command window: >> startIDAE yourUserName
  - Hit intended GUIs in successive GUI windows (three clicks alone)
  - Then the Level 1 Window of the intended package will pop up.
- Now, observe the L1W for completion statuses of subject-analysis block GUIs (the main GUI matrix)
  - Visit the subject-analysis block GUI that shows the lowest completion percentage
  - In the Level 2 Window that pops up, look for interactive (=i; darker green) and quality control (=c; lighter green) processes that display ‘r’ (=ready) on GUIs. Just visit/complete the process. Then, ‘r’ turns to ‘c’ for completed.
  - Once interactive and/or quality control processes are completed on intended subjects, highlight their subject GUIs (hit GUIs) on L1W and hit the ‘Perform’ GUI.
    - ≈ IDAE will stop processing at the first interactive or quality control (QC) process to work on in individual subjects
  - Repeat the sequences until all processes are done on all subjects / scans.
- Above performance principles apply to all IDAE packages that are shown in ‘Analysis Flowchart’

# Starting an IDAE Session



Sequences for starting an analysis package of a project (Indicated by blue arrows; 3 clicks alone):

- Hit 'Start Analysis' in the IDAE Control Module (left)
- Hit the GUI of the intended project in the Project Selector window (middle)
- Select the intended package from the package list of the project (lower panel)
- Then, the Level 1 Window of the package (prepMPfsx) will be generated (next slide)

# Carrying on Analyses with IDAE

## Level 1 Window (L1W)

Perform	i / c	Recover	Exit
Subjects	IDAE4MRI	IDAE4VOIs	IDAE4PET
S0001	85%	50%	90%
S0002	85%	50%	90%
S0003	85%	50%	0%
S0005	85%	50%	90%
S0006	85%	50%	90%
S0009	85%	50%	0%
S0011	85%	50%	0%
S0012	85%	25%	0%
S0013	85%	25%	0%
S0014	85%	25%	0%
S0016	85%	25%	0%
S0017	0%	25%	0%
S0018	85%	25%	0%
S0020	85%	25%	0%
S0021	85%	25%	0%
S0024	0%	25%	0%
Log	scanDB	Help	TAC2MPE
			sumRes

Analysis  
Blocks

Subjects

## Level 2 Window (L2W)

Update	Perform	Next	Exit
Subject	S0012		
Condition 1	[11C]raclopride, baseline		
Condition 2	[11C]raclopride, post-dose, 3h		
Condition 3	[11C]raclopride, post-dose, 8h		
Condition 4	[11C]raclopride, post-dose, 24h		
Condition m	MRI or common to all scans		
	1 2 3 4 m	Task descriptions	
i	- - - -	p generate scripts to run Freesurfer (FS)	
a	- - - -	c reformat FS-derived MRI (.mgz > .nii)	
i	- - - -	c define ACPC points on FS-derived MRI	
a	- - - -	c crop FS outputs around the brain	
o	r r r r	r plot left vs. right VOI volumes	
c	- - - -	c review/approve gray matter segmentation of FS	
d	- - - -	r correct FS81 VOIs, if needed (for local managers; MRI #1 of singleFS)	
o	- - - -	- review status of FS VOI revisions (MRI #1 of singleFS)	
o	- - - -	- review original GM outlines on MRI (MRI #1 of singleFS)	
	- - - -	*** No more tasks ***	
	Help	IDAE4MRI	IDAE4VOIs
		No function	IDAE4PET

Workflow

General sequences of performing analyses with IDAE:

- Observe the Level 1 Window (left) for completion statuses of subject-analysis block GUIs (the main GUI matrix)
- Hit the subject-analysis block GUI that shows the lowest completion percentage to get the Level 2 Window (right)
  - Look for interactive (=i; darker green) and quality control (=c; lighter green) processes that display 'r' (=ready) on GUIs.
  - Just visit/complete the process. Then, 'r' turns to 'c' for completed.
- Once interactive and/or quality control processes are completed on the intended subjects, highlight their subject GUIs (hit GUIs) on L1W and hit the 'Perform' GUI (above 'Subjects' GUI).
  - IDAE will stop processing at the first interactive or quality control process to work on in individual subjects
- Repeat the sequences until all are done

# Installation of IDAE

- Plan & create the following folders for IDAE
  - One folder for IDAE codes (e.g., C:\idae; referred to as ‘IDAE folder’)
  - Folders (one per user) for execution of IDAE (e.g., C:\users\UserName)
  - One folder to dump intermediate files (e.g., C:\tmp)
    - ≈ Place ‘scratch.m’ (any content; using MATLAB editor) in the dump folder
- Download the IDAE package from GitHub to the code folder and unzip it (unzip ‘here’)
  - Look for patches/additional releases occasionally. Do the same for them.
- Prepare a startup.m using IDAE-supplied template and place it to the directory where MATLAB looks when it is stated
  - See the section of ‘Preparation of startup.m’ for details
- Prepare the local adaptor file in the dump folder
  - See the section of ‘construction of local adaptor file’ for details

# Initial Set-up for IDAE (JM)

- Preparation for using IDAE:
  - Mount shared drive/server hosting IDAE
    - ≈ We trust you do not explore other directories of K due to presence of HIPPA sensitive materials.
  - Create a folder to dump intermediate files (C:\tmp)
    - ≈ Place 'scratch.m' (any contents) in the dump folder
  - Copy X:\tmp\startup\_K.m to where MATLAB looks in when started (typically C:\Users\junhua\Documents\MATLAB) and rename it to startup.m
    - ≈ Restart MATLAB and confirm the you have K:\mxxs12 folders in your path
- Setting the first project
  - Let's set it in a primitive way (more user-friendly ways later)

```
>> iv2_serFolders('dxetc4hkx', 'junhua', 'IDAEc01', 2);
```

    - ≈ Note that quotation marks are not copied correctly.
    - ≈ Create X:\users\junhua\idae if above line does not work well.
    - ≈ Replace your IDAEc01\_scanDB.m with lines 1 through 32 of my IDAEc01\_scanDB.m (folder: X:\users\hiroto\idae\IDAEc01).
    - ≈ Then, index your IDAEc01\_scanDB.m as follows:

```
>> iv2_register X:\users\junhua\idae\IDAEc01\IDAEc01_scanDB.m junhua
```
    - ≈ Create X:\tmp\Freesurfer\junhua (added on 1/20/22)

# Preparation of startup.m

	<ul style="list-style-type: none"> <li>Take a directory where you have processed PET-related files: X:\abc\fdaha\PET220211\am\103123\pet_data</li> </ul>
	<ul style="list-style-type: none"> <li>Let's assume you choose to place files from IDAE in subfolders 'idae': X:\abc\fdaha\PET220211\am\103123\pet_data\idae</li> <li>Identify the subject ID segment, segments that are shared with the PET-MRI server, and segments that vary.</li> </ul>
	<ul style="list-style-type: none"> <li>Replace the special segments with designated special segment strings X:\abc\\$\\link_seg_1#\link_seg_2\pet_data\idae</li> <li>Note that 'fixed' segments between special segments are treated as varying segments</li> </ul>

# Construction of the Local Adaptor File

- IDAE assumes the following 4 computer classes

Computer classes	Descriptions	Supported OS
Users' workstation	PCs or workstations to run IDAE	Windows 10 / Linux
Local file server	To store outputs from IDAE <ul style="list-style-type: none"><li>• will be generated by IDAE</li><li>• organized by subjects and PET &amp; MRI scans</li></ul>	Windows / Linux
PET & MRI server	To provide reconstructed PET and MRI files	Windows / Linux
Linux machine	To run Linux-based applications for IDAE	Linux

- They could be physically identical (e.g., local file server = PET & MRI server)
- The local IDAE manager is requested to generate the local adaptor file:
  - Once alone
  - Starting template: `inq_windows10.m` (if Window > Linux) or `inq_Linux.m` otherwise
    - ≈ See next slide for more explanations
  - Once the template is done, submit it to `iv2_gen_dxetc4xxx.m` as follows:  
`>> iv2_gen_dxetc4xxx('inq_whichever', 'dxetc4whatever')`  
where the second input is the name of local adaptor file of your choice.

# Construction of the Local Adaptor File

[reminders for later use]

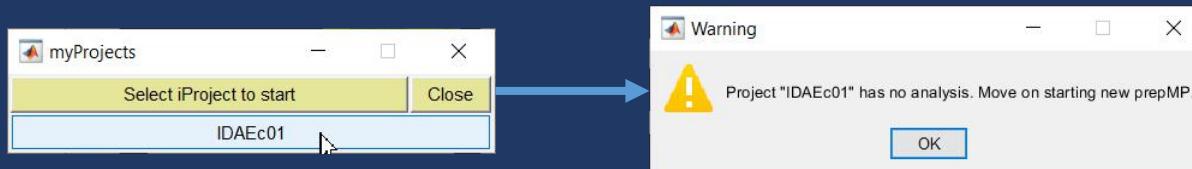
- Setting for Freesurfer
  - Set dxetc4xxx such that >> x = dxetc4xxx('fsd','avatar948') returns:
    - ≈ x.fs.home: the full path of the folder to place IDAE-generated scripts to run Freesurfer
    - ≈ x.fs.linux: the same as x.fs.home but the full path in the Linux system where Freesurfer is installed
    - ≈ x.fs.subj: the full path of the Freesurfer's working directory (e.g.,  
/home/avatar948/freesurfer/subjects)
  - Place a text file (name: FS\_done.txt; any contents) in your x.fs.subj
- Yong Du kindly agree to be a test site for preparation of the local adaptor file
  - Ours: dxetc4hkx.m
  - Two ways we can test:
    - ≈ Junhua gets into their system and complete the local adaptor file
    - ≈ Yong or his people construct the file using the instruction
  - Whichever, we need to provide the distribution set Junhua created.

# Setting the first project

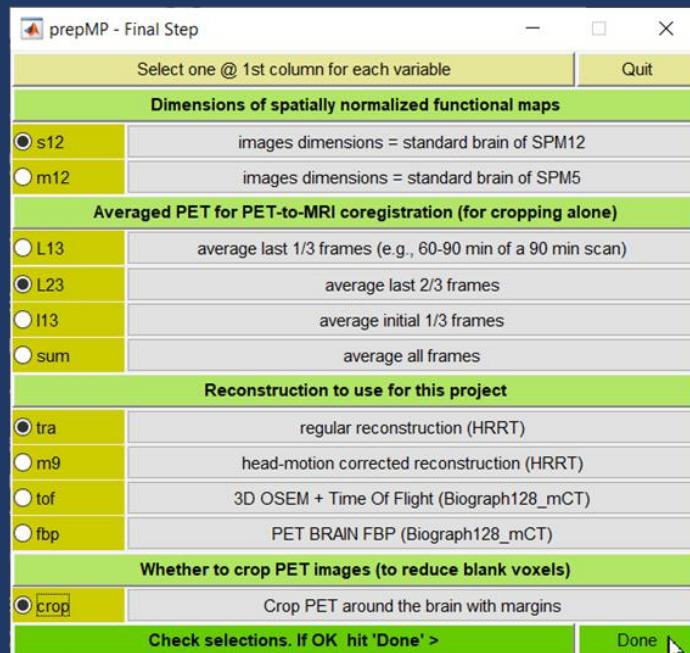
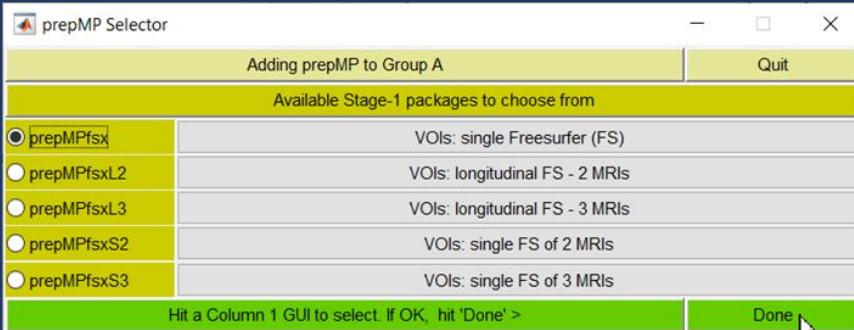
- The IDAE team suggest to set the first project in a manual approach
  - Why manual approach? To help users understand the basic mechanisms better
    - ≈ Users can find GUI-based approaches here
  - Hypothetical strings of this manual. Need to replace them by actual strings
    - ≈ ‘dxetc4xxx’ stands for your local adaptor file.
    - ≈ ‘avatar948’ stands for a hypothetical IDAE user.
    - ≈ ‘IDAEc01’ stands for a demonstration project.
  - Type (and hit return) as follows MATLAB command (>> indicate MATLAB command lines):  
`>> iv2_serFolders('dxetc4xxx', 'avatar948', 'IDAEc01', n);`
    - ≈ n stands for the number of PET scans per subject in the project
    - ≈ Note that quotation marks are often not copied correctly to MATLAB command window
    - ≈ Don’t forget to create the user folder (See Installation of IDAE).
    - ≈ The database template (X:\users\avatar948\idae\IDAEc01\_scanDB.m in this manual) will be generated and opened for editing
  - Edit the scanDB.m as instructed therein:
    - ≈ Once completed, save & index it as follows:  
`>> iv2_register X:\users\avatar948\idae\IDAEc01\IDAEc01_scanDB.m avatar948`
    - ≈ Again, need to replace hypothetical strings with actual ones
    - ≈ If the indexing is successful, move on the next step.

# Setting Stage 1 Package for Projects

- Enter as follows in the command window:  
`>> startIDAE avatar948 dxetc4xxx`
  - To open the myProject module (left)
    - ≈ The module display one project alone since this is the first project
    - ≈ The number will grow as more projects are accumulated (See ‘Starting an IDAE Session’).
- Hit the project GUI (‘IDAEc01’).
  - It is ‘as-expected’ to get a warning sign (right panel).
  - Just hit ‘OK’ to proceed to composing the first Stage 1 package for the project (next slide)



# Preparation Stage 1 Packages

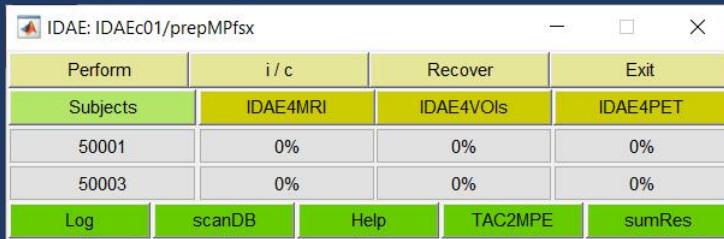
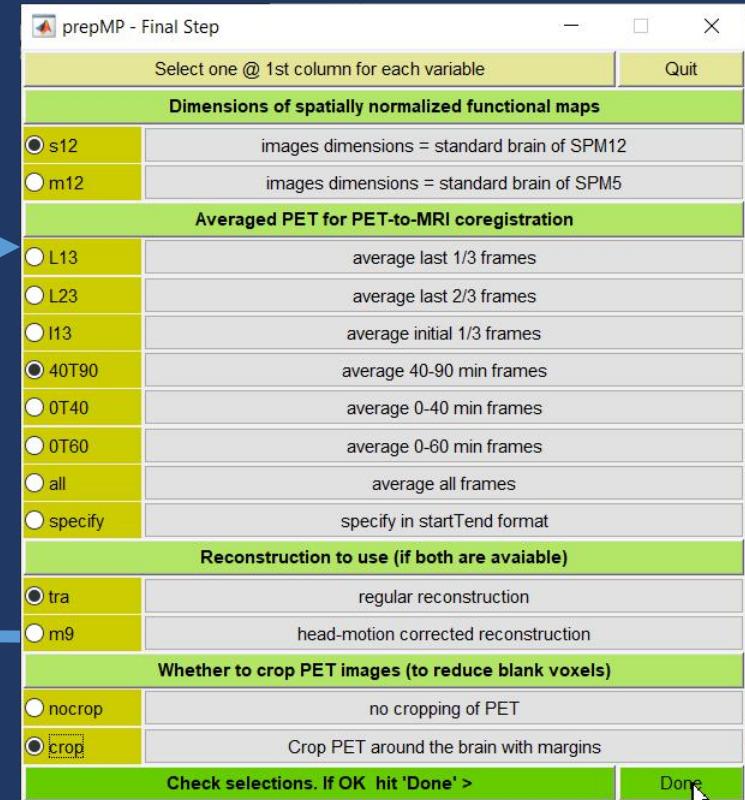


To set locally

- Just 7 clicks (< 10 s) to get ready to start the analysis with a Stage-1 package
  - Select 'prepMPfsx', the only Stage-1 package in this release and hit 'Done' (upper panel)
- Select parameters in the 4 sections in the next module (lower panel) and hit 'Done'
  - Read 'Information' tabs (light green)
  - Averaged PETs are used for obtaining a global TAC to understand if individual scans have any problems (such as early termination, scan breaks)
    - ≈ Available options are convenient for this purpose which may need to cope with different durations of scans
    - ≈ For example, L23 will use 30-45 min frames if the scan terminated prematurely at 45 min instead of the planned 90 min
    - ≈ Note that 'sum' is a good option as well
  - The local IDAE manager needs to set the last two sections (reconstruction & cropping) in the local setting file (dxetc4xxx.m)
- Then, Level 1 Window (L1W) will pop up. Users are ready to start the analyses.

# Completing Stage 1 Packages

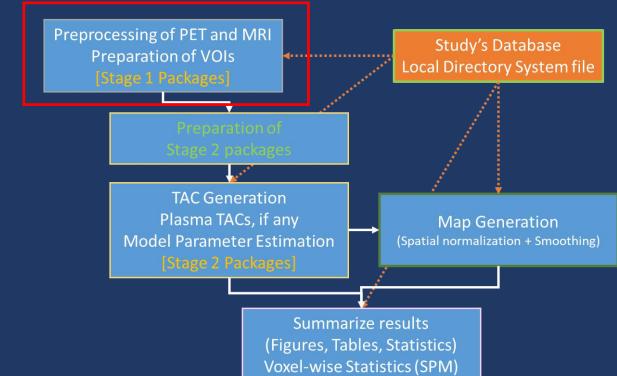
- Just 7 clicks to the completion of a Stage-1 package:
  - Select ‘prepMPfsx’, the only Stage-1 package in this release and hit ‘Done’
  - Select recommended parameters in the next module (right panel) and hit ‘Done’
    - ≈ Read ‘Information’ tabs (light green)
    - ≈ Averaged PET is primarily used for cropping PET in Stage-1 (not so critical)
  - Then Level 1 Window will pop up (left bottom). You are set to start the analysis.



# Outlines of 'prepMPfsx'

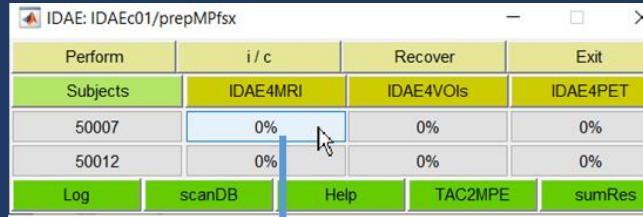
Three analysis blocks in prepMPfsx

- Automated parcellation of brain regions using the Freesurfer software\* for (block name: IDAE4MRI). Major steps include:
  - Generation of scripts for running Freesurfer outside IDAE (to avoid stalling MATLAB)
  - Visual confirmation of the outputs using outlines of gray matter regions
    - ≈ Manual correction of insufficiencies, if any (optional)
- \*Available at: <https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki>
- VOI-related operations (IDAE4VOIs) (VOI = volume of interest):
  - Selection of VOIs to refine (to focus) and reference regions
  - Manual refinement of above-mentioned (and added non-Freesuefer) VOIs
- PET-related operations (IDAE4PET):
  - Cropping of PET frames around the brain with margins, if selected.
  - Initial coregistration of averaged PET to the Freesurfer-derived MRI
    - ≈ Visual evaluation/correction, if needed of the coregistration
    - ≈ Visual evaluation of head motion

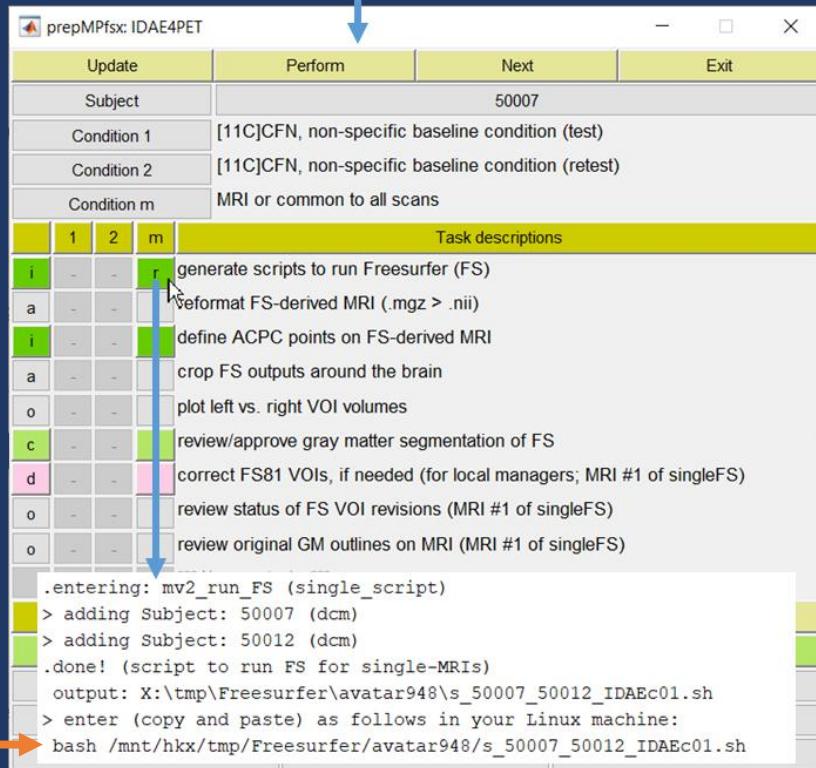


# Generate scripts to run Freesurfer (FS)

L1W



L2W



General sequences of performing analyses apply here as well:

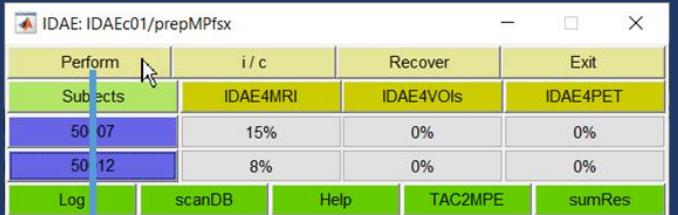
- Visit the subject-analysis block with the lowest complete percentage in L1W
- Visit the first interactive (=i; darker green) or quality control (=c; lighter green) processes that displays 'r' (=ready)
  - The application opens with files selected
  - In this step, the command line to submit to your Linux machine (→) will be displayed on MATLAB command line (bottom row). Just copy and paste/submit it.
  - Up to 3 MRIs were submitted at one time

[Some technical notes]

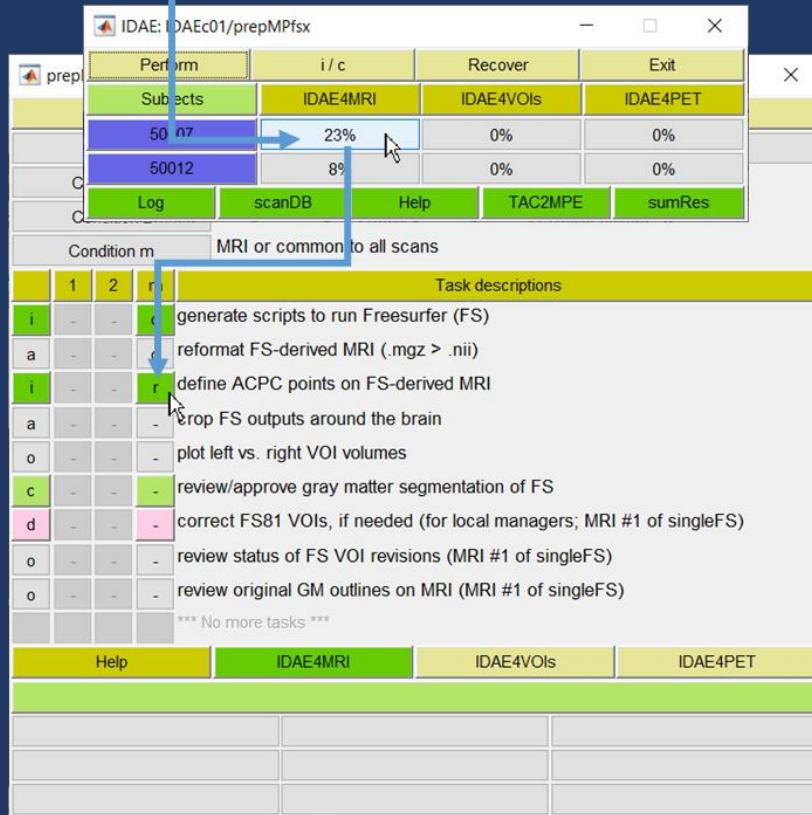
- information on the access to Freesurfer, etc. is defined in your local adaptor file.
- IDAE chose to run Freesurfer outside IDAE to avoid stalling MATLAB while execution of Freesurfer (~6 hours per MRI)

# Define ACPC Points

L1W

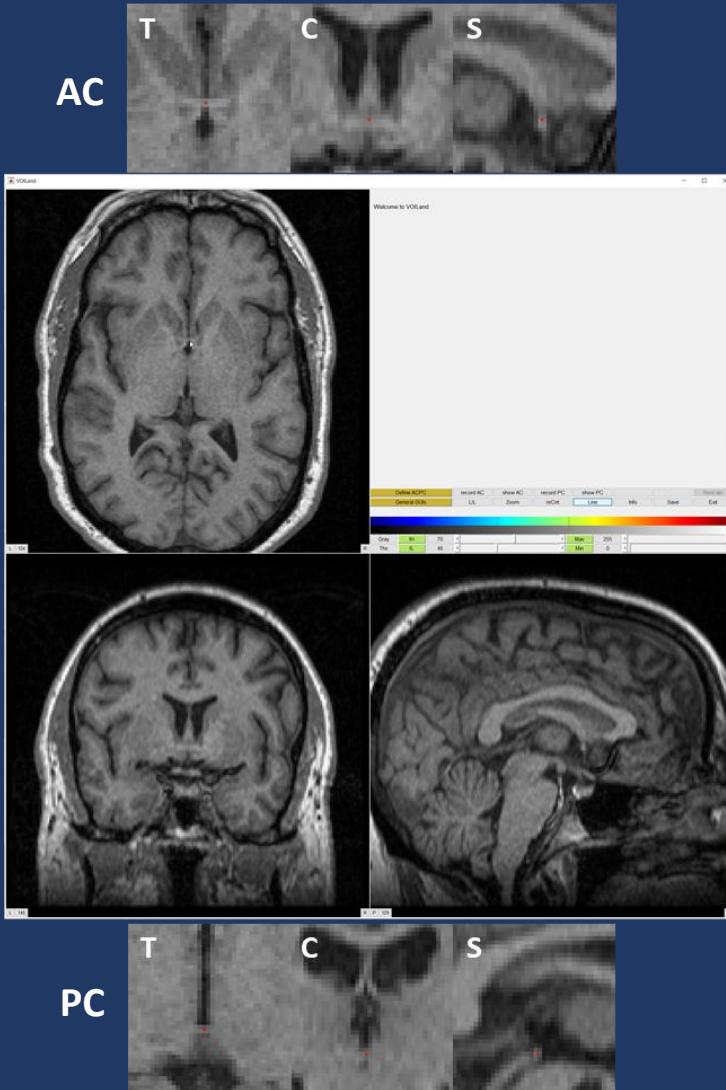


L2W



- Assume that the Freesurfer script was submitted yesterday, and the user revisited the project/package
  - The percent completion statuses increased on GUIs under IDAE4MRI.
  - So, highlight subject GUIs (now deep blue) and hit the ‘Perform’ GUI in L1W to perform available automatic processes (= ‘a’ in L2W)
  - Completion statuses increased on the first subject (15 to 23%) but not for the second subject [i.e., Freesurfer not completed yet].
  - Open L2W (middle then bottom panels)
  - Look for the first dark or light green GUI with ‘r’ (=ready) which is ‘define APCP points on FS-derived MRI’ (right column) in this example
  - Hit the ‘r’ GUI to open the application, VOILand with files selected (next slide).

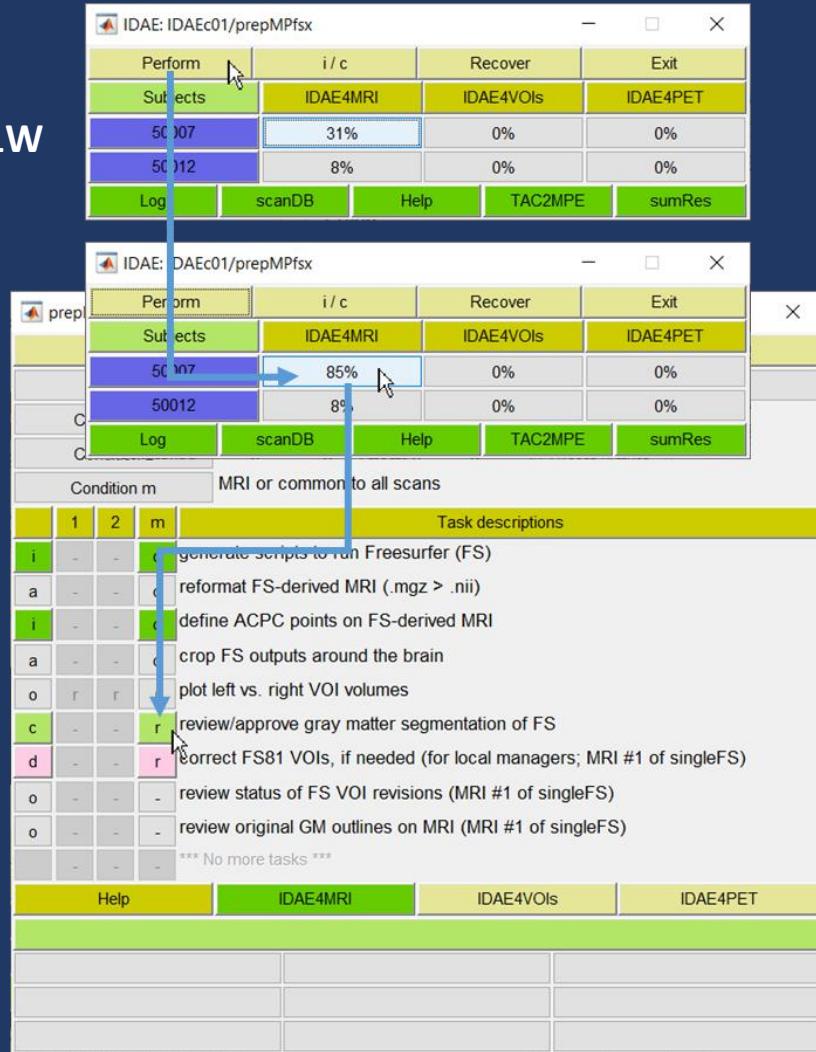
# Defining ACPC Points



- Define the anterior and posterior commissure points (AC and PC) on the MRI
  - To be consistent with SPM12 which assumes the AC as the origin of the image coordinate system
- Procedures:
  - Navigate images to display the AC point in all orthogonal images (middle panel)
    - ≈ Image navigation: Hit u/n keys (for up/down in axial direction), i/m keys (towards the inion/nasion, but m), </> keys (towards your left/right)
    - ≈ Click at any point on the colormap bars when above keys do not respond
  - Hit at the AC point (arrow in the trans-axial image) to display red dots (one per view)
    - ≈ Fine adjustments using number keys: Hit 8/2 keys to displace the dots in anterior/posterior directions, 4/6 to keys to towards your left and right, and 9(Pg Up)/3(Pg Dn) in the up(=cranium)/down directions
    - ≈ Target: Slightly above the center of the AC point (See upper panel)
    - ≈ Hit ‘save AC’ GUI when done
  - Repeat the same for the PC points
    - ≈ But at the middle of PC (bottom panel)
  - Make sure to click on ‘Save’ then ‘Exit’ GUIs (after seeing ‘safe to exist’ message).

# review/approve gray matter segmentation of FS

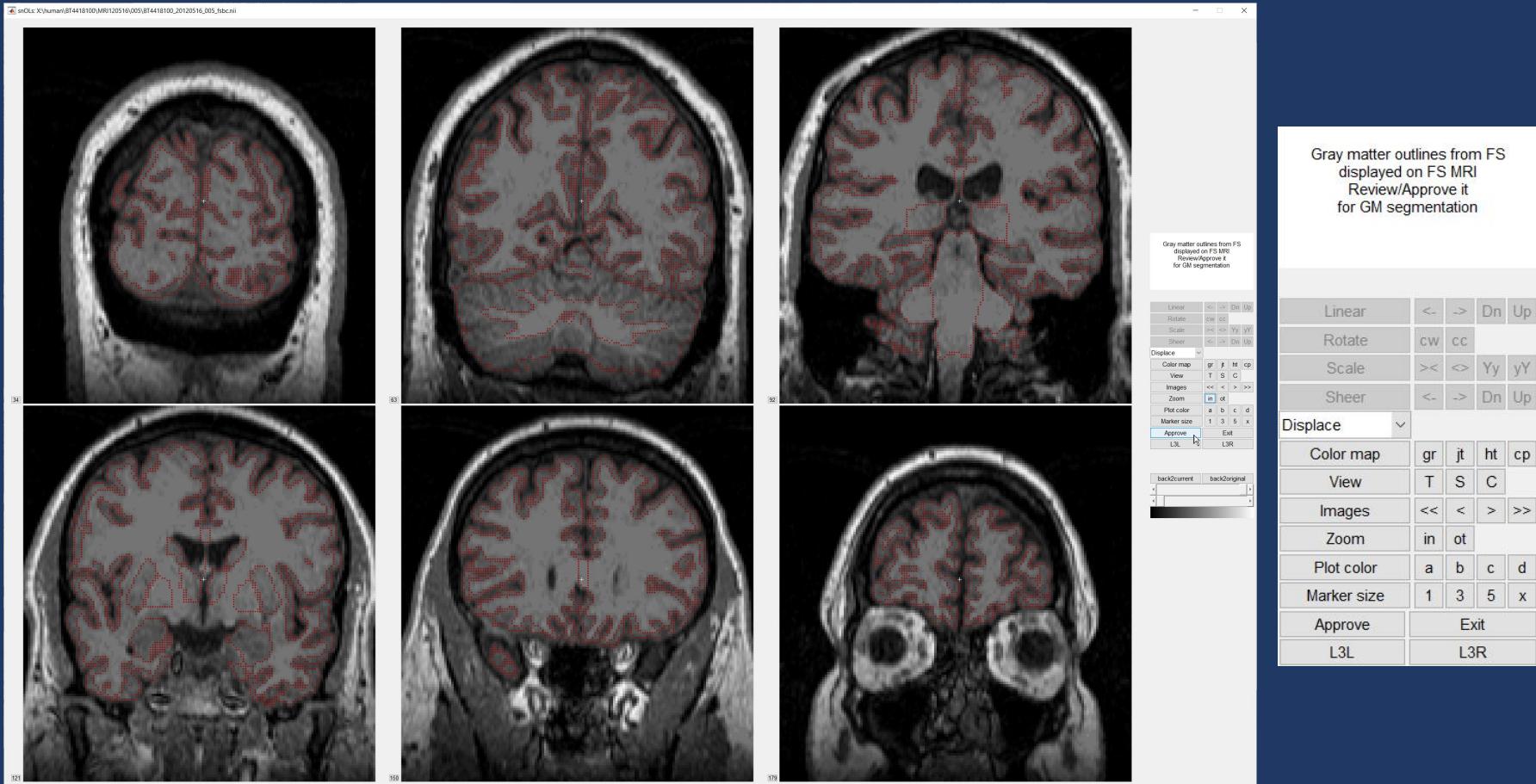
L1W



L2W

- The percent completion status increased since the ACPC points were set.
  - Hit the ‘Perform’ GUI on L1W to run automatic processes through the next interactive or QC process.
  - Once done with increased percentages, hit the subject-block GUI again.
  - Now, the first dark or light green GUI with ‘r’ (=ready) says it’s time to ‘review/approve gray matter segmentation of FS’
  - Hit the GUI to open the application (snOLs.m) for visual inspection (See next slide).
- Consequences:
  - Move on to the next block (for this subject) if you approve the outputs from Freesurfer
  - If not (i.e., some problems), move on the correction of Freesurfer-derived VOIs
    - ≈ Only trusted users (defined in dxetc4xxx) are allowed to access this optional step (pink)

# Review/Approve GM segmentation of Freesurfer



The outlines of gray matter (with all GM VOIs merged) from Freesurfer are projected on MRI in three orthogonal views in turn (5 s per view)

- Evaluate if GM outlines agree with GM of the MRI. Hit 'Approve' GUI if OK (arrow)
  - Use T (trans-axial), S (sagittal), and C (coronal) GUIs under 'view' to change views.
  - Use arrow GUIs under 'Images' to navigate 'slices'

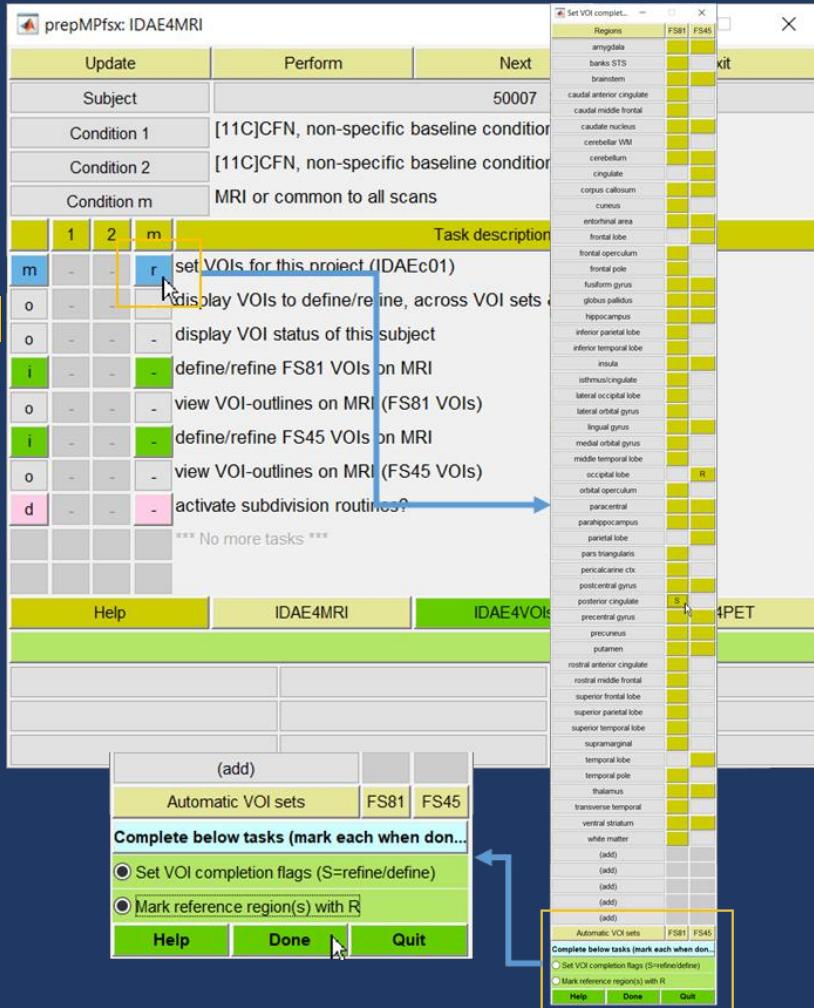
# To Make Interactions with IDAE Enjoyable

- Sometimes users could be frustrated by the behavior of IDAE
- Most of them are caused by users' unexpected behaviors in our experience.
- Thus, keep in mind:
  - GUIs are often left 'active' after a GUI is clicked. Thus, MATLAB (and IDAE) will be confused if any GUI is hit before on-going instruction is completed.
  - So, please be patient until the emitted task is completed.
  - The development team try to include 'be patient .. ' messages as much as possible
  - MATLAB command window shows the 'busy' sign at the bottom
    - ≈ When questionable, hit 'return' in the command window. The sign may appear if it is processing. If you do not see the 'busy' sign, you are good to emit the next command

# IDAE4VOIs

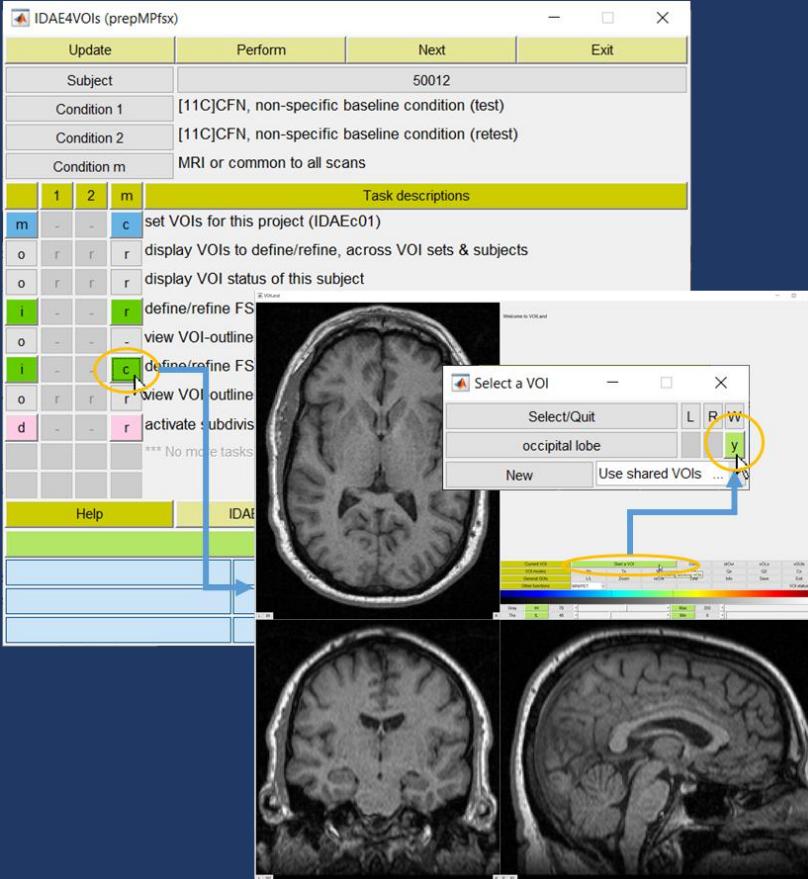
- Set VOIs to refine/define for the project
  - Background: IDAE makes use of Freesurfer-generated VOIs. It appears to be practically impossible to refine all the VOIs (>85) in every MRI.
    - ≈ IDAE provides two sets of VOIs for the sake of convenience: **FS81** that are almost identical to original Freesurfer VOIs; and **FS45** with VOIs re-organized to be conventional larger VOIs.
  - IDAE's strategies to cope with the issue:
    - ≈ To set & refine a subset of the VOIs that are critical for the project (denoted as 'S' VOIs)
    - ≈ To set & define from scratch those VOIs that are not generated by Freesurfer (= 'S' VOIs also)
    - ≈ To set & refine/define reference regions (target-free regions; need one even none) (= 'R' VOIs)
  - Set the S/R VOIs at 'set VOIs for this project' (the first task of IDAE4VOIs)
    - ≈ Hit the GUIs of intended VOIs (toggles among 'no-mark', 'S', and 'R') in the module which pops up when the task GUI is hit on L2W.
    - ≈ Record the selections when done (See next slide) as a set of VOIs
    - ≈ Users can add 'S' and 'R' VOIs later as needed (changes from 'S'/'R' to 'no-mark' are not allowed). The displayed selections will be saved as a new set upon completion of the saving processes.
- Refine/Define 'S' and 'R' VOIs, separately for FS81 and FS45
  - Visit FS81 and/or FS45 versions according to the setting of 'S' and 'R' VOIs

# IDAE4VOIs: ‘Set VOIs for this project’



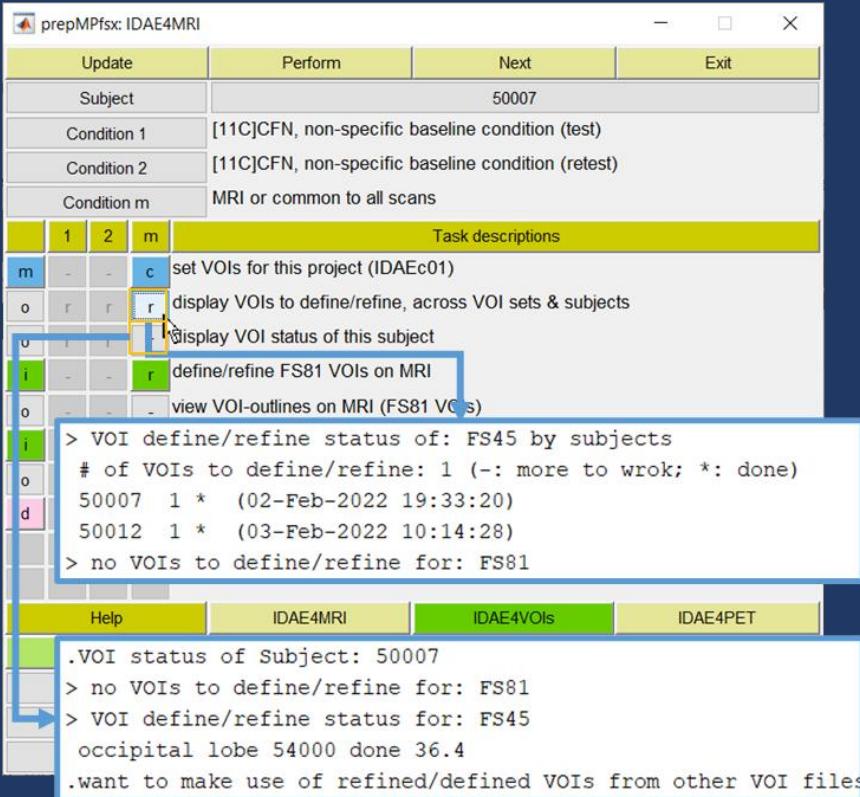
- Popup the VOI setter module
  - Hit the first GUI (arrow & orange rectangle)
- Columns are for:
  - FS81: almost identical to Freesurfer VOIs
  - FS45: a reorganized version of FS81 into conventional larger VOIs
  - Colored GUIs indicate available VOIs from Freesurfer
- Hit the GUI of the intended VOI in the module
  - Toggles among ‘no-mark’, ‘S’, and ‘R’
  - Hit a ‘(add)’ GUI to add non-Freesurfer VOIs
  - Selections shown in this manual are for demonstration purpose alone
- Once all intended VOIs are marked:
  - Check if all ‘S’ VOIs are marked (none is OK)
  - Check if all ‘R’ VOIs are marked (at least one)
  - Then, hit ‘Done’
- Make use of 2<sup>nd</sup> and 3<sup>rd</sup> tasks (‘display VOI...; marked by a orange bar) of L2W to monitor completion status of the ‘S’ and ‘R’ VOIs in individual subjects
  - It’s convenient to know which MRI to work

# Define/Refine VOIs



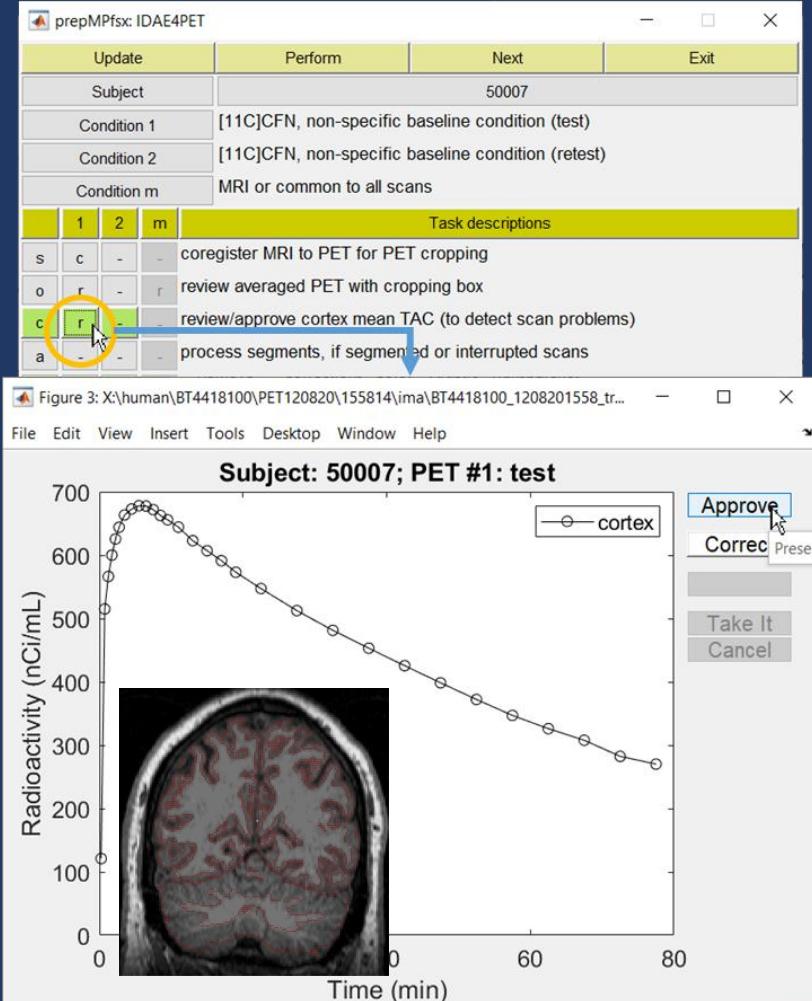
- Hit the green (One each for FS81 or FS45 VOIs) GUI (left orange circle):
  - The application, VOILand will open with input (MRI) and output (VOI) files selected.
- Hit 'start a VOI' GUI on the VOILand window to open the VOI selector (inset)
  - The 'S' and 'R' VOIs will be listed here.
    - ≈ The occipital lobe in this example which is defined in FS45 set alone. Therefore, the FS45 set was hit (the second green GUI).
    - ≈ 'y' means not worked yet.
  - See the VOILand manual to learn how to refine/define VOIs.
- Good to know:
  - IDAE generates one set each of FS81 and FS45 VOIs to be shared by users.
    - ≈ Users are not allowed to edit the shared sets
  - User-defined 'S' and 'R' VOIs were copied from the shared sets to users' personal files, if present.
  - Both shared and personal VOI files are used when to generate time-activity curves, TACs.

# Convenient Option Processes for VOIs



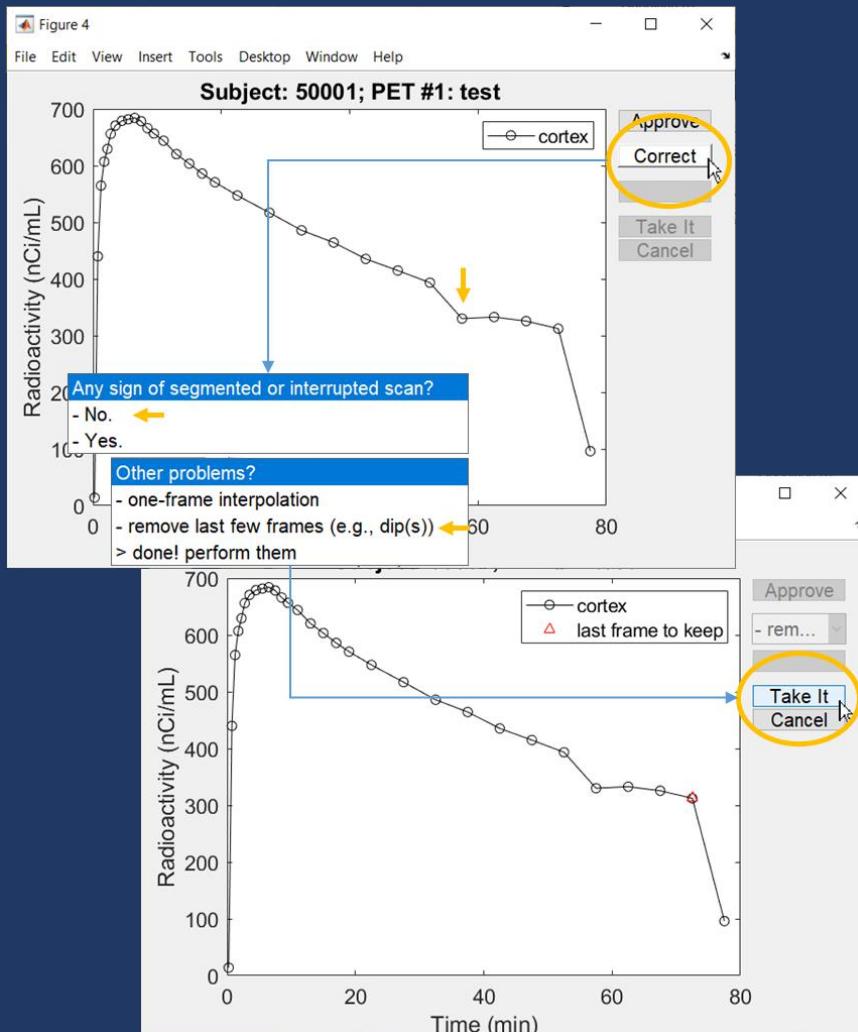
- Two optional processes could be very useful to know which VOIs of the 'S' and 'R' VOIs are left incomplete
- 'Display VOIs to define/refile, across VOI sets & subjects' (upper GUI)
  - Will list # of VOIs to define/refine (i.e., 'S' + 'R') and completion statuses of individual subjects (- if left incomplete; \* if completed with date/time of completion)
  - Thus, the user can visit those incomplete sets and subjects.
- 'Display VOI status of this subject' (lower)
  - Will list VOIs to define for this subject, separately for FS45 and FS81 VOI sets.
- In sum, know which subject to work from the upper GUI, and which VOIs to work for the subject from the lower GUI
  - In addition, a GUI (VOI status) is provided to display VOI completion statuses of the 'S' and 'R' VOIs on the VOILand window.

# IDAE4PET: Mean Cortex TACs



- Review/approve cortex mean TAC
  - Derivation of the cortex mean TAC
    - ≈ Marginal voxels of gray matter (red dots of the inset) were transferred to the PET according to the PET-to-MRI coregistration parameters and applied to successive PET frames
    - ≈ The user of marginal voxels is expected to be sensitive to head motion, if any
  - Hit the first light green GUI (arrow in orange circle) of L2W to display the plot
    - ≈ Look for any sudden dips (often suggestive of bathroom breaks), or shorter than expected scans (early termination).
    - ≈ If no such problems, ‘approve’ it (arrow)
    - ≈ Otherwise, visit ‘Correct’ GUI. Note that the local IDAE managers need to set this section according to local conventions
- Once it is approved:
  - Highlight those subjects for whom mean TACs are newly approved in L1W and hit ‘Perform’ GUI to process a group of subjects, or
  - Hit ‘Perform’ GUI of L2W (top row) to process ready-to-run automatic processes of current subject

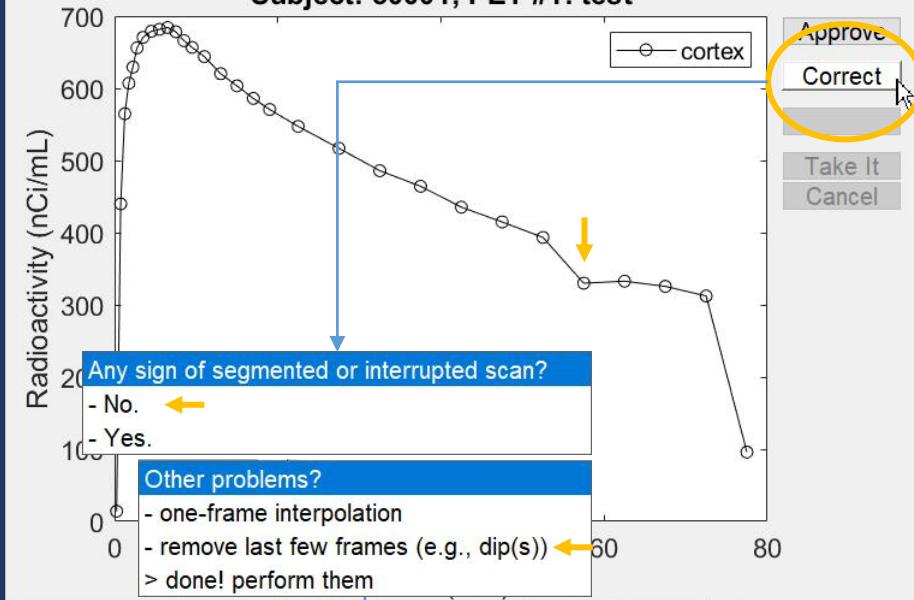
# Correction of Potential Scan Problems



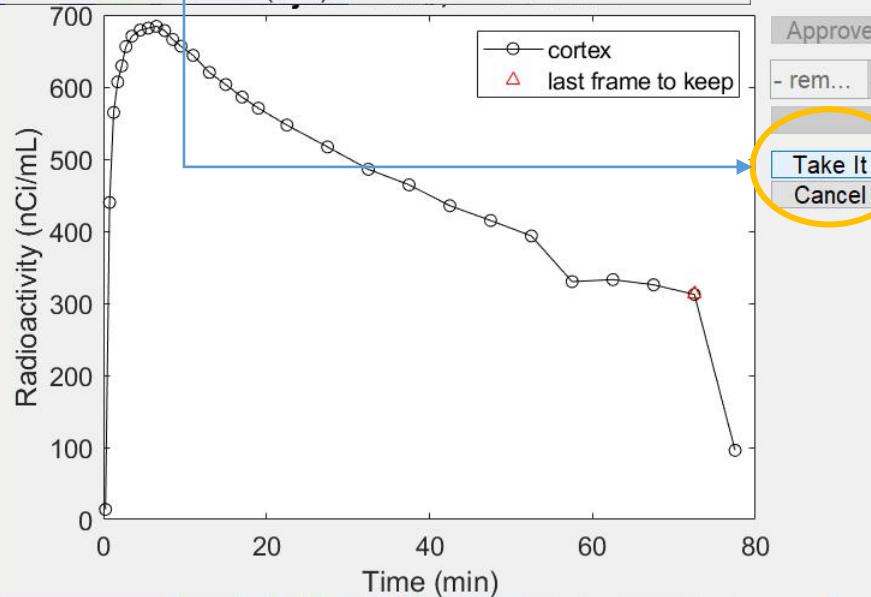
- Some of scan problems can be ‘corrected’ at this stage, if any
- In this example, the mean cortex TAC had a dip at the last frame and lesser dips just before 50 min (vertical arrow).
  - The dip at the last frame may not be ‘corrected’ but it is possible to eliminate the last frame from further analysis.
  - It may be possible to ‘correct’ the lesser dips by the head motion correction approaches
  - So, let’s eliminate the last frame
- Procedures:
  - Hit ‘Correct’ GUI (upper orange circle)
  - Respond to successive inquiries
    - ≈ Correction approaches for segmented (by e. g., bathroom breaks) or interrupted (often planned) scan are site-specific (reconstruction approaches). Thus, those approaches are not included in the distribution set.
  - Point at the last frame to keep (red triangle) and hit ‘Take It’ GUI, if OK
  - The frames up to the red triangle (inclusive) will be used in subsequent analyses.

Figure 4

File Edit View Insert Tools Desktop Window Help

**Subject: 50001; PET #1: test**

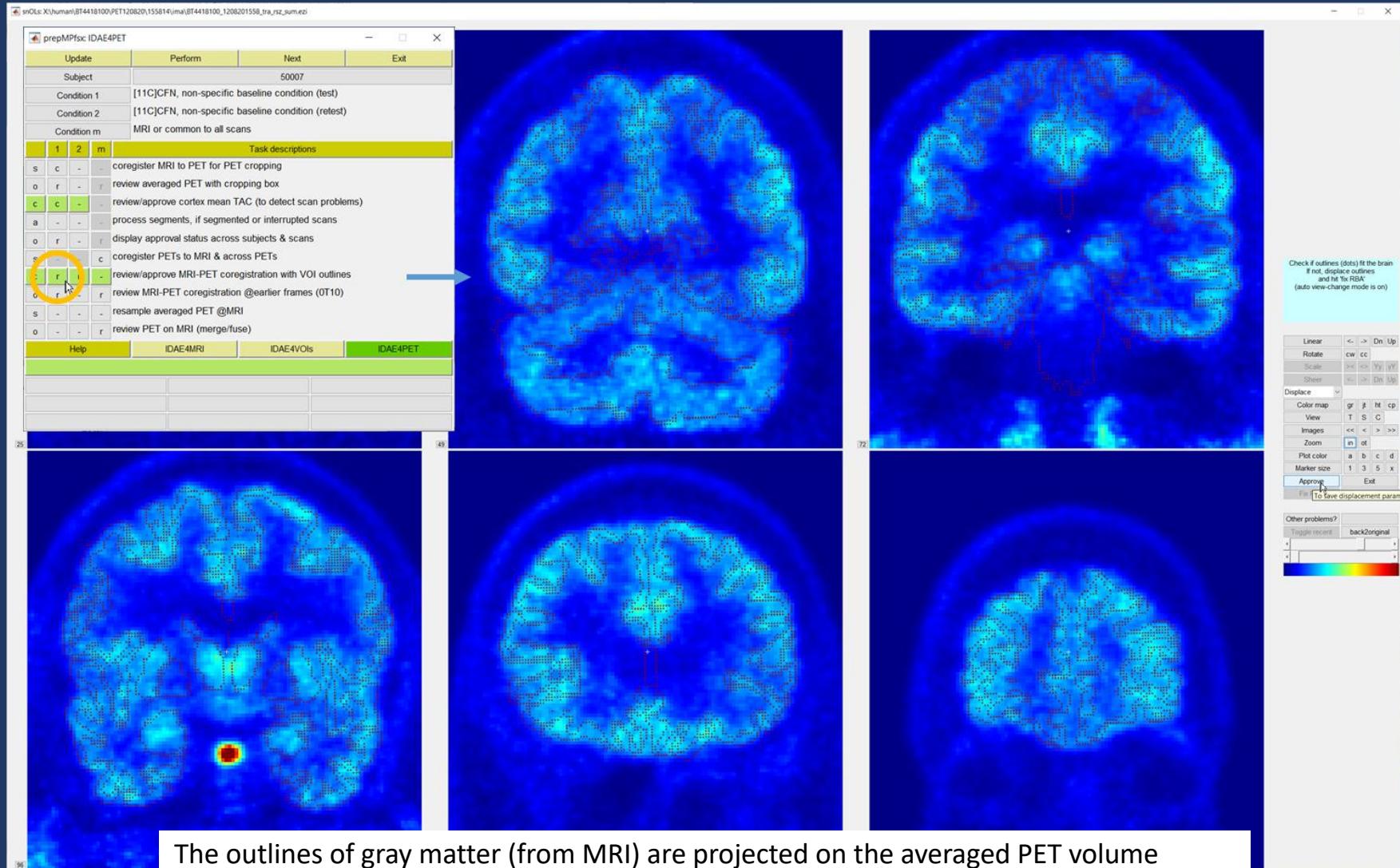
Approve  
Correct  
Take It  
Cancel



Approve  
- rem...  
Take It  
Cancel

Approve  
- rem...  
Take It  
Cancel

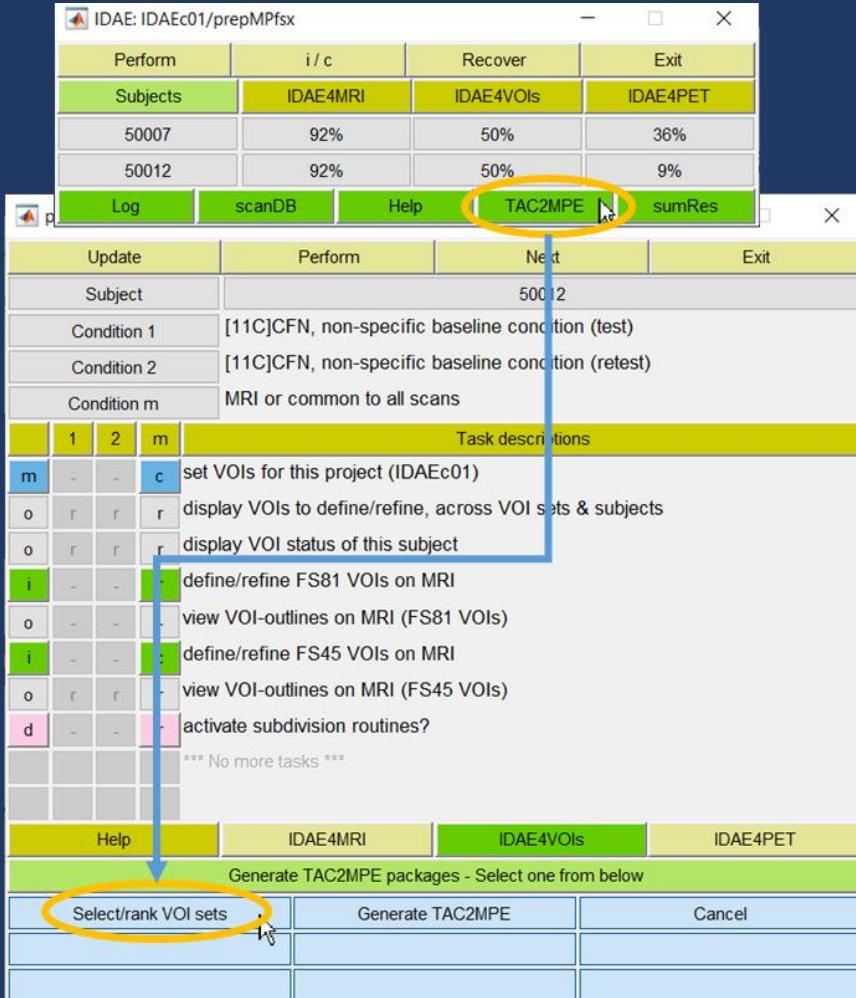
# IDAE4PET: Coregistration QC



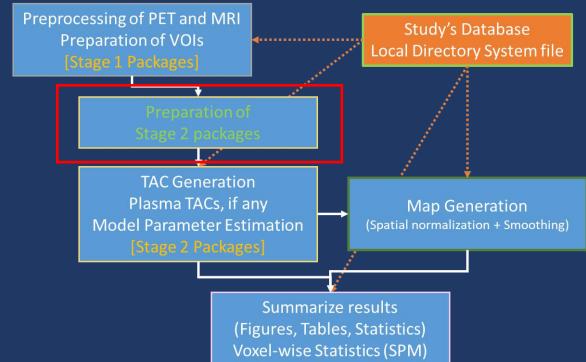
The outlines of gray matter (from MRI) are projected on the averaged PET volume

- Evaluate if GM outlines agree with the PET volume. Hit ‘Approve’ GUI if OK (arrow)
  - Use T (trans-axial), S (sagittal), and C (coronal) GUIs under ‘view’ to change views.
  - Use arrow GUIs under ‘Images’ to navigate ‘slices’

# Preparation of Stage 2 Packages



- Stage-2 packages are to generate TACs and perform model parameter estimation (MPE)
  - Usually there will be several Stage-2 packages per prepMPfsx due to:
    - ≈ Revisions of 'S' and 'R' VOIs
    - ≈ Selections of the parameters in the next step
- Start the preparation with 'TAC2MPE' GUI of L1W (upper orange circle)
- Two potential scenarios (lower GUIs of L2W)
  - To define 'VOI sets', select 'Select/rank VOI sets' tab (lower orange circle)
    - ≈ Move on to understand what are 'VOI sets'
  - To apply a new set of 'other' parameters to a VOI set, hit 'Generate TAC2MPE' GUI

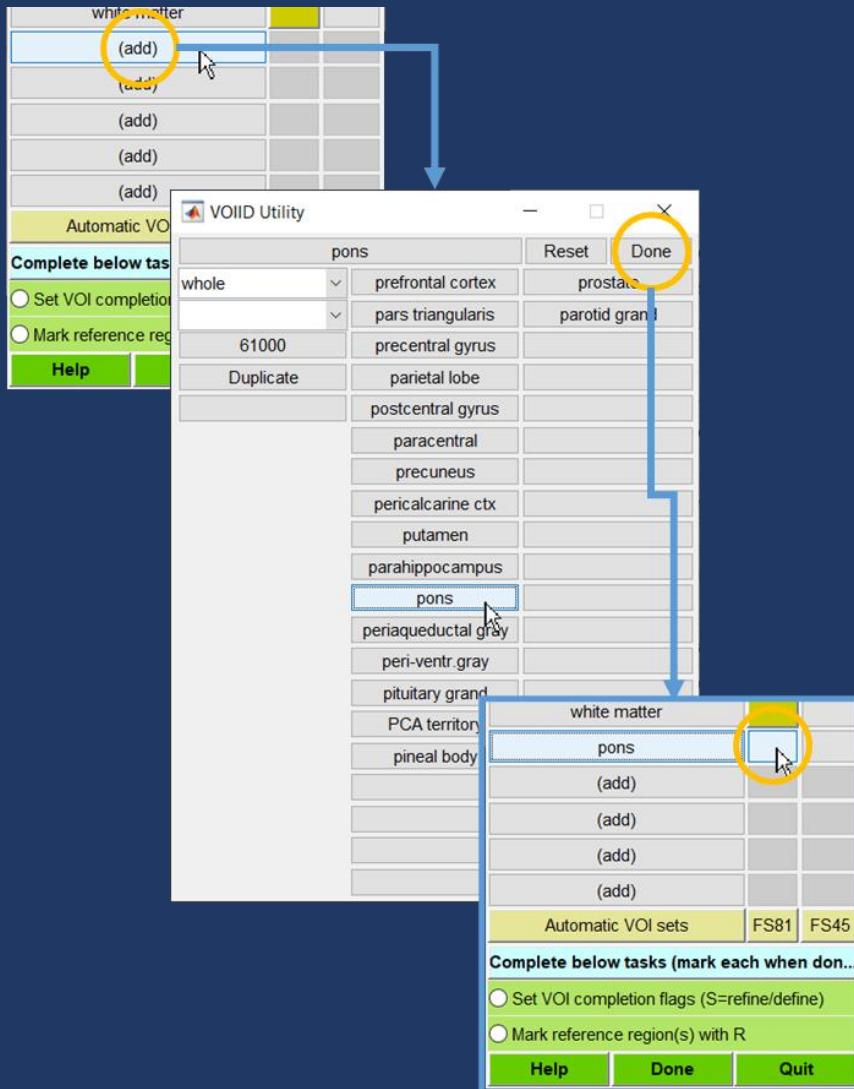


# Setting VOI Sets



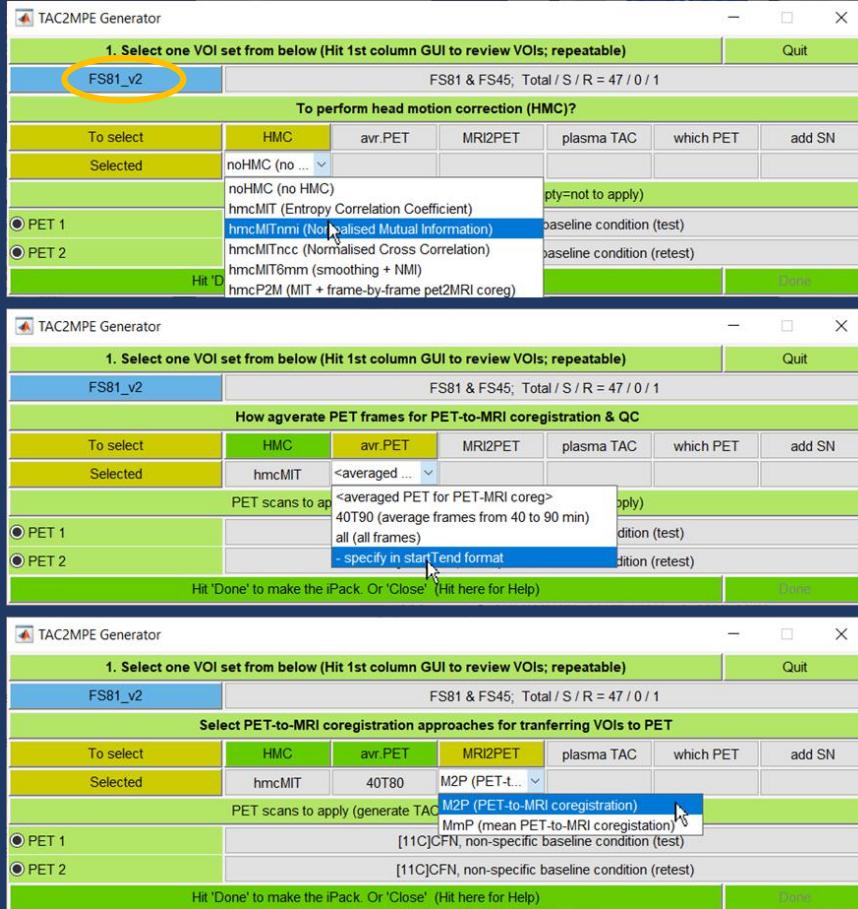
- When the ‘Select/rank VOI sets’ tab was hit in L2W, the VOI selector module pops up
  - Previously defined VOIs to refine/define and VOIs for reference regions are indicated by ‘S’ and ‘R’, respectively
    - It is OK to have no ‘S’ VOIs as in this example.
    - But there must be at least one ‘R’ VOI
  - Dark gold regions are available VOIs. No revisions are allowed in this stage
- Recall that F45 is consisted of merged VOIs from FS81.
  - It is strongly recommended to select the F81 set.
    - A later function allows calculation of the values of any outcome variables for merged VOIs as weighted means (by volumes) of FS81 VOIs.
- In this example:
  - The FS81 set was selected (as 1 and only 1; bottom left circle)
  - Then, the FS81 VOIs are shown in light green (right panel)
  - The VOI for the occipital lobe, reference region for the tracer was set to refine in the F45 set since it is available on this side alone.
    - Just hit the VOI’s GUI to include the VOI to the VOIs to report (orange circle, right panel) (hit it one more time to deselect).
  - Hit the ‘Done’ GUI to set the next module

# Adding Unlisted VOIs



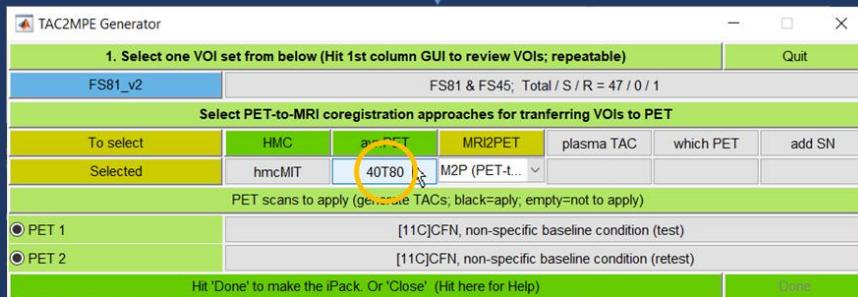
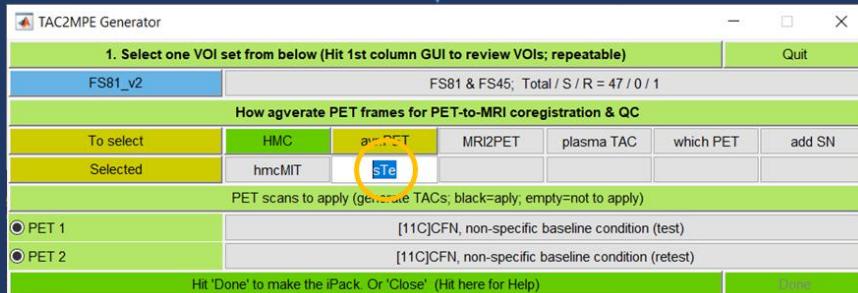
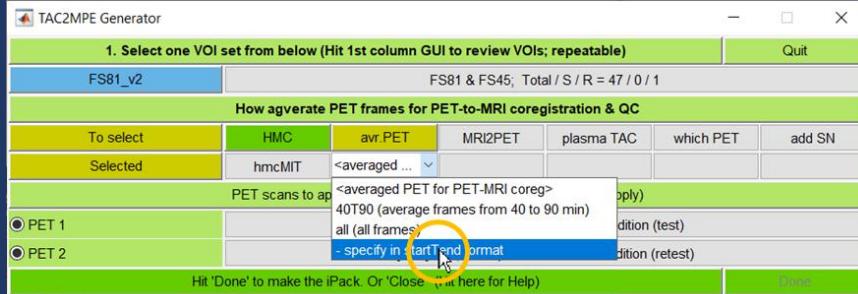
- Instructions for adding VOIs that are not listed under FS81 or FS45 using the pons as an example
  - Hit an (add) GUI (upper orange circle) in the VOI selector module to open the VOIID Utility module
  - Hit the key 'p' to list structures starting with p (middle panel)
    - ≈ Middle column: Brain structures
    - ≈ Right column: Non-brain structures
  - Hit 'pons' GUI to bring up the structure
  - ≈ Leave 'whole' on
  - Hit 'Done' GUI (right upper, middle panel)
    - ≈ The added structure will appear in the VOI selector module (lower panel)
- The newly added VOIs are not defined by Freesurfer. Therefore ..
  - The user must specify it to 'S' or 'R', i.e., to define manually from scratch as a target ('S') or reference 'R' region, respectively
  - The VOI could be included in 'FS81' (orange circle) or 'FS45' set, depending on which is going to be the primary VOI set.

# Setting Options for TAC2MPE: 1



- TAC2MPE Generator module lists the VOI sets the user has for this project
  - The name 'FS81-v2' (orange circle) was assigned to the VOI set that was set in the last slide
  - Next GUI explains the set: 47 VOIs from FS81 and FS45 (the occipital lobe alone) sets with 0 'S' and 1 'R' VOIs
    - ≈ Most VOIs have left and right VOIs
  - Hit the VOI GUI, and confirm the VOIs to start selecting options in succession
- **HMC: Head motion correction**
  - No HMC or select one from the mutual information theory-based approaches using SPM12's coregistration module.
- **'avr. PET': Frames to average for PET-to-MRI coregistration (second round)**
  - '40T90' and 'all' are generic, suggestive choices
  - Consult with the study's framing protocol (See next slide, if applicable)
- **MRI2PET: Approaches for PET-to-MRI coregistration (second round)**
  - M2P is strongly recommended

# Specify Start/End Times for Frame Averaging



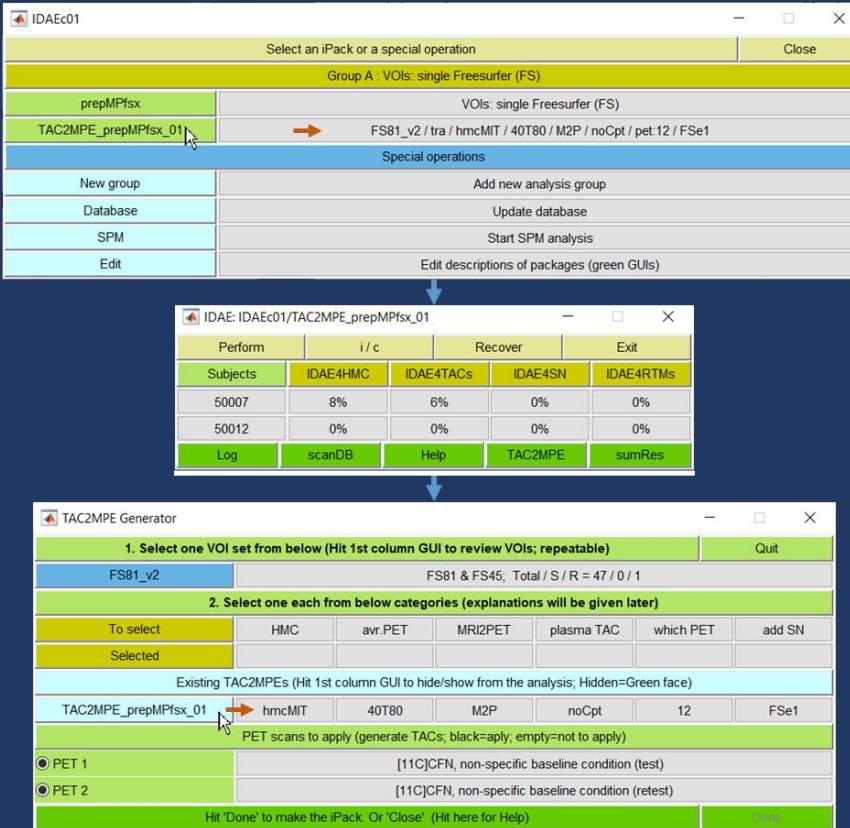
- Aim: To specify PET frames to average for the purpose of PET-to-MRI-coregistration To transfer VOIs from MRI to PET spaces
- Factors to consider:
  - Planned scan durations may be consistent across scans most studies but may be variable to learn the best scan durations for the tracers
    - ≈ There could be a common frames to use even in the latter case
  - To take earlier (e.g., 0-10 min frames; close to CBF images & higher counts) or later segments (e.g., 40-90 min frames; images are closer to the distributions of target molecule, thus critical for modeling)
- How to specify frames in the module:
  - Select ‘- specify ..’ tab (upper orange circle). It turns to be editable.
  - Remove sTe (middle orange circle; to remind users to use the startTend format; e.g., 30T60 to mean to average 30-60 min frames) and enter yours (40T80 in the example; lower orange circle)
  - Make sure to hit return when done. Then, the next selection will appear

# Setting Options for TAC2MPE: 2

The figure consists of three vertically stacked screenshots of the TAC2MPE Generator software. Each screenshot shows a window with a green header bar containing the title 'TAC2MPE Generator' and a '1. Select one VOI set from below (Hit 1st column GUI to review VOIs; repeatable)' button. Below the header is a status bar showing 'FS81\_V2' and 'FS81 & FS45; Total / S / R = 47 / 0 / 1'. The main area contains a table with columns: 'To select', 'HMC', 'avr. PET', 'MRI2PET', 'plasma TAC', 'which PET', and 'add SN'. A dropdown menu is open over the 'plasma TAC' column, listing several options: 'noCpt (no plasma data)', 'TAD (estimate tracer arrival delay)', 'noTAD (generic plasma flag)', 'HPLC1 (another generic flag)', 'HPLC1 (generic)', and 'HPLC2 (generic)'. The second screenshot shows a similar interface but with the 'noCpt' option selected. The third screenshot shows the 'Done' button at the bottom right.

- Plasma TAC:
  - Select ‘noCpt’ if no plasma data
  - Select one of generic flags or enter the user’s own flag (postpended to the plasma files)
    - ≈ Note the descriptions of individual flags using the ‘NoteLine’ function of IDAE (add later)
- Which PET:
  - Indicate which PET scans to apply this TAC2MPE package using check boxes of PET 1 and so on
    - ≈ Check scans to apply, and select ‘done’
- Add SN: Whether to add spatial normalization of functional PET volumes
  - SPM12’s unified segmentation method
  - Templates: SPM-supplied or IDAE-supplied
  - Sampling distances for SPM12’s special normalization routine
  - MRI-based spatial normalization + PET-to-MRI coregistration will be used for spatial normalization of PET volumes
- Review selections
  - Hit a GUI (e.g., 40T80 under avr. PET) to revise the selection
  - Hit ‘Done’ if all are as intended. Then, the package will be generated. Restart the project

# Starting Stage-2 Packages



- The newly added Stage-2 Package will be listed under group A (=prepMPfsx) when the project is revisited (upper panel)
  - Selected options are listed on the right GUI (upper horizontal arrow) in the order of selection items in TAC2MPE Generator (arrow in bottom panel)
- Level 1 Window of the package (middle panel) pops up when it is selected
  - It may be a good idea to review individual blocks by opening them at this point
- Newly generated Stage-2 packages will be listed in TAC2MPE Generator (lower panel) when the user revisits the TAC2MPE routine

# Starting Stage-2 Packages

The figure consists of three vertically stacked screenshots of software windows:

- Top Window:** A dialog titled "Select an iPack or a special operation". It shows a list of items under "Group A": "VOIs: single Freesurfer (FS); Spacial normalization (SN): SPM12". Below this is a table with rows for "prepMPfsx" (selected), "FS81\_v2\_tbaa\_noCpt\_FSe1" (highlighted with a red box), and other options like "New group", "Database", "SPM", and "Edit".
- Middle Window:** A sub-dialog titled "IDAE: IDAEc01/TAC2MPE\_prepMPfsx\_FS81\_v2\_tbaa\_noCpt...". It has tabs for "Perform", "i / c", "Recover", and "Exit". The "i / c" tab is selected. It displays progress for two subjects: "50007" at 8% and "50012" at 0%. Buttons at the bottom include "Log", "scanDB", "Help", "TAC2MPE", and "sumRes".
- Bottom Window:** A window titled "TAC2MPE Generator". It has two main sections: "1. Select one VOI set from below (Hit 1st column GUI to review VOIs; repeatable)" and "2. Select one each from below categories (explanations will be given later)". Under section 1, "FS81\_v2" is selected. Under section 2, "To select" includes HMC, avr.PET, MRI2PET, plasma TAC, which PET, and add SN. Under "Selected", "FS81\_v2\_tbaa\_noCpt" is selected. A table below lists existing TAC2MPEs: "FS81\_v2\_tbaa\_noCpt" with columns hmcMIT, 40T80, M2P, noCpt, 1, and FSe1. A note says "PET scans to apply (generate TACs; black=apply, empty=not to apply)". Under "PET 1", "[11C]CFN, non-specific baseline condition (test)" is listed. Under "PET 2", "[11C]CFN, non-specific baseline condition (retest)" is listed. A note at the bottom says "Hit 'Done' to make the iPak Or 'Close' (Hit here for Help)".

- Stage-2 Packages will be listed under group A (=prepMPfsx) when the project is revisited (upper panel)
  - Selections of options are listed on the right GUI in the order of selection items in TAC2MPE Generator (hmc, avr, m2p, cpt, pet, and SN)
- Level 1 Window of the package (middle panel) pops up when it is selected
  - It may be a good idea to review individual blocks by opening them at this point
- Newly generated Stage-2 packages will be listed in TAC2MPE Generator (lower panel) when the user revisits the TAC2MPE routine

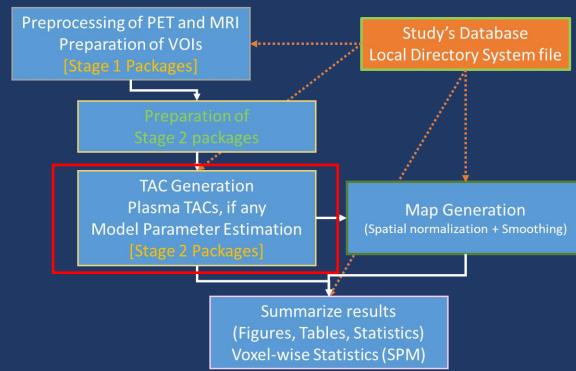
# Managing Stage-2 Packages

The figure consists of three vertically stacked screenshots of software interfaces:

- TAC2MPE Generator:** A window titled "TAC2MPE Generator". It shows a table of existing TAC2MPEs with columns: To select, HMC, avr PET, MRI2PET, plasma TAC, which PET, and add SN. Two rows are selected: "FS81\_v2" (highlighted in blue) and "TAC2MPE\_prepMPfsx\_01". Below the table, there are sections for "PET scans to apply" and "PET 1" and "PET 2" options.
- TAC2MPE Generator:** Similar to the first, but the table shows three rows: "FS81\_v2", "TAC2MPE\_prepMPfsx\_01", and "TAC2MPE\_prepMPfsx\_02". The "TAC2MPE\_prepMPfsx\_02" row is highlighted in blue.
- IDAEc01:** A window titled "IDAEc01". It has a header "Select an iPack or a special operation" and a "Close" button. Below is a table with two rows: "prepMPfsx" and "TAC2MPE\_prepMPfsx\_03". The "TAC2MPE\_prepMPfsx\_03" row is highlighted in blue. At the bottom, there are sections for "Special operations" and "Edit".

- It is very common to have several Stage-2 packages. IDAE
- Major reasons for multiple Stage-2 packages:
  - Revisions of VOIs to refine / define ('S' and 'R' VOIs). Newly added VOI sets will be listed under current FS81\_v2
  - Changes in any of option items
- Explanation by example (totally hypothetical)
  - The user wanted to try averaging 0-10 min frames (0T10) for PET-to-MRI coregistration. The resulting package was 'TAU2MPE\_prepMPfsx\_02' since this is the second package
  - Later, the user wanted to try 30T60 to see if this performed any better than 40T80 (upper panel)
  - Now, the user has 3 Stage-2 packages (lower)
  - Comparing results from the 30T60 and 40T90 sets, the user chose not to use the 40T90 set
  - Hit the tab to remove (arrow, lower panel). It toggles between green (disabled) and black (enabled) face colors.
  - Disabled package will not show on the selection of packages (no 01 package, lower panel)
- Apply the same procedures to any types of changes (i.e., major reasons), if any

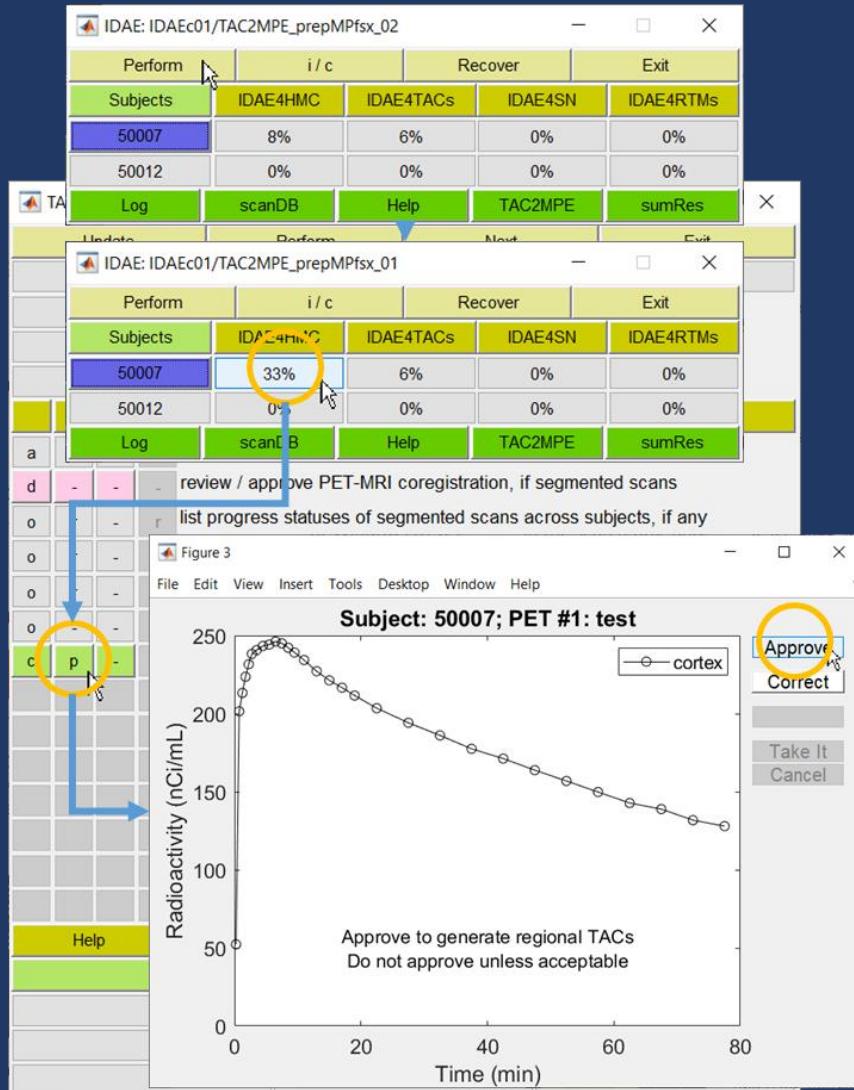
# Carrying on with TAC2MPE (a.k.a., Stage-2 Packages)



# Automatic Processes of TAC2MPE with HMC

- Frame-by-frame head motion correction using SPM12's coregistration module with the user-selected cost function (optional)
- Coregistration of PET to the MRI:
  - Averaging PET frames as selected during the generation of TAC2MPE
  - PET-to-MRI coregistration with SPM12's coregistration module
  - In the QC process, the gray matter outlines from the MRI are projected on the averaged PET volume (See 'Coregistration QC @IDAE4TACs)
    - ≈ If the coregistration is not acceptable, the user can displace the GM outlines to fit with gray matter of the PET volume to repeat the coregistration using the current guesses as the initial guesses for the optimization process
- Generation of regional TACs:
  - Specified VOIs will be transferred from the MRI to PET spaces according to the PET-to-MRI coregistration parameters, and applied to successive PET frames to obtain regional TACs
- Spatial normalization of the MRI
  - All spatial normalization processes will be performed the unified segmentation method of SPM12
  - In the QC process, the gray matter outlines in the MNI space (generated using the probabilistic maps of spatially normalized gray matter VOIs) are projected on the spatially normalized MRI of the subject
    - ≈ No correction measures are available. The user can eliminate the subjects with failed spatial normalization
- Lastly, perform MPE and summarize results.

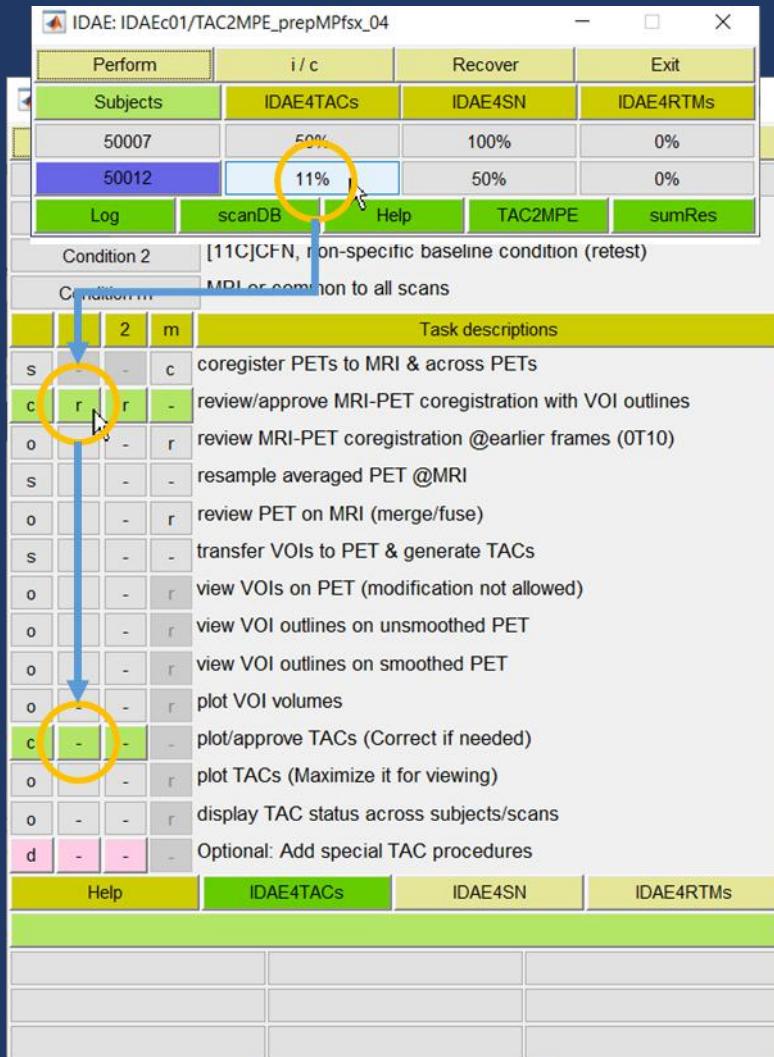
# TAC2MPE with HMC



- Just follow the principle of IDAE-managed analyses: Perform automatic processes first
  - Highlight the subject to perform (upper panel) and hit 'Perform' GUI (arrow)
  - ≈ In this case, frame-by-frame head motion correction will be performed using SPM12's coregistration module with the specified cost function
- When done, visit the first subject x analysis-base GUI with an increased completion status % (orange circle at 33%)
- Look for the first light green GUIs with 'r' (=ready) or 'p' (=pending). Hit it
  - ≈ The plot of mean cortex TAC will appear
- Approve it, if the TAC is reasonably smooth
  - ≈ No further correction measures at after HMC except removing the last (or a few last) frames.
- The 'd' process (special processes that are applicable to certain cases) are not applicable without 'correction' approaches for the scans with 'interrupted' or 'segmented' frames
- Once the QC process is done, repeat processing automatic processes

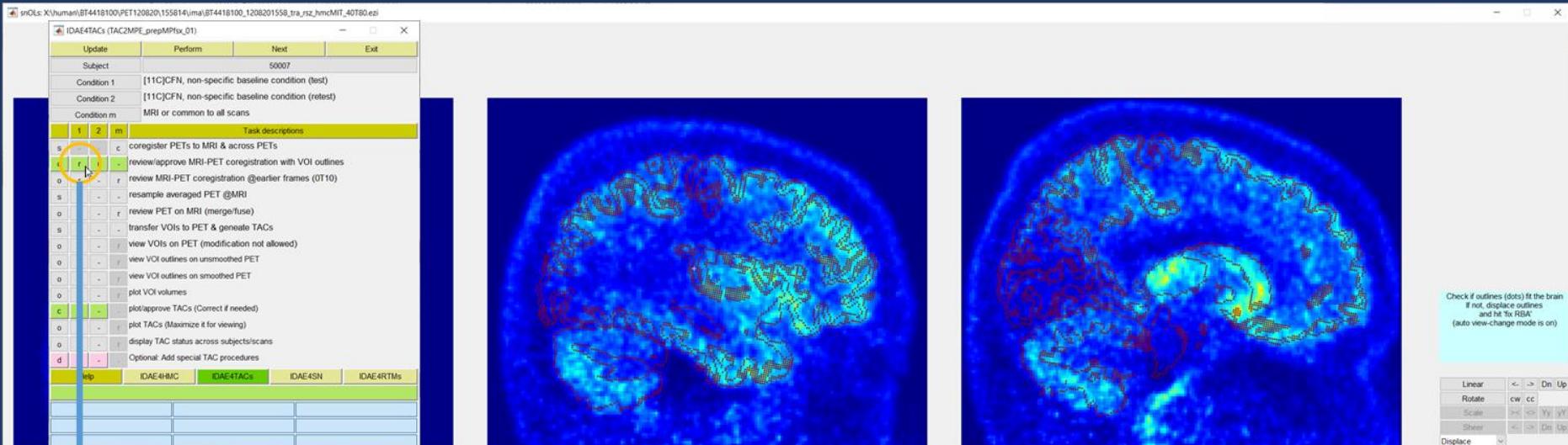
Note that IDAE4SN (spatial normalization) will be processed as well since the block involves MRI alone

# TAC2MPE without HMC



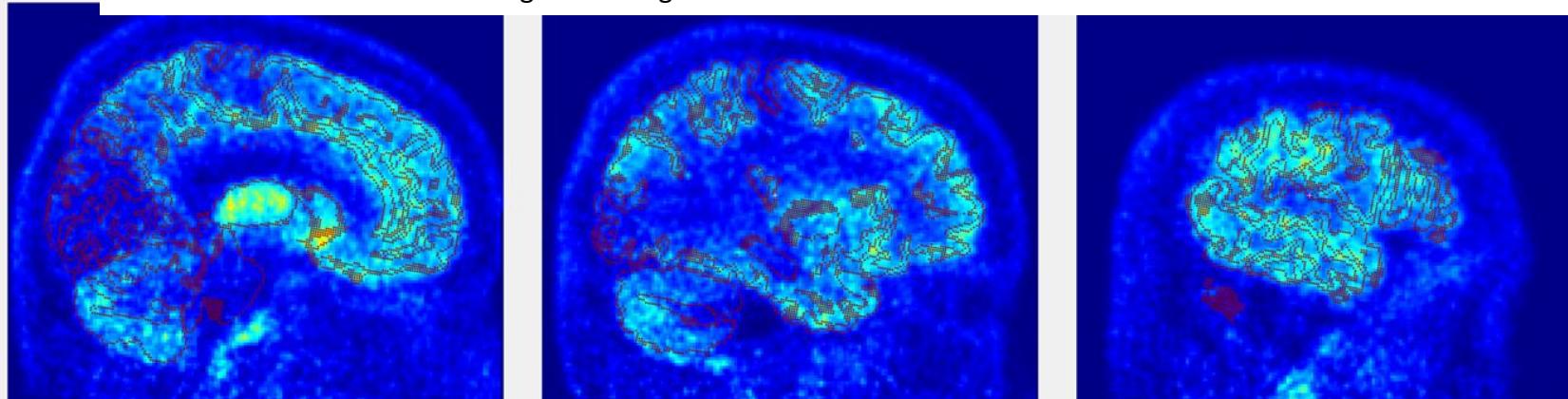
- TAC2MPE without HMC is identical in the core structure to the version without HMC except that this version lacks IDAE4HMC
- Again, just follow the principle of IDAE-managed analyses
  - Perform available automatic processes
  - Visit the first subject x block GUI what is expected to have an interactive process (upper)
  - Visit the first light-green GUIs displaying ‘r’ (middle circle)
    - ≈ Then, the QC process of PET-to-MRI coregistration opens (the same as the next slide)
  - When it is done, hit ‘Perform’ GUI in L1W.
  - Then the second row of light-green GUIs (lower circle) will show ‘r’ (See the slide of ‘Review/approve regional TACs’ downstream)

# Coregistration QC @ IDAE4TACs

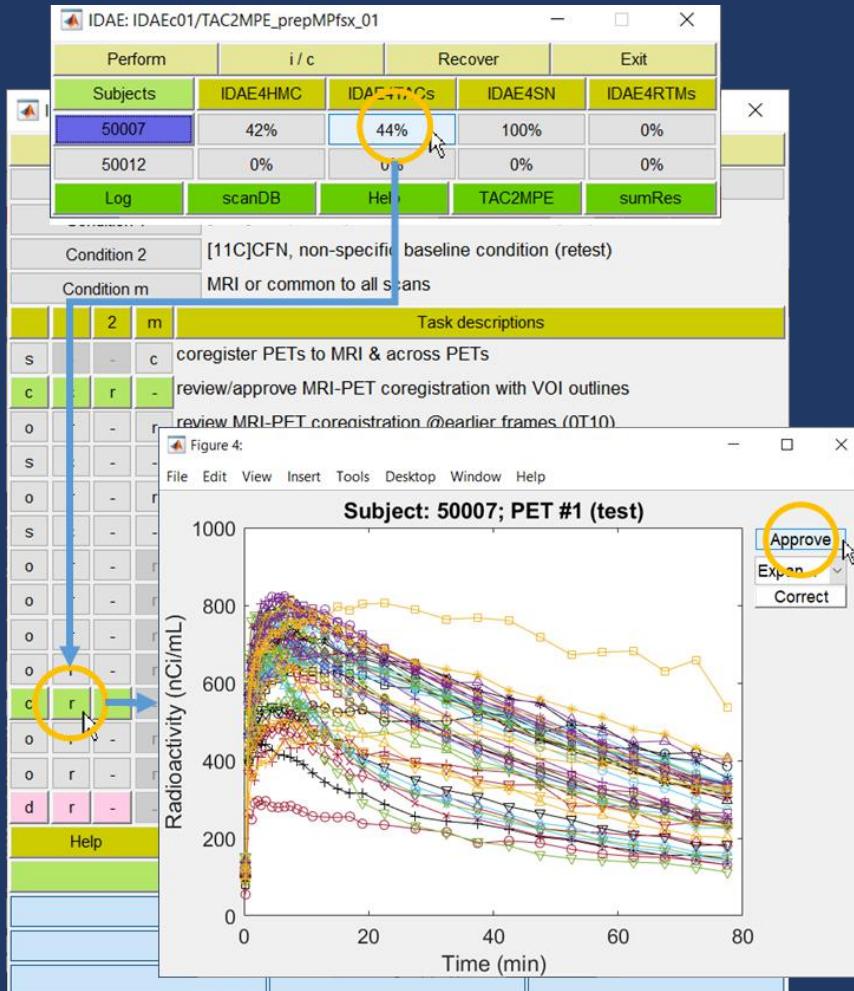


Evaluate if the outlines of gray matter (from MRI) agree with gray matter of the averaged PET volume

- Use T (trans-axial), S (sagittal), and C (coronal) GUIs under ‘view’ to change views.
- Use arrow GUIs under ‘Images’ to navigate ‘slices’



# Review/Approve Regional TACs



- Again, hit the first subject x block GUI with ‘increased’ completion status % (orange circle), and visit the first QC (light green) GUI with ‘r’ (or ‘p’) on it.
- Then, plots of regional TACs will pop up
  - Approve it if TACs look OK (orange circle)
  - ‘Correct’ GUI has no functions at this stage
  - Users can set regions to display. See the next slide for the procedure

# Using VOI Selector Module

The figure shows two windows of the vL2 VOI Selector Module. The top window is a grid of anatomical regions, and the bottom window is a detailed view of the 'Existing VOIs' list.

**vL2 VOI selector (Top Window):**

Existing VOIs	L	R	W
Amygdala (Am)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Banks STS (bT)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Brainstem (BS)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Caudal anterior cingulate (cAC)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Caudal middle frontal (cmFr)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Caudate nucleus (CN)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Cerebellar WM (CW)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Cerebellum (Cb)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Corpus callosum (CC)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Cuneus (Cu)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Entorhinal area (ER)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

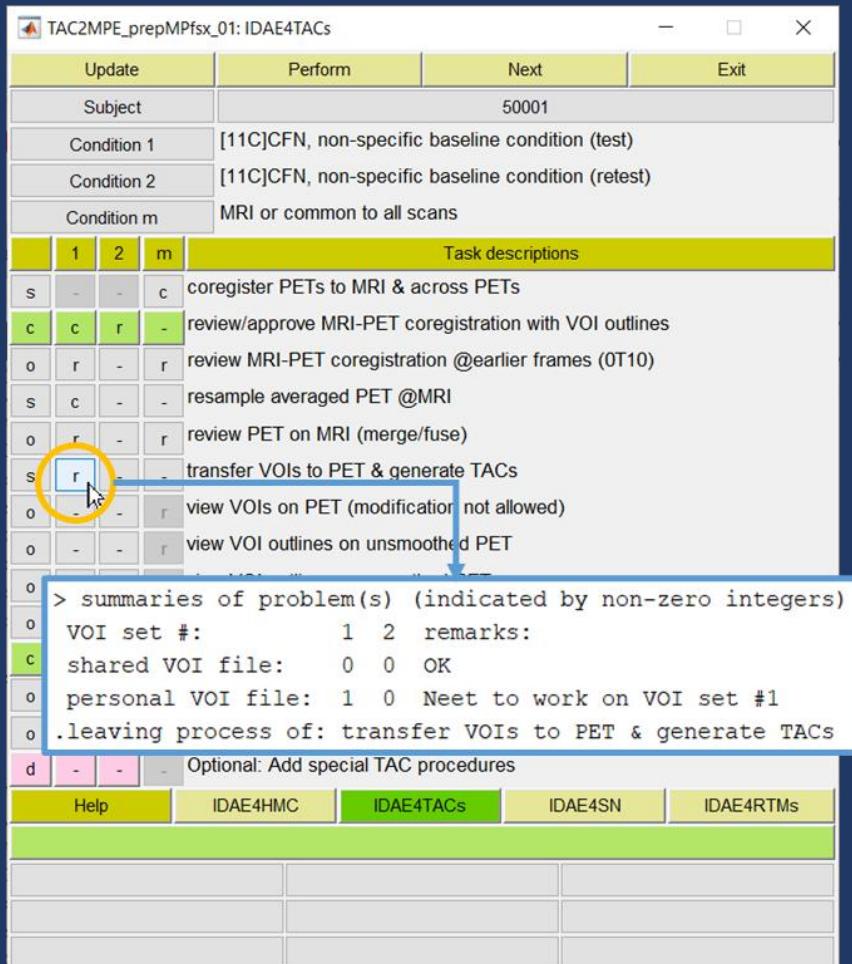
The bottom window shows the 'vL2 VOI selector' interface with the 'Existing VOIs' list:

Existing VOIs	L	R	W
Amygdala (Am)	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Banks STS (bT)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Brainstem (BS)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Caudal anterior cingulate (cAC)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Caudal middle frontal (cmFr)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Caudate nucleus (CN)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Cerebellar WM (CW)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Cerebellum (Cb)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Corpus callosum (CC)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Cuneus (Cu)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Entorhinal area (ER)	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

An orange arrow points from the 'Brainstem (BS)' row in the top window to the 'Brainstem (BS)' row in the bottom window, highlighting the selection status. A blue arrow points from the top window to the bottom window, indicating the relationship between the two views.

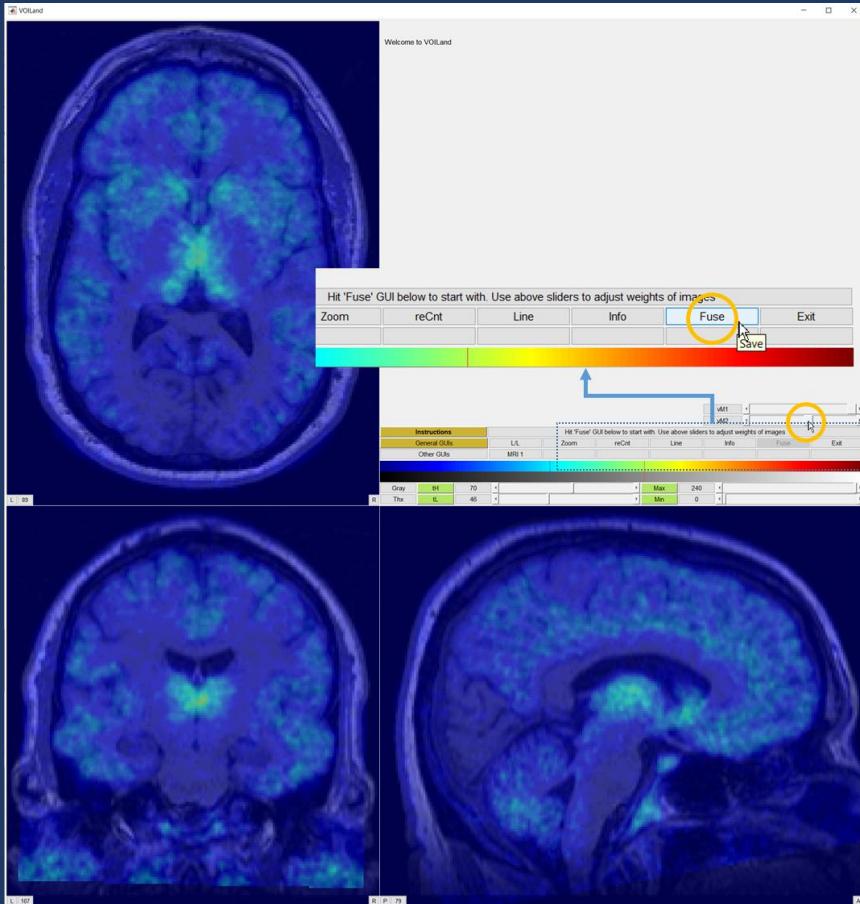
- The VOI selector module pops up together with plots of regional TACs
- Users can control which regions to include the plots via the VOI selector module:
  - Anatomical labels of all available VOIs are listed in 4 primary columns
  - Each primary column (the first column magnified) lists 3 secondary columns for the left (L), right (R), and whole (W; left-right merged) regions (orange circle)
    - ≈ The columns of L and R are disable for those VOIs that are defined for the left-right merged VOIs alone, as for the brainstem (orange arrow)
    - Current selections are checked (black fill)
      - ≈ Users can change the selection statuses by clicking on the checkboxes
      - ≈ Users can change the statuses of all regions of respective categories using 'L', 'R', and 'W' GUIs

# When TACs Are Not Generated



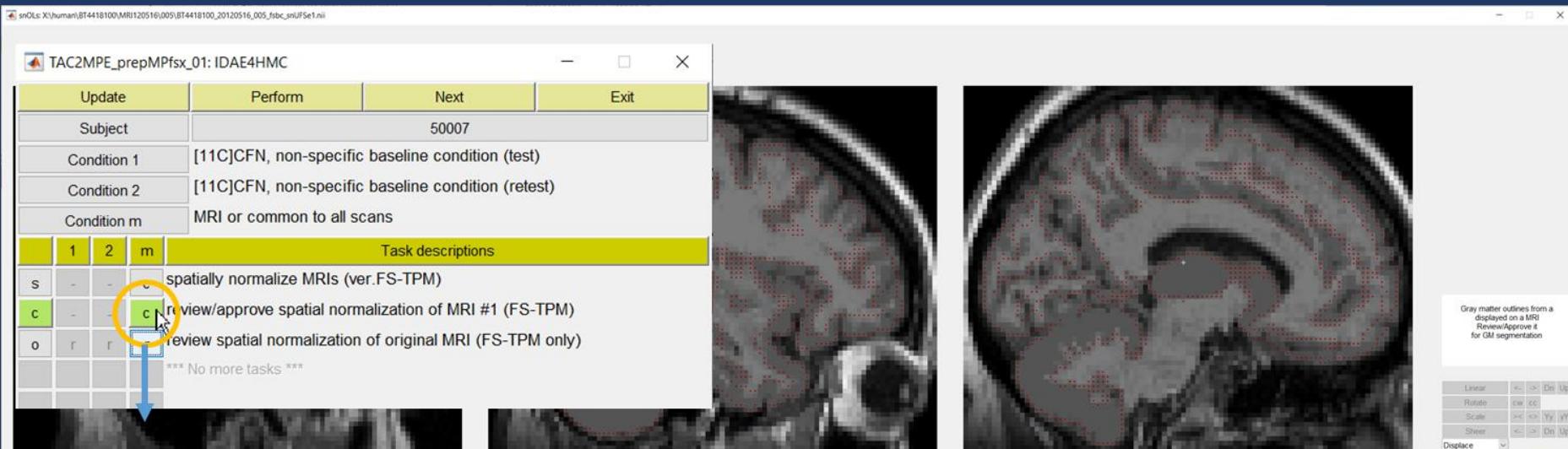
- After performance of automated regions, the step of ‘transfer VOIs to PET & generate TACs’ could remain incomplete (‘r’ is ready to perform). Two major reasons for such instances
  - The mean cortex TAC has not been approved for the scan.
    - That may not be the case if the MRI-to PET coregistration is performed (in this case)
  - Not all VOIs od specified VOI sets are not ready.
    - Users will get a summary of the problems IDAE found for the VOIs in MATLAB command window (insert)
    - Two types of VOI files
      - ≈ Shared VOI sets: VOIs that are straight from Freesurfer and shared by local users. Only local manage is allowed modify defective VOIs.
      - ≈ Personal VOI sets: User-defined ‘S’ or ‘R’ VOIs. The user must complete them as ‘complete’ or ‘as good as possible to be used for VOIs. Shared VOIs will be used for non-‘S’ or ‘R’ VOIs.
    - Revisit the steps of define/define VOIs to complete ‘S’ and ‘R’ VOIs and revisit this step.

# Optional Processes of IDAE4TACs



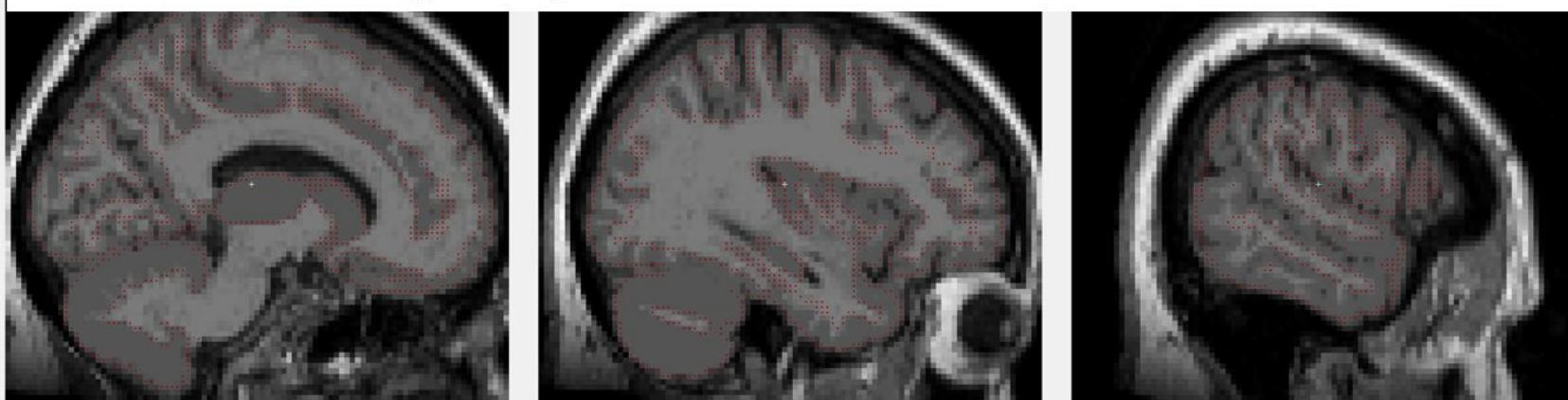
- Feel free to visit optional processes ('o' in the first column)
- Review PET on MRI (merge/fuse)
  - Aim: To display the averaged PET images on the MRI for visual inspection.
  - Procedures: Hit 'Fuse' GUI (upper circle), and adjust intensities of the MRI (upper slider) and PET (lower slider, lower circle)
  - Image navigation:
    - ≈ Hit at any point on a image to display orthogonal images through that point
    - ≈ Hit up/down, i/m (next to u/n), and </> keys to navigate cranium/neck, inion/nasion, and left/right directions, respectively
    - ≈ Hit 'q' key to navigate 30 images in the current direction: e.g., 'u' then 'q' to navigate 30 images toward the cranium
- Display TAC status across subjects/scans

# QC of Spatial Normalization @IDAE4SN



Evaluate if the outlines of gray matter (from standard MRI) agree with gray matter of spatially normalized MRI

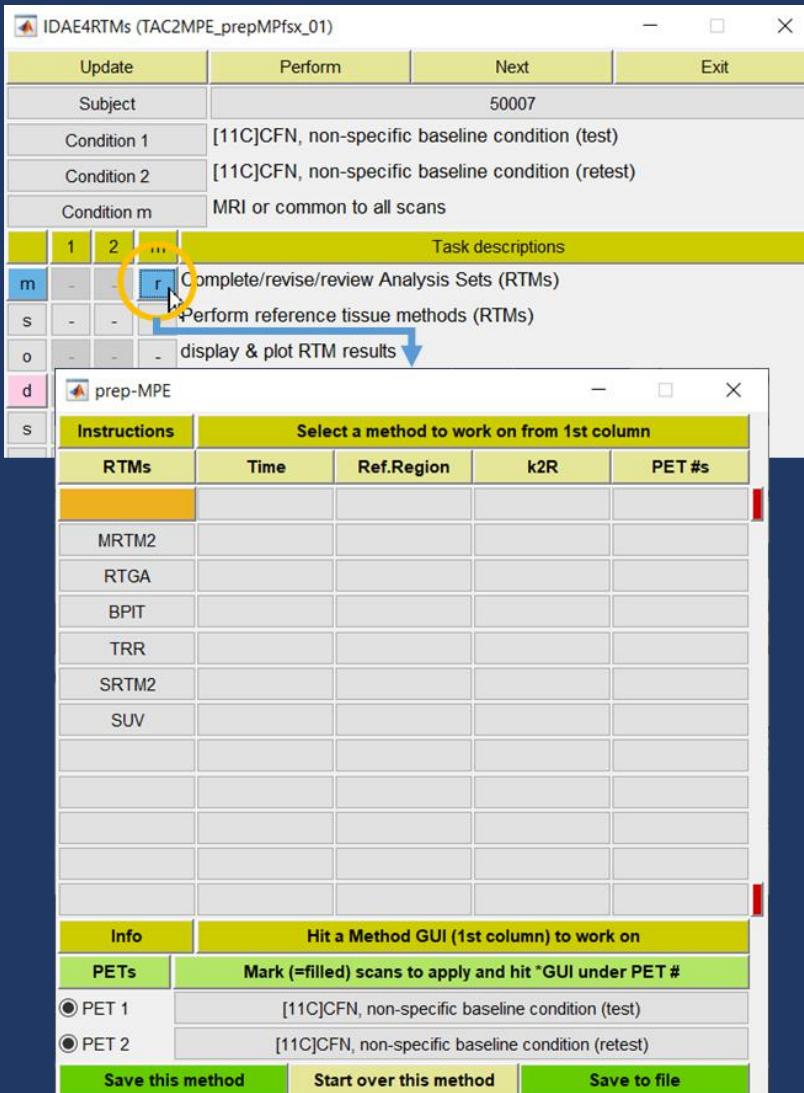
- Use T (trans-axial), S (sagittal), and C (coronal) GUIs under 'view' to change views.
- Use arrow GUIs under 'Images' to navigate 'slices'



Freesurfer-defined gray matter is inserted in this version of MRI. Visit the next step to display SN'ed original MRI

To Set / Perform RTMs

# Setting RTMs: Overview



- Aim: To set reference tissue methods (RTMs) and their parameters for the package
- Major procedures:
  - First, set the MPE preparation module (lower panel) by clicking the designated GUI (orange circle; upper panel)
  - Follow instructions given in the 1<sup>st</sup> row
  - Bring in a method from the 1<sup>st</sup> column GUIs to set relevant parameters (2<sup>nd</sup> to 4<sup>th</sup> columns)
    - ≈ See the quick guide (next slide) for methods
    - ≈ Hit 'Save this method' (bottom left) when done to move on to the next method
  - Go inclusive in the first cycle (i.e., for all PETs) to be selective in the second cycle.
    - ≈ Hit 'Save to file' if no more methods to set (= the end of the first cycle)
  - Visit already-selected (light green) methods one-by-one in the second cycle
    - ≈ Adjust applicable PET sans and hit 'Save this method' to move on to the next method
      - e.g., 20T90 for PET 1 (tracer A) and 40T90 for PET 2 (tracer B) for PRGA
  - ≈ Hit 'Save to file' when all methods are done (= the end of second cycle)

# RTMs: Quick Guide

Methods	Explanations
MRTM2	<p>Multilinear reference tissue method with 2 parameters (Ichise et al., 2003)</p> <p>Treatment of k2R (<math>k_2</math>, the brain-blood clearance constant of the reference region):</p> <ul style="list-style-type: none"> <li>Median k2R: Use the median values of k2R (across regions) from the 3-parameter fit</li> <li>Optimize: Optimize k2R by minimizing the total RSS across regions. Referred to as optk2R here.</li> <li>Fix as RTGA: fix k2R at the user-entered k2R value(s) for PRGA (need to set)</li> </ul>
RTGA	<p>Reference tissue graphical analysis (Logan et al., 1996)</p> <ul style="list-style-type: none"> <li>RTGA will be performed in two ways: Fixing k2R at the user-entered k2R value(s), and optimizing k2R by minimizing the total RSS across regions (Referred to as optk2R)</li> </ul>
BPIT	Bolus-plus-infusion transformation (Kuwabara et al., 2013)
TRR (SUVR)	Target-reference tissue ratio
SRTM2	<p>Simplified reference tissue method with 2 parameters (Lammertsma and Hume, 1996)</p> <ul style="list-style-type: none"> <li>Not recommended by IDAE because SRTM2 yields practically identical values of BPND to MRTM2, while computationally more demanding.</li> <li>Wu and Carson, 2002 should be credited for the 2 parameter version</li> </ul>
SUV	Standard uptake value

## On the circulation times for data analysis

IDAE's $t^*TT_{end}$ Format	All RTMs assumes the conditions for a method are met a segment of the total scan from the start-analysis time (denoted by $t^*$ ) and the end-analysis time ( $T_{end}$ ). In IDAE, the start- and end analysis can be specified by a $t^*TT_{end}$ format (e.g., 20T80 for a $t^*$ of 20 min, and an end-analysis time of 80 min)
--------------------------------	--

# Setting MRTM2: First cycle

prep-MPE

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info														
RTMs		Time	Ref.Region	k2R	PET #s														
<b>MRTM2</b>	5T90	<input checked="" type="radio"/> Oc 54000	<input type="radio"/> median k2R	in Step 2															
MRTM2	*	<input checked="" type="radio"/> optimize	<input type="radio"/> fix as RTGA																
RTGA																			
BPIT																			
TRR																			
SRTM2																			
<table border="1"> <thead> <tr> <th>Time</th> <th>Time</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td>5T90</td> <td>5T90</td> <td>5T90</td> </tr> <tr> <td>*</td> <td>10T90</td> <td>0T90</td> </tr> <tr> <td>*</td> <td>*</td> <td>*</td> </tr> </tbody> </table>					Time	Time	Time	5T90	5T90	5T90	*	10T90	0T90	*	*	*			
Time	Time	Time																	
5T90	5T90	5T90																	
*	10T90	0T90																	
*	*	*																	
Info		Step 1: Complete Columns from Time through k2R																	
PETs		Mark (=filled) scans to apply and hit *GUI under PET #																	
<input checked="" type="radio"/> PET 1	[11C]CFN, non-specific baseline condition (test)																		
<input type="radio"/> PET 2	[11C]CFN, non-specific baseline condition (retest)																		
<b>Save this method</b>		<b>Start over this method</b>			<b>Save to file</b>														

- Hit MRTM2 to start with.
  - MRTM2 will be shown in the orange GUI while GUIs for other methods are disabled
- Default parameters will be shown initially. Users can modify them as needed as follows:
  - Time: the circulation time for the analysis in startTend format: 5T90 to use 5-90 min frames
    - ≈ Hit an available GUI (5T90 initially) to modify it. The GUI becomes editable. Enter your values and hit ‘enter’ to quit the editable mode.
    - ≈ Hit the GUI with \* (arrow in left insert) to set another circulation time (by the start time increase by 5 min; thus 10T90) (middle insert)
    - ≈ Hit the GUI to modify it as show above. And hit return when done (right insert)
  - Reference region: Pre-selected reference regions ('R' regions) will appear here.
    - ≈ Go inclusive in the first cycle. For example, select all reference regions when reference regions differ among tracers of the scans (PET 1, 2, etc.).
  - See ‘Quick Guide’ for k2R
    - ≈ all checked will be performed
    - ≈ Need to add RTGA if to use the ‘fix as RTGA’ option
  - Hit ‘Save this method’ GUI when done

# Setting RTGA: First Cycle

prep-MPE

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
RTMs	Time	Ref.Region	k2R	PET #s					
RTGA	10T90	Oc 54000	Recommen... ▾	in Step 2					
MRTM2	*		Recommended k2Rs:						
RTGA			[11C]CFN						
BPIT			0.104						
TRR			< select one and edit, if needed						
RTMs	Time	Ref.Region	k2R	PET #s					
RTGA	5T80	Oc 54000	0.104	in Step 2					
MRTM2	10T80		*						
RTGA	15T80								
BPIT	*								
TRR									
Info Step 1: Complete Columns from Time through k2R									
Mark (=filled) scans to apply and hit *GUI under PET #									
<input checked="" type="radio"/> PET 1	[11C]CFN, non-specific baseline condition (test)								
<input checked="" type="radio"/> PET 2	[11C]CFN, non-specific baseline condition (retest)								
<b>Save this method</b>		<b>Start over this method</b>		<b>Save to file</b>					

- Hit RTGA to start with
  - MRTM2 which was set in the previous slide is marked by light green, although it is disabled along with other non-RTGA methods
- Default parameters are shown initially
  - The values of k<sub>2</sub> of the reference region (k<sub>2R</sub>) must be provided for RTGA. Users can:
    - ≈ Use IDAE-recommended values, then edit them if needed
    - ≈ If the value is unknown yet, run MRTM2 and obtain mean k<sub>2R</sub> across subjects
    - ≈ When the study involve multiple tracers of different k<sub>2R</sub> values, enter all in the first cycle and make them tracer-specific in the second cycle
  - An example of RTGA setting is shown in insert
    - ≈ Three values for t\* (the start of asymptote for RTGA plots) were set to examine which t\* is appropriate to [11C]CFN
- Hit ‘Save this method’ GUI when done
  - If no more RTMs to define, hit ‘Save to file’ GUI

# Setting MRTM2: Second Cycle

prep-MPE

Expand mode. Check/Set applicable PETs for each approach				
RTMs	Time	Ref.Region	k2R	PET #s
MRTM2	5T90	Oc	optk2R	1,2
MRTM2	0T90	Oc	optk2R	2
RTGA				
BPIT				
TRR				
SRTM2				
SUV				
Info Expand mode: One approach per row				
PETs	Mark (=filled) scans to apply and hit *GUI under PET #			
<input type="radio"/> PET 1	[11C]CFN, non-specific baseline condition (test)			
<input checked="" type="radio"/> PET 2	[11C]CFN, non-specific baseline condition (retest)			
<b>Save this method</b>		<b>Start over this method</b>	<b>Save to file</b>	

- Assume that ‘Save to file’ GUI was hit after setting MRTM2 and RTGA
  - Then, the module goes into the second cycle (pink instruction GUI)
  - Select a method among green GUIs (MRTM2 in this case)
  - Now each line shows one set of MRTM2 analysis
- Making analysis set scan-specific (tracer-specific in fact):
  - Note that we cannot do much for making analysis sets to be tracer-specific in this study because the tracer is the same for PET 1 and 2
  - Assume (although very hypothetical) that the 0T90 set is applicable to PET 2 alone. Then, unmark PET 1 alone (orange circle), then hit a GUI under ‘PET #s’ (arrow). It turns now that the 0T90 analysis is ‘applicable to PET 2 alone’
- Hit ‘Save this method’ when all rows are OK
  - Note that the GUI of MRTM2 turns to a darker green color indicating that the second cycle is done for MRTM2

# Setting RTGA: Second Cycle

prep-MPE

Instructions					Expand mode. Check/Set applicable PETs for each approach
RTMs	Time	Ref.Region	k2R	PET #s	
RTGA	5T80	Oc	0.104	1,2	
MRTM2	5T80	Oc	optk2R	1,2	
RTGA	10T80	Oc	0.104	1,2	
BPIT	10T80	Oc	optk2R	1,2	
TRR	15T80	Oc	0.104	1,2	
SRTM2	15T80	Oc	optk2R	1,2	
SUV					
Info					
Expand mode: One approach per row					
PETs		Mark (=filled) scans to apply and hit *GUI under PET #			
<input checked="" type="radio"/> PET 1	[11C]CFN, non-specific baseline condition (test)				
<input type="radio"/> PET 2	[11C]CFN, non-specific baseline condition (retest)				
<b>Save this method</b>		<b>Start over this method</b>		<b>Save to file</b>	

- Again, each row lists an analysis set of RTGA in the second cycle.
  - In this example, 6 analysis sets will be performed: 3 user-entered analysis circulation time sets x 2 k2R sets (to fix at 0.104 and to optimize the value for the scan which is automatically added by IDAE).
  - Note that we cannot do much in terms of making analysis sets to be tracer-specific in this study because the tracer is the same for PET 1 and 2
- Hit ‘Save this method’ when all rows are OK
  - Note that the GUI of RTGA turns to a darker green color indicating that the second cycle is done for PRGA
  - Hit ‘Save to file’ GUI if there are no more ‘light green’ GUIs. This is the end of RTM setting.

# Further on the 2<sup>nd</sup> Cycle: 1

The image displays two screenshots of the prep-MPE software interface. The top screenshot shows the 'Instructions' mode, which lists various modeling approaches (RTMs, MRTM2, RTGA, BPIT, TRR, SRTM2) with their corresponding time points (e.g., 5T90, 10T90, etc.) and reference regions (e.g., CW, median k2R). The bottom screenshot shows the 'Expand mode', where each approach is expanded into multiple rows, allowing for individual parameter settings like k2R values (optk2R, fitk2R, mdk2R) and PET counts (1, 2, 3). Both screenshots include tabs for 'Info' and 'PETs' at the bottom.

Approach	Time	Ref.Region	k2R	PET #s
MRTM2	5T90	CW 90400	median k2R	in Step 2
MRTM2	10T90		optimize	
RTGA	15T90		fix as RTGA	
BPIT	20T90			
TRR	*			
SRTM2				

Approach	Time	Ref.Region	k2R	PET #s
MRTM2	5T90	CW	optk2R	1
MRTM2	5T90	CW	fitk2R	1
RTGA	5T90	CW	mdk2R	1
BPIT	10T90	CW	optk2R	1
TRR	10T90	CW	fitk2R	1
SRTM2	10T90	CW	mdk2R	1
SUV	15T90	CW	optk2R	1
	15T90	CW	fitk2R	1
	15T90	CW	mdk2R	1
	20T90	CW	optk2R	1
	20T90	CW	fitk2R	1
	20T90	CW	mdk2R	1

- In the 1<sup>st</sup> cycle of this example:
  - Four t\*, the starting time for MRTM2 were entered (but all ending at 90 min)
  - One reference region was entered (CW or the cerebellar white matter)
  - Two approaches for k2R, k2 of reference region were entered
    - ≈ Median k2R in which median of regional k2R values from MRTM3 will be obtained / fixed in MRTM2 (original MRTM3 and MRTM2)
    - ≈ Optimize k2R to minimize the total sum of square sums across regions (modified MRTM2)
  - Altogether, 12 modeling approaches (= 4 x 1 x 3) are specified in the 1<sup>st</sup> cycle
- In the 2<sup>nd</sup> cycle:
  - The 12 modeling approaches will be listed one per row
    - ≈ Page up / down GUIs (red GUIs) will be activated when more than 12 approaches are present.
  - Since this is a one-scan study, the role of the 2<sup>nd</sup> cycle is limited to just confirm presence of individual modeling approaches.
    - ≈ See the next slide for multi-PET a study

# Further on the 2<sup>nd</sup> Cycle: 2

The screenshot displays the prep-MPE software interface in two main panels:

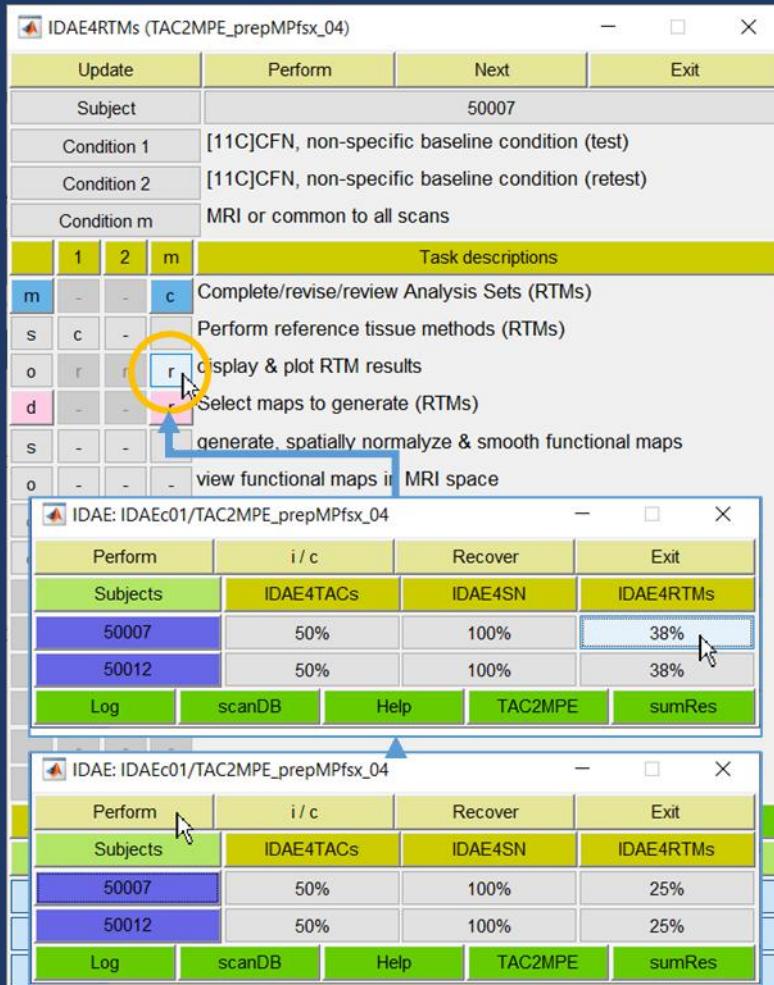
- Top Panel:** Titled "Expand mode. Check/Set applicable PETs for each approach". It lists modeling approaches (RTMs) along with their time points, reference regions, k2R values, and applicable PET numbers. The data is as follows:

RTMs	Time	Ref.Region	k2R	PET #s
RTGA	25T90	Cb	0.149	1,2,3,4
MRTM2	25T90	Cb	0.048	1,2,3,4
RTGA	25T90	Cb	optk2R	1,2,3,4
BPIT	25T75	Cb	0.149	1,2,3,4
TRR	25T75	Cb	0.048	1,2,3,4
SRTM2	25T75	Cb	optk2R	1,2,3,4

- Bottom Panel:** Titled "Expand mode: One approach per row". It shows the selection of PET scans for different PET types (PET 1, PET 2, PET 3, PET 4) across different scans (PIB scan 1, PIB scan 2, DASB scan 1, DASB scan 2).

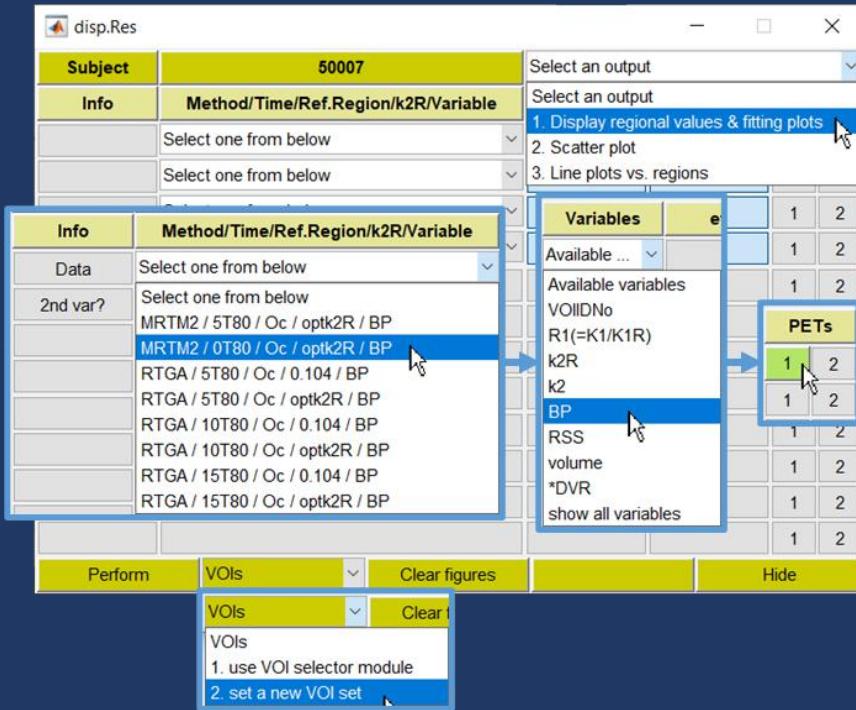
- In the 1<sup>st</sup> cycle (not shown) of this example:
  - Two circulation time pairs were set for RTGA (20T90 and 25T75)
  - One reference region was entered (Cb or the cerebellar)
  - Two approaches for k2R, k2 of reference region were entered
    - ≈ Two fixed k2R values for PIB and DASB (0.149 and 0.48 min<sup>-1</sup>, respectively) were entered
    - ≈ Optimize k2R by minimizing the total sum of square sums across regions (denoted as optk2R)
  - Altogether, 6 modeling approaches (= 4 x 1 x 3) were specified for RTGA in the 1<sup>st</sup> cycle
- Set the applicable PETs in the 2<sup>nd</sup> cycle:
  - The 6 modeling approaches will be listed one per row to be applicable to all scans (1, 2, 3, and 4) initially (upper panel)
  - Now set the applicable scans for PIB scans
    - ≈ Deselect PET 3 and 4 (bottom PET area)
    - ≈ Hit GUIs of the rows of k2R = 0.149 min<sup>-1</sup> under 'PET#s' (e.g., at the cursor) to change applicable PET scans to all to 1 and 2
  - Repeat the same procedures for DASB after activating PET 3 and 4 alone

# Perform / Review RTMs



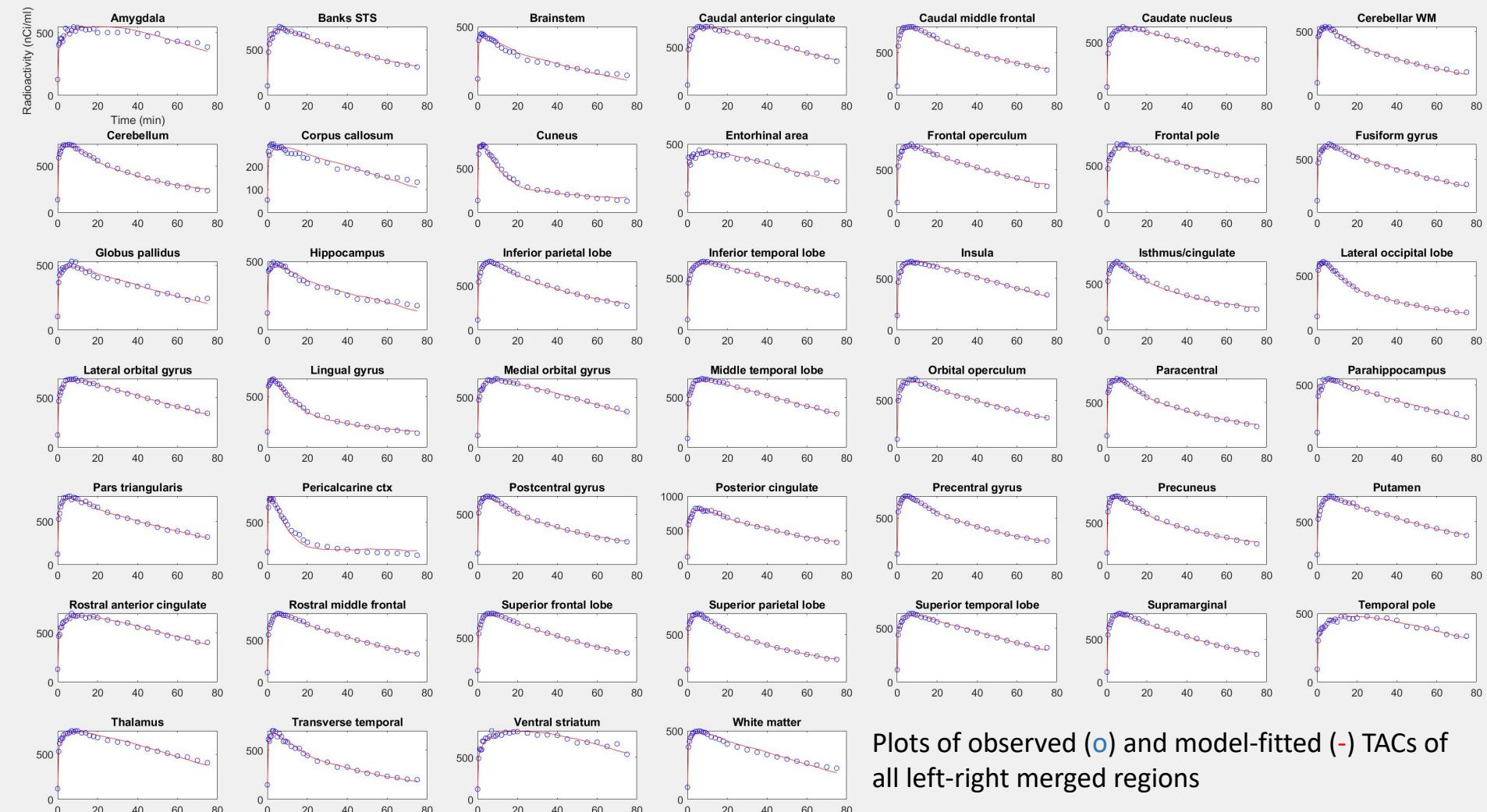
- It is very simple to perform RTMs
  - Just highlight subjects to perform RTMs (judged from completion status) and hit 'Perform GUI' (lower insert)
  - Once the automatic processes are done, the completion statuses increase (upper insert)
- Users can review results of RTMs of a subject as follows
  - Visit the subject x block GUIs (under IDAE4RTMs) of any subject to open L2W
  - Hit 'r' GUI (orange circle) @'display & plot RTM results'

# Display / Plot RTM Results



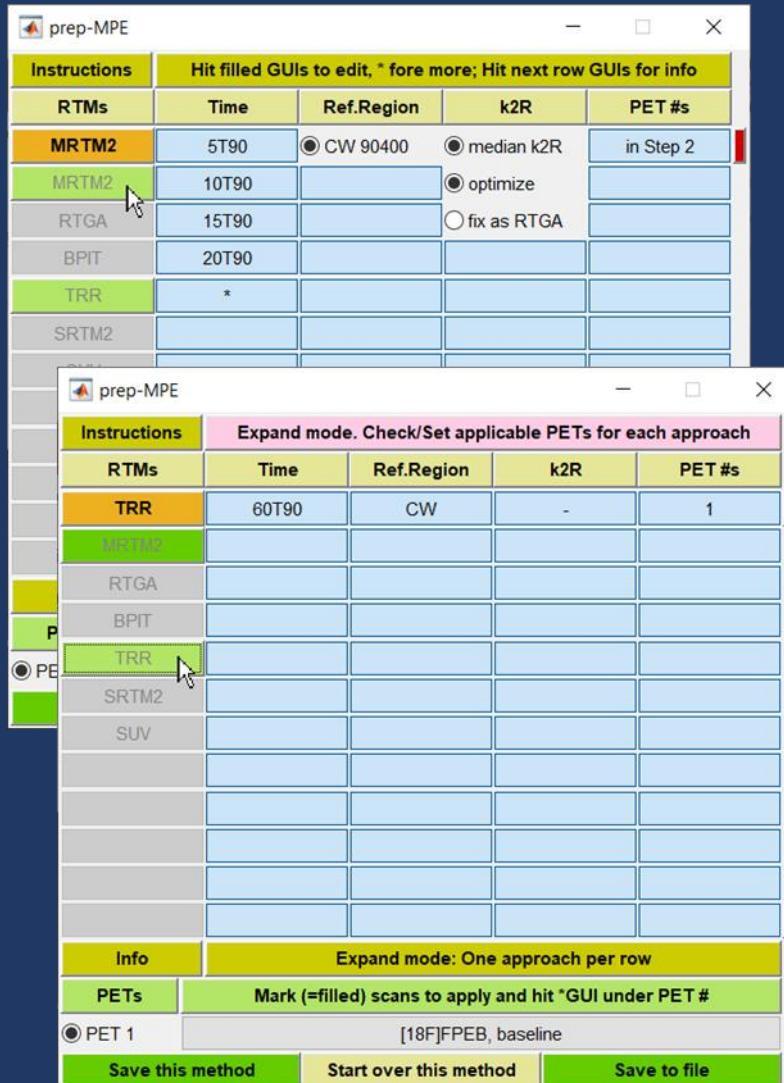
- Hit the 'r' GUI @'Display / plot RTM results' of L2W (IDAE4RTMs) to set the result display module (background)
- Select an output from the menu (top right)
  - Display regional values ... (shown here)
  - Scatter plot of regional data of a variable between scan 1 vs. scan 2 and so on
  - Line plots vs. regions: Spaghetti plots
- Select one analysis approach from the list (left insert)
  - Approaches are shown by 5 elements of 'method flag' (acronyms), 'circulation time for analysis', 'acronym of reference region', 'treatment of k2R', and 'primary variable'.
- Select the variable to display (middle insert)
  - Select 'show all variables' to display them all
- Select the scan to display (right insert)
  - Light green = available; darker green = selected
- Set the VOIs to display (bottom)
  - See the section of the VOI selector module
- Hit 'Perform' GUI (bottom left)

# Example of Observed and Fitted TACs: MRTM2



Plots of observed (○) and model-fitted (-) TACs of all left-right merged regions

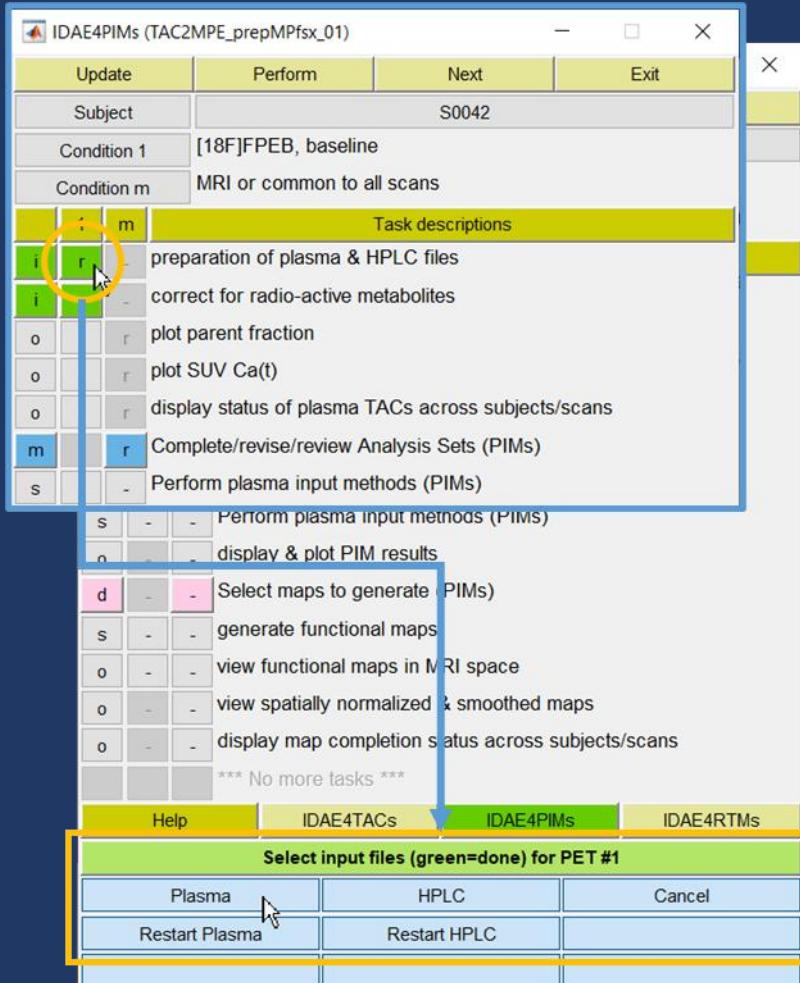
# Revise / Review RTM Approaches



- First, hit ‘c’ GUI at ‘Complete/review/revise’ Analyses Sets’ of L2W to bring up the MPE preparation module (upper panel)
    - Previously set RTM approaches will be highlighted in light green
    - Hit a highlighted approach to review / revise
    - Bring in / set a new approaches, as needed
    - Hit ‘Save this method’ to update the working approach
    - Hit ‘Save to file’ when all approaches are done (= the end of the 1<sup>st</sup> cycle)
      - ≈ Leave those approaches not intended to review / revise unattained
  - In the 2<sup>nd</sup> cycle (lower panel):
    - Hit a highlighted approach to review / revise
    - Hit ‘Save this method’ to update the approach
      - ≈ Reviewed / revised approaches will be highlighted in darker green (MRTM2 in this example)
    - Hit ‘Save to file’ when done (= the end of the 1<sup>st</sup> cycle)
      - ≈ Leave those approaches not to review / revise unattained

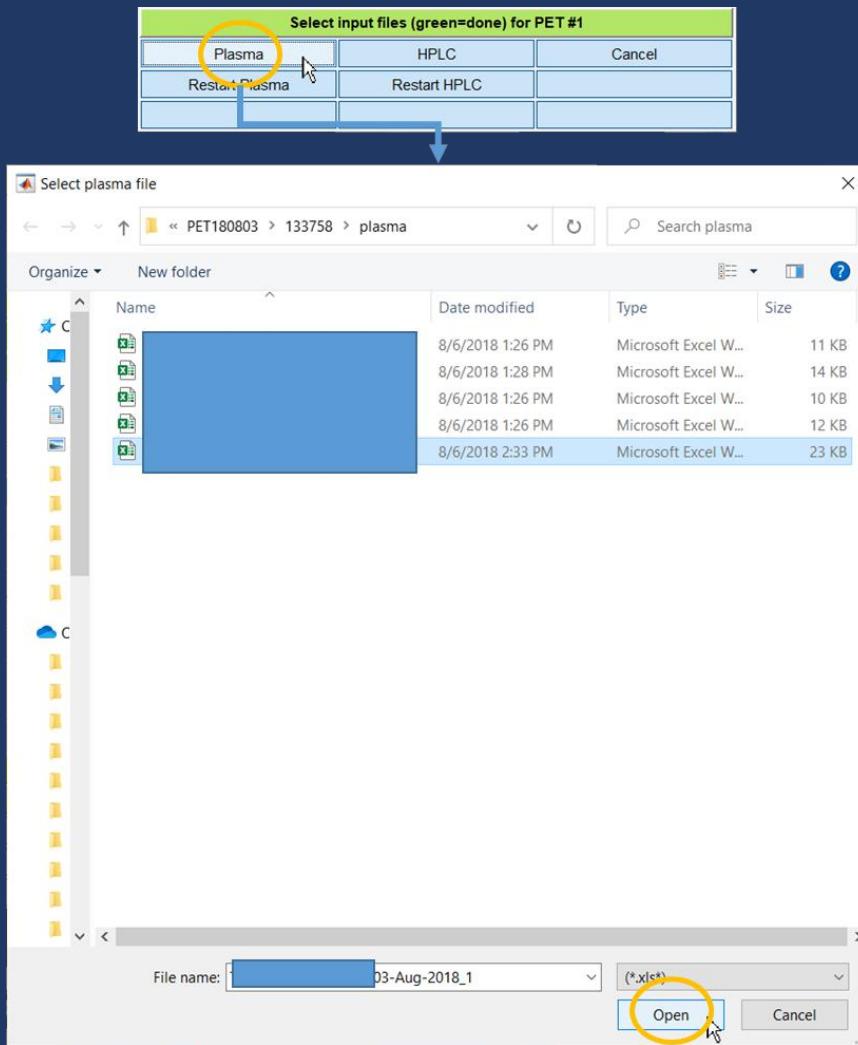
To Prepare Plasma and HPLC Data

# Preparation of Plasma & HPLC files



- When the ‘preparation’ step is activated (upper orange circle), L2W’s utility GUIs will be set for the purpose (orange rectangle)
  - The function of ‘Plasma’ GUI is to prepare a file of plasma data of this scan of the subject
    - ≈ Here, the term ‘plasma data’ refer to a two-column matrix of sampling times and radioactivity values in user-specified unit
  - The function of ‘HPLC’ GUI is to prepare a file of HPLC data
    - ≈ The term ‘HPLC data’ refers to a two-column matrix of sampling times and fractions of metabolites in percentage
- The ‘Plasma’ and ‘HPLC’ GUIs will not function until the local manager set the local system file (dxetc4xxx.m)
  - This is to cope with the fact that individual PET centers or Labs prepare plasma and HPLC files in their own formats and store them according to their own conventions.
- To local IDAE managers:
  - See help messages from cv2\_getCPT.m
  - See also the next two slides

# Site-Specific Operations: Plasma



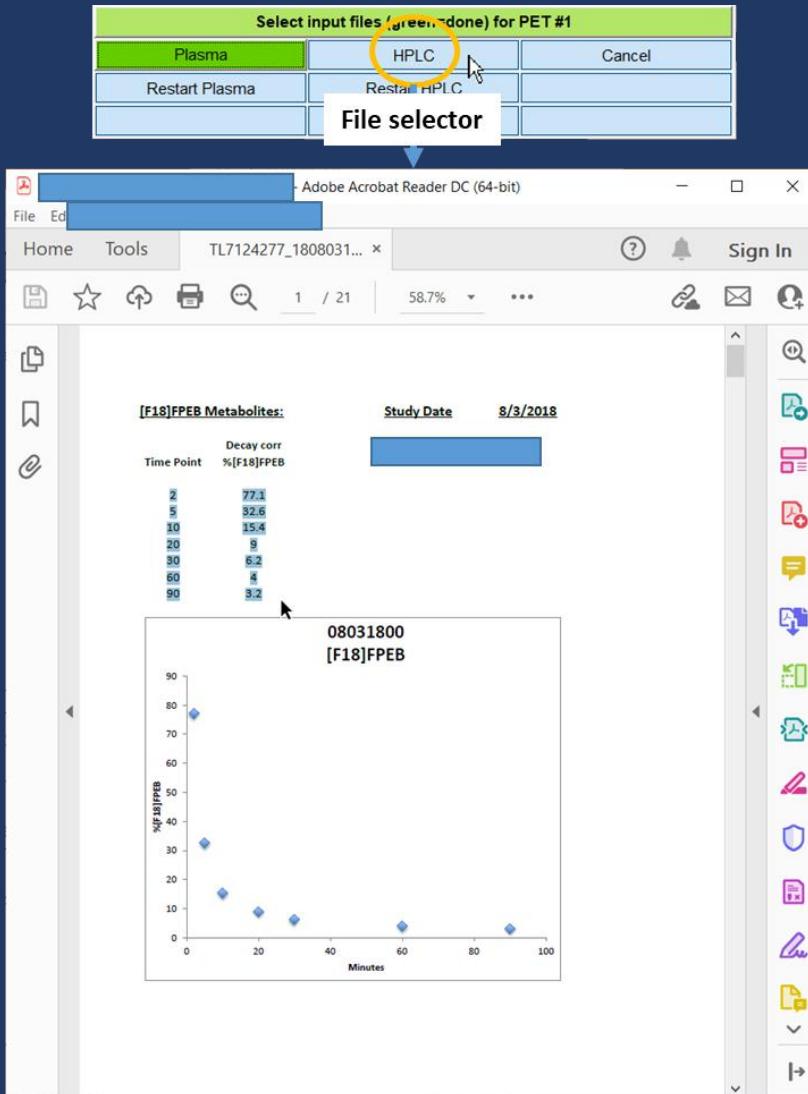
- In this example, MATLAB's file selector will pop up when 'Plasma' GUI is hit.
  - Note that the folder was pre-selected
  - Files of target format (\*.xls\*) alone are listed
  - When the target file is selected (lower orange circle), the plasma data will be extracted and saved in IDAE-requested format
  - The GUI will be marked in darker green
    - ≈ Use 'Restart Plasma' GUI to start over
- To local IDAE managers:
  - The callback function of 'Plasma' GUI is:

```
dxetc4xxx('get_plasma',input_2)
```

where input\_2.ofl contains the IDAE-generated output plasma file, and input\_2.fbc lists [figure # of L1W, subject #, scan #]
  - Set a subfunction 'local\_get\_plasma' in your dxetc4xxx.m and set the following measures:
    - ≈ To find the plasma file. A MATLAB function of uigetfile.m was utilized in this example
    - ≈ To convert the plasma data into a two-column matrix of sampling times and radioactivity values in user-specified unit
    - ≈ To save it to input\_2.ofl in 8-digit ASCII format (add '-ascii')
    - ≈ To update the Plasma GUI (to green) add the following line just after the 'save' line

```
cv2_getCPT('check', 1)
```

# Site-Specific Operations: HPLC



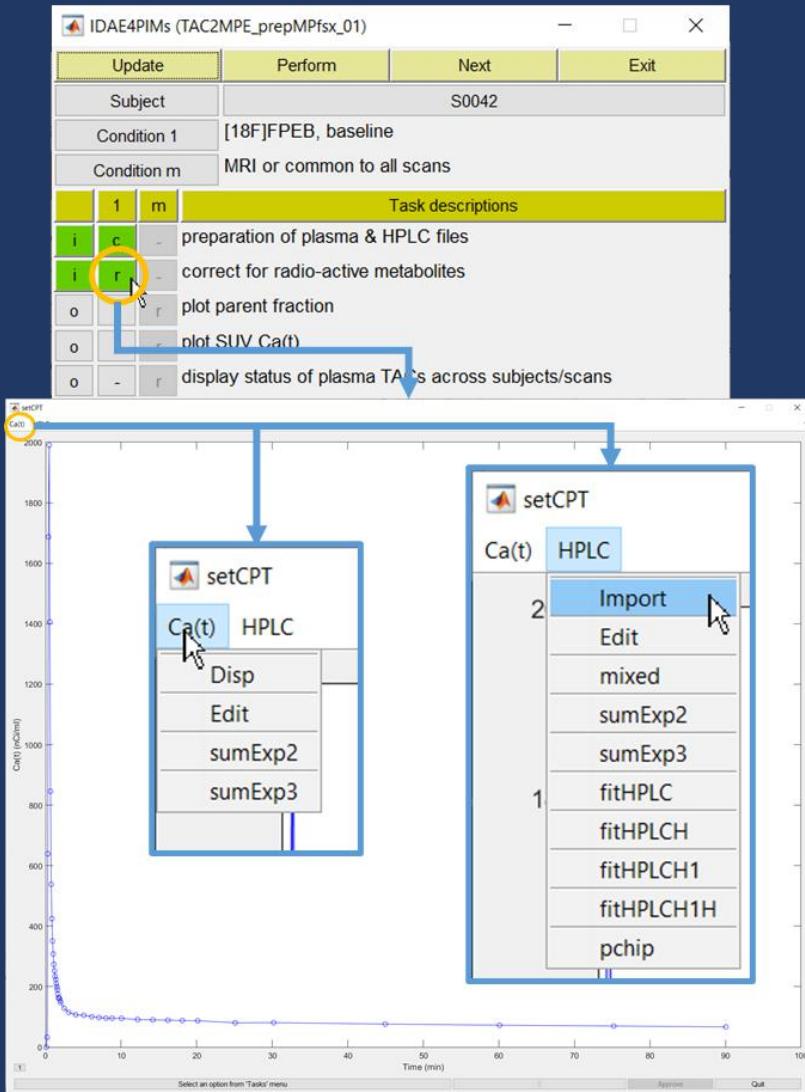
- In this example, MATLAB's file selector will pop up when 'HPLC' GUI is hit.
  - Open the target PDF file (lower panel) as shown in previous slide. Copy / paste time and parent fractions to the MATLAB command as instructed therein
    - ≈ The manual method was selected since the function to read PDF requires a specific MATLAB toolbox
  - The GUI will be marked in darker green
  - ≈ Use 'Restart HPLC' GUI to start over
- To local IDAE managers:
  - The callback function of 'Plasma' GUI is:

```
dxetc4xxx('get_hplc',input_2)
```

where input\_2.ofl contains the IDAE-generated output HPLC file, and input\_2.fbc lists [figure # of L1W, subject #, scan #]
  - Set a subfunction 'local\_get\_hplc' in your dxetc4xxx.m and set the following measures
    - ≈ To find the HPLC file. A MATLAB function of uigetfile.m was utilized in this example
    - ≈ To convert the plasma data into a two-column matrix of sampling times and radioactivity values in user-specified unit
    - ≈ To save it to input\_2.ofl in 8-digit ASCII format (add '-ascii')
    - ≈ To update the HPLC GUI (to green) add the following line just after the 'save' line

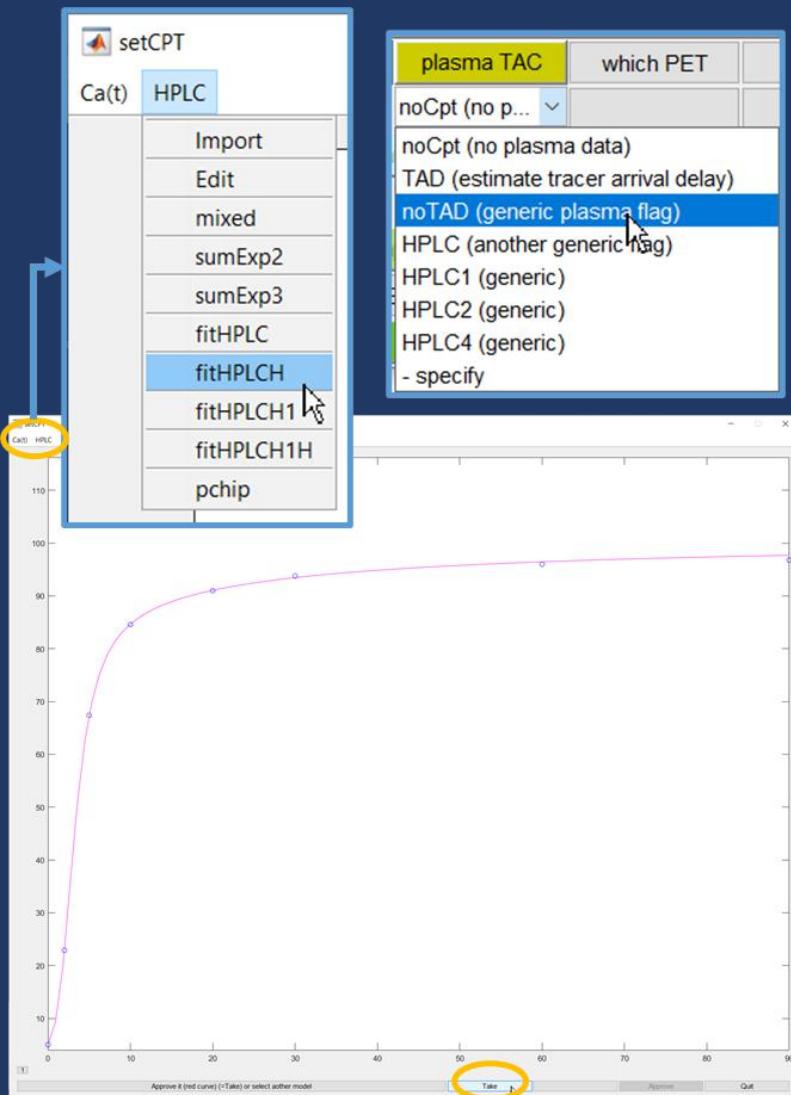
```
cv2_getCPT('check', 2)
```

# Correct for Radioactive Metabolites: 1



- The setCPT module will pop-up with plot of the plasma TAC (total) (lower panel) when the GUI of the 'correct ..' step is clicked (orange circle)
- Observe the plasma TAC
  - Some corrective measures for the plasma TAC are provided (left insert; under Ca(t))
  - Consult the tabs for functions
    - ≈ sumExp2/3 refer to sums of exponential functions
- Import HPLC data, if plasma TAC is OK

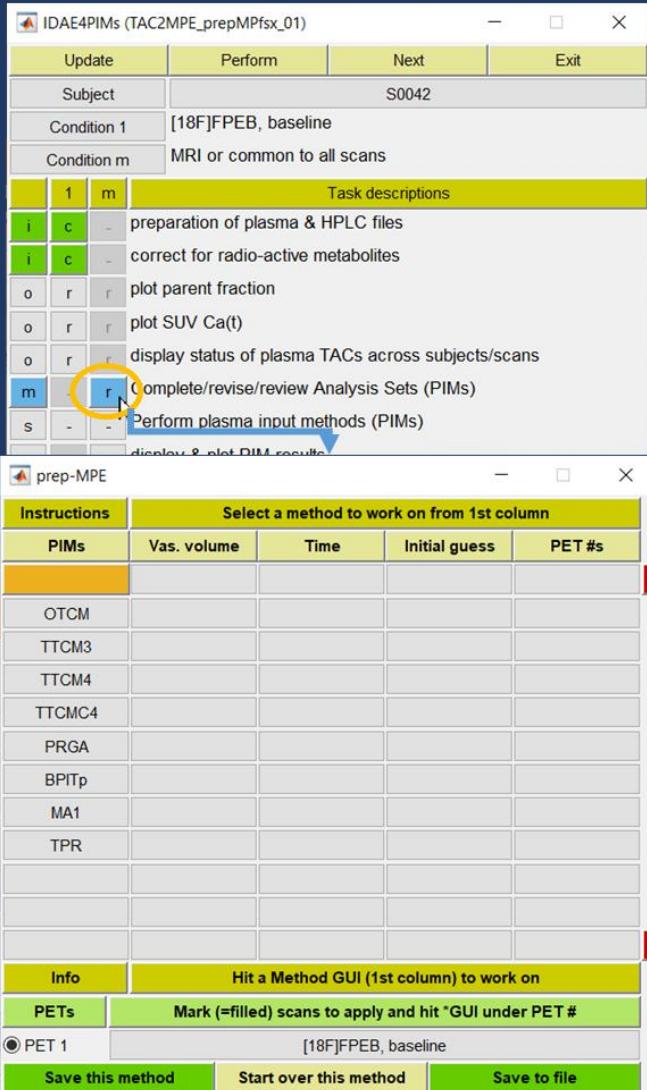
# Correct for Radioactive Metabolites: 2



- Observe plot of the HPLC data (blue circles in lower panel)
  - Note that the HPLC data show total metabolites in percentages (= 100 – parent fraction in percentage)
  - Fit the HPLC data by one of IDAE-supplied functions (3<sup>rd</sup> tab and on; upper panel)
    - ≈ The IDAE team suggest using ‘mixed’, ‘fitHPLC’, one of ‘fitHPLCH\*’, or ‘pchip’
      - ‘pchip’ refers to the shape-preserving piecewise cubic interpolation of MATLAB (interp1.m)
    - ≈ Employ one approach across scans of a study
  - Hit ‘Take’ (lower orange circle), ‘Apply’, and ‘Approve’ GUIs sequentially. It’s done!
  - Associate the fitting approaches with the IDAE-supplied generic terms for plasma data
    - The generic terms including ‘noTAD’ and ‘HPLC\*’ are presented during generation of Stage-2 packages (TAC2MPE)
    - The IDAE team recommends to make site-wide rules, for example to use ‘noTAD’, ‘HPLC’, and ‘HPLC1’ for ‘fitHPLC’, one of ‘fitHPLCH\*’, and ‘pchip’, respectively.

To Set / Perform PIMs

# Setting PIMs: Overview



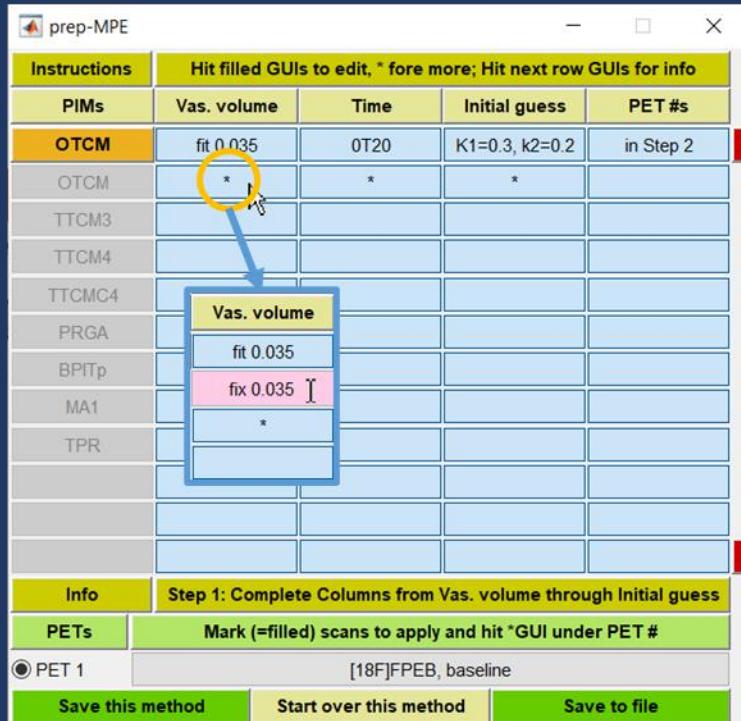
- Aim: To set plasma input methods (PIMs) and their parameters for the package
- Major procedures:
  - First, set the MPE preparation module (lower panel) by clicking the designated GUI (orange circle; upper panel)
  - Follow instructions given in the 1<sup>st</sup> row
  - Bring in a method from the 1<sup>st</sup> column GUIs to set relevant parameters (2<sup>nd</sup> to 4<sup>th</sup> columns)
    - ≈ See the quick guide (next slide) for methods
    - ≈ Hit ‘Save this method’ (bottom left) when done to move on to the next method
  - Go inclusive in the first cycle (i.e., for all PETs) to be selective in the second cycle.
    - ≈ Hit ‘Save to file’ if no more methods to set (= the end of the first cycle)
  - Visit already-selected (light green) methods one-by-one in the second cycle
    - ≈ Adjust applicable PET sans and hit ‘Save this method’ to move on to the next method
      - e.g., 20T90 for PET 1 (tracer A) and 40T90 for PET 2 (tracer B) for PRGA
    - ≈ Hit ‘Save to file’ when all methods are done (= the end of second cycle)

# PIMs: Quick Guide

Labels	Descriptions	Parameters	Outcome Variables
OTCM	One tissue compartment model	$K_1, k_2', V_0$	$V_T = K_1/k_2'$
TTCM3	Two tissue compartment model irreversible (no $k_4$ )	$K_1, k_2, k_3, V_0$	$K_i = K_1 \cdot k_3 / (k_2 + k_3)$
GPGA	Gjedde-Patlak plot	Slope of asymptote	$K_i$ : slope
TTCM4	Two tissue compartment model reversible (with $k_4$ )	$K_1, k_2, k_3, k_4, V_0$	$V_T = K_1/k_2 (1 + k_3/k_4)$ $BP_{ND} = k_3/k_4?$
TTCM4C	TTCM with the $K_1/k_2$ ratio fixed at the reference tissue value	$K_1, k_3, k_4, V_0$	$V_T = K_1/k_2 (1 + k_3/k_4)$ $BP_{ND} = k_3/k_4$
PRGA	Plasma reference graphical analysis (Logan et al., 1990)	Slope of asymptote	$V_T$ : Slope $BP_{ND} = V_T/V_T^R - 1$
MA1	A multi-linear version of PRGA		
BPITp	Bolus-plus-infusion transformation		$V_T$ : Plateau height

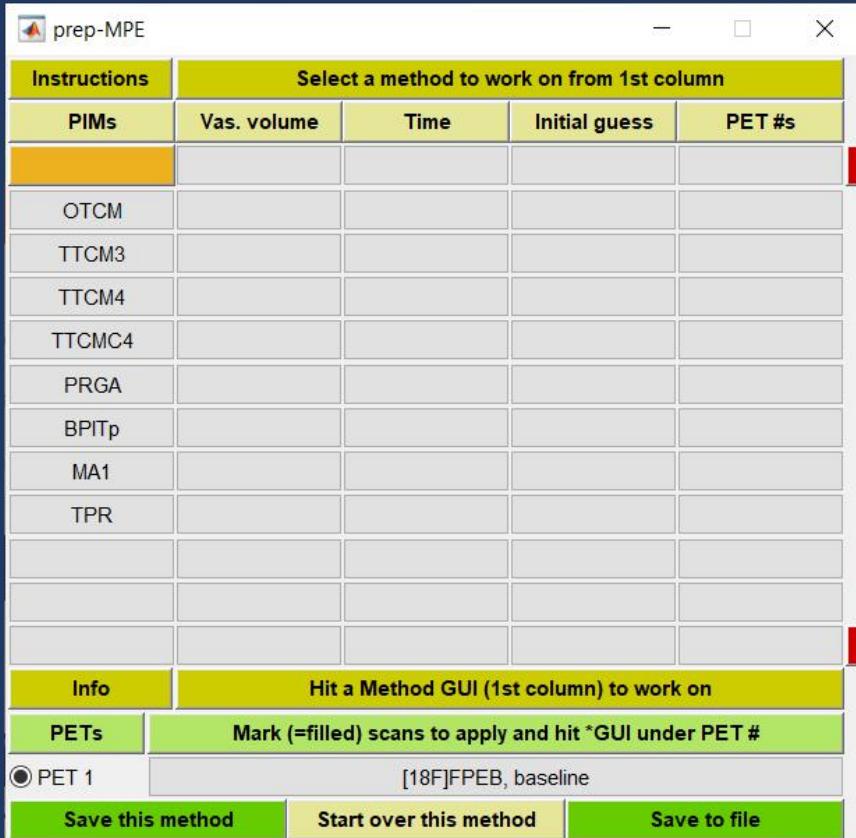
$K_1, k_2$ : BBB clearance constants;  $k_3 = B_{max}/k_{on}$ ;  $k_4 = k_{off}$ ;  $V_0$ : tissue vascular volume  
 TTCM3 etc (yellow highlight): Not working for now (need to fix by submission)

# Setting PIMs: General Points



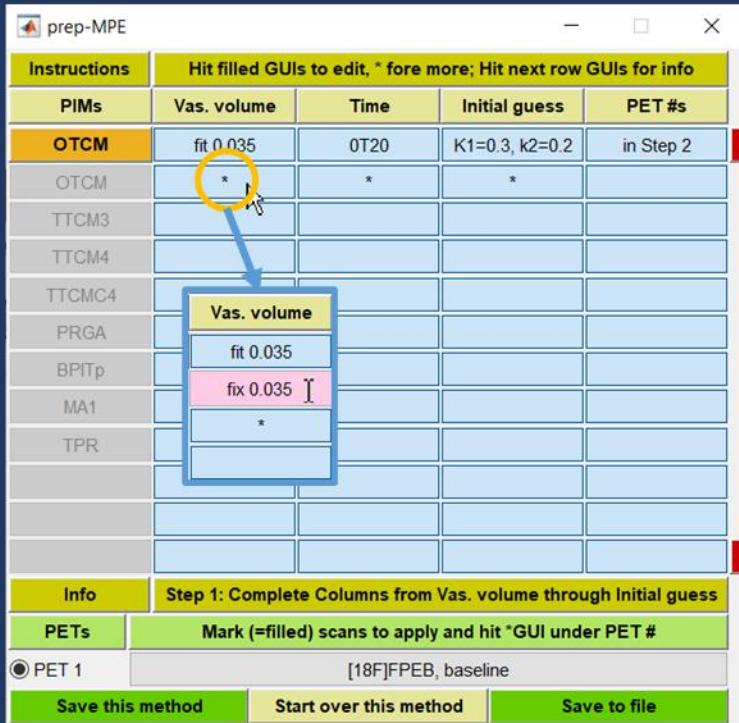
- Hit a method to set (OTCM in this example)
  - The method will be shown on the 'Orange' GUI
  - Suggested entries will be shown in columns of 'Vas. volume', 'Time', and 'Initial guesses'
- Complete columns:
  - Hit a filled GUI to modify it, as needed
    - ≈ The GUI turns in the 'edit' mode (pink)
    - ≈ Follow the displayed format: e.g., for the initial guesses, enter 'K1 = new value, k2 = new value'
    - ≈ Empty it to remove the entry
    - ≈ Hit the 'return' key when done (no longer in pink)
  - Hit a \* GUI to create a new entry (orange circle)
    - ≈ The GUI turns in the edit mode (pink) with a new suggested entry (insert)
    - ≈ Follow the displayed format: e.g., 'fix new value' to fix the vascular volume at the new value
    - ≈ Empty it to remove the entry
    - ≈ Hit the 'return' key when done (no longer in pink)
- Hit 'Save this method' GUI when it is done for the method.
- Hit 'Save to file' GUI when all intended methods are done
- Repeat the same in the second cycle to individualize the methods to scans

# When to Employ TTCM4 Family



- See the 'Quick Guide' to know IDAE's acronyms for PIMs
- IDAE is set to perform TTCM4 & TTGMC4 with regionally adjusted initial guesses of parameters, if OTCM and PRGA are also performed
  - Initial guesses of  $K_1$  through  $k_4$  will be calculated from the estimates of  $K_1$  from OTCM (with a short circulation time such as OT20) and estimates of  $V_T$  from PRGA.
  - In our experience, the measure decreased # of outliers of  $V_T$  (e.g.,  $> x5$  of the maximal regional  $V_T$  value from PRGA)
  - Thus, IDAE chose to adopt the feature.
- In sum, set OTCM and PRGA if the user intend to set TTCM4 and/or TTGMC4

# Setting OTCM: First Cycle



- Vas. Volume: vascular volume in tissue  $v_0$ .
  - Default (initial suggestion): ‘fit 0.035’ to fit  $v_0$  while setting the initial guess to 0.035 mL/mL
  - ‘fix value’ is also valid to fix  $v_0$  at the value (e.g., 0.035 mL/mL)
    - ≈ Enter ‘fix 0’ to ignore the vascular volume in tissue
- Circulation time:
  - Start- and end-frame time of the analysis
  - Use the startTend format
    - ≈ The initial suggestion is ‘0T20’ specifying to use 0-20 frames for the model parameter estimation
      - This is to obtain regional values of K1 because OTCM can fit TACs very well if initial 20 min of the scan is used (see ‘When to Employ TTCM Family’)
    - ≈ Add other sets (e.g., 0T90) to test OTCM in longer scan durations.
    - ≈ The start-frame time should be 0 in OTCM
- Initial guesses:
  - The generic one (K1=0.3, k2=0.2) should work well for OTCM
  - ‘Save this method’ to move on to set the next method

\*Second (or more) entries for ‘fit’ and ‘fix’ of ‘vas. volume’ (e.g., ‘fix 0.03’ and ‘fix 0.05’) and ‘initial guesses’ work only when they are made scan-specific in the second cycle (e.g., ‘fix 0.03’ for scans 1 & 2 and ‘fix 0.05’ for scans 3 & 4). Otherwise, second (and more) entries will be ignored (due to common output file names).

# Setting TTCM4 and TTMC4

Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s
TTCM4	fit 0.035	0T90	OTCM+PRGA	in Step 2
OTCM	*	*		
TTCM3				
TTCM4				

Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s
TTCM4C	fit 0.035	0T90	<input checked="" type="radio"/> CW 90400	in Step 2
OTCM	*	*		
TTCM3				
TTCM4				

- Columns of ‘Vas. volume’ and ‘Time’ are accessible for TTCM
  - The entry, ‘OTCM+PRGA’ under ‘Initial guesses’ indicates that initial guesses of K1, k2, k3, and k4 are calculated from outputs of OTCM and PRGA
- Columns of ‘Vas. volume’ and ‘Time’ are accessible for TTMC4
  - Select applicable reference regions from the list
    - ≈ Filled = selected; empty = not to use
    - ≈ The K1-k2 ratio of the scan will be obtained from TTCM4 of the reference region to be fixed to estimate K1, k3, and k4 alone in other regions
- Leave 0 of OTend (e.g., 0T90) for OTCM, TTCM4, and CCTMC4 because there is no justification for ignoring the initial portions of TACs in these methods

# Setting PRGA, MA1, and BPITp

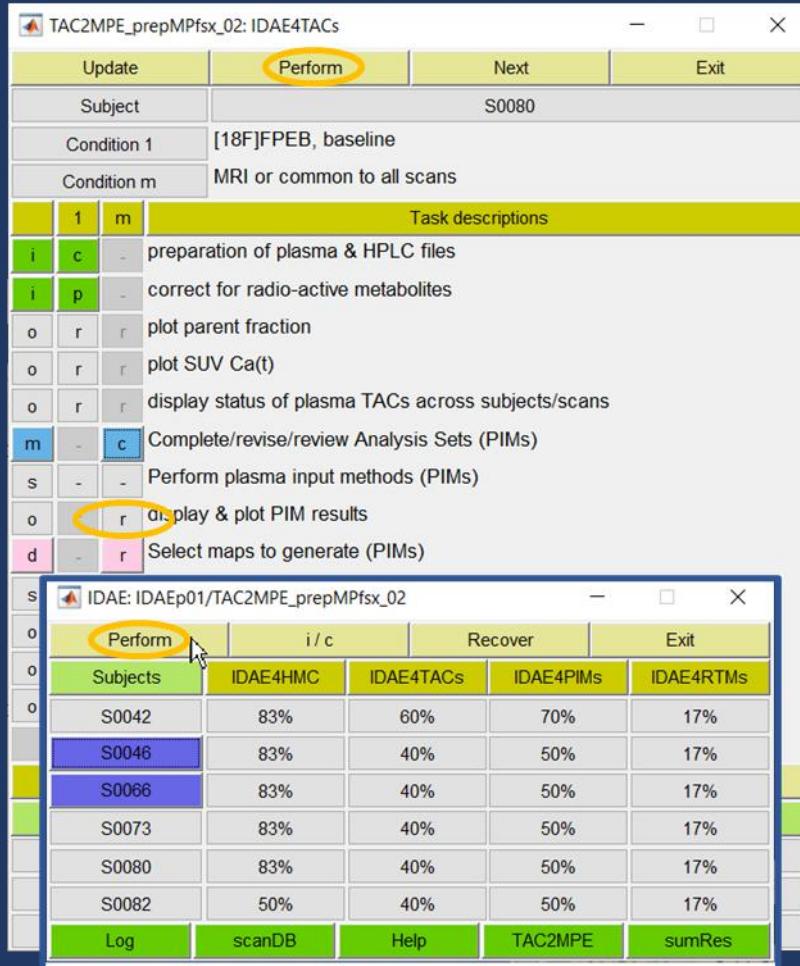
Instructions Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s
PRGA	-	10T90	-	in Step 2
OTCM		15T90		
TTCM3		20T90		
TTCM4	*			

Instructions Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s
MA1	-	20T90	-	in Step 2
OTCM		*		
TTCM3				
TTCM4				

Instructions Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s
BPITp	-	40T90	-	in Step 2
OTCM		*		
TTCM3				
TTCM4				

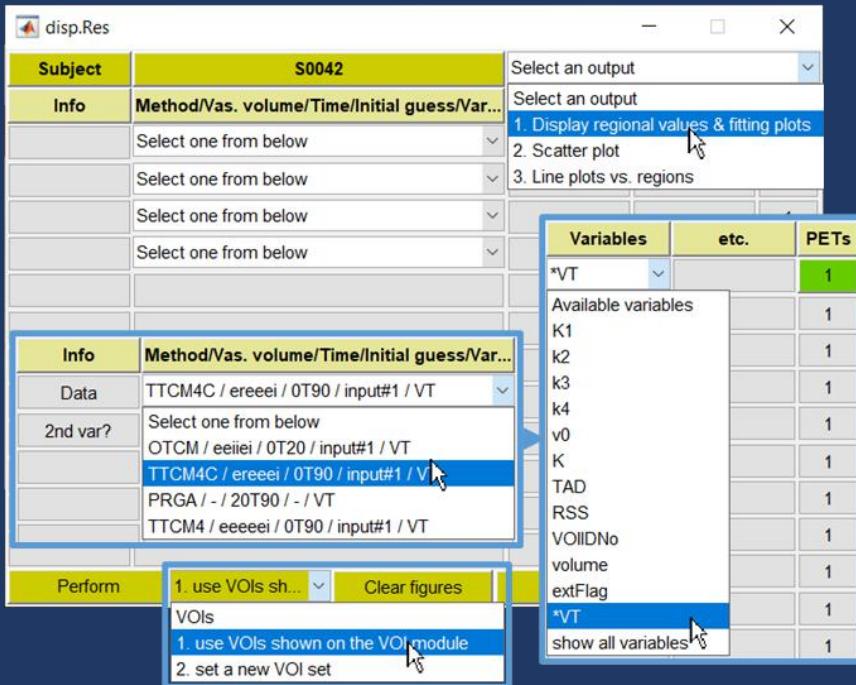
- Complete the column of ‘Time’ alone for PRGA, MA1, and BPITp
  - Again, use the t\*Tend format where t\* stands for the start time of asymptotes and ‘end’ stands for the circulation time for the analyses
  - Hit the GUI with \* to start a new entry
    - ≈ Edit it (in pink) as needed.
  - Hit an existing GUI to edit it.
- Make sure to include PRGA if to employ TTCM4 or TTGMC4

# Performing PIMs



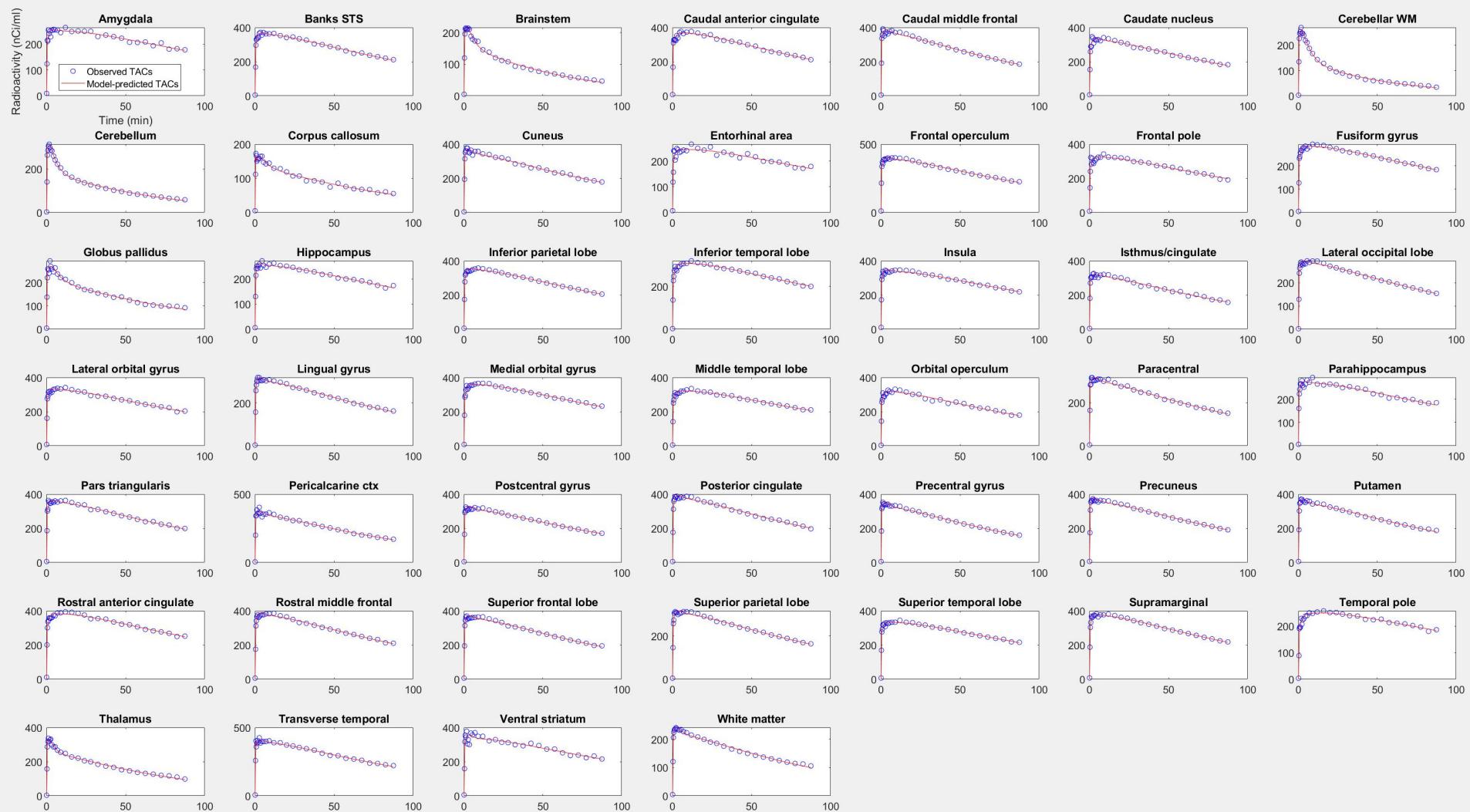
- To perform PIMs on this subject alone:
  - Hit ‘Perform’ GUI (top orange circle) of IDAE’s Level 2 window
  - Hit ‘r’ GUI of the designated task (middle orange circle)
- To perform PIMs on multiple subjects:
  - Highlight subjects to perform on Level 1 window and hit ‘Perform’ (bottom orange circle)

# Display / Plot PIM Results



- Hit the ‘r’ GUI @’Display / plot PIM results’ of L2W (IDAE4RTMs) to set the result display module (background)
- Select an output from the menu (top right)
  - Display regional values ... (shown here)
  - Scatter plot of regional data of a variable between scan 1 vs. scan 2 and so on
  - Line plots vs. regions: Spaghetti plots
- Select one analysis approach from the list (left insert)
  - Approaches are shown by 5 elements of ‘method flag’ (acronyms), ‘fit flag’ (e = to estimate; c = to fix; I = to ignore for K1, k2, k3, k4, and v0), ‘circulation time for analysis’, ‘acronym of initial guesses’, and ‘primary variable’.
- Select the variable to display (right insert)
  - Select ‘show all variables’ to display them all
- Select the scan to display (right insert)
  - Light green = available; darker green = selected
- Set the VOIs to display (bottom)
  - See the section of the VOI selector module
- Hit ‘Perform’ GUI (bottom left)

# Example Fitting Plots: TTCM



# Revise / Review PIM Approaches

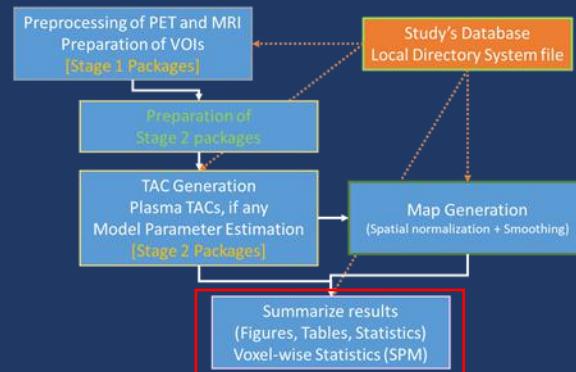
The figure consists of two side-by-side screenshots of a software window titled 'prep-MPE'.

**Screenshot 1 (Top):** The title bar says 'prep-MPE'. The main area has a table with columns: 'Instructions' (highlighted in yellow), 'PIMs' (highlighted in light green), 'Vas. volume', 'Time', 'Initial guess', and 'PET #s'. The rows list various PIM methods: OTCM, TTGCM3, TTGCM4, TTGCM4C, PRGA, BPITp, and MA1. The first row (OTCM) is highlighted in light green.

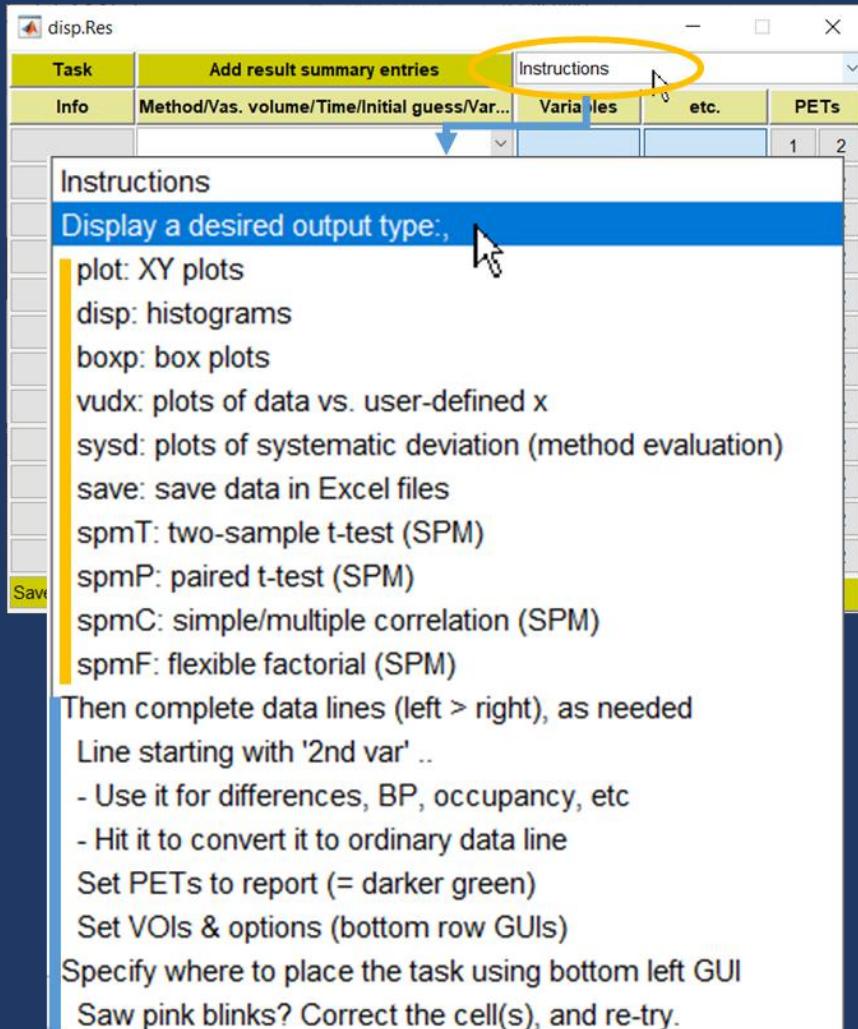
**Screenshot 2 (Bottom):** The title bar says 'prep-MPE'. The main area has a table with columns: 'Instructions' (highlighted in pink), 'PIMs' (highlighted in light green), 'Vas. volume', 'Time', 'Initial guess', and 'PET #s'. The rows list the same PIM methods. The second row (OTCM) is highlighted in light green. A sidebar on the left shows buttons for 'PE' and 'PET'. Below the table, there's an 'Info' section with 'Expand mode: One approach per row' and a 'PETs' section with 'Mark (=filled) scans to apply and hit \*GUI under PET #' and 'PET 1 [18F]FPEB, baseline'. At the bottom are buttons: 'Save this method', 'Start over this method', and 'Save to file'.

- To review / revise saved PIM approaches
- Hit 'c' GUI at 'Complete/revise/review Analyses Sets' to bring up the MPE preparation module (upper panel)
  - Previously set PIM methods will be highlighted in light green
  - Hit a highlighted method to review / revise
  - Bring in / set yet-set methods, as needed
  - Hit 'Save this method' to update displayed method
  - Hit 'Save to file' when done (= the end of the 1<sup>st</sup> cycle)
    - ≈ Leave those methods not to review / revise unattained
- In the 2<sup>nd</sup> cycle:
  - Hit highlighted methods to review / revise
  - Hit 'Save this method' to update displayed method
    - ≈ Reviewed / revised methods will be highlighted in darker green (e.g., TTGCM4 in this example)
  - Hit 'Save to file' when done (= the end of the 1<sup>st</sup> cycle)
    - ≈ Leave those methods not to review / revise unattained

# Result Summary

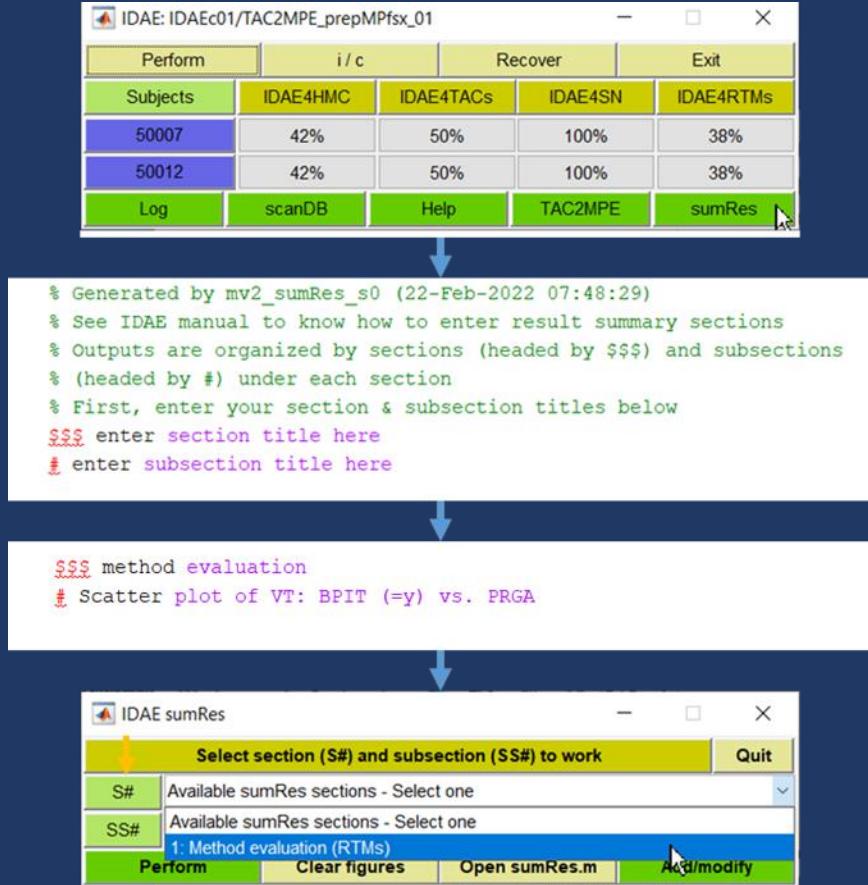


# Introduction



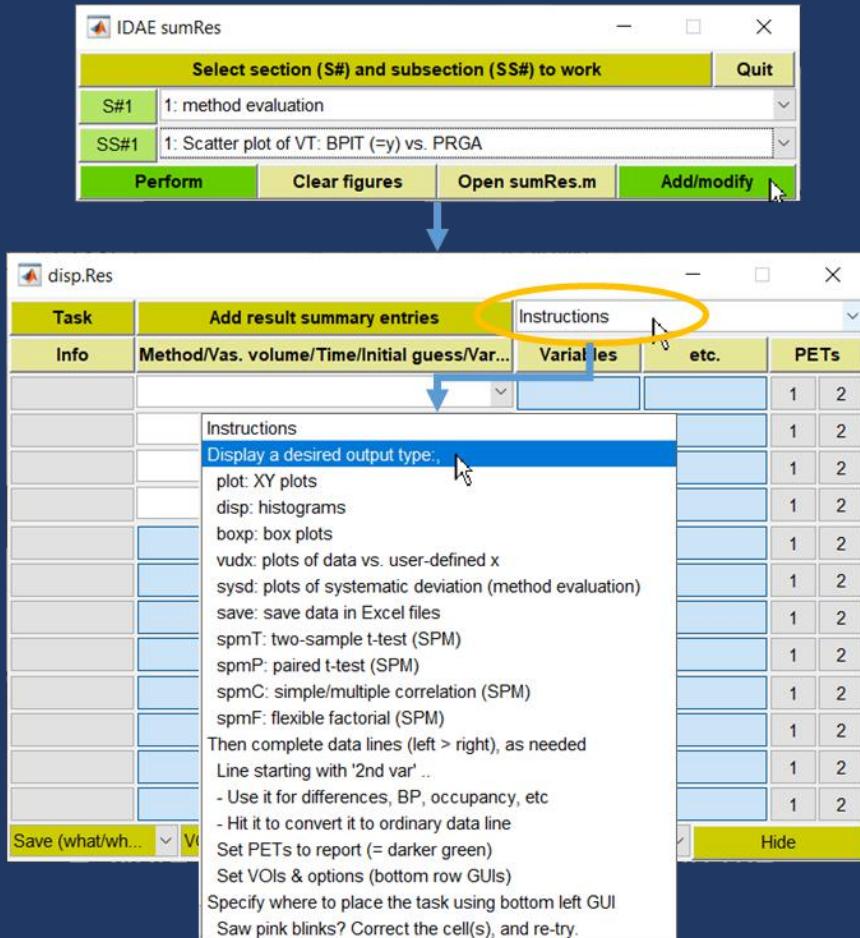
- Aim: To make figures and tables for reports and manuscripts
- One set of outputs (figures or a table) is defined in one cycle of actions that includes:
  - Selection of the output type
    - ≈ Available output types are listed on the menu bar (foreground, orange lines) of the disp.Res module (background)
  - Successive selections about details of the outputs, all done by GUIs
    - ≈ outlined in the tab, blue lines
  - Execution of so-generated commands
- Management system:
  - IDAE adopt the following system to make it possible to re-generate outputs at will
    - ≈ The command lines from one cycle are stored as a 'subsection' in the sumRes.m file (plain text) of the study
    - ≈ Subsections are organized under sections, both with user-defined titles
      - The user choose where to place the new subsection in the file at the end of a cycle i.e., such as under which section and above or below which subsection

# First sumRes Cycle



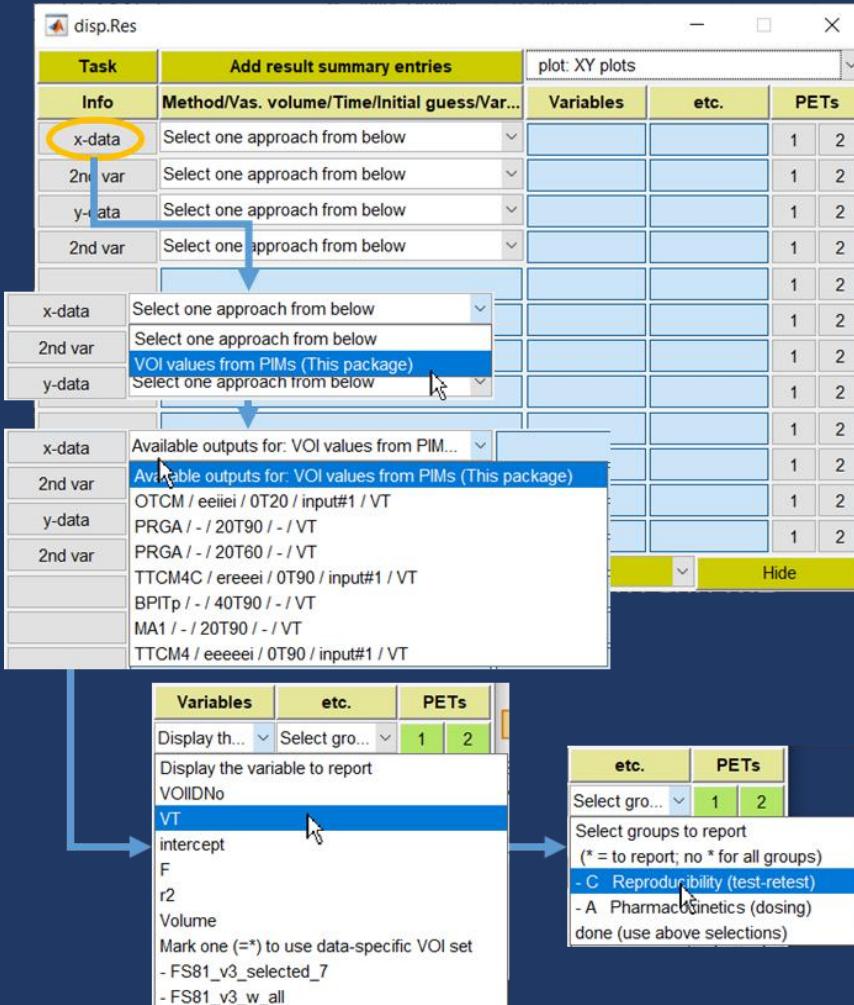
- Hit the ‘sumRes’ (for result summary) GUI of L1W to start with
- A designated file (referred to as sumRes.m) will be generated / opened
  - It will be organized by sections (start with \$\$\$) which hold several subsections (start with #)
    - ≈ Initially, one each alone (second panel)
  - The user manage section/subsection titles while IDAE inserts executable contents
    - ≈ Examples of user-edited section and subsection titles are shown in the third panel
  - Make sure to save it before moving on.
- Hit the ‘sumRes’ GUI one more time to display the sumRes module (bottom).
  - Select the section to work on first from the upper menu bar (headed by S# under orange arrow), then the subsection at SS# (subsection #)
    - ≈ Now the user is ready to add the executable contents (move on to the next slide)
  - **Good to remember:** Always start with the section first to update the section and subsection titles after revisions.

# Before Setting Outputs



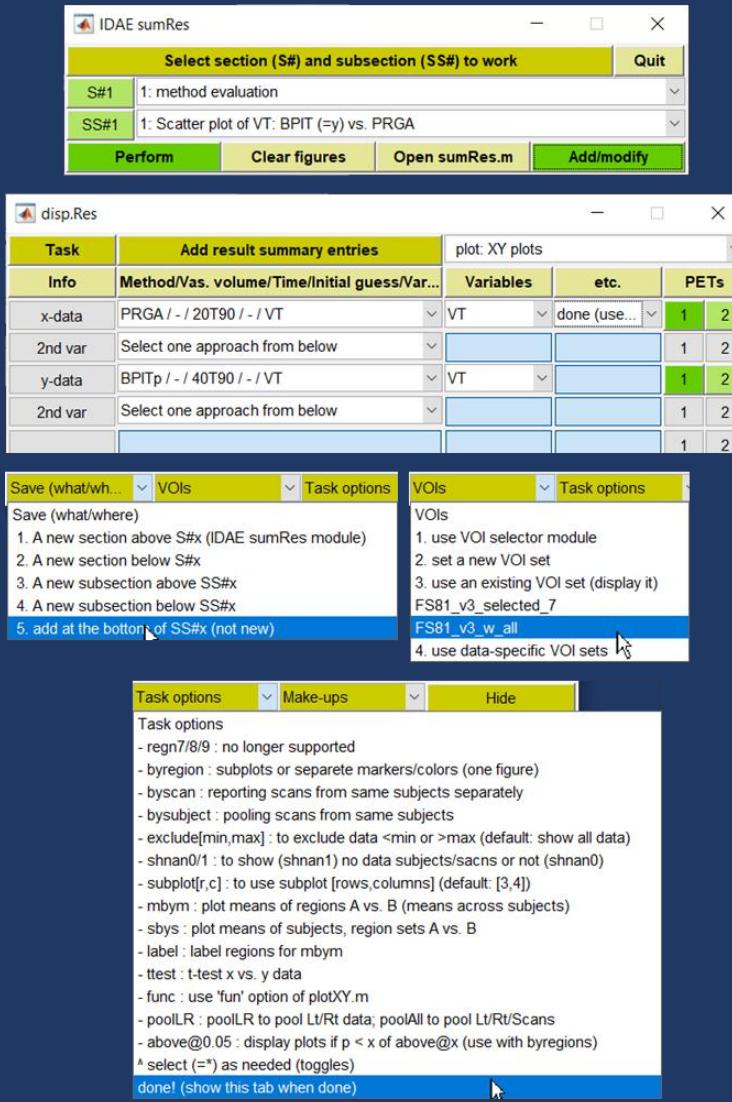
- Hit 'Add/modify' of the sumRes module (top) to display the 'Display Results' (disp.Res) module (bottom, background)
  - The sumRes module indicates that the user is intended to add the executable content for the subsection of the section
    - ≈ In this example, 'Scatter plot of VT: BPIT (=y) vs. PRGA' under 'Method evaluation (RTMs)'.
- Read the instruction menu carefully
  - Available output types are listed at top under 'Display a desired output' (@cursor)
    - ≈ Each selection shows the type flag followed by simple description
    - ≈ Just display the intended output type
      - In this example, the user intends to make 'XY plots' according to the user-defined subsection title
    - ≈ At least one example each output category will be described in this manual.
  - Once the intended output type is selected, the main GUI matrix of the disp.Res module become available for selections (next slide)

# Selecting Variables to Report: XY Plots



- Once ‘XY plots’ is selected (top right), GUIs for x- & y-data become available (left column)
    - Use the row of 2<sup>nd</sup> var to specify relational variables such as differences, ratios, or occupancy estimates, as needed
  - Complete data lines, one line at a time from left to right (showing for ‘x-data’ first)
    - Select the primary method classification
      - ≈ The highlighted selection means ‘regional V<sub>T</sub> value from this package’ (= VOI-based analysis)
        - ‘Map-value from PIM (from this package) will become available when VT images were generated for this package.
        - Data from ‘other’ packages will become available if other packages are generated / processed
    - Select the method (middle foreground panel)
      - ≈ Not sure about the method identification format?  
Review sections of RTMs and PIMs
    - Select the variable to report (bottom left)
    - Select the groups to report and display ‘done’
      - ≈ No need to select groups to report all groups
    - Lastly, select the scans to report
      - ≈ Applicable PETs are shown by light green
  - Repeat the same for ‘y-data’

# Setting Remaining Parameters: XY Plots



- The user's intention in this example (review):
  - To make a scatter plot of  $V_T$  data, BPIT (=y) vs. PRGA (@SS#1, upper panel) as a part of 'model evaluation' (@S#1 = section title)
  - Accordingly, it was set that  $V_T$  data of scan #1 of all subjects were used in the plot (middle panel)
- Set the remaining parameters using bottom row GUIs of the disp.Res module:
  - Set VOIs to report (third panel, right)
    - ≈ It is recommended to set VOI sets using VOI selector module to be consistent among trials
      - Review the section of 'Setting a New VOI Set'
    - ≈ A previously prepared VOI set was used here
  - Set output options (bottom panel)
    - ≈ Each selection shows the option flag followed by simple description
    - ≈ Most descriptions are self-explanatory. But ..
      - Need to replace r (# of rows) and c (# of columns) with integers in sumRes.m when to use subplot[r,c] (subplot[3,4] will display 3 rows x 4 columns of subfigures in one figure window).
    - ≈ Multiple options may be selected, as needed (denoted by \*, as the user select)
  - Lastly, specify where to place the executable lines
    - ≈ Select #5 for this example because both section and subsection titles are present (top panel)

# Setting a New VOI Set

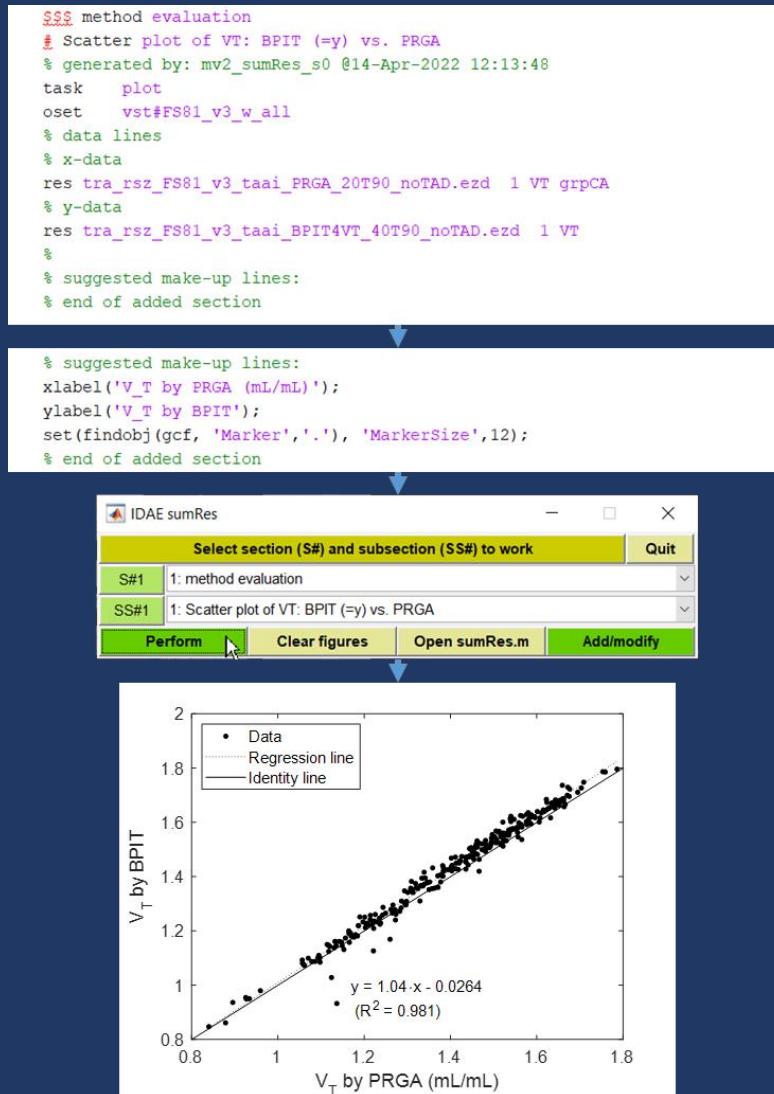
The screenshot shows two instances of the vL2 VOI selector interface. The top instance has the tab '2. set a new VOI set' selected, indicated by a blue highlight. The bottom instance has the tab 'FS81\_v2\_All\_w\_noWM' selected. Both instances show a grid of VOIs with L/R/W checkboxes. A large blue arrow points from the top instance down to the bottom instance.

VOIs	Task option	VOIs	Task option
1. use VOI selector module		1. use VOI selector module	
2. set a new VOI set		2. set a new VOI set	
FS81_v2_All_w_noWM	FS81_v2_All_w_noWM		
VOIs	VOIs		
Frontal operculum (FO)	Frontal operculum (FO)	Frontal operculum (FO)	Frontal operculum (FO)
Amygdala (Am)	Amygdala (Am)	Amygdala (Am)	Amygdala (Am)
Banks STS (bT)	Banks STS (bT)	Banks STS (bT)	Banks STS (bT)
Brainstem (BS)	Brainstem (BS)	Brainstem (BS)	Brainstem (BS)
Caudate nucleus (CN)	Caudate nucleus (CN)	Caudate nucleus (CN)	Caudate nucleus (CN)
Cerebellar WM (CW)	Cerebellar WM (CW)	Cerebellar WM (CW)	Cerebellar WM (CW)
Cerebellum (Cb)	Cerebellum (Cb)	Cerebellum (Cb)	Cerebellum (Cb)
Corpus callosum (CC)	Corpus callosum (CC)	Corpus callosum (CC)	Corpus callosum (CC)
Cuneus (Cu)	Cuneus (Cu)	Cuneus (Cu)	Cuneus (Cu)
Entorhinal area (ER)	Entorhinal area (ER)	Entorhinal area (ER)	Entorhinal area (ER)
L	R	L	R
Frontal pole (FP)	Fusiform gyrus (Fs)	Frontal pole (FP)	Fusiform gyrus (Fs)
Globus pallidus (GP)	Hippocampus (Hp)	Globus pallidus (GP)	Hippocampus (Hp)
Inferior parietal lobe (iPa)	Inferior temporal lobe (iTp)	Inferior parietal lobe (iPa)	Inferior temporal lobe (iTp)
Insula (In)	Isthmus/cingulate (IC)	Insula (In)	Isthmus/cingulate (IC)
Lateral occipital lobe (lOc)	Lateral orbital gyrus (lOG)	Lateral occipital lobe (lOc)	Lateral orbital gyrus (lOG)
Lingual gyrus (LG)		Lingual gyrus (LG)	
Medial orbital gyrus (mdOG)	Middle temporal lobe (mTp)	Medial orbital gyrus (mdOG)	Middle temporal lobe (mTp)
Occipital lobe (Oc)	Orbital operculum (OO)	Occipital lobe (Oc)	Orbital operculum (OO)
Paracentral (pC)	Parahippocampus (PH)	Paracentral (pC)	Parahippocampus (PH)
Pars triangularis (PT)	Pericalcarine ctx (pCx)	Pars triangularis (PT)	Pericalcarine ctx (pCx)
Postcentral gyrus (PS)	Posterior cingulate (pCg)	Postcentral gyrus (PS)	Posterior cingulate (pCg)
Precentral gyrus (Pc)	Precuneus (Pr)	Precentral gyrus (Pc)	Precuneus (Pr)
Putamen (Pu)		Putamen (Pu)	
Rostral anterior cingulate (rAC)		Rostral anterior cingulate (rAC)	
Rostral middle frontal (rmFr)		Rostral middle frontal (rmFr)	
Superior frontal lobe (sFr)		Superior frontal lobe (sFr)	
Superior parietal lobe (sPa)		Superior parietal lobe (sPa)	
Superior temporal lobe (sTp)		Superior temporal lobe (sTp)	
Supramarginal (SM)		Supramarginal (SM)	
Temporal pole (TP)		Temporal pole (TP)	
Thalamus (Th)		Thalamus (Th)	
Transverse temporal (tT)		Transverse temporal (tT)	
Ventral striatum (vS)		Ventral striatum (vS)	
White matter (WM)		White matter (WM)	

The users can define a VOI set when the ‘display result’ module is in the result summary mode.

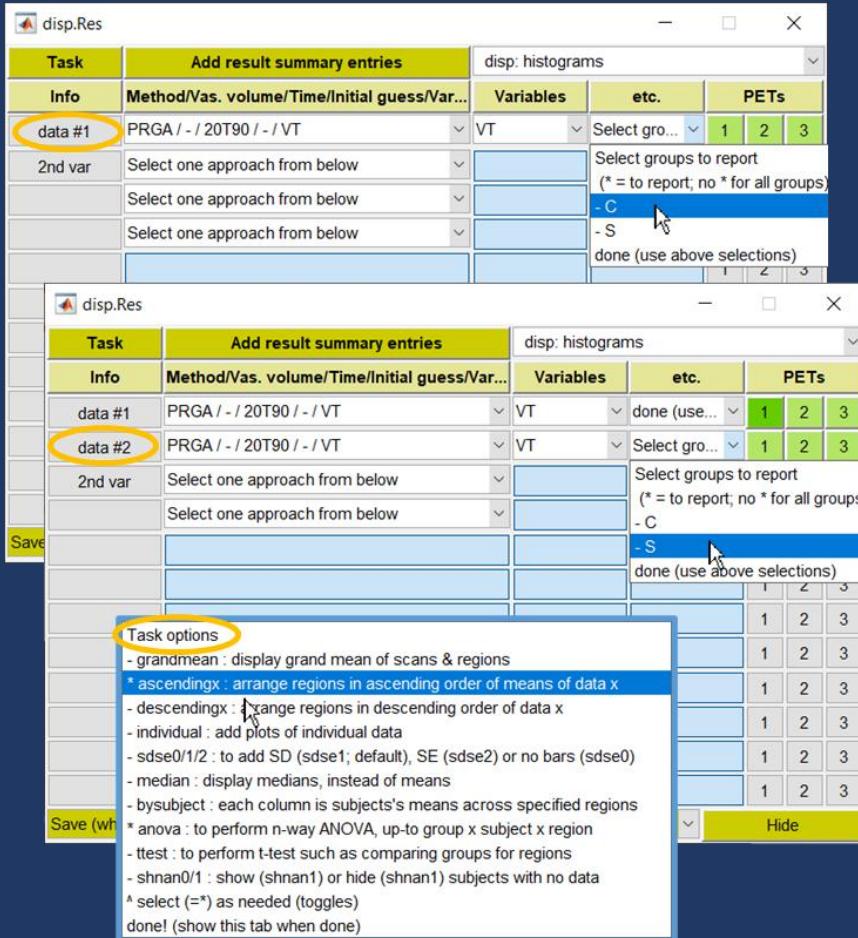
- Select the ‘set a new VOI set’ tab under ‘VOIs’
- Check the VOIs to include in the new set: L/R/W GUIs for bulk operations of the left, right, and whole (i.e., left-right merged) VOIs, respectively; Hit a checkbox to set it ‘on’ (filled) or ‘off’ (blank) one-by-one
- Empty the tab (Set a VOI set? ...) and enter a concise name. Note that the name of current VOIs set (FS81\_v2) will be prepended automatically (i.e., All\_w\_noWM alone was entered in this case)

# Generation of XY Plots



- Once ‘Save’ is done, ‘Not-right’ GUIs blinks in pink on the disp.Res module
  - Make corrections until the sumRes.m is updated
- If successful, the executable lines will be inserted to the sumRes.m file (and opened)
  - No need to check the executable lines (it’s IDAE’s responsibility)
  - The user can add command lines (second panel) for make-up
    - ≈ In this example, command lines for x- and y-labels were added. The third line is to make dots bigger
    - ≈ Hit ‘make-ups’ GUI of the disp.Res module to display useful sample command lines
    - ≈ The users can test / add the command lines after generation of the plot.
  - Make sure to save the sum.Res file, if any changes are made
- Hit ‘Perform’ GUI of the sumRes module (arrow, 3<sup>rd</sup> panel)
- Repeat the sumRes sessions, as needed.

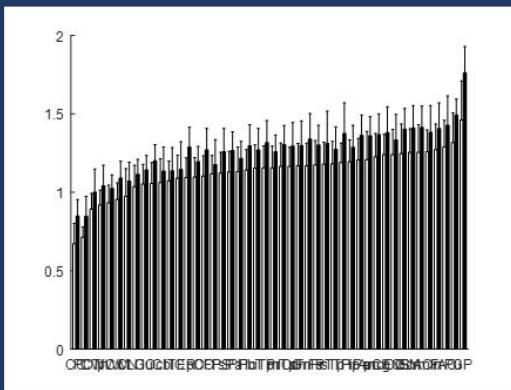
# Preparation for Histograms



- Presentation of the demonstration case:
  - To generate histograms of regional  $V_T$  values of two groups side by side, in an ascending order of Group C under a new section of ‘Figures for Manuscript #1’
- On the disp.Res module:
  - Select ‘histograms’ tab
  - For Data #1 (upper panel):
    - ≈ Select the method and variable to report
      - Use the line of 2<sup>nd</sup> var to calculate relational variables, if needed
    - ≈ Select Group C for data #1
    - ≈ Select PET #1 (=baseline scan)
  - For Data #2 (middle panel):
    - ≈ Hit ‘2<sup>nd</sup> var’ GUI to display ‘data #2’
    - ≈ Select Group S this time.
  - Options are quite self explanatory
    - ≈ Multiple options may be selected (denoted by \* if selected). And display ‘done!’ tab (bottom)
  - Select ‘2. New section below S#x’ to place the section in the intended location in the file
    - ≈ Because it was intended to create a new section in this example
  - ≈ Correct errors at GUIs that blink in pink when to ‘Save’ the subsection

# Generation of Histograms

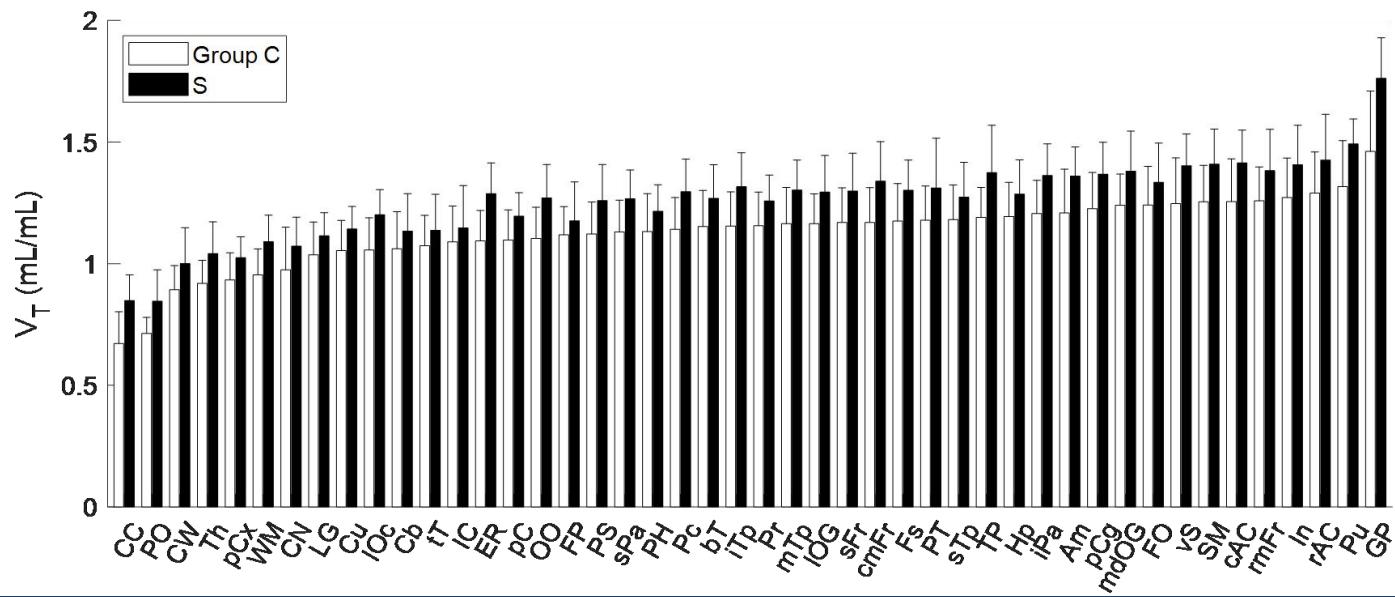
```
sss enter section title here
# enter subsection title here
% generated by: mv2_sumRes_s0 @14-Apr-2022 15:09:35
task disp ascendingx anova
oset vst#FS81_v3_w_lessBS
% data lines
% data #1
res tra_rsz_hmcMIT_FS81_v3_tbaa_PPGA_20T90_HPLC2.ezd 1 VT grpC
% data #2
res tra_rsz_hmcMIT_FS81_v3_tbaa_PPGA_20T90_HPLC2.ezd 1 VT grpS
%
% suggested make-up lines:
% end of added section
```



```
% suggested make-up lines:
set(gca, 'FontSize',13);
ylabel('V_T (mL/mL)');
pos = get(gcf, 'Position');
set(gcf, 'Position',[200,200,pos(3).*2,pos(4)]);
set(gca, 'XTickLabelRotation',60);
legend('Group C','s', 'location','northwest');
% end of added section
```

- When successfully saved, the file (sumRes.m) will open for checking / editing
  - First, revise the section and subsection titles according to the user's preferences
  - Some option strings require edition as written in the 'task option' menu bar
    - ≈ In this example, 'ascendingx' has to be revised to 'asending1' to sort regions by regional mean  $V_T$  values of Group C (= the intention)
      - Warning messages will be issued if option strings that require editions are left unchanged.
    - Then, hit 'Perform' GUI of the sumRes module to generate the histograms (middle panel)
- Try and error approach for figure make-ups:
  - List points of improvements
    - ≈ The y-axis label is missing
    - ≈ Region labels are not readable
    - ≈ Histograms are too close to each other
    - ≈ Legend is missing
  - Hit 'make-ups' GUI of the disp.Res module (bottom) to display suggested lines for make-ups
    - ≈ Copy / paste the lines for above list to the sumRes.m file and fine tune values
    - ≈ Acceptably good make-up lines are shown in bottom panel. See the next slide together with the ANOVA table

# Example Histograms

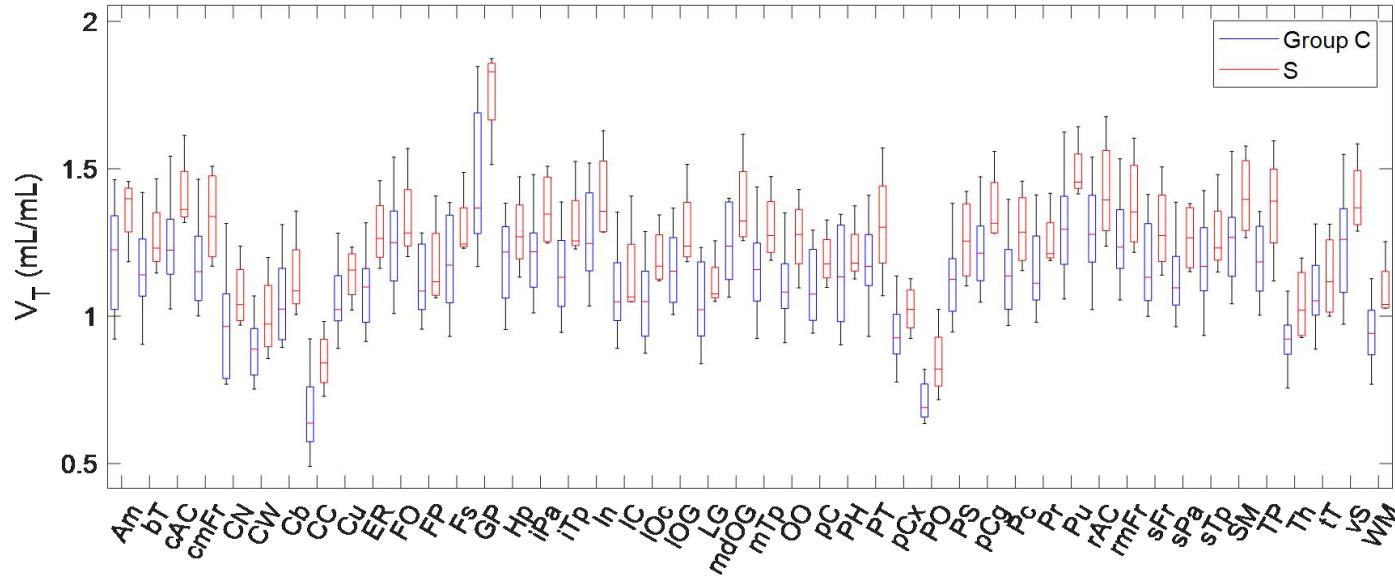


Analysis of Variance					
Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
<hr/>					
group	2.2317	1	2.23168	115.5	9.50046e-25
region	13.8347	45	0.30744	15.91	2.33903e-75
Error	11.5354	597	0.01932		
Total	27.6018	643			

Constrained (Type III) sums of squares.

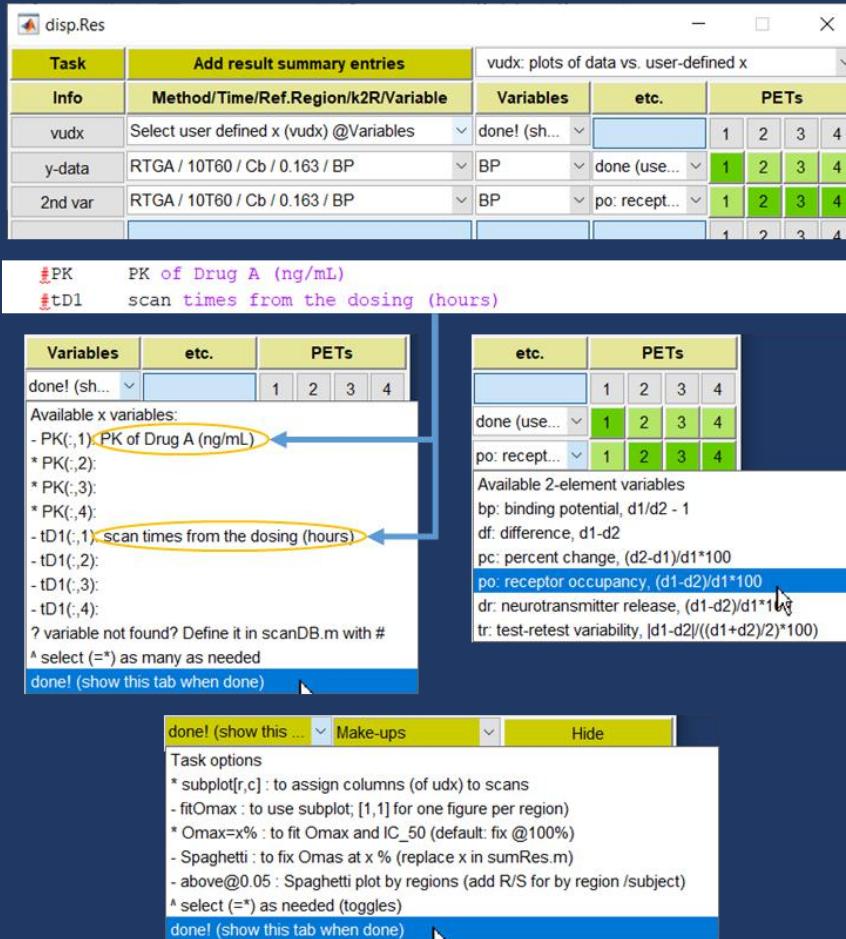
- Histograms from the example case after make-ups.
- The ANOVA table shows strong group and region effects in the dataset.

# Example Box Plots



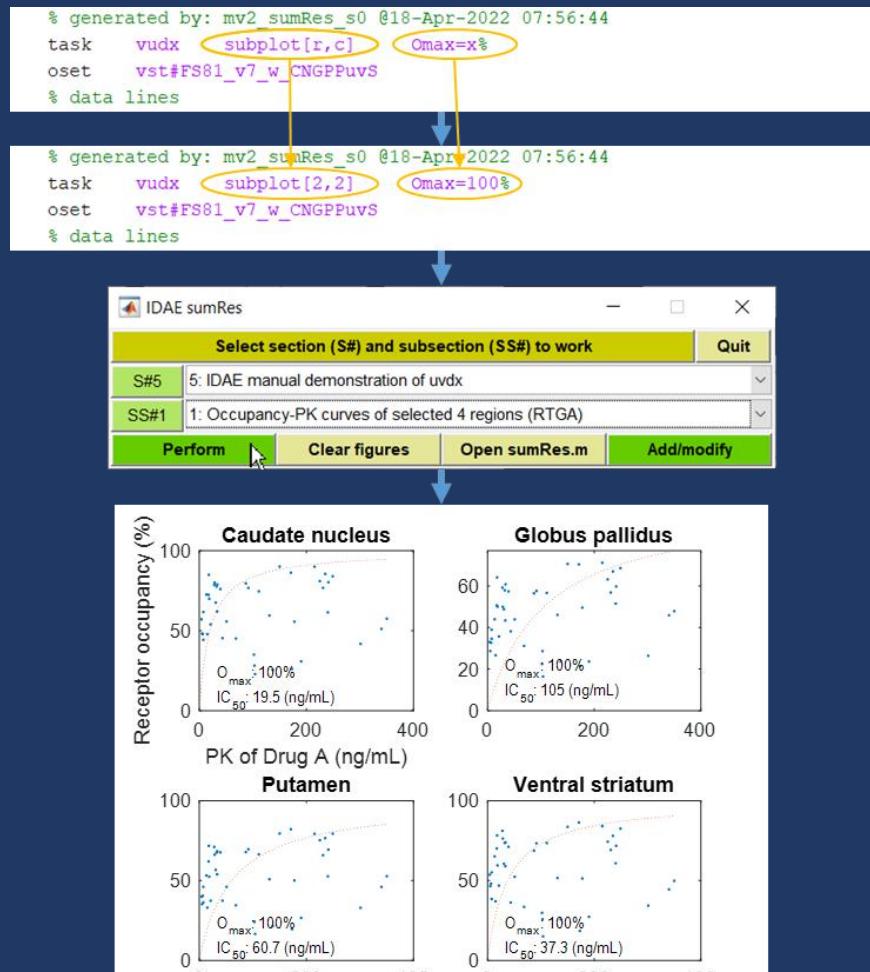
- For generation of ‘box plots’, follow the procedures of histogram sessions, except that the box plots option have less sub-options.
- The following make-up procedures were used, in addition to those applied to example histograms
  - To find ‘boxes’: `>> h = findobj(gca, ‘Tag’,’Box’);`
  - Sorting h from left to right: `hps = cell2mat(get(h, ‘XData’)); [x, is] = sort(hps(:,1)); h(:) = h(is);`
  - Changing colors of ‘S’ group to red: `set(h(2:2:end),’Color’,’r’);`
  - To add the legend: `legend(h(1:2), {‘Group C’,’S’});`

# Plots of data vs. user-defined x



- Demonstration case:
  - Subjects had PET scans at baseline and at three time point after a single-dose of drug A.
    - ≈ Concentrations of the drug (PK) were measured and entered to the database (scanDB.m)
  - To define occupancy-PK curves for the drug
    - ≈ Occupancy values at PET 2, 3, 4, will be calculated using PET 1 (no drug) as reference
- Most variables may be defined as described before except that:
  - Variables to use for 'vudx' must be entered in the scanDB.m file and defined in the info lines
    - ≈ 'PK' and 'tD1' are defined as shown in 2<sup>nd</sup> panel inf this demonstration example
  - Those variables will be listed in the menu bar of 'Variables' of the 1<sup>st</sup> data row (headed by 'vudx')
  - ≈ Select all variables to use (\* = selected), and display 'done!' tab (bottom) (3<sup>rd</sup> left)
  - Available 2-element variables will be displayed on the menu bar of the '2<sup>nd</sup> var' row (3<sup>rd</sup> right)
  - Mark options (\* = selected; as needed) and display 'done!' tab of the options (bottom)
    - ≈ Edit options as needed in sumRes.m file
      - Subplot[r,c]: replace r (# of rows) and c (# of columns with integers for sub-figures in a figure
      - Omax=x%: replace x with a desired value

# Generation of 'vudx' Plots



Junhua, this the only study in which data failed align along the model prediction (dotted curves). I will replace this with other reasonable ones later

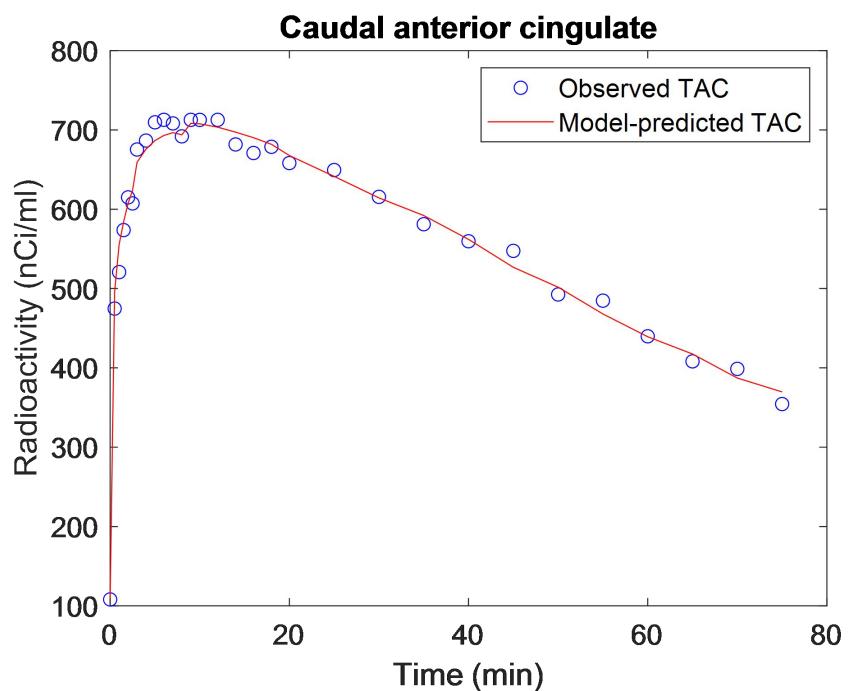
- Once the subsection of 'vudx' plots is completed successfully, the sumRes.m will be opened.
  - Replace titles of the section and subsection
  - Edit output options as needed
    - It may be appropriate to make 2 x 2 of sub-figures for the 4 regions
    - It is reasonable to set  $O_{max}$  at 100%
    - Always read the option tabs (bottom panel) carefully for the need for manual editions
  - Save it
- Display the intended section and subsection titles in the sumRes module (3<sup>rd</sup> panel)
  - Restart from selection of the section to display updated titles
  - Hit the 'Perform' GUI to generate the figure (bottom)
- Post-hoc make-ups:
  - Enter make-ups in the sumRes.m file between '% suggested make-up lines:' and '% end of added section'
  - Make use of the 'make-up' tab of the disp.Res module to display suggestions

# Plots of Systematic Deviations

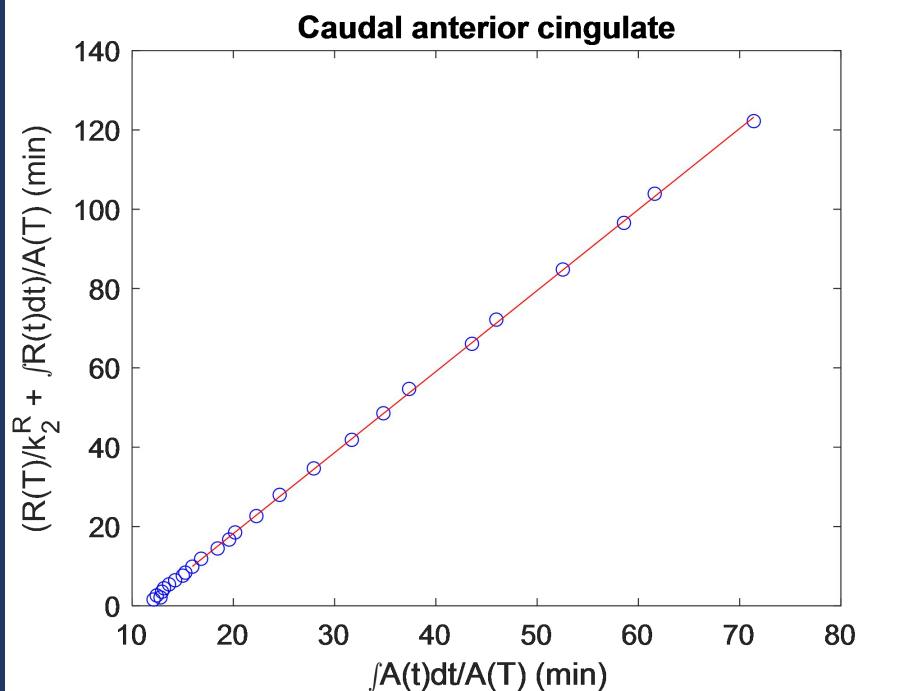
- This result-summary function may be particularly useful for tracer evaluation
- When movements of a tracer in regions of interest are governed by the blood-brain barrier and association to / dissociation from target molecules, the tracer may be useful only when:
  - Time activity-curves are fitted by a two-compartmental tissue model (TTCM) acceptably well, and
  - Plots of the plasma reference graphical analysis (PRGA; Logan et al., 1990) approach asymptotes
- Currently, no solid criteria for above necessary conditions have been established
  - Empirically, the normalized systematic deviations, NSDs of regions (across subjects) fell within  $\pm 5\%$  for ‘validated’ (in the literature) tracers ( $n > 20$ ; unpublished data from us)
  - NSDs may be useful for determination of  $t^*$ , the start of asymptote for PRGA and other approaches
- It is recommended to make use of NSDs to confirm published  $t^*$  for PRGA and other approaches in users’ own data

# Mean Normalized Deviations

## MRTM2



## RTGA

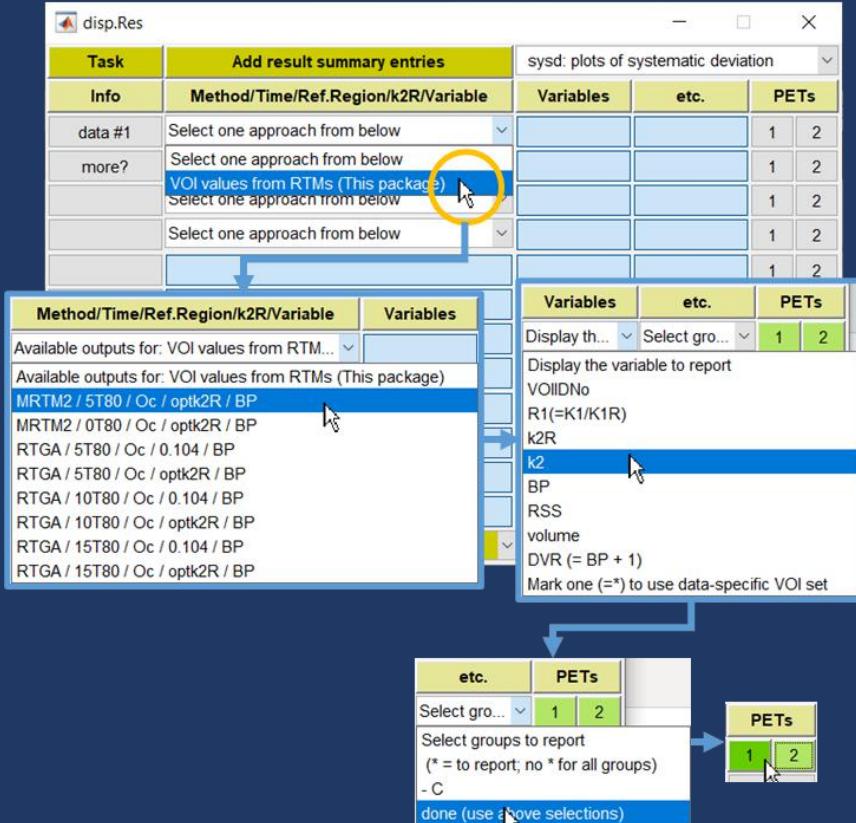


Plots of observed and model-fitted TACs of one region by MRTM2 and PRGA.

NSDs are defined as the sum of measured less model-predicted TACs over mean observed TAC in individual regions ( $\sum (\text{blue circle} - \text{red line}) / \text{mean blue circle}$ )

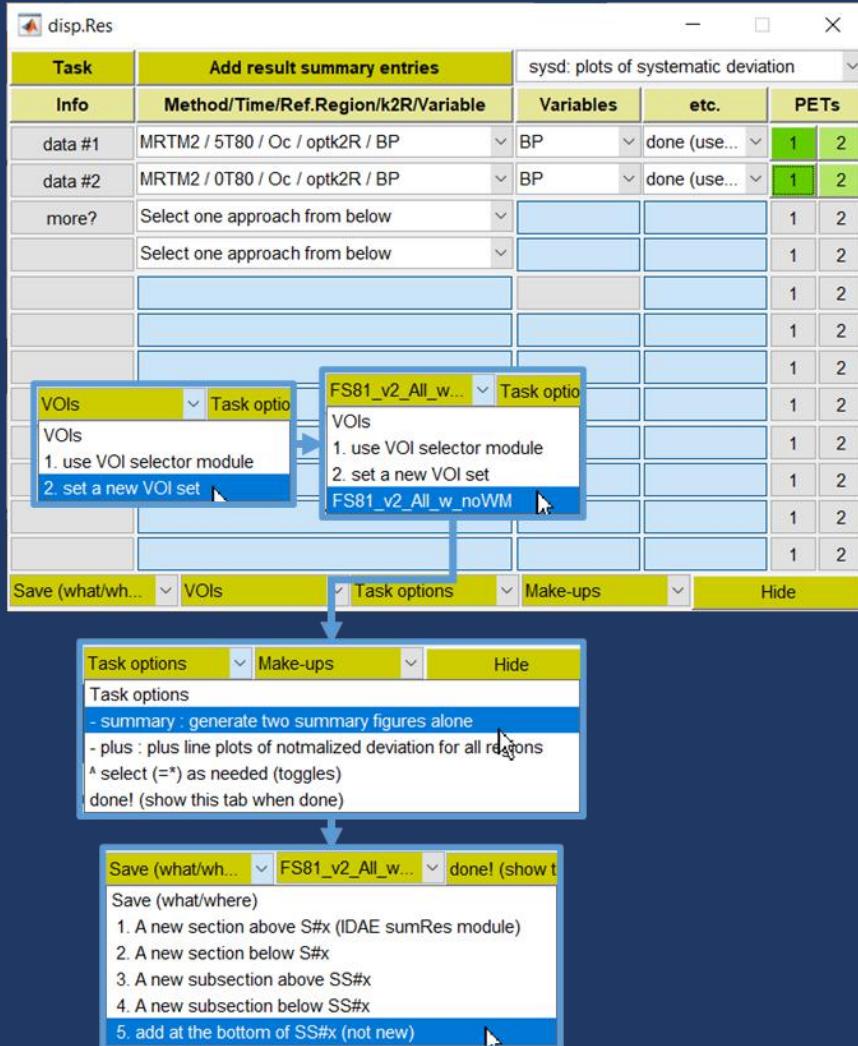
NSD is defined for a regions as the mean across subjects or scans.

# Procedures for NSD Plots



- Generally, users end up with many analysis approaches (not rate to exceed 100).
  - Thus, the search for an approach start with identification of categories
    - ≈ The first category is ‘VOI values from RTMs (This package)’ (and the only for this example)
    - ≈ ‘VOI values from maps (This package) will be added to the list once the user generate functional volumes (a.k.a., functional maps)
      - Regional values of the variable of the map from the same VOIs
    - ≈ ‘VOI values from RTMs (approach ID)’ will be added to the list once other MPE are done
      - In this example, this approach = with HMC; another approach = without HMC
    - ≈ ‘VOI values from maps (approach ID)’ will be added when maps are generated for ‘other’ approaches.
  - Select intended approach from the list (middle left insert)
  - Select the variable to display (middle right)
  - Select the group, if applicable
    - ≈ Display the ‘done’ tab
  - Select applicable PET(s)
    - ≈ Light green GUIs: Set to perform (not by presence)
    - ≈ Darker green GUIs: Selected.

# Setting Other Parameters for NSD Plots



- Once output approaches are defined (background), define ..
- VOIs to report:
  - Use VOI selector module: Report all checked VOIs on the module which may be convenient but hard to reproduce
  - Set a new VOI set: See the slide of ‘Setting a New VOI Set’
    - ≈ Make the name descriptive enough to remember
- Set options
  - Display ‘done!’ tab when done
- Specify where to insert specified set
  - Always relative to the section + subsection combination which is on display on the sumRes module
  - In this example, the section (S#1) and subsection (SS#1) titles were defined. So, it is appropriate to insert the output lines ‘at the bottom of SS#x’ (Selection #5)
- The process is sort-of fool-proof.
  - GUIs with any insufficiency, if any will blink with pink. Visit the GUI and fix the issues.

# Command Lines in sumRes.m

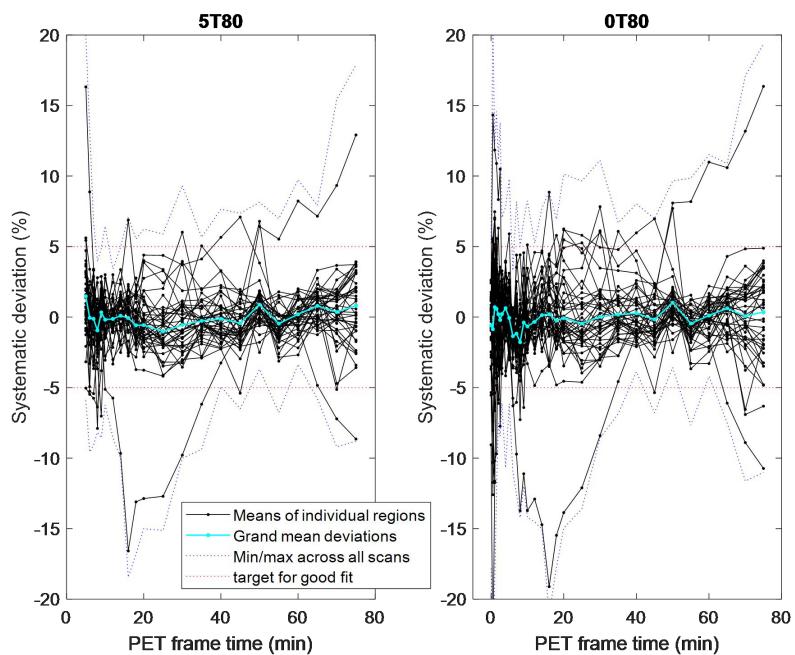
The diagram illustrates the workflow. At the top is a code editor window displaying MATLAB command lines. A vertical orange line on the left marks the start of the 'added section'. A yellow arrow points from the command '% suggested make-up lines:' to the bottom of the code. Below the code editor is a screenshot of the 'IDAE sumRes' GUI. The first row shows 'S#1: Method evaluation (RTMs)' and 'SS#1: 1: Normalized deviations: MRTM2'. The second row shows 'Perform' as the active button. A blue arrow points down to the second screenshot of the 'IDAE sumRes' GUI. This second screenshot shows 'S#1: Method evaluation (RTMs)' and 'SS#2: 2: Normalized deviations: RTGA'. The 'Perform' button is again highlighted.

```
sss Method evaluation (RTMs)
Normalized deviation: MRTM2
% generated by: mv2_sumRes_s0 @22-Feb-2022 12:11:45
task sysd summary
oset vst#FS81_v2_All_w_noWM
% data lines
% data #1
res tra_rsz_hmcMIT_FS81_v2_tbaa_MRTM2_5T80_Oc.ezd 1 BP grpC
% data #2
res tra_rsz_hmcMIT_FS81_v2_tbaa_MRTM2_0T80_Oc.ezd 1 BP grpC
%
% suggested make-up lines:
% end of added section
```

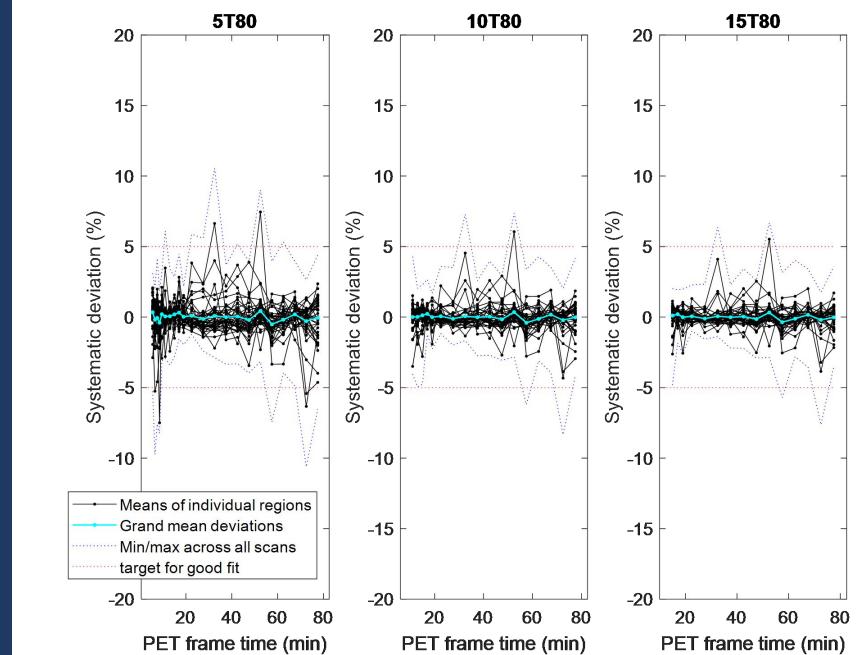
- Then (i.e., when the ‘at the bottom of SS#x’ tab was selected), command lines will be inserted to the file (studyName\_sumRes.m) together with some comment lines (top panel; denoted by vertical orange line)
  - Do not alter the command lines unless the user knows what to do
  - However, the user can insert make-up lines at orange arrow
    - ≈ Select ‘coming soon’ tab under the ‘Make-ups’ GUI of the ‘display result’ (disp.Res) module
- Hit ‘Perform’ GUI to generate a figure displaying plots mean normalized deviations of MRTM2.
- Then, a new subsection was added in similar manner for 5T80, 10T80, and 15T80 all with k2R fixed at  $0.104 \text{ min}^{-1}$ .
  - The new request is registered as ‘2: Normalized deviation: RTGA’
  - The ‘Perform’ GUI was hit to generate a figure displaying mean normalized deviations of RTGA

# Example Plots of NSDs

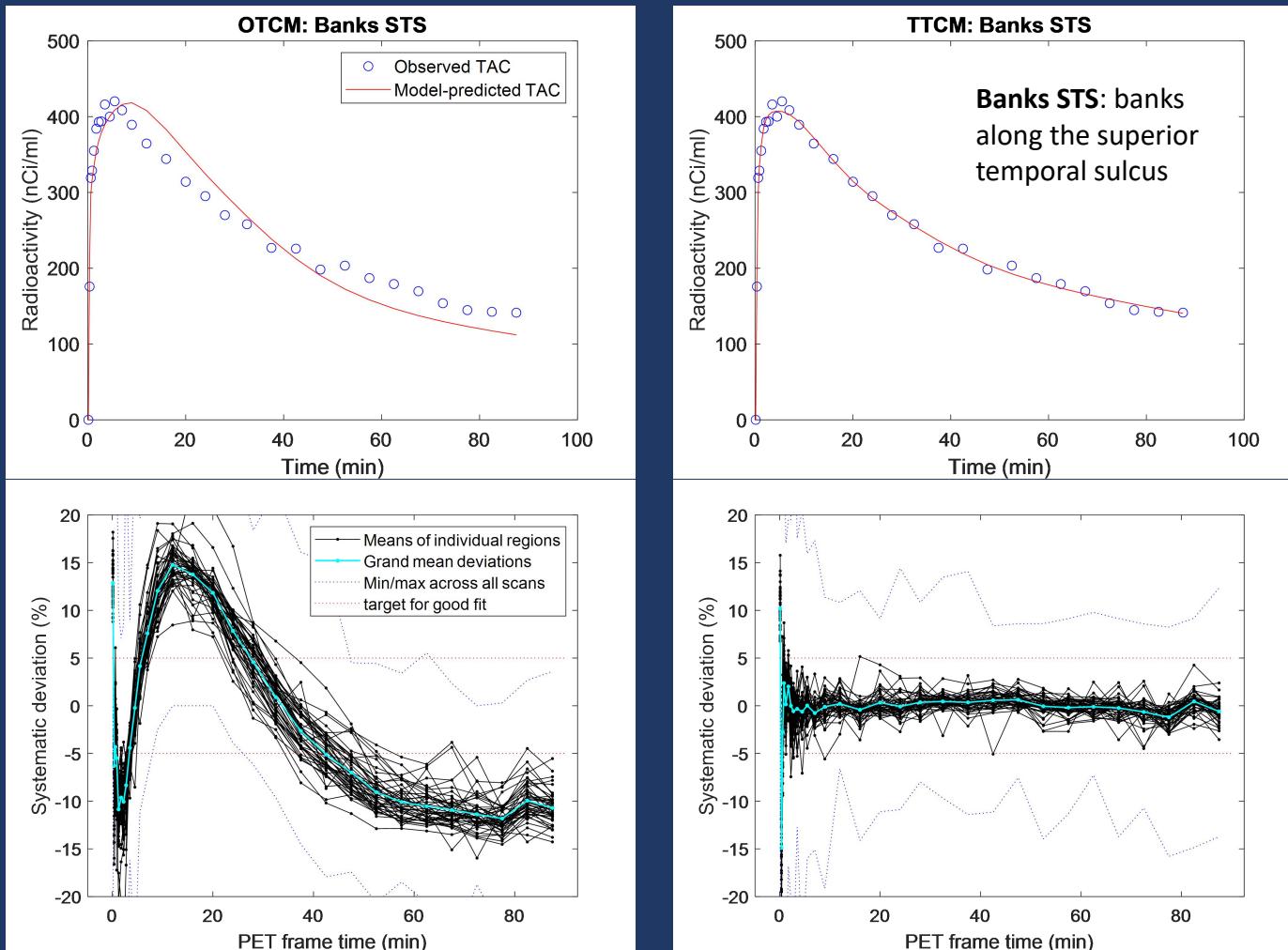
MRTM2



RTGA

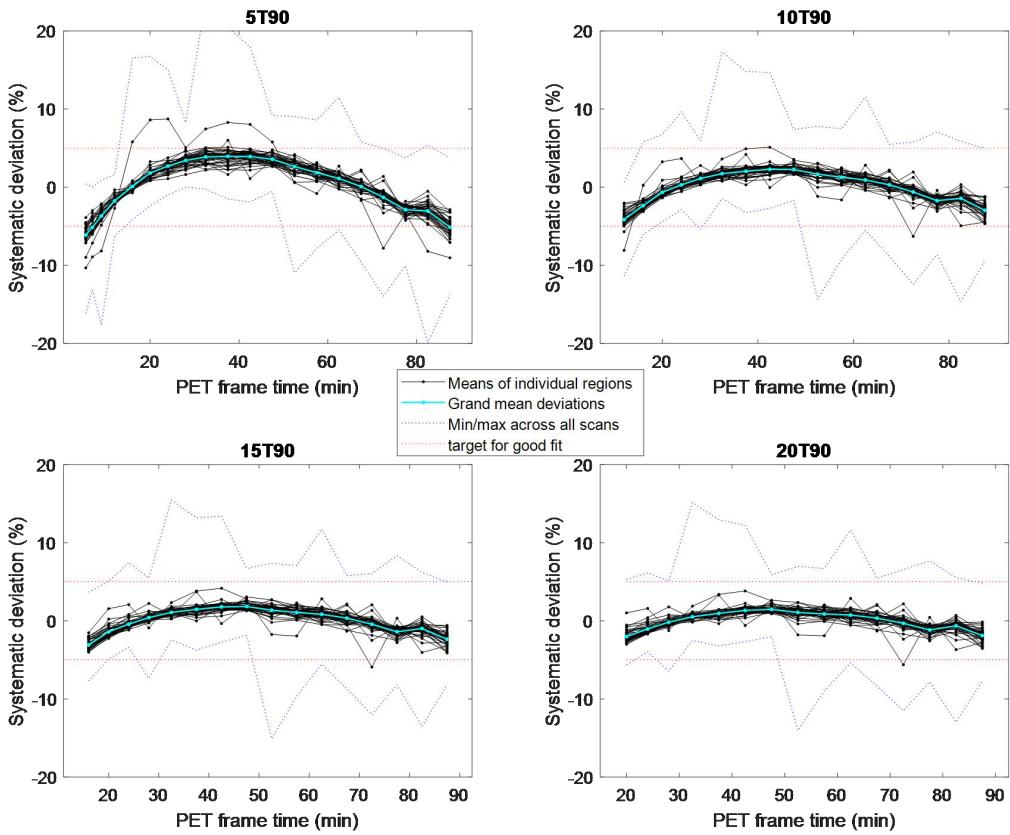
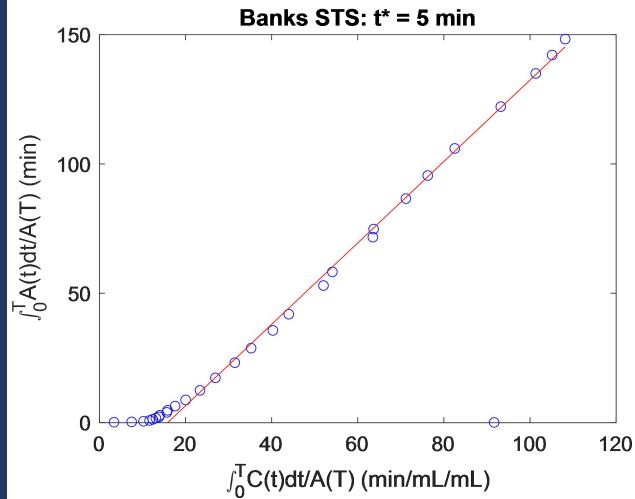


# Example NSDs: OTCM vs. TTCM



Plots of observed and model-predicted TACs of the banks of the superior temporal sulci (STS) from a subject of a tracer under evaluation for OTCM (left) and TTCM (upper panels). Plots of regional and grand means of normalized deviations fell within  $\pm 5\%$  for TTCM but not OTCM. Thus, the tracer cleared the necessary condition for TTCM.

# Example NSDs: PRGA for $t^*$



A PRGA plot (open circles) and an asymptote (red line) with  $t^*$ , the start of asymptote set at 5 min of the banks of STS from a subject (left panel). Plots of regional and grand means of normalized deviations across the six scans (model-predicted less observed TAC over mean of observed TACs). The plots fell within  $\pm 5\%$  for PRGA when  $t^*$  was set at 20 min. Thus,  $t^*$  was set at 20 min for the tracer.

# Want to Use IDAE?

- Operating systems:
  - Windows 10 + Linux Subsystem.
    - ≈ See <https://docs.microsoft.com/en-us/windows/wsl/install-win10>
  - Mac OS
  - Linux, tested on Ubuntu 18.04
- Matlab 2020a/b
  - Users need to create a script that adds IDAE code paths to the path list
- IDAE codes
  - JHU users: connect to our server for the newest distribution sets
    - ≈ Users can obtain the link from [anandi1@jhmi.edu](mailto:anandi1@jhmi.edu)
  - Non JHU users: Need to talk to [hkuwaba1@jhmi.edu](mailto:hkuwaba1@jhmi.edu) (discouraged)
    - ≈ IDAE codes will become available at a public deposit (e.g., GitHub)
      - We look for people who are experienced in this regard
    - ≈ Updates will come as zip files per request
  - Users need to create one file **dxetc4xxx.m** (xxx stands for a site-specific string) to make use of IDAE
    - ≈ A sample code is provided (sample\_dxetc4xxx.m)
    - ≈ This code includes subfunctions to make PET & MRI files available to IDAE