Neuroscience Information Toolbox

Manual

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1. What can you do by NIT

1. Batch processing of the fMRI data analysis;
2. Data preprocessing based on SPM8;
3. Removing nuisance signals from fMRI data such as linear trend, head motion, white, CSF and global signals, and band-pass filtering;
4. Calculating functional connectivity density (FCD);
5. Calculating FOur dimensional (spatio-temporal) Consistency of local neural Activities (FOCA);
6. Parallel computing for data preprocessing, nuisance signals removing, FCD and FOCA calculating;
7. Extract features from cleaned EEG data, such as event onsets, power and ERP amplitudes;
8. Marking interested events (e.g. epileptic discharges) in EEG data;
9. **EEG-fMRI fusion: 1) fMRI-informed EEG analysis (NEtwork-based SOurce Imaging, NESOI); 2) EEG-informed fMRI analysis.**
10. Identify and classify original DICOM data;
11. Viewing threshold of T-map.

2. Installation

1. NIT was tested in MATLAB 2013a for 64 bit Win 7 system (Linux). MATLAB 2010-2014 are recommended (For MATLAB 2015, only *NIT EEG Toolbox 1.0* CANNOT be used).
2. Unzip NIT package, start MATLAB, and add the NIT folder (*\NIT_toolbox) to MATLAB: Click ‘set path’ -> Click ‘add folder’ -> Select the ‘NIT folder’ -> Click ‘ok’ -> Click ‘save’ (Fig. 2.1).

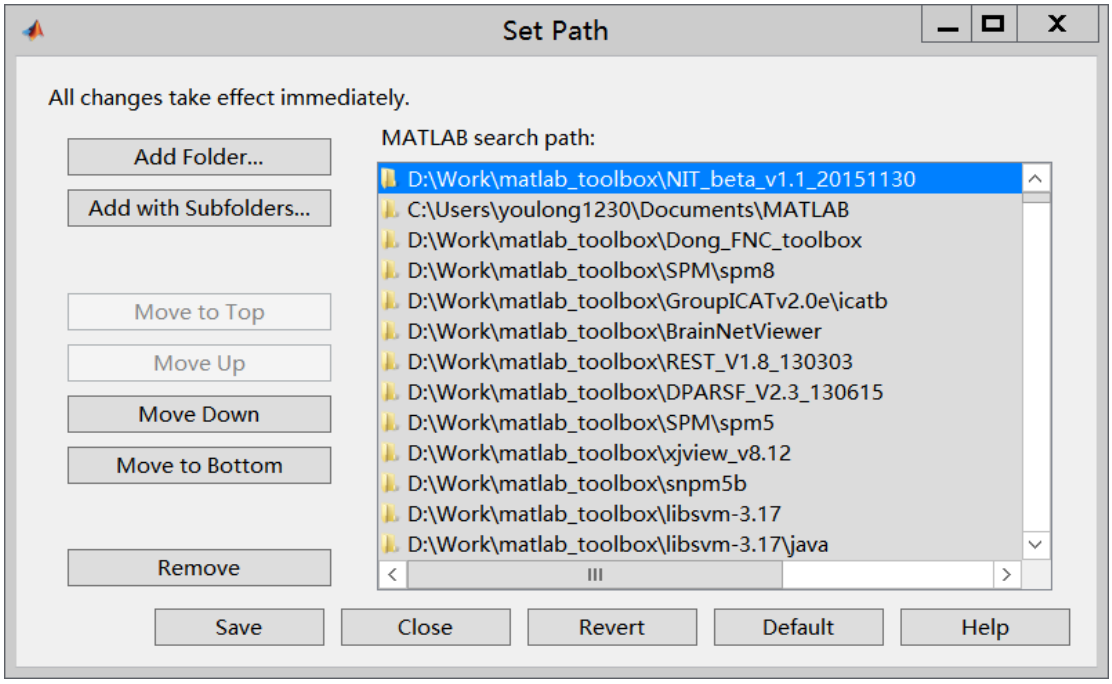


Fig. 2.1: Adding NIT paths to MATLAB.

3. Enter ‘nit’ in the command line in MATLAB, the NIT GUI interface will popup (Fig. 2.2).

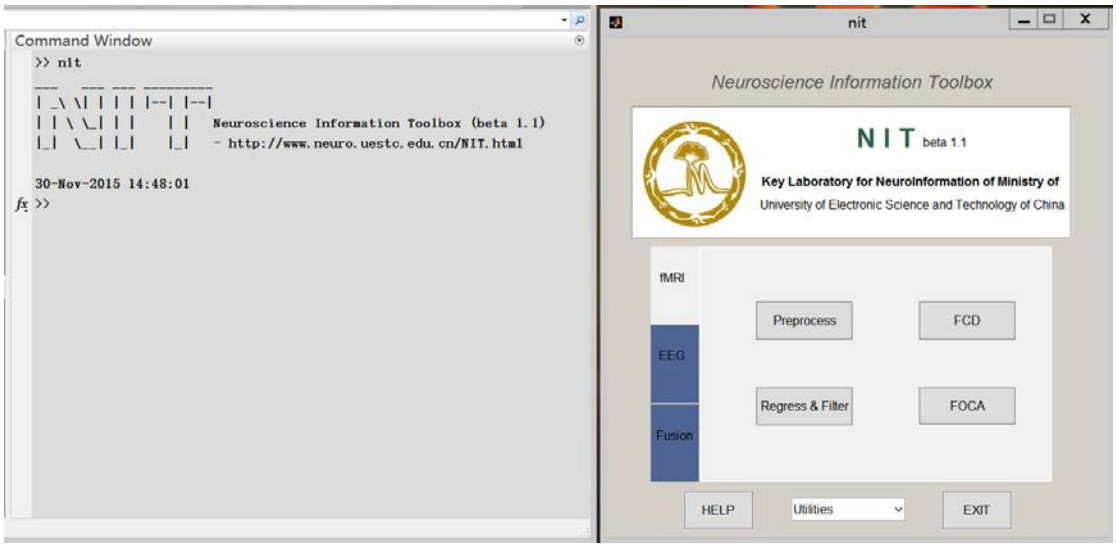


Fig. 2.2: NIT main interface.

3. Introduction

3.1 fMRI analysis

3.1.1 Preprocess

It is inconvenient that manually setting the SPM8 batch for preprocessing fMRI data of each subject, and the leaving the intermediate images in one folder during preprocessing. Here, NIT can automatically generate the SPM preprocess batch file

and preprocess the fMRI data based on SPM8 functions. Meanwhile, images generated from each preprocessing step are classified and saved.

As an example, the original fMRI images (*.img files) of two healthy adult subjects are provided (TR = 2).

3.1.2 Regress & Filter

Before analyzing fMRI data such as calculating functional connectivity and resting-state measures etc., nuisance signals, such as head motion, linear trend, global, white and CSF signals, may be removed from fMRI data first. Here, in NIT, linear regress model is utilized to remove these nuisance signals, and band-pass filter is also realized in the NIT to reduce the noise.

The fMRI data during 510 s resting state (two healthy adults, TR = 2 s) are provided as an example to show the NIT function. Slice time correction, realignment, spatial normalization (3 mm × 3 mm × 3 mm) were analyzed using SPM8.

3.1.3 FCD

The high cognitive performance of humans may be supported by brain networks with energy-efficient hubs. Then, Tomasi et al. (Tomasi and Volkow, 2010; Tomasi and Volkow, 2011) have been proposed an novel measure, named local functional connectivity density (lFCD) to characterize the distributions of hubs in the brain. Here, the NIT can calculate the FCD measure in MATLAB using parallel computing.

The fMRI data during 510 s resting state (two healthy adults, TR = 2 s) are provided as an example to show the NIT function. Slice time correction, realignment, spatial normalization (3 mm × 3 mm × 3 mm) were analyzed using SPM8.

3.1.4 FOCA

As yet, the local coherence of a region in the temporal domain has also been examined by numerous studies in recent years. Zang et al. proposed a regional homogeneity (ReHo) measure of a time series per voxel with those of its nearest 26 neighbors (Zang et al., 2004). Similarly, with Pearson's correlation, a measure of integrated local correlation (ILC) was introduced to assess the local coherence in fMRI data (Deshpande et al., 2009). More recently, a novel measurement, named local functional connectivity density (local FCD), was proposed to characterize the functional homogeneity in fMRI data (Tomasi and Volkow, 2010). All above-mentioned measures emphasize the temporal consistency in the local region; however, they may ignore the effect of spatial correlation in the local region in neighboring time. We may understand the brain functions spatio-temporally as we understand the time and space. It may be useful for functional brain imaging and may increase our understanding of brain function.

Here, we hypothesized that the local functional brain consistency could contain two aspects: a temporal correlation between voxels and a local spatial correlation between neighboring time points. And, we proposed a new measure, named Four-dimensional (spatio-temporal) Consistency of local neural Activities (FOCA), to characterize the local consistency by integrating temporal and spatial information in the local region (Dong et al., 2015a). The FOCA measure has several advantages. 1)

Because FOCA measure integrates temporal and spatial information in a local region, it is more flexible to characterize the local spontaneous activity. It emphasizes both temporal homogeneity of local adjacent voxels, and regional stability of brain activity states between neighboring time points, which may be considered to reflect local functional states. 2) It is a data-driven method without prior knowledge and practical choices of the key parameter settings. 3) It also has a good reproducibility and reliability.

The fMRI data during 510 s resting state (two healthy adults, TR = 2 s) are provided as an example to show the NIT function. Slice time correction, realignment, spatial normalization (3 mm × 3 mm × 3 mm) have been analyzed using SPM8.

3.2 EEG analysis

Electroencephalogram (EEG) is a noninvasive and high temporal resolution neuroimaging technology for brain function. However, due to folded structures of gray matter and volume conductions of CSF, skull and scalp, its spatial resolution is limited. Therefore, in simultaneous EEG-fMRI, EEG can be used to a point where a specific EEG feature of interest over the time course of the recording can be extracted. In EEG-informed fMRI analysis, several features of the EEG are useful, such as epileptic discharge events (Gotman and Pittau, 2011; Murta et al., 2014), ERP amplitudes (Debener et al., 2006) and the power within specific EEG frequency bands (Mantini et al., 2007; Moosmann et al., 2003). Here, the NIT can extract the EEG features, which can be used for EEG-informed fMRI analysis. Simultaneous EEG data of a juvenile myoclonic epilepsy patient is provided as an example. The EEG data were cleaned by removing gradient and BCG artifacts, filtering (1-30 Hz) and resampling (to 250 Hz). The onset times of epileptic discharges which were independently identified by two experienced neurologists with both agreements are provided instead of original EEG data.

3.3 Fusion analysis

Decoding the brain functions and dysfunctions continues to be grand challenge of the 21st century, and functional neuroimaging has shown tremendous promise in better understanding the brain (Friston, 2009). As yet, noninvasive imaging technologies such as Magnetic Resonance Image (MRI), electroencephalogram (EEG) and magnetoencephalogram (MEG) have been widely used in neuroimaging research. Considering their respective strengths and weaknesses in temporal and spatial resolution (see Fig. 3.1), integrating multimodal information (especially EEG-fMRI) may provide high-resolution spatiotemporal neuroimaging that further our understanding of the brain functions and dysfunctions (Biessmann et al., 2011; Huster et al., 2012; Laufs, 2012). For the EEG-fMRI fusion, there are the three most influential approaches for EEG-fMRI integration (He et al., 2011; Huster et al., 2012; Rosa et al., 2010) are the following (see Fig. 3.2): (1) fMRI-informed EEG, in which spatial information from the fMRI is utilized to assist the inverse problem of electromagnetic source reconstruction; (2) EEG-informed fMRI, in which the fMRI benefits from extracted EEG feature in specific frequency or time; and (3) symmetric

EEG-fMRI fusion, in which EEG and fMRI data are analyzed jointly through a common generative model or in a common data space. The NIT realizes the functions of 1) fMRI-informed EEG analysis and 2) EEG-informed fMRI analysis.

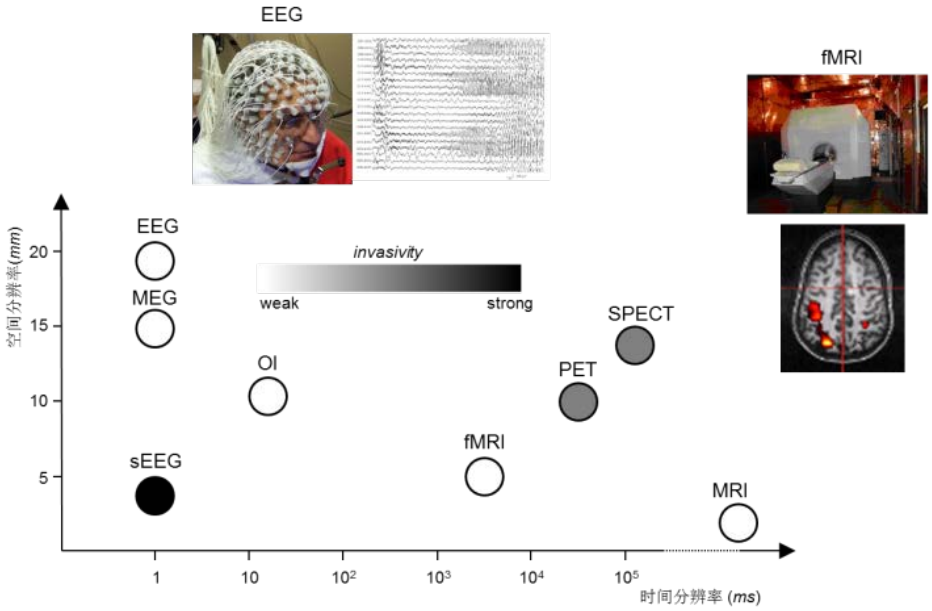


Fig. 3.1: The emotion of fusion: complementary advantages of spatial and temporal resolution.

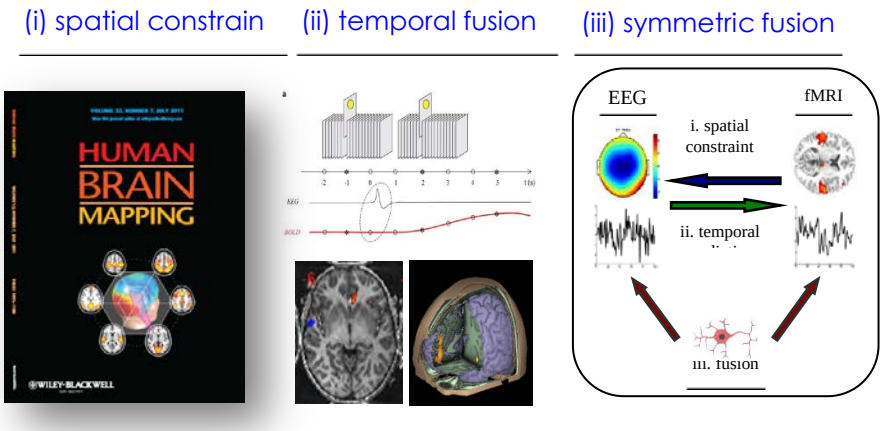


Fig. 3.2: Three most influential approaches for EEG-fMRI integration: (i) fMRI-informed EEG analysis; (ii) EEG-informed fMRI analysis; (iii) symmetric EEG-fMRI fusion.

3.3.1 fMRI-informed EEG analysis

Spatial integration of EEG-fMRI typically utilizes the fMRI maps as a priori information to inform the locations of the EEG sources, such as fMRI-constrained dipole fitting and the fMRI-constrained/weighted source imaging. With the spatial constrains, the ill-posedness of the original inverse problem can be moderated.

Considering brain networks represent the interactions between different brain areas, and understanding such networks may facilitate electroencephalography (EEG) source estimation. We proposed a new method, termed NEtwork-based SOurce Imaging (NESOI) (Lei et al., 2010; Lei et al., 2011), to reconstruct the EEG source using Parametric Empirical Bayesian (PEB). NESOI produces a good solution by combining the high temporal resolution of EEG and the high spatial resolution of fMRI. The NIT realizes the functions of NESOI.

Simultaneous EEG-fMRI recording data during an auditory novelty oddball (target processing) are provided as an example. Here, P300 was first extracted from preprocessed EEG data using temporal independent component analysis (ICA), and then NESOI was used to reconstruct the EEG source while using networks (fMRI spatial ICA components) as the covariance priors. Further details regarding the task were observed in a previous article (Dong et al., 2014; Strobel et al., 2008).

3.3.2 EEG-informed fMRI analysis

Temporal integration of EEG-fMRI typically utilizes the EEG dynamic features in the time or frequency domain, such as onset times of epileptic discharges, event related potentials, powers in the specific band etc., to inform the statistical mapping of fMRI. These quantities obtained from EEG are typically convolved with a canonical hemodynamic response function (HRF) and then regressed with BOLD signals on the voxel-level to identify the statistical fMRI activation/deactivation maps corresponding to the electromagnetic temporal signatures. A classic example is using onset times of epileptic discharges obtained from EEG to study the Blood Oxygenation Level Dependent (BOLD) changes related to the scalp EEG discharges, and providing useful information for epileptic mechanism research and clinical diagnosis (Gotman and Pittau, 2011; Murta et al., 2014).

However, there are also some problems for the analysis of simultaneous EEG-fMRI data in epilepsy: one is the variation of HRFs, and another is low signal-to-noise ratio in the data. Therefore, we proposed a new multimodal unsupervised method, termed local multimodal serial analysis (LMSA), which may compensate for these deficiencies in multimodal integration (Dong et al., 2015b). The NIT realizes the functions of LMSA and GLM.

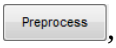
Simultaneous EEG and fMRI (TR = 2s) recording data during resting state in familial cortical myoclonic tremor and epilepsy (FCMTE) patients are provided as an example. The onset times of epileptic discharges which were independently identified by two experienced neurologists with the best agreement are provided instead of original EEG data. More details can be seen in the paper (Dong et al., 2015b).

4. Walkthrough and Description

4.1 fMRI analysis

4.1.1 Preprocess

A. Step by step:

1. After clicking the 'fMRI' button at the NIT main interface (Fig. 2.2), clicking 'Preprocess' button 

, then the preprocess GUI will popup (Fig. 4.1.1).

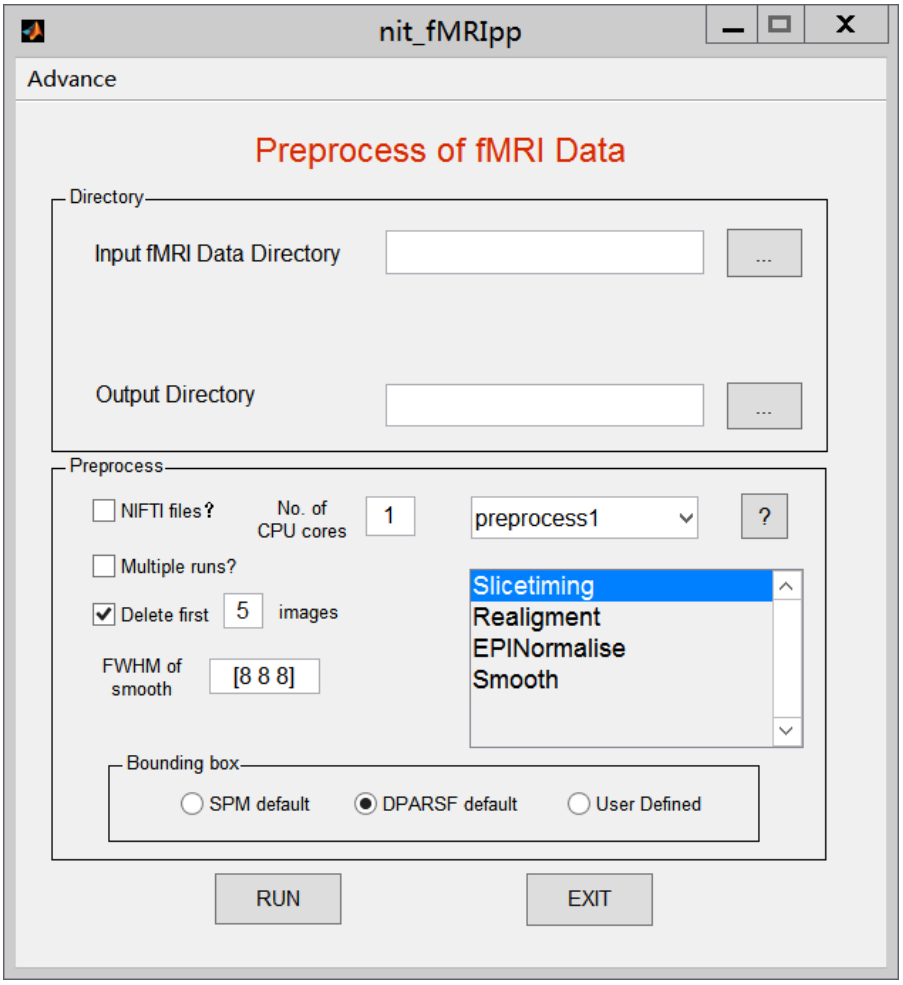


Fig. 4.1.1: Preprocessing interface。

2. Three preprocess types are provided：Preprocess 1 which contains slice time correction, realignment, spatial normalization (using EPI template to normalize) and spatial smoothing; Preprocess 2 which contains slice time correction, realignment, spatial normalization (using parameters from individual T1 segmentation), and Preprocess 3 which contains realignment, spatial normalization (using EPI template to normalize) and spatial smoothing.

   Input fMRI Data Directory: Directory of input data. The data are images files such as *.img and *.nii (NIFTI format), or original DICOM data. Support subfolders (multiple subjects) of a directory and subfolders (multiple sessions or runs) of a subject folder.

   Input T1 Data Directory: Directory of T1 data. This dialog will appear, if

choose the Preprocess 2. Support subfolders (multiple subjects) of a directory and subfolders (multiple sessions or runs) of a subject folder. If multiple sessions or runs exist, corresponding T1 image must be contained in each T1 session/run folder.

Output Directory: Directory of output.

Preprocess: The pull-down menu 

can select:

Preprocess 1: slice time correction, realignment, spatial normalization (using EPI template to normalize) and spatial smoothing. Images will be prepended with a 'z', if the initial character of image names is 'a' or 'A'.

Preprocess 2: slice time correction, realignment, spatial normalization (using parameters from individual T1 segmentation) and spatial smoothing. T1 images prefixed with 'co' (co*.img/co*.nii) are priority images to read. The parameters of segmentation are default settings in SPM8.

Preprocess 3: realignment, spatial normalization (using EPI template to normalize) and spatial smoothing. Images will be prepended with an 'a', if the initial character of image names is NOT 'a' or 'A'.

Smooth： Smooth image volumes with a Gaussian kernel of a specified width.

Notes: Parameters such as TR, slice number can be automatically identified using an image file. If you want to set the parameters of Slice timing and normalize, click the Parameter menu in the Advance (Top left).

NIFTI files? : If the data are *.img or *.nii files (NIFTI format), please check this option. If the data are DICOM files, uncheck it.

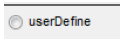
No. of CPU core: Number of CPU core used for parallel computing. Start parallel computing, while > 1.

Multiple runs? : If there are multiple session or run subfolders in each subject folder, please check this option. Otherwise, uncheck it.

Delete first ? images: The first ? volumes of each run were first discarded before preprocessing fMRI data. It CANNOT delete your original data! Default is discarding the first 5 volumes.

Smooth FWHM: Full-width at half-maximum of an isotropic Gaussian filter. Default is [8 8 8].

Bounding box: Bounding box. Default is DPARSF bounding box. The parameter of SPM bounding box used in NIT is [-78 -112 -50; 78 76 85] which will generate normalized images with 53×63×46 dimensions (while voxel size is 3×3×3 mm^3). The parameter of DPARSF bounding box is [-90 -126 -72;90 90

108] which will generate normalized images with 61×73×61 dimensions (while voxel size is 3×3×3 mm^3). User can select the button 

to fill user-defined bounding box.

Here, as an example, images files (NIFTI format) were used to illustrate the fMRI data preprocessing (Fig. 4.1.2):

Input Directory: Select directory of data: *\ fMRI_example_data\original_data.

Output Directory: Select output directory : *\preprocess_results.

Preprocess 1: Select this option.

NIFTI files?: Check this option.

Multiple runs?: Uncheck this option.

Delete first ? images： Uncheck this option.

Smooth FWHM: Set as [8 8 8].

Bounding box: Select DPARSF default.

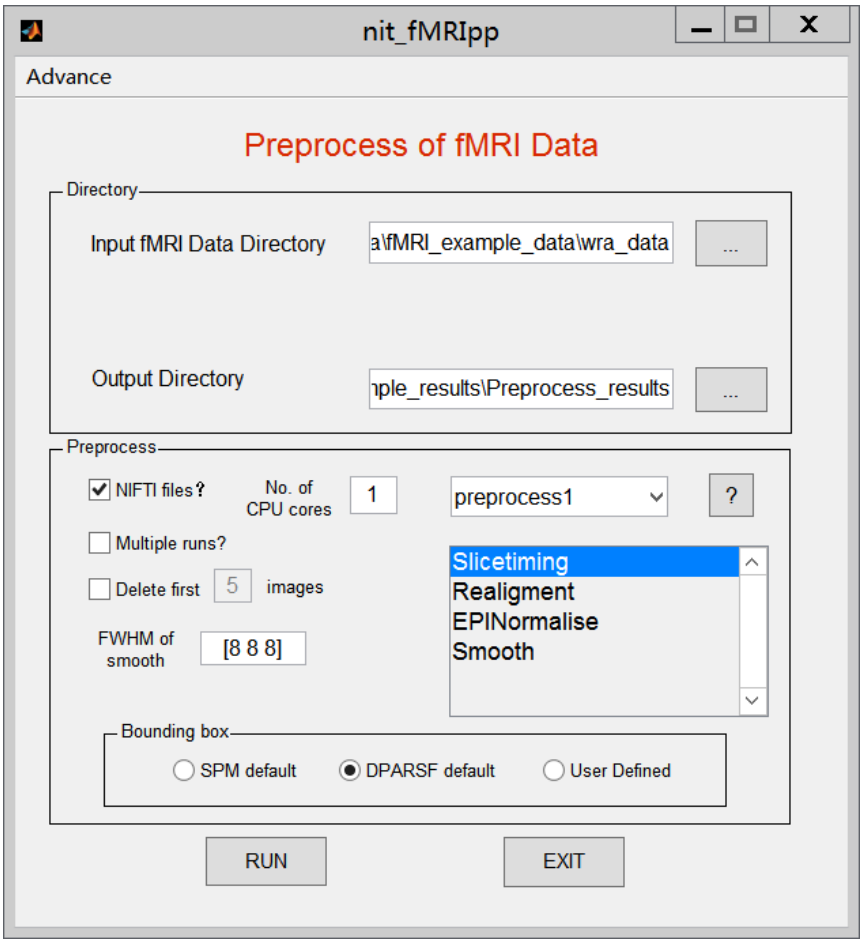


Fig. 4.1.2: Preprocessing interface.

3. Press button 

. The calculating interface can be seen in Fig. 4.1.3.

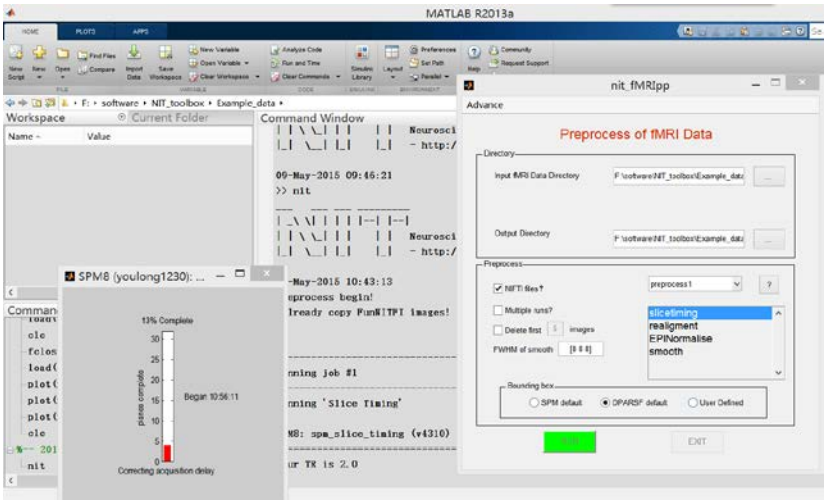


Fig. 4.1.3: The calculating interface of preprocessing.

4. The results are listed below (Fig. 4.1.4):

Preprocess_log.txt: The log file.

FunNIFTI: The images files (NIFTI format). If the format of original data is DICOM, files will be transformed to *.nii image files in this folder.

Slicetiming: Correct differences in image acquisition time between slices. Slice-time corrected files are prepended with an 'a'.

Realign: This routine realigns a time-series of images acquired from the same subject using a least squares approach and a 6 parameter (rigid body) spatial transformation. The folder contains the files: the resliced images (which are named the same as the originals, except that they are prefixed by 'r'), a mean of the resliced image, realignment parameter file named 'rp_*.txt' and the normalisation parameter file named '* sn.mat'.

Normalise: Normalised files prefixed with a 'w'.

Smooth: The smoothed images prefixed with a 's'.

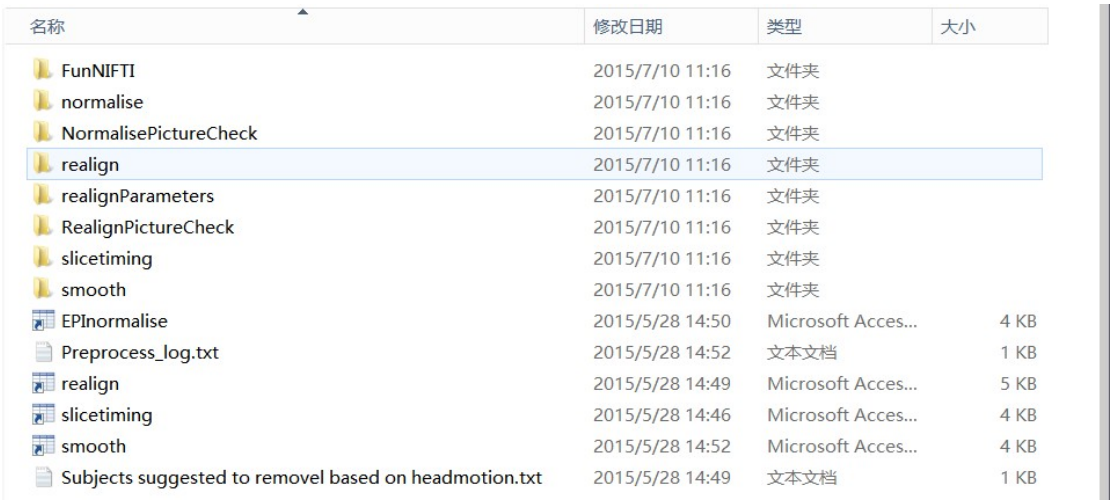
realignParameters: Realignment parameter file named 'rp_*.txt' generated from a 6 parameter (rigid body) spatial transformation.

RealignPictureCheck: Figures of translations and rotations.

NormalisePictureCheck: Figures of normalized images.

Subjects*.txt: The information of head motion.

*.mat: The detailed parameters of each preprocessing step.



名称	修改日期	类型	大小
FunNIFTI	2015/7/10 11:16	文件夹	
normalise	2015/7/10 11:16	文件夹	
NormalisePictureCheck	2015/7/10 11:16	文件夹	
realign	2015/7/10 11:16	文件夹	
realignParameters	2015/7/10 11:16	文件夹	
RealignPictureCheck	2015/7/10 11:16	文件夹	
slicetiming	2015/7/10 11:16	文件夹	
smooth	2015/7/10 11:16	文件夹	
EPInormalise	2015/5/28 14:50	Microsoft Acces...	4 KB
Preprocess_log.txt	2015/5/28 14:52	文本文档	1 KB
realign	2015/5/28 14:49	Microsoft Acces...	5 KB
slicetiming	2015/5/28 14:46	Microsoft Acces...	4 KB
smooth	2015/5/28 14:52	Microsoft Acces...	4 KB
Subjects suggested to removel based on headmotion.txt	2015/5/28 14:49	文本文档	1 KB

Fig. 4.1.4: The list of preprocessing output.

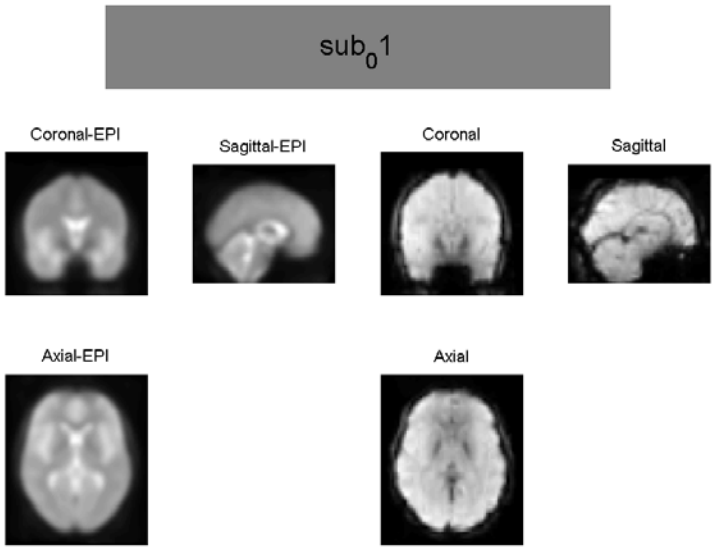


Fig. 4.1.5: The simple illustration of normalized images.

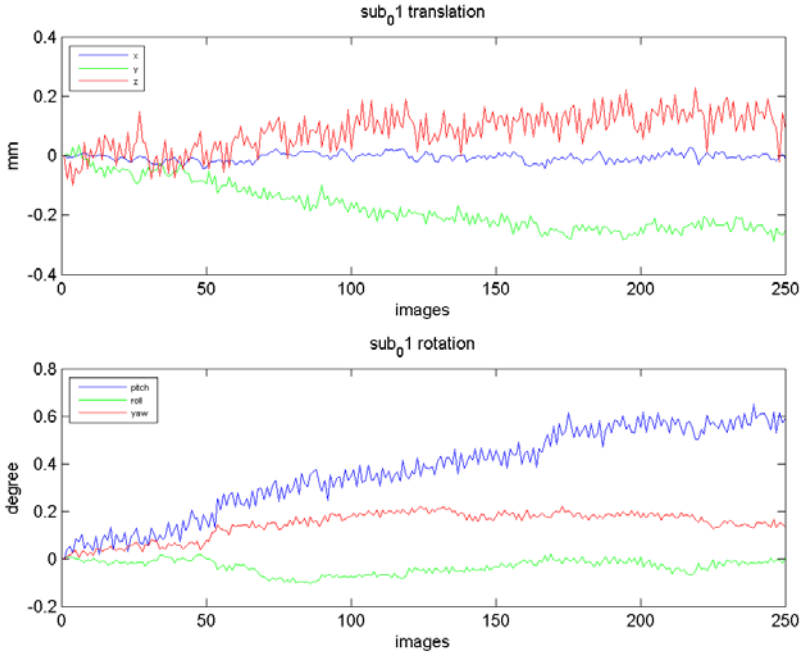


Fig. 4.1.6: The estimated time series of translations and rotations.

B. Note:

1. NIT is designed to automatically generate the SPM8 preprocess batch file using default parameters, and preprocess the fMRI data based on SPM8. If you want to preprocess the fMRI data using specific parameters, SPM8 or other software are recommended.
2. If using Preprocess 2, please confirm that each T1 image is corresponding to the fMRI data. If having several sessions or runs for each subject, corresponding T1 image must be contained in each T1 session/run folder.
3. If fMRI preprocessing is interrupted at a step, you can re-calculate data from interrupted step. For example, if preprocessing is interrupted when doing 'realignment'. Delete the result folder of realignment (folder 'realign') first, and re-start the preprocessing again. The NIT will skip the steps before realignment.
4. If you want to redo fMRI preprocessing, please make sure that the output folder is empty.
5. In slice timing step, the reference slice is the temporally middle slice during scanning. Default slice order is set as interleaved (bottom -> up): [1:2:nslices 2:2:nslices].
6. More details of two preprocessing procedures can be seen in SPM8 manual.

4.1.2 Regress & Filter

A. Step by step:

1. After clicking the 'fMRI' button at the NIT main interface (Fig. 2.2), clicking 'Regress & Filter' button 

, then the interface of Regress & Filter will

popup (Fig. 4.1.7).

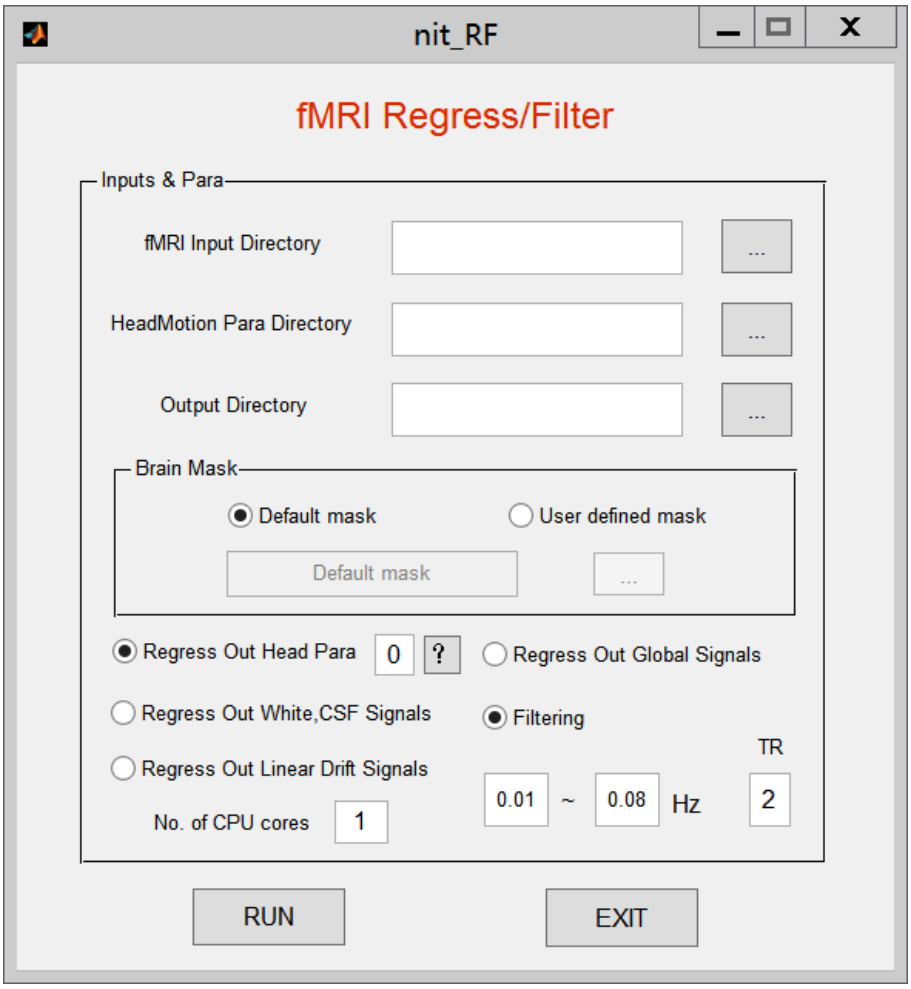


Fig. 4.1.7: Regress & Filter main interface.

2. Setting parameters as below (Fig. 4.1.8):

fMRI Input Directory: Input directory of fMRI data. The data are images files such as *.img and *.nii (NIFTI format). Support subfolders (multiple subjects) of a directory. The example directory is '*\ fMRI_example_data\ wra_data\'.

Head Parameter Directory: Select directory of head motion parameter files (The example directory is *\ fMRI_example_data\headmotion\).

Output Directory: Select output directory. For example, *\Regress_out_results\.

Brain Mask: Select brain mask. The default is a standard brain mask generated from a probabilistic template. Here we use a user-defined brain mask. Select 'User defined mask', and press button [...] to select the brain mask (*\ fMRI_example_data\brainmask.img).

Regress out Head Para: Regressing out head motion parameters.

0: 6 head motion parameters generated from alignment in SPM8 (R = [x, y, z, pitch, yaw, roll]).

1: 12 head motion parameters which contain R and its derivative

([R, diff(R)]) (Power et al., 2014).

2: 24 head motion parameters which contain R, square of R, delay of R and its square ([R, R^2, R_{t-1}, R^2_{t-1}]) (Friston et al., 1996).

3: 36 head motion parameters ([R, R^2, R_{t-1}, R^2_{t-1}, R_{t-2}, R^2_{t-2}]) (Power et al., 2014).

Regress Out White, CSF Signals: Regressing out white matter and CSF signals.

Regress Out Linear Drift Signals: Regressing out linear drift signals.

Regress Out Global Signals: Regressing out global signals.

No. of CPU cores: Number of CPU cores used for parallel computing. Start parallel computing, while > 1.

Filtering: Ideal band-pass filter. Default pass band is 0.01-0.08 Hz, and TR = 2 s.

The nuisance signals defined by user can be regressed out using GLM. Here, as an example, we select all options as below (Fig. 4.1.8):

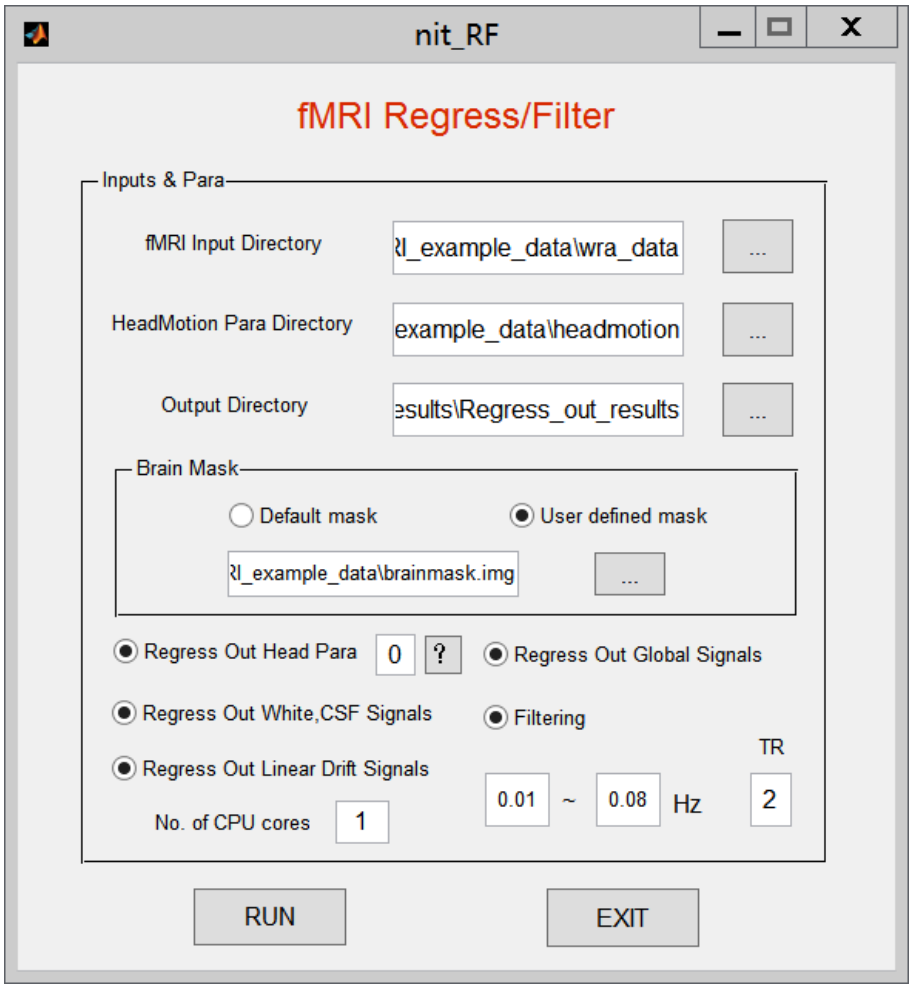


Fig. 4.1.8: Regress & Filter parameter settings.

3. Press RUN button RUN.
4. The results (*.nii image files) will be saved in output folder (Fig. 4.1.9).

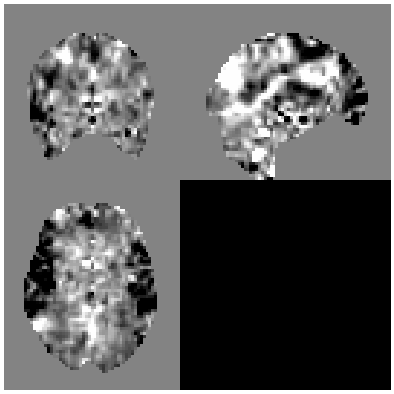


Fig. 4.1.9: The first image after removing the nuisance signals (sub_01).

B. Note:

1. It is important to check the order of head motion parameter files are corresponding to the fMRI data, e.g. '*\sub_01*.img' → '*\headmotion\sub_01*.txt', or '*\headmotion\rp_*_sub_01.txt' etc.
2. The nuisance signals such as white, CSF, linear trend and global signals are extracted from fixed template mask (ROIs). MNI coordinates are listed: White matter ROIs：[-21,-9,36]，[21,-6,36]；CSF ROIs: [-6,0,21]，[6,0,21]；Linear drift: [66,-99,-36]，[-72,-99,-36]，[66,63,66]，[9,69,72]，[-69,60,81]. Two types of masks (53×63×46 and 61×73×61 dimensions, voxel size is 3×3×3 mm^3) are provided corresponding to the general bounding box (SPM bounding box [-78 -112 -50; 78 76 85] and DPARSF bounding box [-90 -126 -72; 90 90 108]). If the image size is not matched to the above two masks, NIT will use MNI coordinates to extract signals from fMRI data.
3. User must select whole brain mask (User defined mask), if the image size is neither 53×63×46 nor 61×73×61 dimensions with voxel size 3×3×3 mm^3.
4. Support the number of time points of each subject are different.
5. The parameter settings of results (RegressFilter_Para.mat) and log (RegressOut_Filter_log.txt) files will be generated after calculating.

4.1.3 FCD

A. Step by step:

1. After clicking the 'fMRI' button at the NIT main interface (Fig. 2.2), clicking 'FCD' button 

(Fig. 4.1.10).

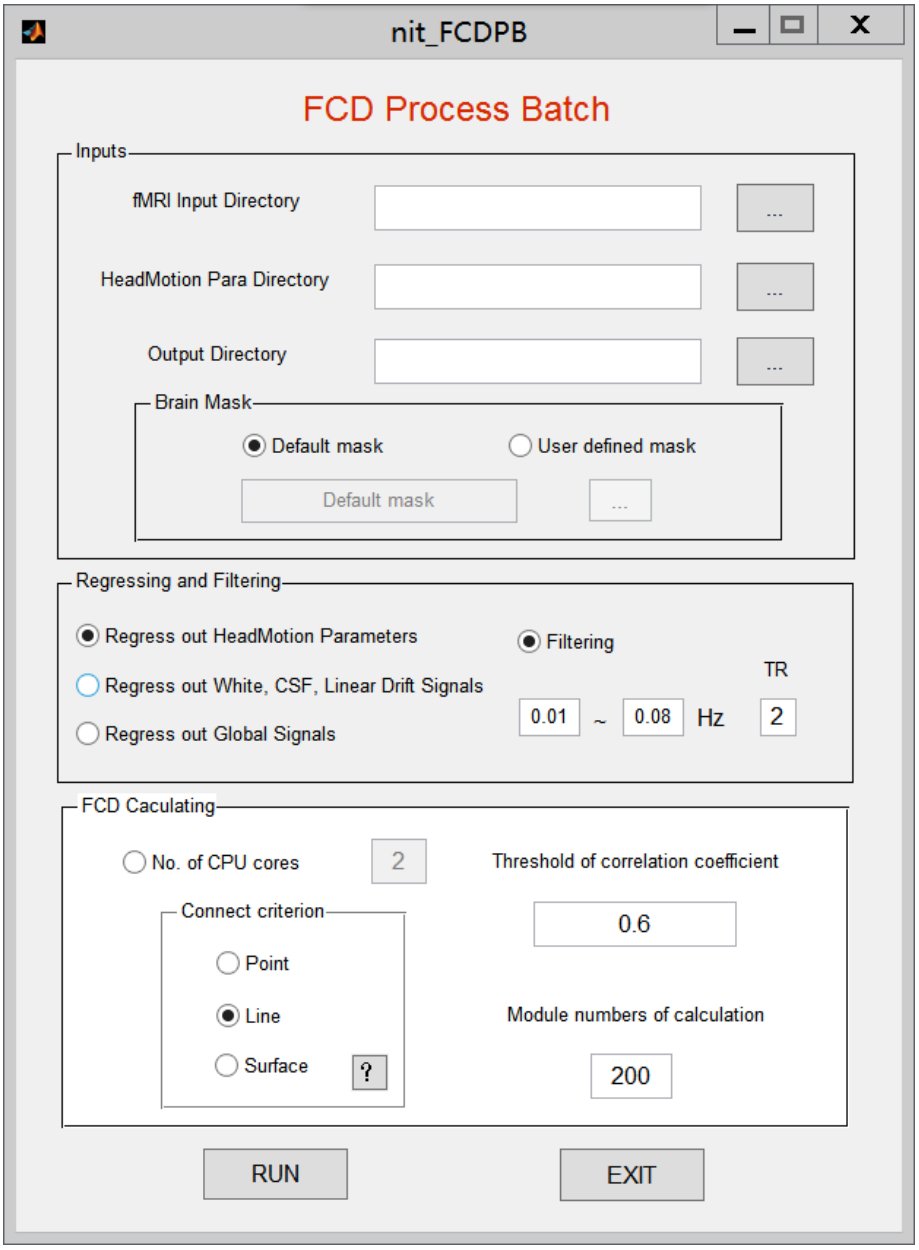


Fig. 4.1.10: FCD interface.

2. Setting parameters as below (Fig. 4.1.11):

fMRI Input Directory：Directory of input data (normalized fMRI data without smoothing). The data are images files such as *.img and *.nii (NIFTI format). Support subfolders (multiple subjects) of a directory. The example directory is '*\ fMRI_example_data\ wra_data\'.

Head Parameter Directory：Select directory of head motion parameter files (The example directory is *\ fMRI_example_data\headmotion\). Support subfolders (multiple subjects) of a directory.

Output Directory：Select the output directory, for example, *\FCD_results.

Brain Mask： Select brain mask. Default is standard brain mask generated from a probabilistic template. Here we use a user-defined brain

mask. Select ‘User defined mask’, and press button [...] to select the brain mask (*\ fMRI_example_data\brainmask.img).

Regress out Head Parameters: Regressing out 6 head motion parameters.

Regress out White, CSF, Linear Drift Signals: Regressing out the white matter, CSF and linear drift signals.

Regress out Global Signals: Regressing out global signals.

Filtering: Ideal band-pass filter. Default pass band is 0.01-0.08 Hz, and TR = 2 s.

Connect criterion: The connect criterion is the definition of spatial voxel connection. ‘Point’: 26-connected neighborhood; ‘line’: 18-connected neighborhood and ‘surface’: 6-connected neighborhood. Default is ‘line’ criterion (SPM definition).

No. of CPU cores: The number of CPU cores used for parallel computing. E.g. if the test computer has 4 cores, then fill in 4.

Threshold of correlation coefficient: The threshold of correlation, default is 0.6.

Calculate module number: The number of calculating module for parallel computing. Default is 200.

As an example, we select ‘Regress out Head Parameter’, ‘Regress out White, CSF, Linear Drift Signals’ and ‘Filtering’ options. Pass band is 0.01-0.08Hz and TR = 2 s.

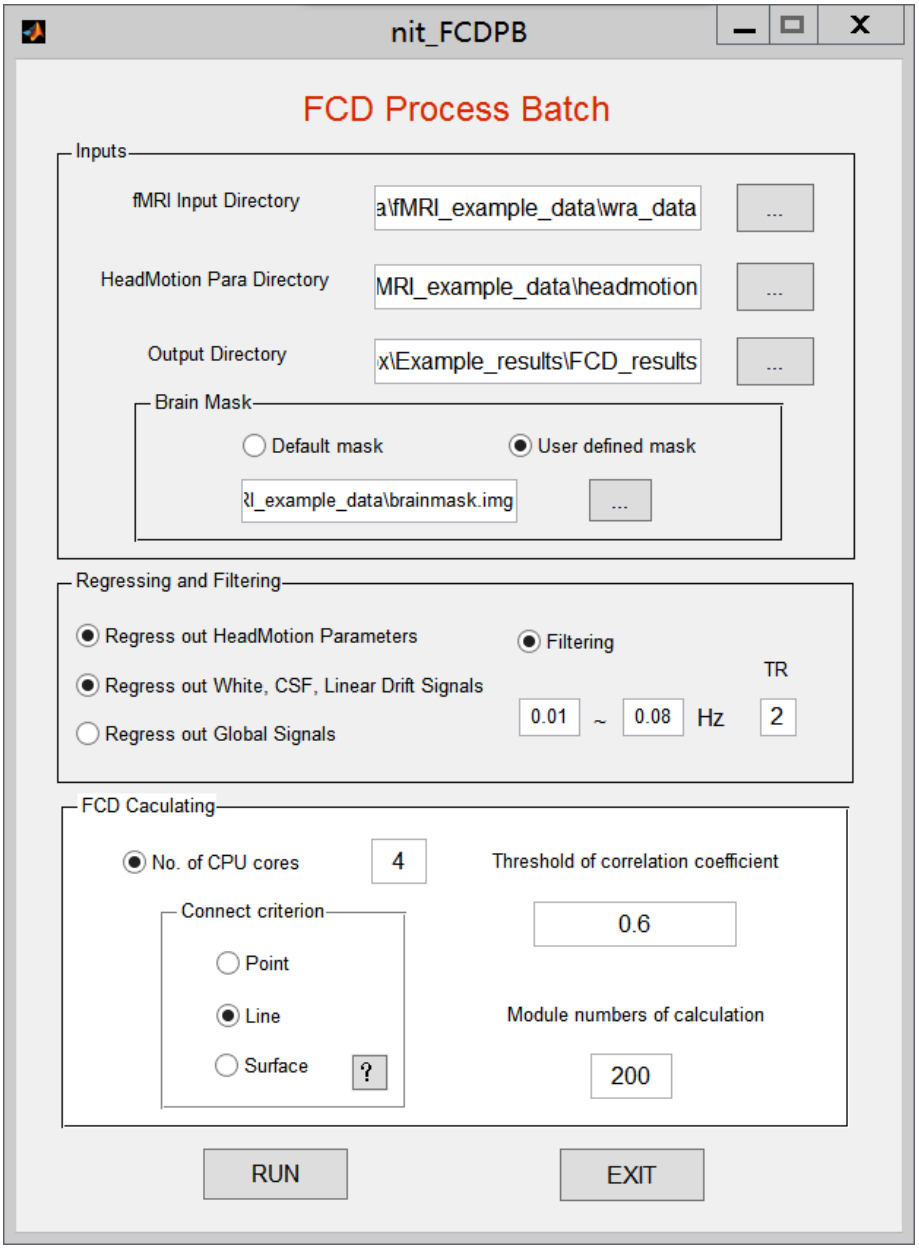


Fig. 4.1.11: FCD parameter settings.

3. Press RUN button RUN.
4. The output files are listed below (Fig. 4.1.12):

   FCD_log.txt: Log file.

   FCD_Para.mat: The parameter settings.

   globalFCD: The global functional connectivity density maps (*.nii).

   localFCD: The local functional connectivity density maps (*.nii).

   longRangeFCD: The long range functional connectivity density maps (*.nii). They are defined as global connectivity density subtracts local connectivity density.

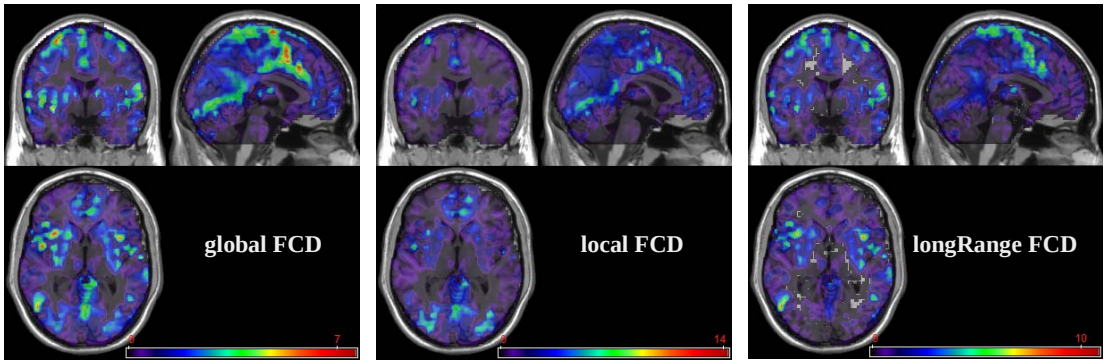


Fig. 4.1.12: The results of FCD maps (sub_01).

B. Note:

1. The correlation threshold of FCD is set at 0.6, according to the paper of Tomasi et al. However, if you want to calculate FCD under the different threshold, you can fill the threshold vector in the input box, e.g. [0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9].
2. The No. of CPU cores should be less than (or equal to) the true core numbers.
3. The default of calculate module number is 200. In general, there is no need to be changed.
4. The nuisance signals such as white, CSF, linear trend and global signals are extracted from fixed template mask (ROIs). MNI coordinates are as follows: White matter ROIs：[-21,-9,36]，[21,-6,36]；CSF ROIs: [-6,0,21]，[6,0,21]；Linear drift: [66,-99,-36]，[-72,-99,-36]，[66,63,66]，[9,69,72]，[-69,60,81]. Two types of masks (53×63×46 and 61×73×61 dimensions, voxel size is 3×3×3 mm^3) are provided corresponding to the general bounding box (SPM bounding box [-78 -112 -50; 78 76 85] and DPARSF bounding box [-90 -126 -72;90 90 108]). If the image size is not matched to the above two masks, NIT will use MNI coordinates to extract signals from fMRI data.
5. Two types of whole brain masks (53×63×46 and 61×73×61 dimensions, voxel size is 3×3×3 mm^3) are also provided, corresponding to the general bounding box (SPM bounding box [-78 -112 -50; 78 76 85] and DPARSF bounding box [-90 -126 -72;90 90 108]). If the data image size is not matched to the above two masks, customer must select user-defined brain mask.
6. Different number of time points of each subject is allowed.
7. It is important to check the order of head motion parameter files are corresponding to the fMRI data, e.g. '*\sub_01*.img' → '*\headmotion\sub_01*.txt', or '*\headmotion\rp_*_sub_01.txt' etc.
8. DO NOT smooth the fMRI date before calculating FCD. Spatial smooth is conducted after calculating FCD.

4.1.4 FOCA

A. Step by step:

1. After clicking the 'fMRI' button at the NIT main interface (Fig. 2.2), clicking 'FOCA' button FOCA (Fig. 4.1.13).

2. Setting the parameters as below:

fMRI Input Directory: Directory of input data (normalized fMRI data without smoothing). The data can be images files such as *.img and *.nii (NIFTI format). Support subfolders (multiple subjects) of a directory. The example directory is '*\ fMRI_example_data\ wra_data\'.

Head Parameter Directory: Select directory of head motion parameter files (The example directory is *\ fMRI_example_data\headmotion\).

Output Directory: Select the output directory, for example, *\FOCA_results.

Brain Mask: Select brain mask. Default is a standard brain mask generated from a probabilistic template. Here we use a user-defined brain mask. Select 'User defined mask', and press the button  to select the brain mask (*\ fMRI_example_data\brainmask.img).

Regress Out 6 HeadMotion Parameters: Regressing out 6 head motion parameters.

Regress Out White, CSF, Linear Drift Signals: Regressing out the white matter, CSF and linear drift signals.

TR (sec): fMRI TR time. Unit is second. Default is 2 s.

No. of CPU cores: The number of CPU cores used for parallel computing. E.g. if the test computer has 2 cores, then fill in 2.

Connect criterion: The connect criterion is the definition of spatial voxel connection. 'Point': 26-connected neighborhood; 'line': 18-connected neighborhood and 'surface': 6-connected neighborhood. Default is 'point' criterion.

As an example, we select the 'Regress Out 6 HeadMotion Parameters' and 'Regress Out White, CSF, Linear Drift Signal' options. Select 'point' option in connection criterion box. TR is set at 2 (default TR = 2 s).

3. Press 'RUN' button .

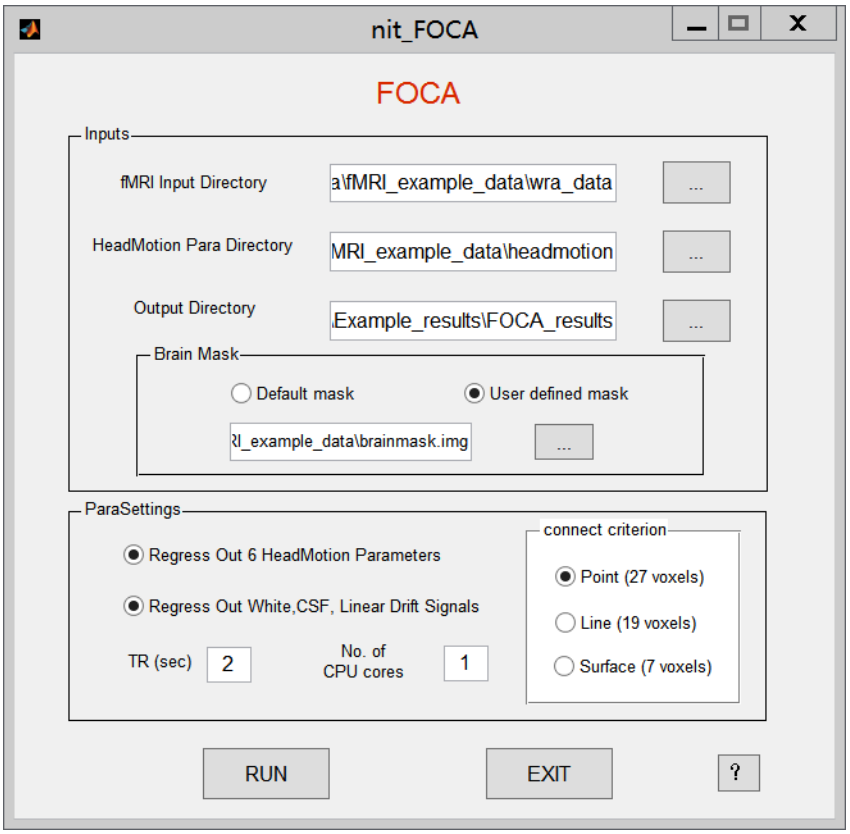


Fig. 4.1.13: FOCA interface and parameter settings.

4. The results are listed below (Fig. 4.1.14):
   FOCA_log.txt: Log file.
   FOCA_Para.mat: Parameter settings.
   FOCA_*.nii: FOCA value maps.
   mFOCA_*.nii: Normalized FOCA maps by dividing FOCA value by the mean FOCA of the whole brain for each subject.
   mFOCA-1_*.nii: The normalized FOCA maps which are subtracted by 1.

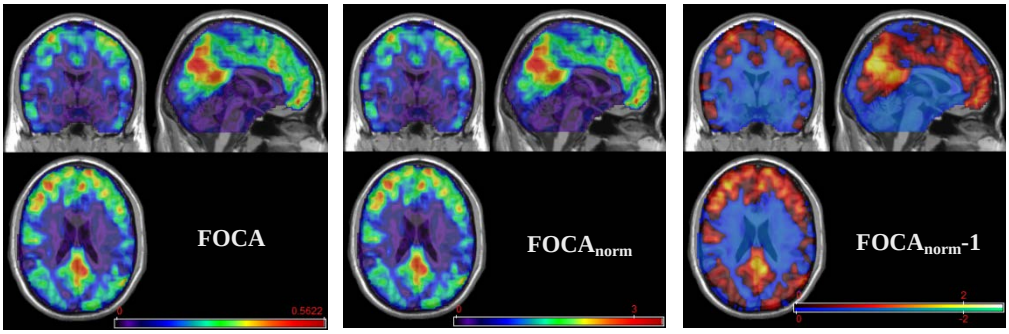


Fig. 4.1.14: The results of FOCA maps (sub_01).

B. Note:

1. DO NOT smooth the fMRI date before calculating FOCA. Spatial smooth can be conducted after calculating FOCA.
2. DO NOT filter the fMRI data before calculating FOCA.

3. Nuisance signals such as head motion, linear drift, white and CSF signals are suggested to be removed from data before calculating FOCA. It is also important to check the order of head motion parameter files are corresponding to the fMRI data, e.g. '*\sub_01*.img' → '*\headmotion\sub_01*.txt', or '*\headmotion\rp_*_sub_01.txt' etc.
4. The nuisance signals such as white, CSF, linear trend and global signals are extracted from fixed template mask (ROIs). MNI coordinates are as follows: White matter ROIs：[-21,-9,36]，[21,-6,36]；CSF ROIs: [-6,0,21]，[6,0,21]；Linear drift: [66,-99,-36]，[-72,-99,-36]，[66,63,66]，[9,69,72]，[-69,60,81]. Two types of masks (53×63×46 and 61×73×61 dimensions, voxel size is 3×3×3 mm^3) are provided corresponding to the general bounding box (SPM bounding box [-78 -112 -50; 78 76 85] and DPARSF bounding box [-90 -126 -72;90 90 108]). If the image size is not matched to the above two masks, NIT will use MNI coordinates to extract signals from fMRI data.
5. Two types of whole brain masks (53×63×46 and 61×73×61 dimensions, voxel size is 3×3×3 mm^3) are also provided corresponding to the general bounding box (SPM bounding box [-78 -112 -50; 78 76 85] and DPARSF bounding box [-90 -126 -72;90 90 108]). If the data image size is not matched to the above two masks, customer should select user defined brain mask.
6. Different number of time points of each subject is allowed.
7. $FOCA_{norm}$ (mFOCA_*.nii) or $FOCA_{norm}$-1 (mFOCA-1_*.nii) maps are suggested to do statistical analysis. For example, use mFOCA-1_*.nii files to do one sample t-test or two sample t-test. Spatial smoothing is suggested to conduct before statistical analysis (e.g. FWHM is 6 mm or 8 mm).
8. The spatial correlation between distributions in the neighboring time point is calculated by Pearson's correlation, and the neighboring time is equal to TR time.

4.2 EEG analysis

NIT EEG Toolbox is based on EEGLAB functions (EEGLAB version: eeglab12_0_2_6b). The main functions of NIT EEG Toolbox are extracting various features from CLEANED EEG data (simultaneous EEG-fMRI data). These EEG features are used for EEG-informed fMRI analysis. After clicking the 'EEG' button at the NIT main interface, clicking 'EEG Toolbox' button (Fig. 4.2.1).

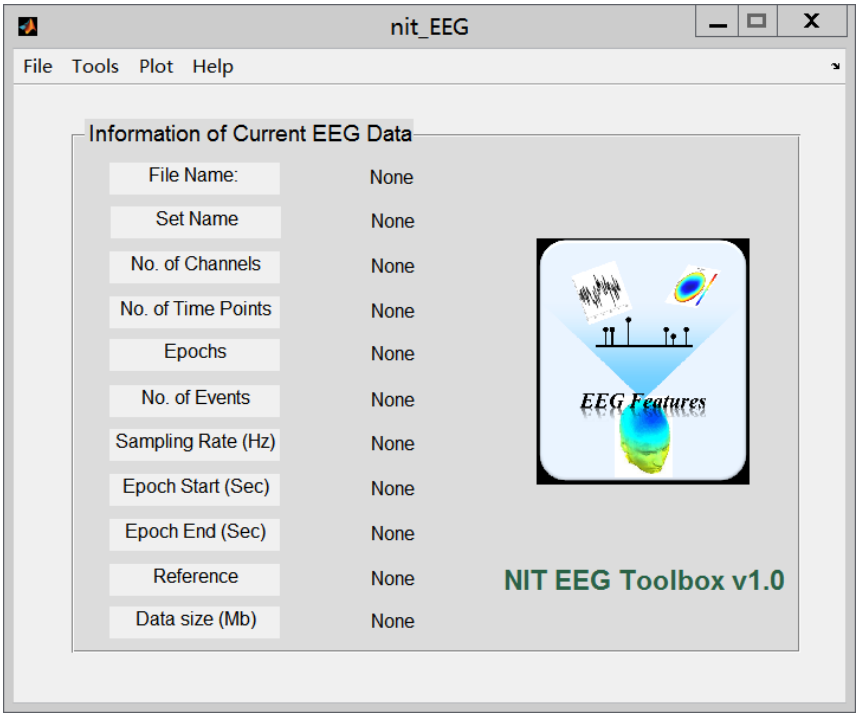


Fig. 4.2.1: The main interface of NIT EEG Toolbox.

4.2.1 Load EEG data

- Import a ASCII/Float File or Matlab array

Select ‘File->Import Data->Load ASCII/Float File or Matlab Array’ (the function is pop_importdata()). Then, click button ‘Browse’ to select data file. Set the sampling frequency, press "OK". Other dataset parameters will be automatically adjusted (Fig. 4.2.2). After successfully loading the data, the main interface of EEG Toolbox will show the main information of EEG data, such as file name, set name, No. of channel and No. of time points etc. (Fig. 4.2.3).

To import continuous data from a Matlab .mat file instead from a Matlab array, scroll the list of choices in the box above that shows "Matlab .mat file". Note: When reading a Matlab .mat file, please confirm that it must contain only one Matlab variable. For reading a (32-bit) binary float-format data file, there are two choices: 'float le' ("little-endian") and 'float be' ("big-endian"). In case the bit ordering is unknown (depending on operating system), try each of them to get correct results.

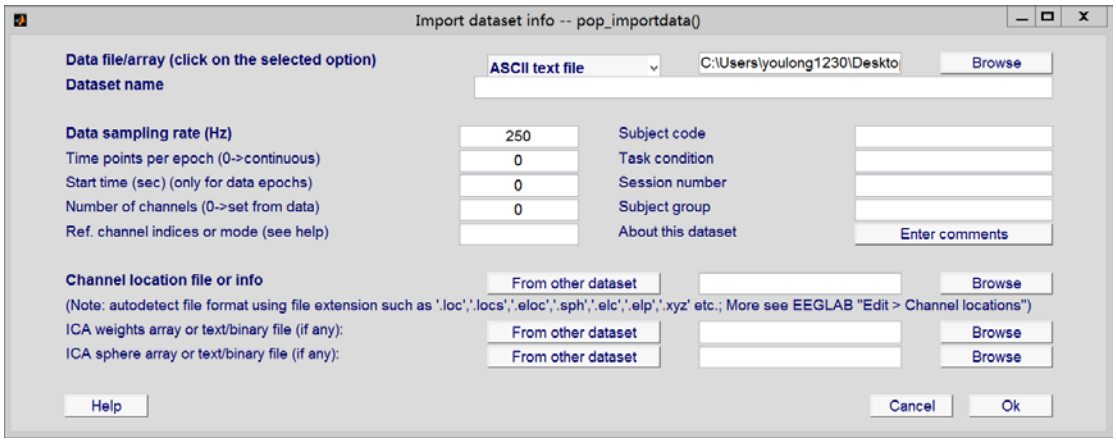


Fig. 4.2.2： The interface of Load ASCII/Float File or Matlab array.

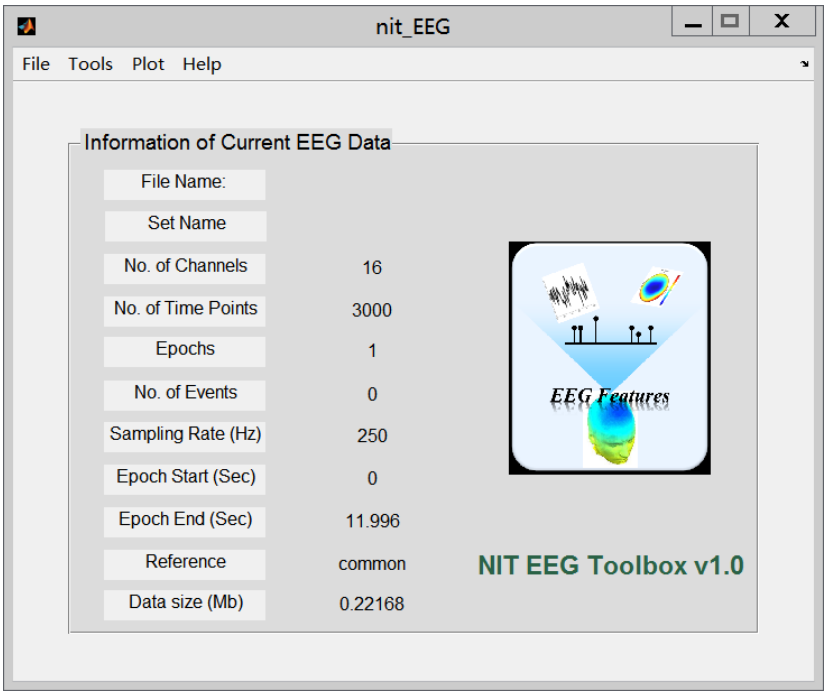


Fig. 4.2.3: After successfully loading the data, the main interface of EEG Toolbox will show the main information of EEG data, including file name, set name, No. of channel, No. of time points, epochs, No. of events, sampling rate, epoch start, epoch end, reference and data size.

- Load EEGLAB .set File

Select ‘File->Import Data->Load EEGLAB .set File’ (pop_loadset()). Then select EEG data (.set) file, and press ‘OK’. It supports reading the EEGLAB dataset files (.set).

- Load Curry 6/7 .dat File

Select ‘File->Import Data->Load Curry 6/7 .dat File’ (pop_loadcurry()). Then, select EEG data file (.dap/.rs3) and press ‘OK’.

It supports the NeuroScan Curry6/7 continuous EEG data files (.dat). Please DO NOT save the MRI slice triggers in cleaned EEG data files. It will be badly displaying

the EEG events in NIT (too many fMRI slice triggers), and it is very hard to mark the interested events.

- Load NeuroScan .cnt File

Select 'File->Import Data->Load NeuroScan .cnt File' (pop_loadcnt ()). Then, select EEG data file (.cnt) and press 'OK' (Fig. 4.2.4). It supports reading the NeuroScan EEG data files (.cnt).

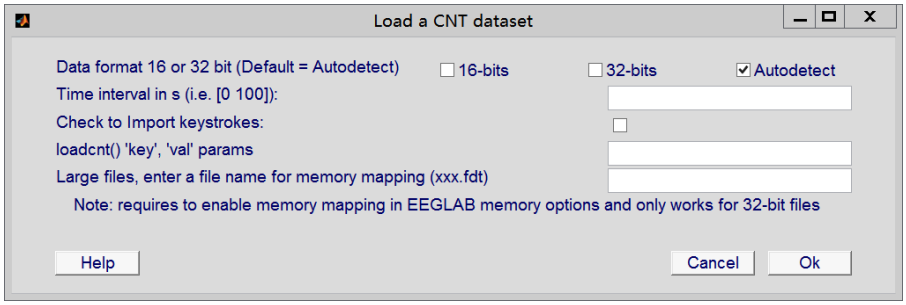


Fig. 4.2.4: The interface of Load NeuroScan .cnt File

- Load NeuroScan .eeg File

Select 'File->Import Data->Load NeuroScan .eeg File' (pop_loadeeg()). Then, select EEG data file (.eeg) and press 'OK' (Fig. 4.2.5).

It supports reading the NeuroScan EEG data files (.eeg). If the .eeg file is epoched data (channels × time points × trials), NIT only supports ICA analysis for epoched EEG data.

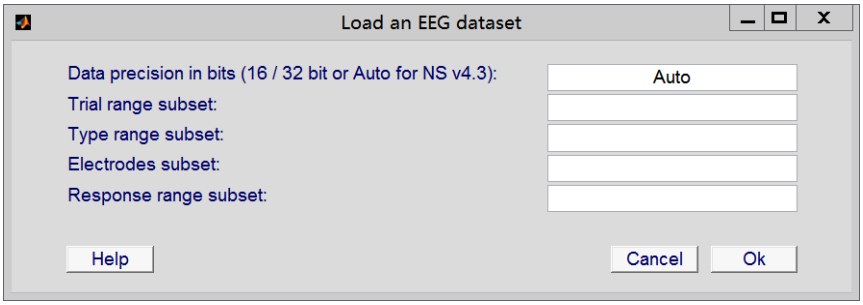


Fig. 4.2.5: The interface of Load NeuroScan .eeg File.

- Load BIOSIG edf/edf+/gdf/bdf File

Select 'File->Import Data->Load BIOSIG edf/edf+/gdf/bdf File' (pop_biosig()).Then, select EEG data file (.edf/.edf+/.gdf/.bdf) and press 'OK' (Fig. 4.2.6). Based on BIOSIG toolbox, it supports reading 16-bit European standard "EDF" (European Data Format), 24-bit BDF (Biosemi Data Format) and BCI2000 .gdf files.

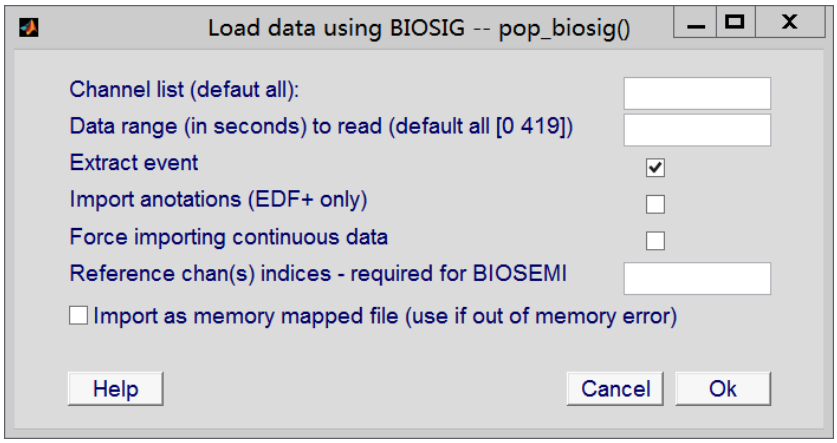


Fig. 4.2.6: The interface of Load BIOSIG edf/edf+/gdf/bdf File.

- Load Biosemi .bdf/.edf File

Select 'File->Import Data-> Load Biosemi .bdf/.edf File' (pop_readbdf()). Then, select EEG data file (.edf/.bdf) and press 'OK' (Fig. 4.2.7). Based on Biosemi functions, it supports reading 16-bit European standard "EDF" (European Data Format) and 24-bit BDF (Biosemi Data Format).

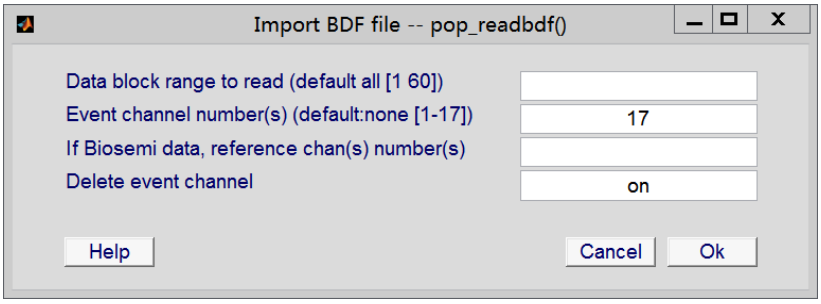


Fig. 4.2.7: The interface of Load Biosemi .bdf/.edf File.

- Load BCI2000 ASCII File

Select 'File->Import Data->Load BCI2000 ASCII File' (pop_loadbci()).Then, select EEG data file (.bci2000), fill the sampling rate (default is 256 Hz) and press 'OK' (Fig. 4.2.8).

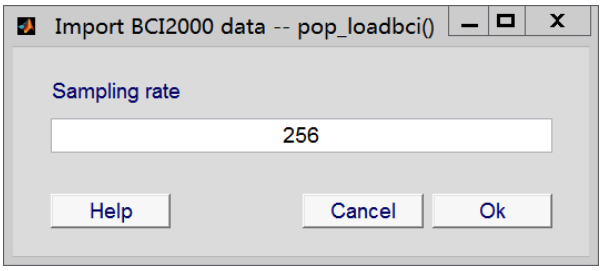


Fig. 4.2.8: The interface of Load BCI2000 ASCII File.

- Load Brain Vis. Rec. .vhdr File

Select 'File->Import Data->Load Brain Vis. Rec. .vhdr File' (pop_loadbv()). Then, select EEG data file (.vhdr), and press 'OK' (Fig. 4.2.9). It supports reading Brain Vision Analyzer data files (.data, .vhdr and .vmrk).

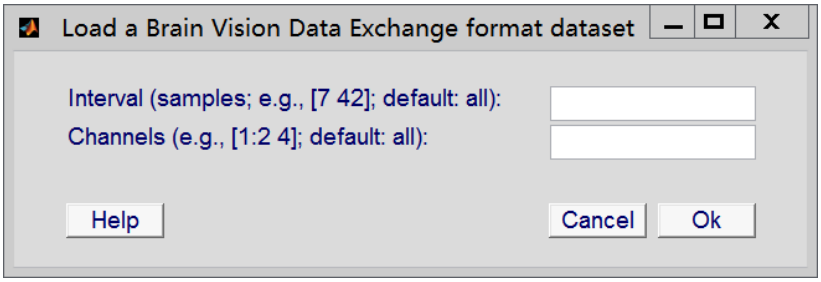


Fig. 4.2.9: The interface of Load Brain Vision Analyzer File.

4.2.2 Save EEG data

Select 'File->Save Current EEG Data As'. The EEG data will be saved as EEGLAB .set file.

4.2.3 Re-reference

Select 'Tools->Re-reference'. Then, set the parameters, and press 'OK' (Fig. 4.2.10). Please exclude non-EEG electrodes using 'Exclude channel indices', if there are non-EEG electrodes.

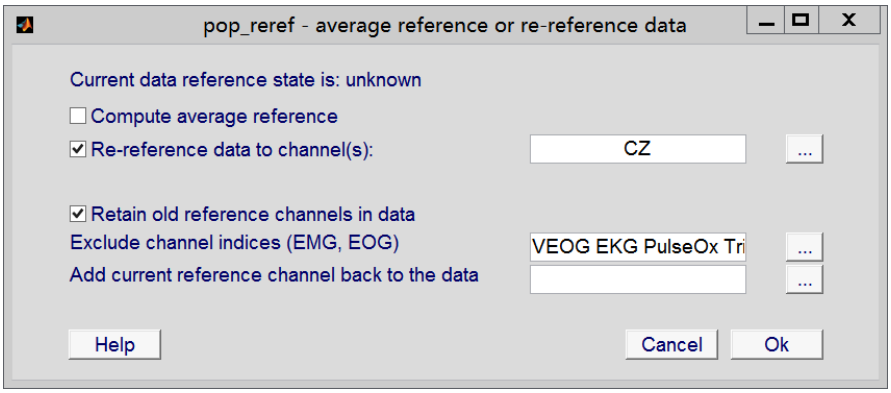


Fig. 4.2.10: The interface of re-reference.

4.2.4 Filtering

Select 'Tools->Filtering'. The function is pop_eegfilt().The parameters are (Fig. 4.2.11):

Lower edge of the frequency pass band (Hz): Lower edge of the frequency pass band (Hz), same as the high-pass cutoff frequency.

Higher edge of the frequency pass band (Hz): Higher edge of the frequency pass band (Hz), same as the low-pass cutoff frequency.

FIR Filter order (default is automatic): The order of finite impulse response (FIR) filter. Length of the filter in points [default is 3*fix(sampling rate/low cutoff frequency)].

Notch filter the data instead of pass band: Use notch filter? It can be used to remove ~50Hz power-line interference.

Use (shaper) FFT linear filter instead of FIR filtering: Use FFT filter instead of FIR filter? If the Matlab Signal Processing Toolbox is present, FIR filter uses the Matlab routine filtfilt(). This applies the filter forward and then again backward, to ensure that there are no phase delays introduced by the filter. If

the Matlab Signal Processing toobox is not present, pop_eegfilt uses a simple filtering method involving the inverse fourrier transform.

Use causal filter: Uses causal filtering? Default is uncheck.

Plot the filter frequency response: Plot the filter frequency response?

Use fir1 (check, recommended) or firls (uncheck, legacy): Filter design method, default is 'firls'. More details can be seen in Matlab functions ‘fir1’ and ‘firls’.

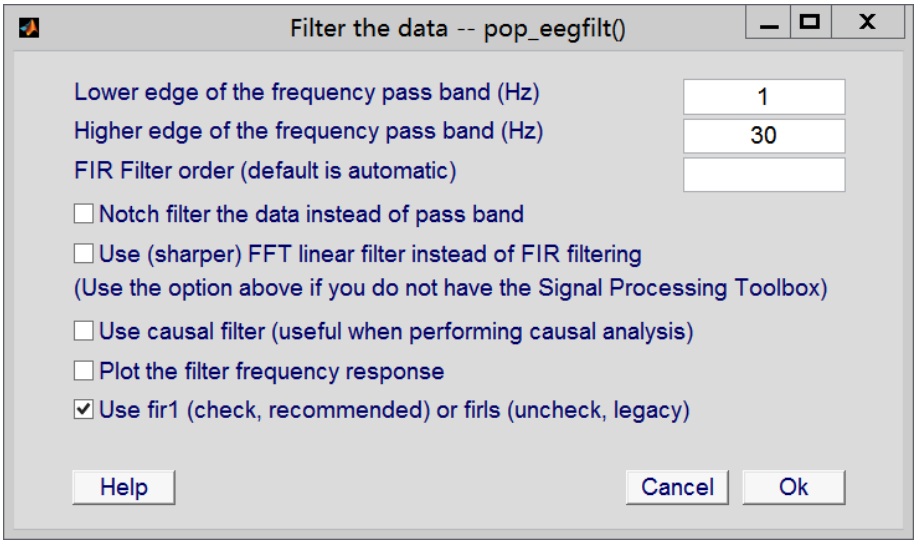


Fig. 4.2.11: The interface of filtering.

If high-pass and low-pass cutoff frequencies are BOTH selected, the filtering routine may not work. To avoid this problem, we recommend first applying the high-pass filtering and then, in a second call, the low-pass filtering (or vice versa).

If press button ‘OK’, the filtered data will instead of EEG data (EEG.data).

4.2.5 ICA analysis

After loading EEG data, select ‘Tools->Run ICA’. The ICA algorithm is temporal informed-ICA (runica()). As an example, ICA analysis is applied on simultaneous EEG data (ECG events). The parameter settings are follows (Fig. 4.2.12):

Select Channels: Select EEG channels. Here we select 62 EEG channels. The labels of selected channels will be listed.

Select Events: Select interested events. Here we select ECG events (label 255). The labels of selected events will be listed.

Epoch Time Range [min max] (msec): Set epoch time range. Defaults are 200 msec before time-locking event (min $\leq$ 0) and 800 msec after time-locking event (max$>$0).

EEG Sampling Rate: EEG sampling rate.

Exclude Event in Bad Block (label 9999): Exclude events in the bad blocks? The label of bad block in NIT is ‘9999’.

No. of ICs: Number of ICA components. Default is number of EEG channels or number of retained PCs. We usually run ICA using many more trials that the sample decomposition presented here. As a general rule, finding N stable components (from N-channel data) typically requires more than kN2 data

sample points (at each channel), where N2 is the number of weights in the unmixing matrix that ICA is trying to learn and k is a multiplier. The value of k will increase as the number of channels increases. When data are insufficient, then using the 'pca' option (Set the number of PCs to retain) to find fewer than N components may be the only good option.

Training blocks (extended-ICA): Perform tanh() "extended-ICA" with sign estimation N training blocks. If N > 0, automatically estimate the number of sub-Gaussian sources. If N < 0, fix number of sub-Gaussian comps to -N [faster than N>0] (default|0 -> off). The "runica" Infomax algorithm can only select for components with a supergaussian activity distribution (i.e., more highly peaked than a Gaussian, something like an inverted T). If there is strong line noise in the data, it is preferable to set the training blocks as 1, so the algorithm can also detect subgaussian sources of activity, such as line current and/or slow activity.

No. of PCs to retain: Number of PCs to retain (i.e. retain first ? PCs). Default is NOT performing PCA analysis. Here, we set it as 20.

Stop Criterion: Stop training when weight-change < this (default is 1e-6).

Max Steps: Max number of ICA training steps. Default is 512.

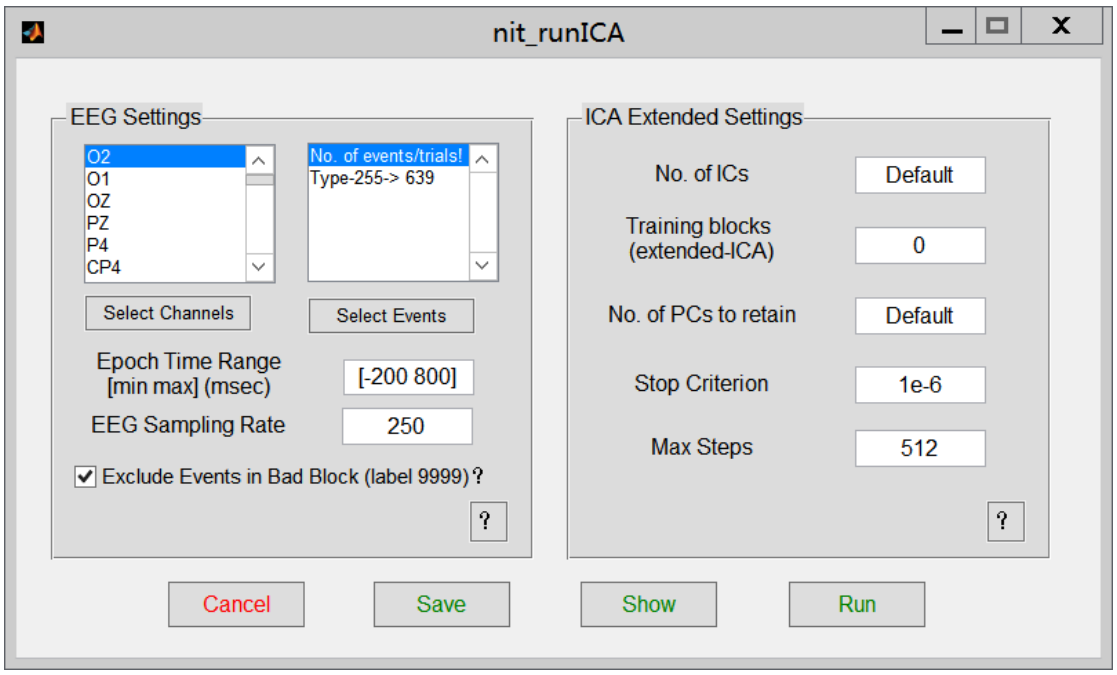


Fig. 4.2.12: The interface of ICA analysis.

Press button 'Run' to calculate (when calculating, the color of 'Run' will be red) ICA. The results ('ICAresults') will be first saved in the Matlab work space. The 'ICAresults' contains:

Settings.SelectedChanns: Selected channels. Settings.epoch: Epoch time range (msec).

Settings.srate: EEG sampling rate.

Settings.BadBlockFlag: 1-> Exclude events in the bad blocks; 0-> Exclude events in the bad blocks.

Settings.ICs: No. of ICs (If set as ‘default’, it will be ‘default’ string). Settings.N: N training blocks.

Settings.PCs: No. of PCs to retain.

Settings.stop: Stop training when weight-change < this. Settings.MaxSteps: Max number of ICA training steps. Results.latencies: Latencies of selected events.

Results.type: Event type (event label). If EEG data is epoched data, type will be ‘default’.

Results.trials: Number of trials (events).

Results.IC_weights: ICA weights (No. of ICs × No. of channels).

Results.IC_timecourses: Temporal ICs (No. of ICs × time points).

You can press button ‘Show’ to see the results of ICs (Fig. 4.2.13), and button ‘Save’ to save the ‘ICAresults’. If channel locations are contained in the EEG data, NIT will plot the topographies of ICs. Otherwise, NIT only plots the ICs as trials and an averaging wave.

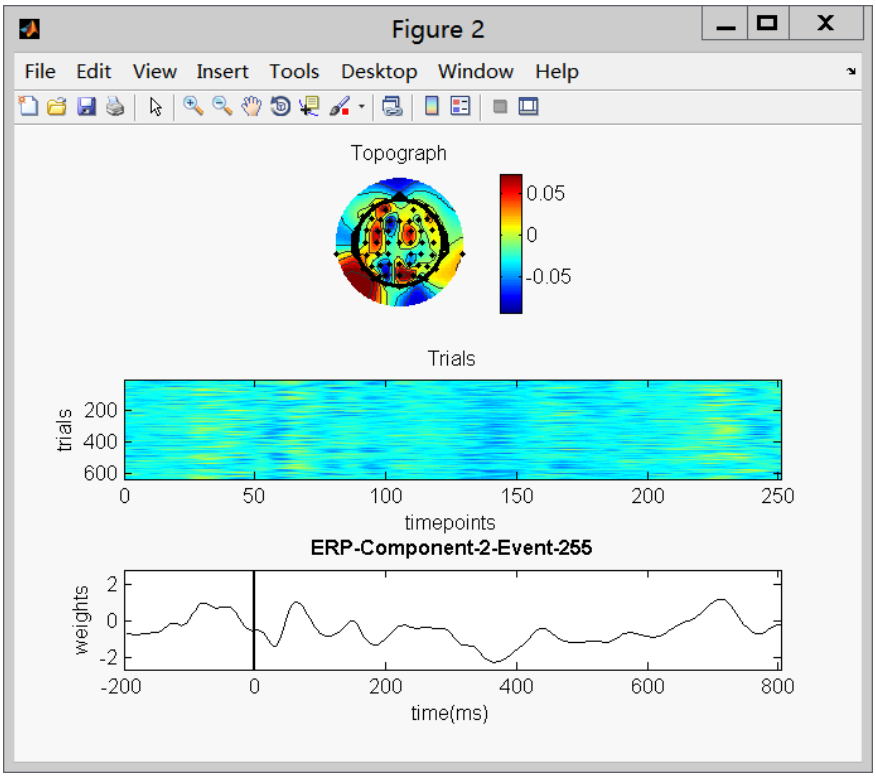


Fig. 4.2.13: Reuslts of ICA (ECG events). For an EEG independent component, the 1st row is topography, the 2nd row is trial image and the 3rd row is averaging wave.

4.2.6 Load Channel Locations

After loading the EEG data, select ‘Tools->Load Channel Locations’. The channel location of example data is based on 10-20 system. Therefore, we select ‘BESA file’, and press ‘OK’ (Fig. 4.2.14). Then, the information of channel locations will be showed in pop-up window (Fig. 4.2.15-4.2.16), and simply press ‘OK’.

The generated channel locations are standard channel locations corresponding to the imported channel labels (for example, Fz) from a channel location file using an extended International 10-20 System. To load a user defined channel locations file,

press the ‘Read Locations’ button (Fig. 4.2.15) and select the sample channel locations file.

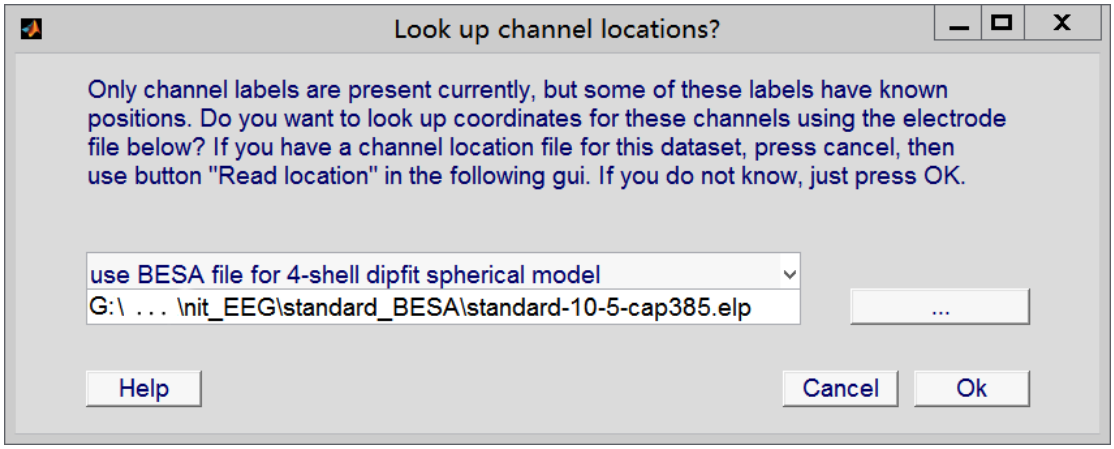


Fig. 4.2.14: The interface 1 of Loading Channel Locations.

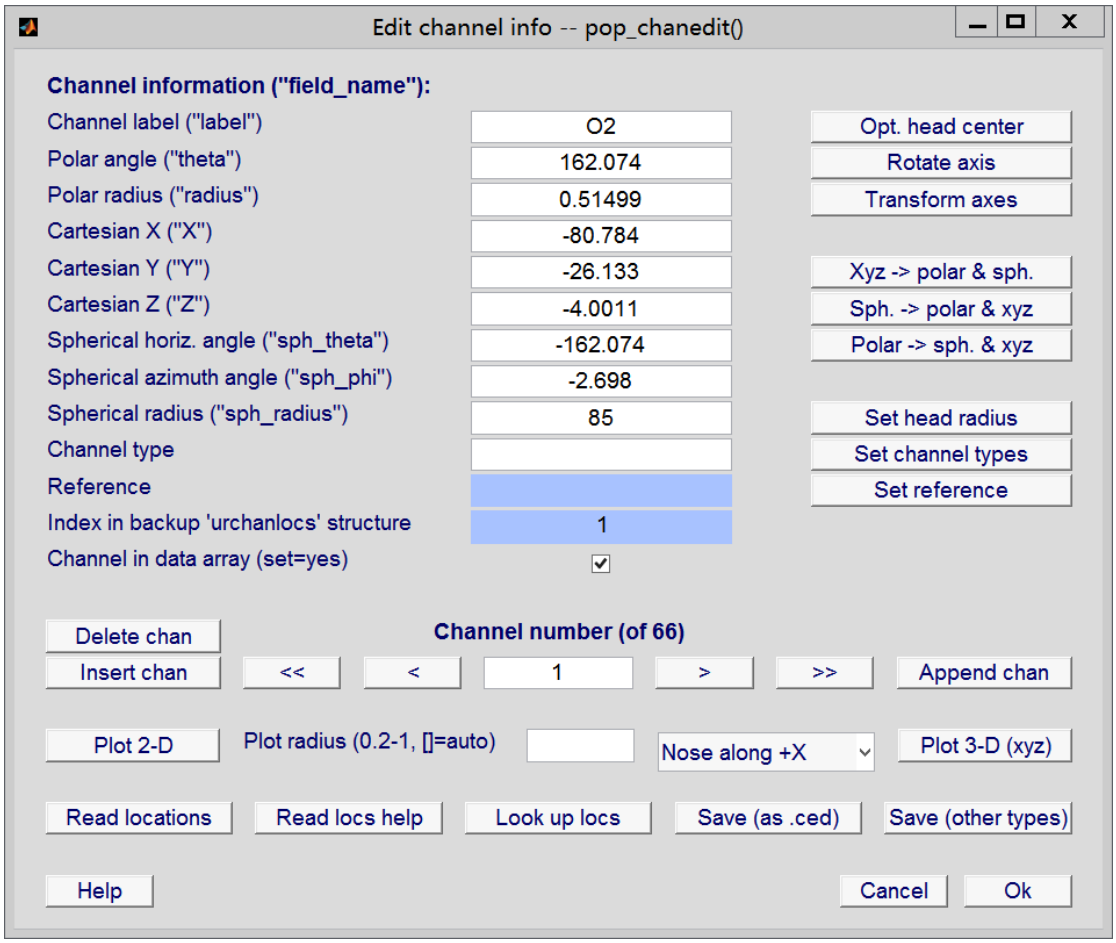


Fig. 4.2.15: The interface 2 of Loading Channel Locations.

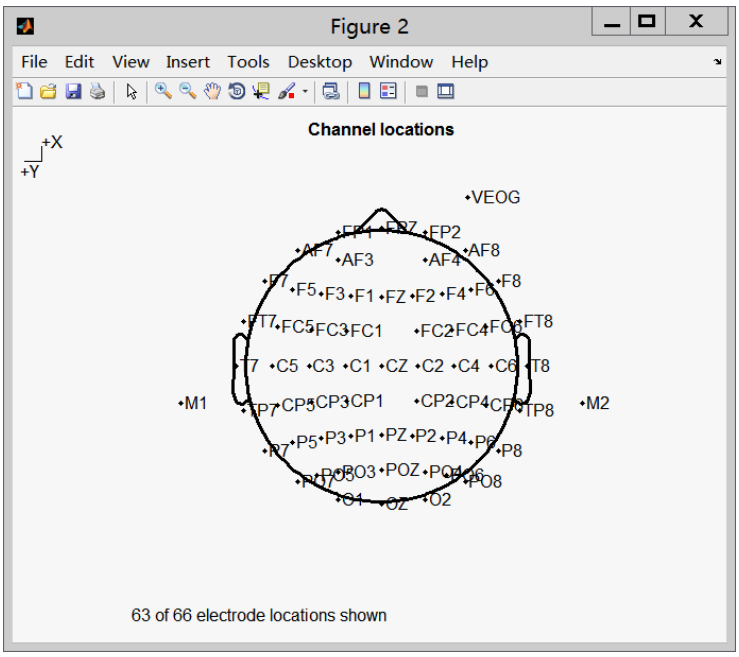


Fig. 4.2.16: 2D Channel locations of the example (NeuroScan Curry7, 62 channels).

4.2.7 Mark Epileptic Events

As an example, re-reference the EEG data to Cz electrode (see 4.2.3) first. Then, select 'Tools->Mark Epileptic Events'. The interface of model selection wills popup (Fig. 4.2.17). Select '16 Channels (NeuroScan Curry7)' (the selected electrodes will be listed), and press 'OK'. The display interface of EEG data wills popup. If you want to mark a continuous EEG data, select continuous data for epileptic events by dragging the mouse over a data region. After marking a portion of the data for epileptic events, keep the mouse in the marked block (gray area), click the right mouse button and select the type of epileptic event. The successfully marked events will be showed immediately (Fig. 4.2.18). If you want to mark an event at a certain time point, put the mouse in the data display area (DO NOT dragging the mouse to mark data), click the right mouse button and select the type of event. The true time of the mouse depends on the displayed time showed below ('Time').

You can use 'Delete Event' button to delete false events one by one (select false event in the 'Events' list first). When completed, press the 'Save Events' button to save the added events to EEG data (structure array 'EEG' in the Matlab workspace). At last, select 'File->Save Current EEG Data As' to save the marked EEG data as a new data file.

Options of displayed models are following (Fig. 4.2.17):

Original Channels: Display all channels of EEG data.

16 Channels (NeuroScan Curry7): Display 16 channels based on NeuroScan (Curry7) system (listed in the file 'NeuroScanCurry7_16Channels.xlsx' and Table 4.2.1).

32 Channels (NeuroScan Curry7): Display 32 channels based on NeuroScan (Curry7) system (listed in the file 'NeuroScanCurry7_32Channels.xlsx' and Table 4.2.1).

16 Bipolar Channels (NeuroScan Curry7): Display 16 bipolar channels based on NeuroScan (Curry7) system (listed in the file 'NeuroScanCurry7_16BipolarChannels.xlsx' and Table 4.2.1).

User Defined Channels: Display user defined channels. User defined channels should be contained in a txt/xls/xlsx file. Generally, channel labels/numbers should be listed as only 1 column in the file. If there are 2 columns (up to 2 columns), NIT will display the temp data, which are the data of first column minus data of second column.

Table 4.2.1: The list of channels.

No.	16 channels	32 channels	16 bioplar channels
1	FP1	FP1	FP1-F3
2	FP2	FP2	F3-C3
3	F3	F3	C3-P3
4	F4	F4	P3-O1
5	C3	C3	O1-P7
6	C4	C4	P7-T7
7	P3	P3	T7-F7
8	P4	P4	F7-FP1
9	O1	O1	FP2-F4
10	O2	O2	F4-C4
11	F7	F7	C4-P4
12	F8	F8	P4-O2
13	T7	T7	O2-P8
14	T8	T8	P8-T8
15	P7	P7	T8-F8
16	P8	P8	F8-FP2
17		AF3	
18		AF4	
19		FC3	
20		FC4	
21		CP3	
22		CP4	
23		PO3	
24		PO4	
25		AF7	
26		AF8	
27		FT7	
28		FT8	
29		TP7	
30		TP8	
31		PO7	

32		PO8	

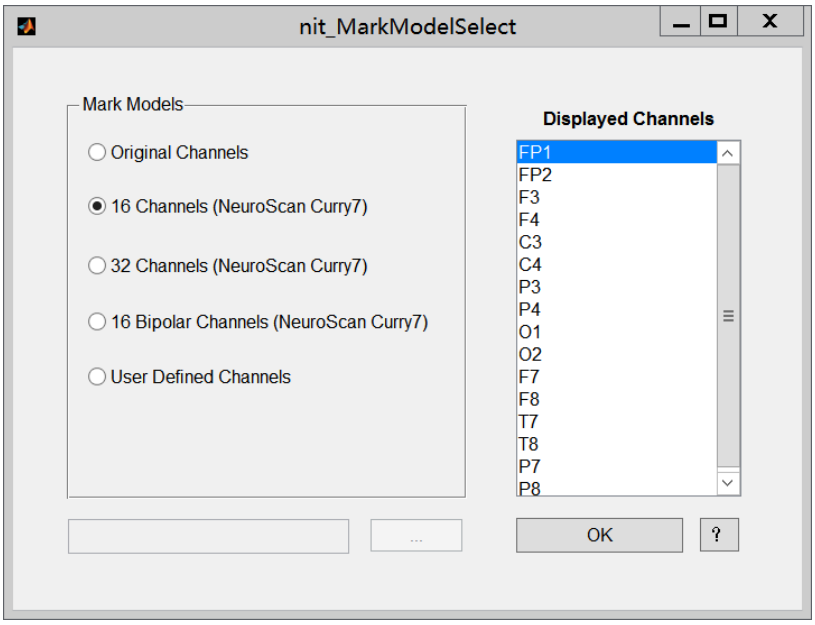


Fig. 4.2.17: The interface of display model selection.

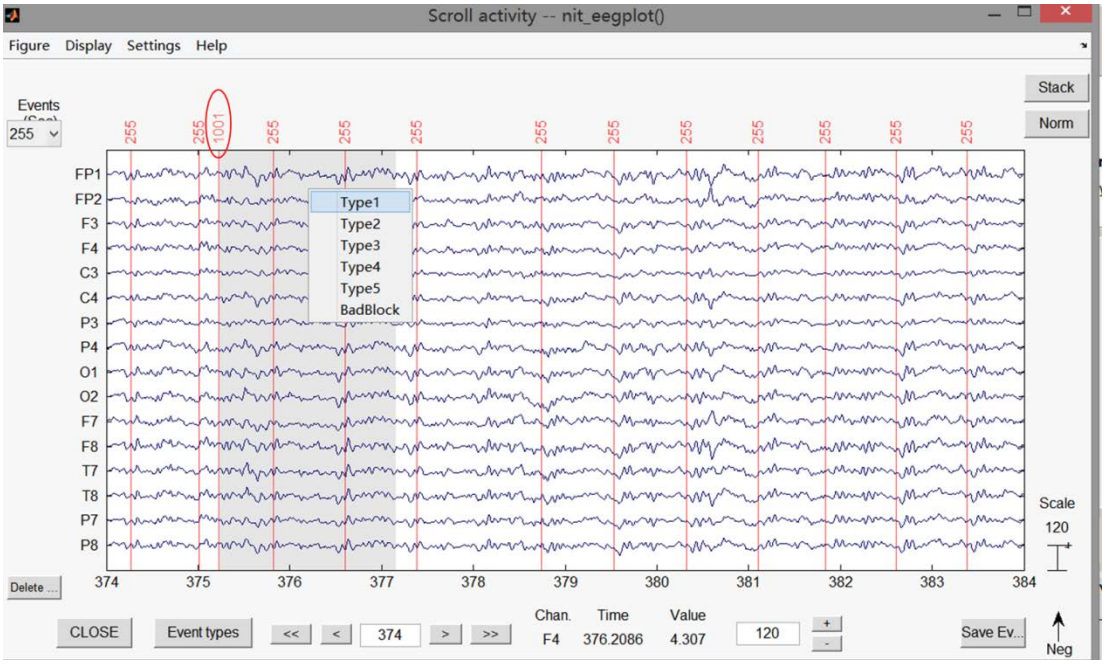


Fig. 4.2.18: Mark the epileptic events. The successfully marked events will be showed immediately (red circle). You can use ‘Delete Event’ button to delete false events one by one (blue arrow). Label ‘255’ is ECG events.

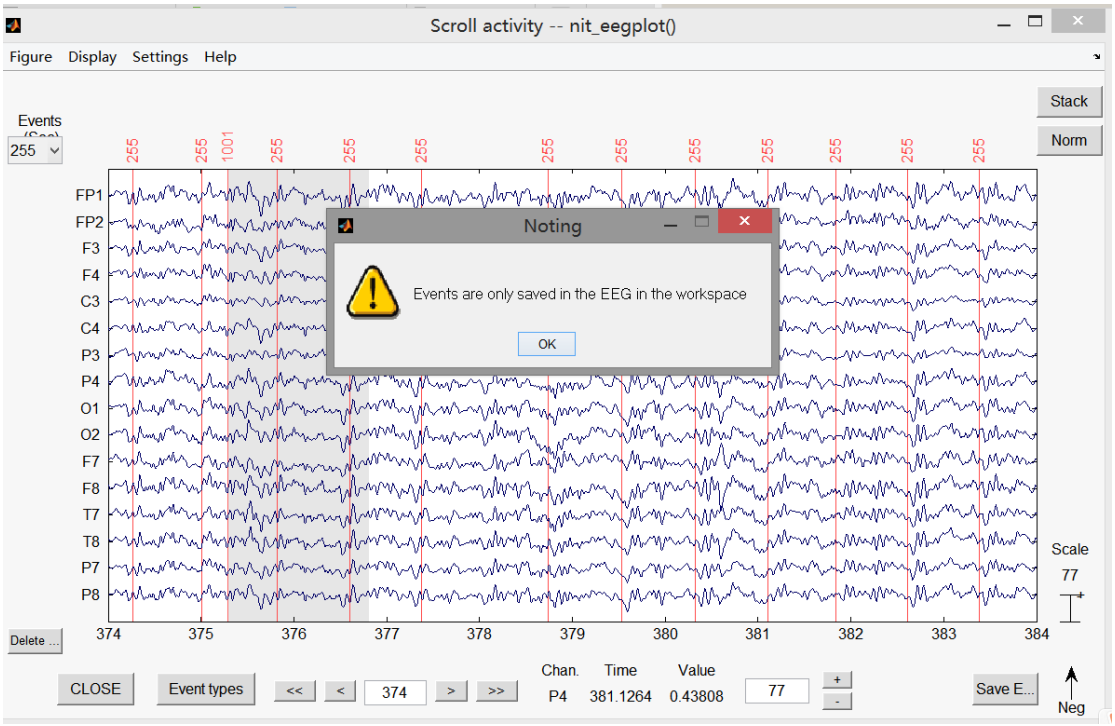


Fig. 4.2.19: Save the events. Pressing 'Save Events' button only saves the events to the structure array 'EEG' in the MATLAB workspace.

4.2.8 Extract EEG features

EEG features including event onset, power (Mantini et al., 2007; Moosmann et al., 2003) and ERP amplitude (Debener et al., 2006) can be extracted for EEG-informed fMRI analysis. Select 'Tools->Extract EEG Features', the interface of feature selection will popup (Fig. 4.2.20).

If you want to extract ERP amplitude, please import/calculate ICA results (ICAresults) first using NIT EEG Toolbox.

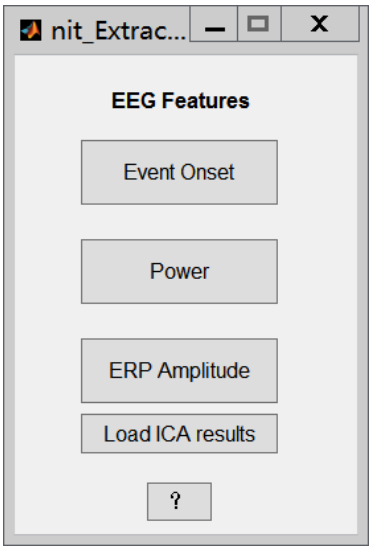


Fig. 4.2.20: Interface of feature selection.

- **Event Onset**

Press button ‘Event Onset’, the interface of event onset will popup (Fig. 4.2.21). Event types will be listed in the left ‘Event list’. Here we select type ‘1001’ (epileptic event). Label ‘225’ is ECG event, and label ‘9999’ is bad block. Events in the period of fMRI scanning are considered (from ‘fMRI onset’ to ‘onset + fMRI duration’).

fMRI Onset (sec): Onset time of fMRI scanning (unit is second). Default is 0, and it should be ≥ 0. As an example, we fill 29.107 sec.

fMRI Duration (sec): Duration of fMRI scanning (unit is second). Default is Inf. Here we fill 510 s. If the value is empty/negative/0, default is Inf. NOTE: In fMRI analysis, the first several (e.g. 5) volumes are always discarded to remove the T1 saturation effects. Therefore, if you want to match onsets to fMRI time scale, please correct the fMRI onset and duration time (i.e. fMRI onset + discarded TR time; fMRI duration - discarded TR time).

Match to fMRI timepoints?: Match onsets to fMRI time scale? If check, unit is TR time points. If uncheck, outputs are onsets in fMRI scanning period (unit is second).

With Event Duration?: Contain event duration?

Exclude Events in Bad Block?:If check, exclude events in the bad block (label ‘9999’).

TR: fMRI repeating time. Unit is second.

Show Info: Show the No. of events in the period of fMRI scanning (also exclude events in the bad block).

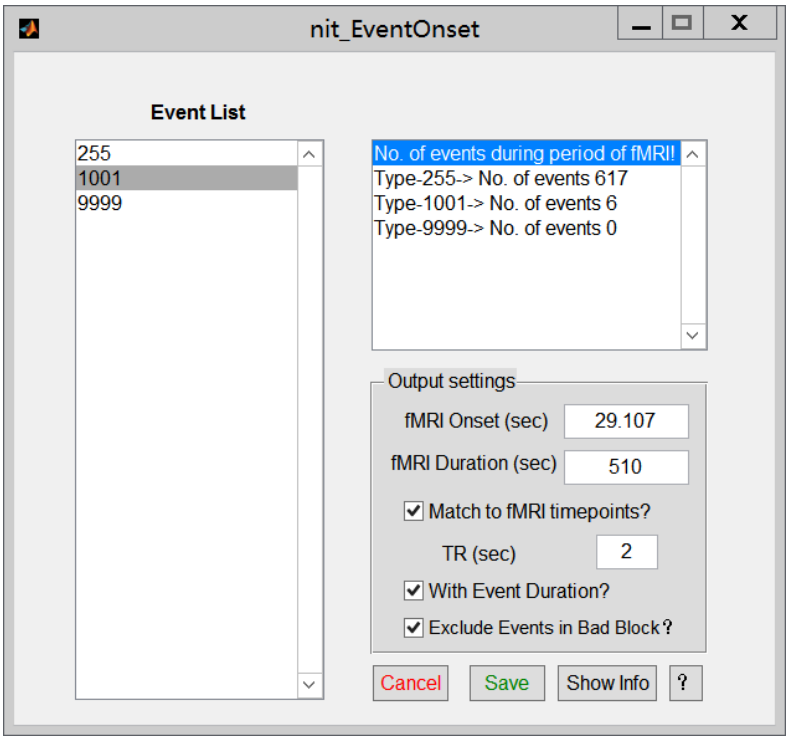


Fig. 4.2.21: The interface of Event Onset.

Press ‘Save’ to save the results as .txt/.xls/.xlsx/.mat file.

Save as .txt/.xls/.xlsx file: first row is event type. 1: yes; 0: no. If the onsets are matched to fMRI temporal scale, this file can be directly used for GLM

analysis in NIT.

Save as .mat file: Matlab structure array ‘Latencies’, which contains latencies of event onsets (‘latency’) and parameter settings (‘ParaSettings’).

- **Power**

Select ’Power’, the interface will popup (Fig. 4.2.22). The power is calculated by time-frequency analysis (timefreq()). The power value is calculated by:

$$Y_{power} = 2 * \frac{\|Y\|^2}{length\ of\ signal}$$

where Y is complex number calculated by FFT, $\|.\|$ is complex modulus operations (using ‘abs’ function of MATLAB).

***EEG settings*:**

Select Channels: Select EEG channels. As an example, we select 7 frontal channels (FP2, FP1, AF4, AF8, AF7, AF3 and FPZ).

Select Event/Type: Select interested event/type. Here we select type ‘1001’ (epileptic event).

‘’~‘’**Hz**: The range of frequency band. Here we select ‘User Defined’ and set 3 ~ 6 Hz.

Model Select: Analysis model of calculating power (Fig. 4.2.23).

Extract Power From Continuous Data: Time-frequency analysis will be conducted in each TR epoch. If uncheck ‘Match to fMRI time points’, the length of epoch is 1 second. This option is suggested for resting-state EEG data.

Extract Power From Discharge Epoch: Time-frequency analysis will be conducted in each epoch of discharge event. This option is suggested for epileptic EEG data. Here, as an example, we select this option.

Extract Power From Event Epoch: Time-frequency analysis will be conducted in each event epoch. This option is suggested for ERP EEG data.

EEG Sampling rate: EEG sampling rate (Hz).

Epoch Time Range [min max] (msec): Set epoch time range. Defaults are 200 msec before time-locking event (min≤0) and 800 msec after time-locking event (max＞0).

Wavelet Cycles: The number of cycles for the time-frequency decomposition. Default is 0. If 0, use FFTs and Hanning window tapering. If a real positive scalar, it is no. of cycles in each Morlet wavelet, constant across frequencies. If [value(1) value(2)], wavelet cycles increase with frequency starting at value(1) and, if value(2) > 1, increasing to value(2) at the upper frequency, or if value(2) = 0, same window size at all frequencies (similar to FFT if value(1) = 1) or if value(2) = 1, not increasing (same as giving only one value for ‘cycles’). This corresponds to pure wavelet with the same number of cycles at each frequencies if 0 < value(2) < 1, linear variation in between pure wavelets (1) and FFT (0).

FFT Tapering Function: FFT Tapering function. Default is ‘hanning’ function.

NOTE: ‘hamming’ and ‘blackmanharris’ functions require MATLAB signal processing toolbox.

Wavelet Method/Progam: Wavelet method/program to use. Default is ‘dftfilt3’. ‘dftfilt2’: Morlet-variant or Hanning DFT; ‘dftfilt3’: Morlet wavelet or hanning DFT (exact Tallon baudry).

Normalize？: Normalize power values to [0, 1], i.e.

$$Power_{normalize} = \frac{Y_{power} - \min(Y_{power})}{\max(Y_{power}) - \min(Y_{power})}$$

Detrend？: Linearly detrend each data epoch before time-frequency analysis.

Exclude Powers in Bad Block (label 9999)?: Exclude values of power in the bad block (label ‘9999’).

Mean Power Across Channels？: Calculate mean power across channels.

fMRI settings

fMRI Onset (sec): Onset time of fMRI scanning (unit is second). Default is 0, and it should be ≥ 0. As an example, we fill 29.107 sec.

fMRI Duration (sec): Duration of fMRI scanning (unit is second). Default is Inf. Here we fill 510 s. If the value is empty/negative/0, default is Inf. NOTE: In fMRI analysis, the first several (e.g. 5) volumes are always discarded to remove the T1 saturation effects. Therefore, if you want to match power values to fMRI time scale, please correct the fMRI onset and duration time (i.e. fMRI onset + discarded TR time, fMRI duration - discarded TR time).

Match to fMRI timepoints?: Match power values to fMRI time scale? If check, the length of power vector is equal to fMRI time points. If uncheck, outputs are power values of all epochs.

TR: fMRI repeating time (sec).

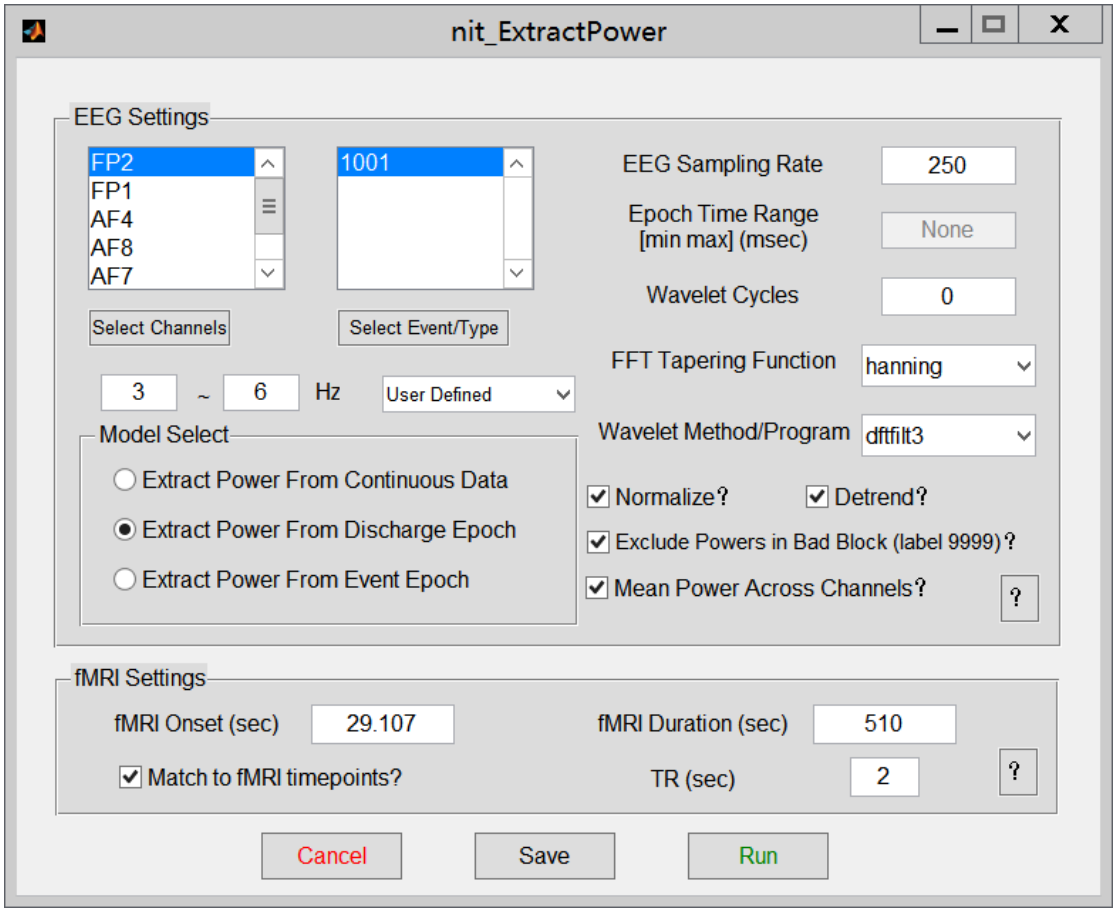


Fig. 4.2.22: The interface of power calculation.

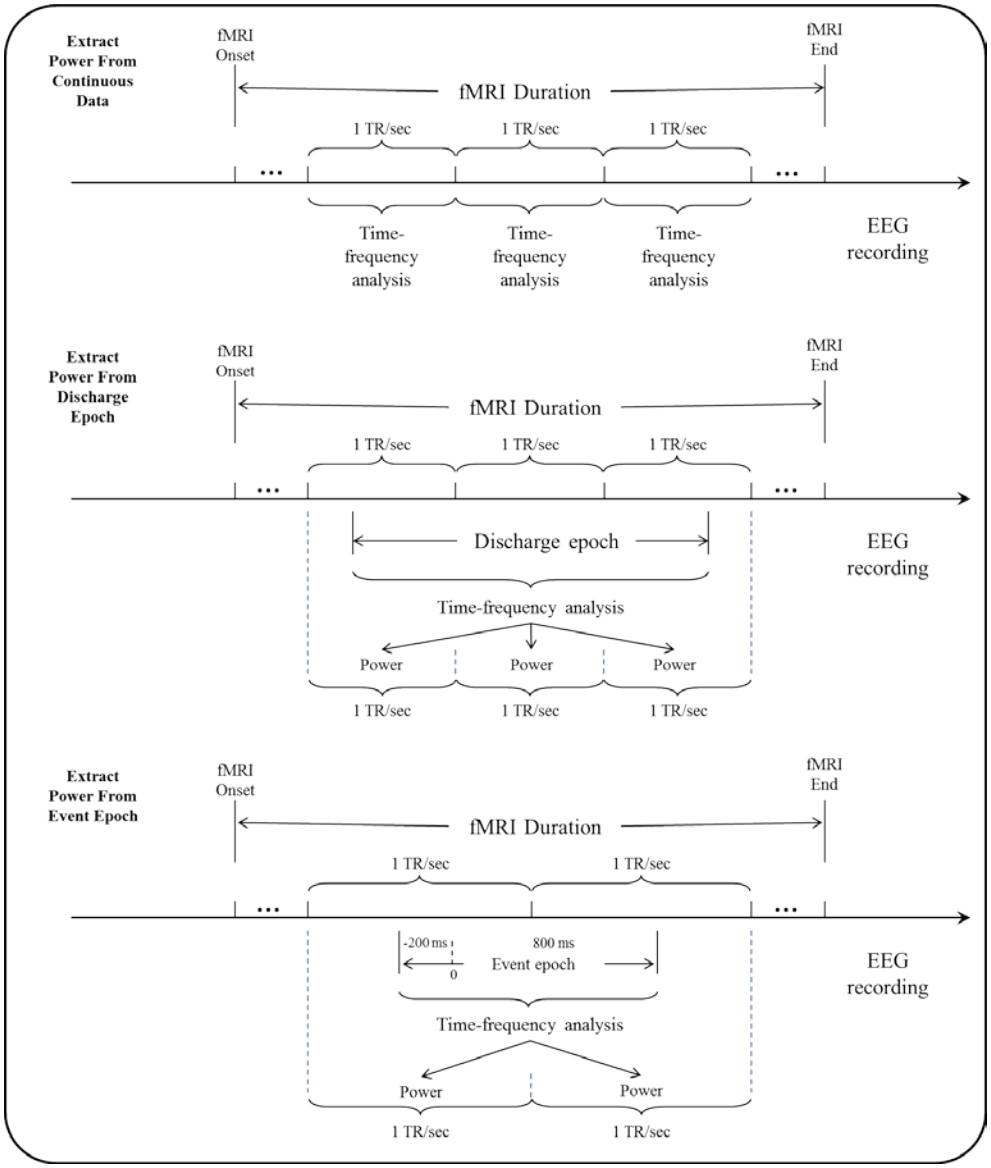


Fig. 4.2.23: Power calculation. *Extract Power From Continuous Data*: Time-frequency analysis will be conducted in each TR epoch. If uncheck 'Match to fMRI time points', the length of epoch is 1 second. This option is suggested for resting-state EEG data. *Extract Power From Discharge Epoch*: Time-frequency analysis will be conducted in each epoch of discharge event. This option is suggested for epileptic EEG data. *Extract Power From Event Epoch*: Time-frequency analysis will be conducted in each event epoch. This option is suggested for ERP EEG data

Press 'Run' to calculate, the results can be seen in MATLAB work space ('MeanPower').
MeanPower.power: Power value.
MeanPower.type: Event type.
MeanPower.label: Frequency band.
MeanPower.channs: Selected EEG channels.
MeanPower.model: model select. 1: Extract Power From Continuous Data; 2: Extract

Power From Discharge Epoch; 3: Extract Power From Event Epoch.

MeanPower.ParaSettings.srate: EEG sampling rate.

MeanPower.ParaSettings.epoch: Epoch time range (msec).

MeanPower.ParaSettings.WaveletCycles: Wavelet cycles.

MeanPower.ParaSettings.TaperingFunction: FFT Tapering function.

MeanPower.ParaSettings.WaveletMethod: Wavelet method.

MeanPower.ParaSettings.NormalizeFlag: 1: normalize; 0: do not normalize.

MeanPower.ParaSettings.DetrendFlag: 1: detrend; 0: do not detrend.

MeanPower.ParaSettings.ExcludeBadBlockFlag: 1: exclude; 0: do not exclude.

MeanPower.ParaSettings.MeanPowerFlag: 1: calculate mean power across channels; 0: do not calculate.

MeanPower.ParaSettings.fMRIOnset: fMRI onset (sec).

MeanPower.ParaSettings.fMRIDur: fMRI duration (sec).

MeanPower.ParaSettings.MatchFlag: 1: match to fMRI scale; 0: do not match.

MeanPower.ParaSettings.TR: fMRI repeating time (sec).

You can reset the parameters to re-calculate the power values, the results will be added to the array 'MeanPower' in MATLAB work space. Press button 'Save' to save the results as .txt/.xls/.xlsx/.mat file. Pressing button 'Cancel' will clean the array 'MeanPower'.

Save as .txt/.xls/.xlsx file: first row is label including event type and frequency band. If the onsets are matched to fMRI time scale, this file can be directly used for GLM analysis in NIT. For each calculation, the parameter, 'Match to fMRI timepoints' (MatchFlag), must be consistent (all 1 / all 0).

Save as .mat file: Matlab structure array 'MeanPower', which contains power values and parameter settings ('ParaSettings').

- **ERP Amplitude**

Press button 'ERP amplitude', the interface will popup (Fig. 4.2.24).

Select Event/Type: Select interested event/type. Here we select ECG event (label '255').

Select ICs: Select ICs.

Method: *Maximal Absolute Value*: for each trial, get the maximal absolute value after onset/stimuli (positive); *Absolute Maximal Value (signed)*: for each trial, get the absolute maximal value after onset/stimuli (with sign); *Maximal Value*: for each trial, get the maximal value after onset/stimuli. Default is 'Maximal Absolute Value'.

EEG Sampling rate: EEG sampling rate.

Baseline Correction？: Baseline correction (for each trial, subtracting mean value of period before onset/stimuli).

Normalize？: Normalize amplitude values to [0, 1], i.e.

$$Y_{normalize} = \frac{Y_{ampli} - \min(Y_{ampli})}{\max(Y_{ampli}) - \min(Y_{ampli})}$$

Match to fMRI timepoints?: Match amplitude values to fMRI time scale? If check, the length of amplitude vector is equal to fMRI time points. If uncheck, outputs are power values of all epochs/trials. Default is uncheck.

fMRI Onset (sec): Onset time of fMRI scanning (unit is second). Default is 0, and it should be ≥ 0.

fMRI Duration (sec): Duration of fMRI scanning (unit is second). Default is empty. NOTE: This value must be > 0 and are divisible by TR time. In fMRI analysis, the first several (e.g. 5) volumes are always discarded to remove the T1 saturation effects. Therefore, if you want to match amplitude values to fMRI time scale, please correct the fMRI onset and duration time (i.e. fMRI onset + discarded TR time, fMRI duration - discarded TR time).

TR: fMRI repeating time (sec).

Then press button 'Run'. The results can be seen in the MATLAB work space (array 'ampli_results'):

ampli_results.type: Event type.

ampli_results.ICs: Selected ICs.

ampli_results.method: method.

ampli_results.srate: EEG sampling rate.

ampli_results.BaselineFlag: 1: baseline correction; 0: no baseline correction.

ampli_results.NormalizeFlag: 1: normalize; 0: do not normalize.

ampli_results.MatchFlag: 1: match to fMRI time scale; 0: do not match.

ampli_results.ampli: amplitude values.

Press button 'Save' to save the results as .txt/.xls/.xlsx/.mat file. Pressing button 'Cancel' will clean the array 'ampli_results'.

Save as .txt/.xls/.xlsx file: first row is label including event type and IC number. If the amplitude values are matched to fMRI time scale, this file can be directly used for GLM analysis in NIT.

Save as .mat file: Matlab structure array 'ampli_results', which contains amplitude values and parameter settings.

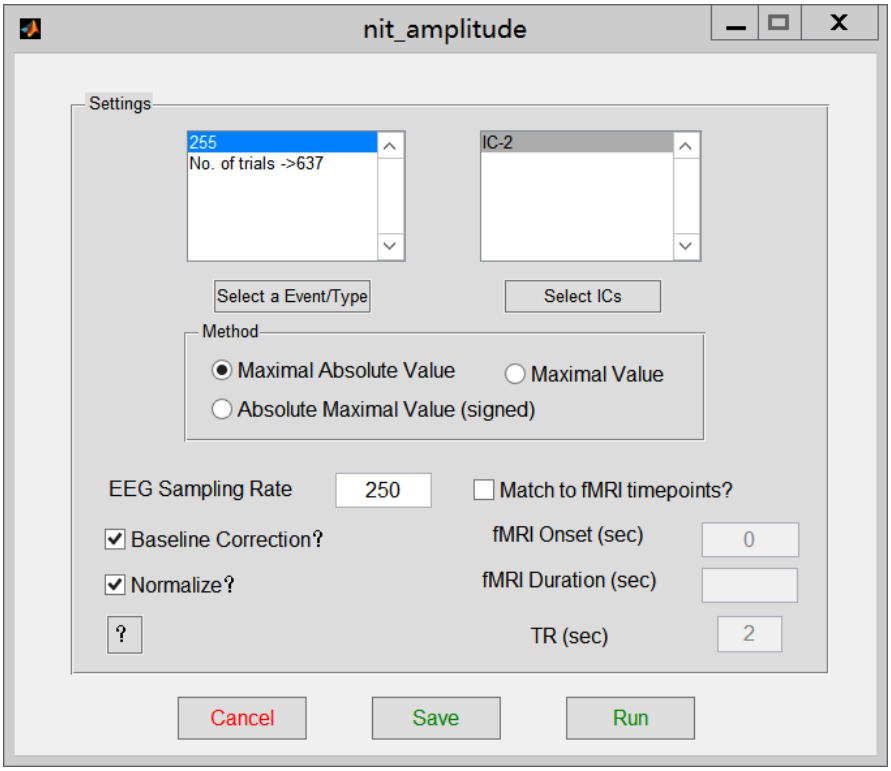


Fig. 4.2.24: The interface of ERP amplitude.

4.2.9 Display EEG

Select 'Plot->Channels Plot' (nit_eegplot()). Default is showing all EEG channels. The vertical axis is negative y-direction (↑Neg).You can press 'Help' to see other functions and settings.

Figure->Save Image: Save image as .JPEG/.TIFF/.BMP/.EPS/.PNG file (24 bit).

Events (Sec): Show the list of events. Click the time of a certain event will show the portion of EEG data corresponding to selected event.

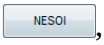
Delete Event: Delete selected event in the array 'EEG'.

Save Event: Save event information in the array 'EEG'.

4.3 Fusion analysis

4.3.1 fMRI informed EEG analysis (NESOI)

A. Step by step:

1. After clicking the 'Fusion' button at the NIT main interface, clicking 'NESOI' button 

, then the NESOI GUI will popup (Fig. 4.3.1).

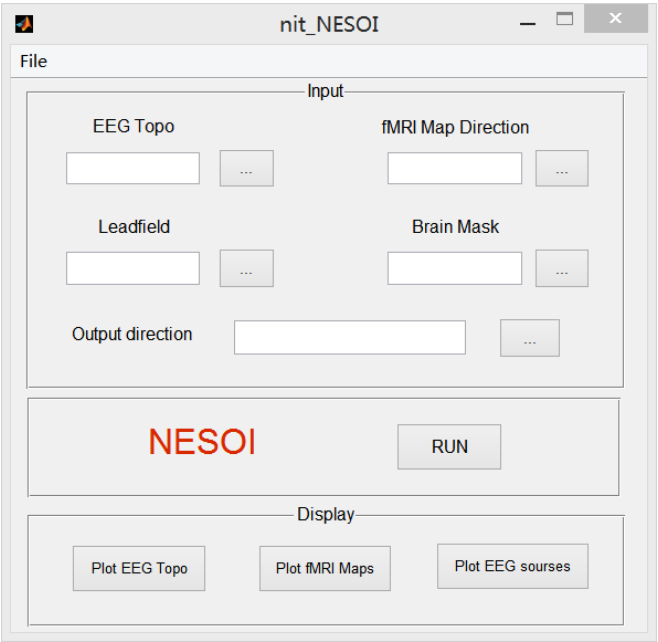


Fig. 4.3.1: NESOI interface.

2. Setting parameters as below (Fig. 4.3.2):

EEG Topo: Select EEG topograph file (e.g. EEG_topo.xlsx). Support *.txt or Office *.xls and *.xlsx files. The data dimension is the number of EEG channels × the number of EEG topographies (e.g. 62 channels × 11 topographies).

Leadfield: Select leadfield file (e.g. leadfield.xls). Support *.txt or Office *.xls and *.xlsx files. The data dimension is the number of EEG sources (dipoles) × the number of EEG channels (e.g. 6144 dipoles × 62 channels).

fMRI Map Direction: Select images which are spatial priors in NESOI (e.g. *\Example_data\NESOI\fmri_ica_maps). The directory only contains 3D *.img or *.nii files (NIFTI format).

Brain Mask: Select brain mask (e.g. brainmask.img). Support 3D *.img or *.nii files (NIFTI format).

Output Direction: Select output directory (e.g. *\Example_results\NESOI).

3. Press RUN button 

(Fig. 4.3.2).

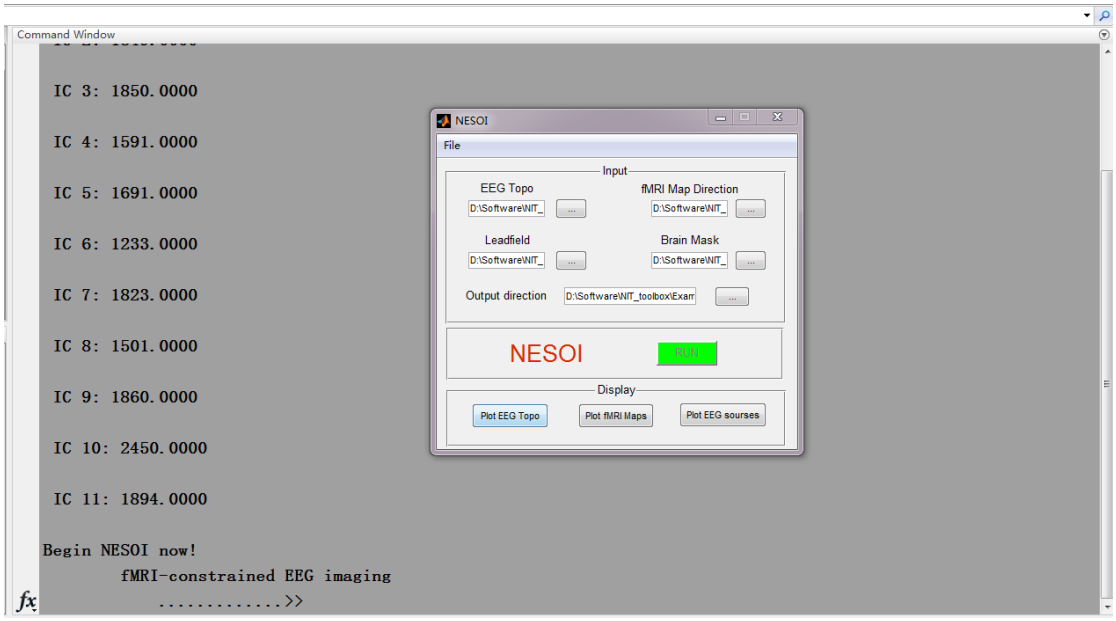


Fig. 4.3.2: NESOI is calculating.

4. The output results are MATALB *.mat files:

   gridICA.mat: The spatial distributions of fMRI priors. The dimension is the number of sources (dipoles) × the number of fMRI prioris (e.g. 6144 dipoles × 11 fMRI components).

   NESOI_results.mat: Source imaging results. The variable 'Phie' is the source result (e.g. 6144 dipoles × the number of EEG topographies), and the variable 'he' is hyper-parameter (e.g. 11 fMRI priors + 24 sparse priors = 35 priors × the number of EEG topographies).

   NESOI_Para.mat: Parameter settings of NESOI.

5. After completing the calculation, press the corresponding plot button in Display box (Fig. 4.3.3-4.3.5).

   Plot EEG Topo: Plot all EEG topographies. Press button Plot EEG Topo , then select channel location file (e.g. layout62.loc).

   Plot fMRI Maps: Press button Plot fMRI Maps to show the fMRI spatial distributions.

   Plot EEG sources: Press button Plot EEG sourses to show the EEG sources.

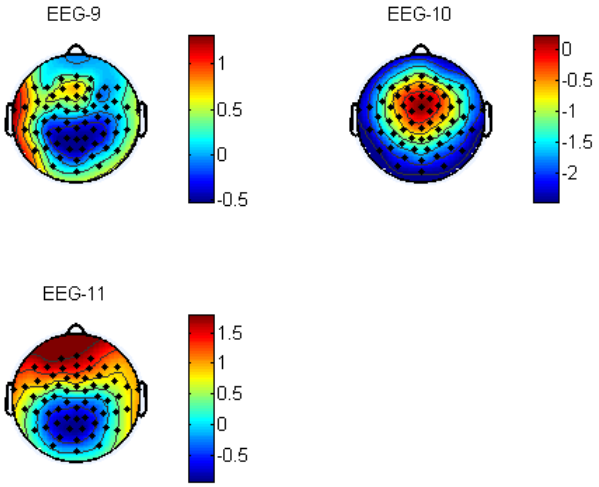


Fig. 4.3.3: EEG topographies.

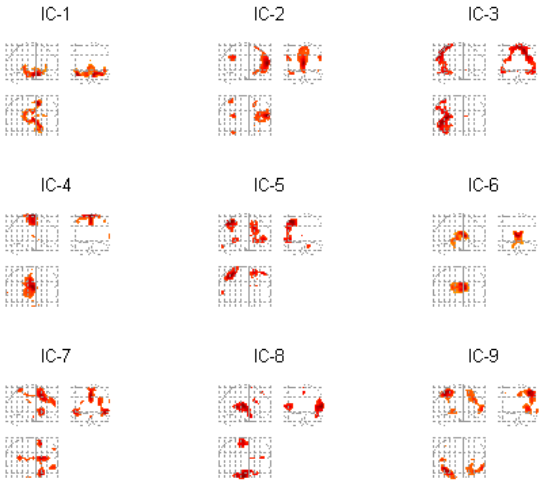


Fig. 4.3.4: The spatial distributions of fMRI functional networks.

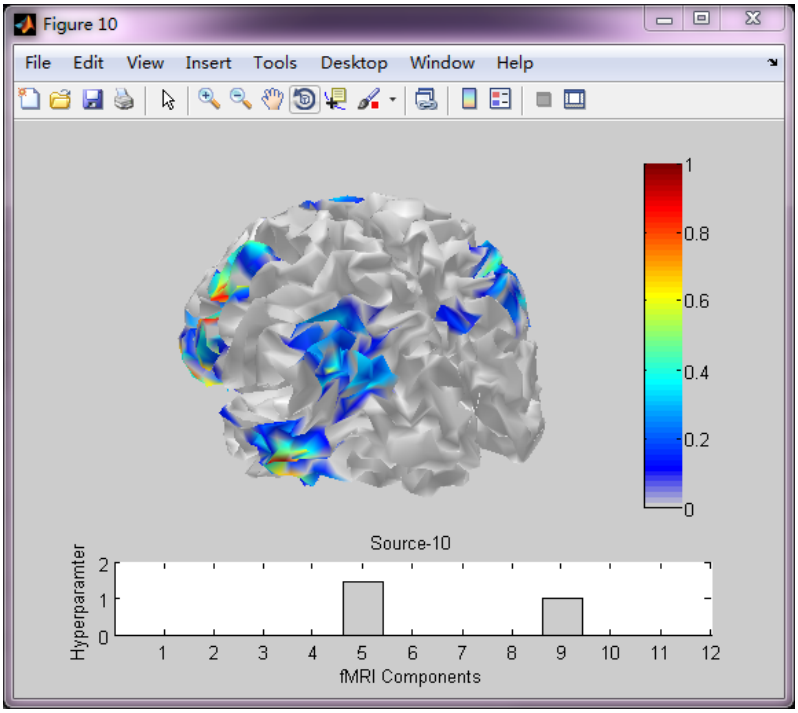


Fig. 4.3.5：The EEG source imaging result of an EEG topography (EEG-10). The upper is the EEG source, and below is hyper-parameters.

B. Note:

1. Advance option:

   In general, you can change these settings if necessary.

   Threshold: The spatial priors are locations in which the T-values or Z-values are above the threshold. Default is 3.

   Number of sparse priors: The number of sparse priors which contains right, left and bilateral hemispheres. Sparse priors are locations where are fMRI priors not included. Default is 8.

   - After clicking the 'Advance' button on NESOI main interface (Fig. 4.3.1), the advance interface will popup (Fig. 4.3.6).

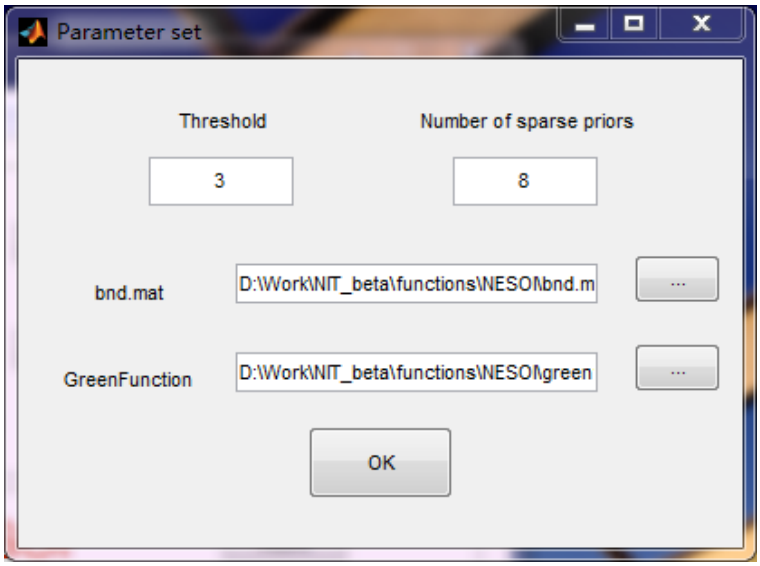


Fig. 4.3.6: NESOI advance interface.

- Fill the value in ‘Threshold’ input box such as 4 (using the same threshold for all fMRI components), or vector [4 4 4 4 4 4 4 4 4 4.5 4.5] (using the specific threshold for each fMRI component).
- Fill the number of sparse priors.
- Press ‘OK’.

2. Source：

In NIT, the assumed sources (6144 dipoles) are defined over a geometrically triangular grid based on the standard brain (Fig. 4.3.8).

- If use these sources (6144 dipoles), you should use the grid file to estimate lead field matrix. The grid file is provided in NIT: *\data\ soure_file.sor. The *.sor file contains the coordinates of nodes (first 3 columns → xyz) and corresponding normal vector directions (the last 3 columns → $x'y'z'$). The triangular grid file is *\functions\NESOI\bnd.mat which contains bnd.face, bnd.vert and bnd.discribe information.
- If you want to show or calculate the coordinates of dipoles, after clicking the ‘Dipoles’ in the ‘File’ and inputting the bnd.mat file and output direction; then, you can click the ‘SHOW’ button to show the dipoles and the ‘SAVE’ button to save the coordinates (Fig. 4.3.7). ‘Scale’ is the scale relative to unit triangular grid.

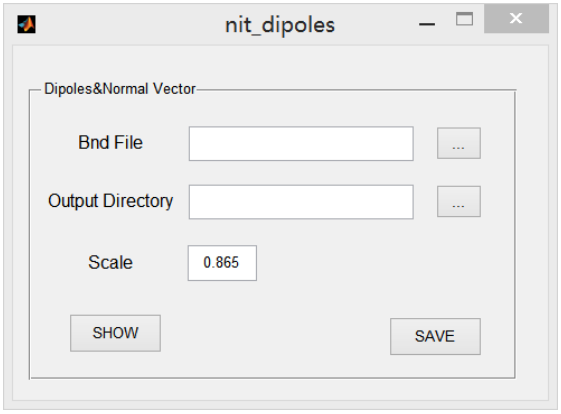


Fig. 4.3.7: interface of dipoles.

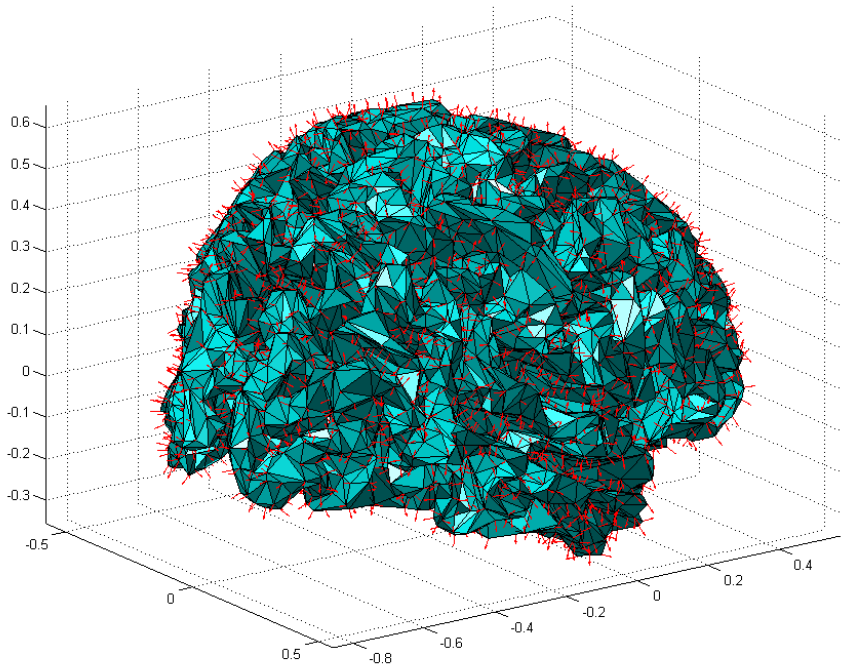


Fig. 4.3.8: The default geometrically triangular grid in NIT which is based on the standard brain and contains 6144 dipoles. Nodes and their normal vector directions are showed.

- If use user-defined EEG sources, you should recalculate the grid (bnd.mat) and Green function (greenfunction.mat), and replace them in advance options. Meanwhile, recalculate the coordinates of nodes and normal vector directions to generate the lead field matrix.

3. Other info
   - Some dipole coordinates (based on geometrically triangular grid showed in Fig. 4.3.8), electrode distribution and leadfield (based on three-shell spherical model) files are also provided in '~\NIT\data\':

     source_file.sor: The *.sor file contains the coordinates of nodes (first 3 columns: xyz) and corresponding normal vector directions (the last 3 columns: x'y'z').

     Layout_61Channels_10-20_BP.loc: Electrode distribution of BP Company based on 10-20 system (only contains EEG channels, 61 channels).

     Leadfield_61Channels_10-20_BP.xlsx: Leadfield (6144 dipoles × 61 channels) based on three-shell spherical model.

     Layout_62Channels_Curry7.loc: Electrode distribution of NeuroScan Company (Curry 7) based on 10-20 system (only contains EEG channels).

     Leadfield_62Channels_Curry7.xlsx: Leadfield (6144 dipoles × 62

channels) based on three-shell spherical model.

4.3.2 EEG-informed fMRI Analysis based on GLM

A. Step by step：

1. Click ‘GLM’ button, then the GLM GUI will popup (Fig. 4.3.9).

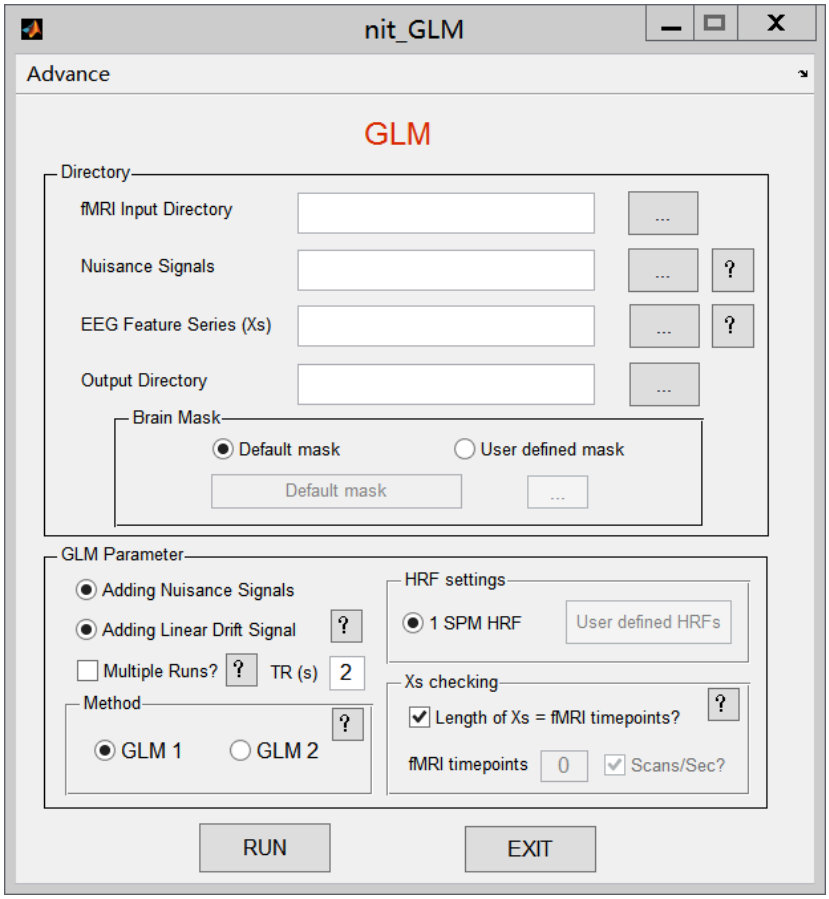


Fig. 4.3.9: GLM interface.

fMRI Input Directory: Directory of input data. The data are images files such as *.img and *.nii (NIFTI format). Support subfolders (multiple subjects) of a directory. The example directory is ‘*\ EEG_informed_fMRI_example_data\fMRI_data\’.

Nuisance Signals: Covariables in the linear regression model. For example, 6 head motion parameters gained from realignment (E.g. ‘*\EEG_informed_fMRI_example_data\HeadMotionPara’).

EEG Feature Series (Xs): The EEG feature series (such as epileptic discharge onset times, ERP amplitudes and power in specific band etc.) in the regression model (*.txt; or Office *.xls and *.xlsx file). Row is time points, and column is number of EEG features. As an example, information of EEG discharge time are provided (‘*\ EEG_informed_fMRI_example_data\discharge\’).

Output Directory: Output directory. E.g. '*\ EEG_informed_fMRI_example _results'.

Brain Mask: Select brain mask. Default is a standard brain mask generated from a probabilistic template. Here we use a user-defined brain mask. Select 'define mask', and press the button [...] to select the brain mask (*\EEG_informed_fMRI_example_data\brainmask.img).

Adding Nuisance Signals: Adding the covariables (such as head motion parameters) in regression model?

Adding Linear Drift Signal: Adding the linear drift signals in regression model?

Multiple Runs?: Multiple runs for each subject?

TR: Repeating time of fMRI (second).

Method: Select the method.

GLM1: General linear regression model. All of regressors are estimated in a regression model. This type is suitable for event or block design fMRI analysis.

GLM2: Design for investigating EEG discharge related BOLD response in epilepsy (Bagshaw et al., 2004). For each voxel, the fMRI data is being analyzed several times (once for each of the different HRFs), and the maximal T value is chosen to account for the activation of this voxel.

HRF settings: Default is a standard HRF generated by SPM (used in GLM1). If you want to change the shape of HRF or select method GLM2, uncheck the default option, and click the 'User defined HRFs'. Then, set the parameters you wanted, and show the HRF curve in the HRF interface (Fig. 4.3.10). Finally, press the 'SAVE' button to save the HRFs. Default HRFs in the HRF interface are Glover HRFs peak at 3, 5, 7, 9 s.

Xs checking: Checking whether Xs is matched to fMRI time courses. If the time points of Xs is equal to fMRI data, check the 'Xs is matched to fMRI?'; otherwise, please set the number of fMRI time points and the unit of Xs (scans or seconds).

As an example, simultaneous EEG-fMRI data of 2 FCMTE patients are provided. The discharges onset times from EEG and preprocessed fMRI data are directly provided. For each subject, 1 type of discharge onset times is included in 1 run. Here, select method 'GLM2', and HRFs are set as Glover HRFs peak at 3, 5, 7, 9 s (Fig. 4.3.10-11).

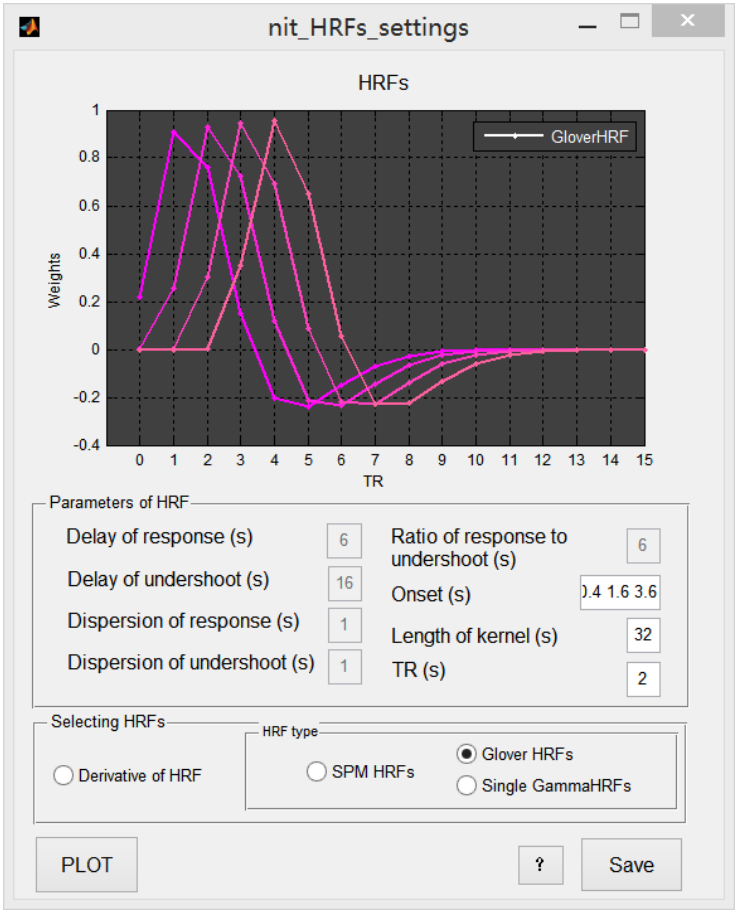


Fig. 4.3.10: HRF interface.

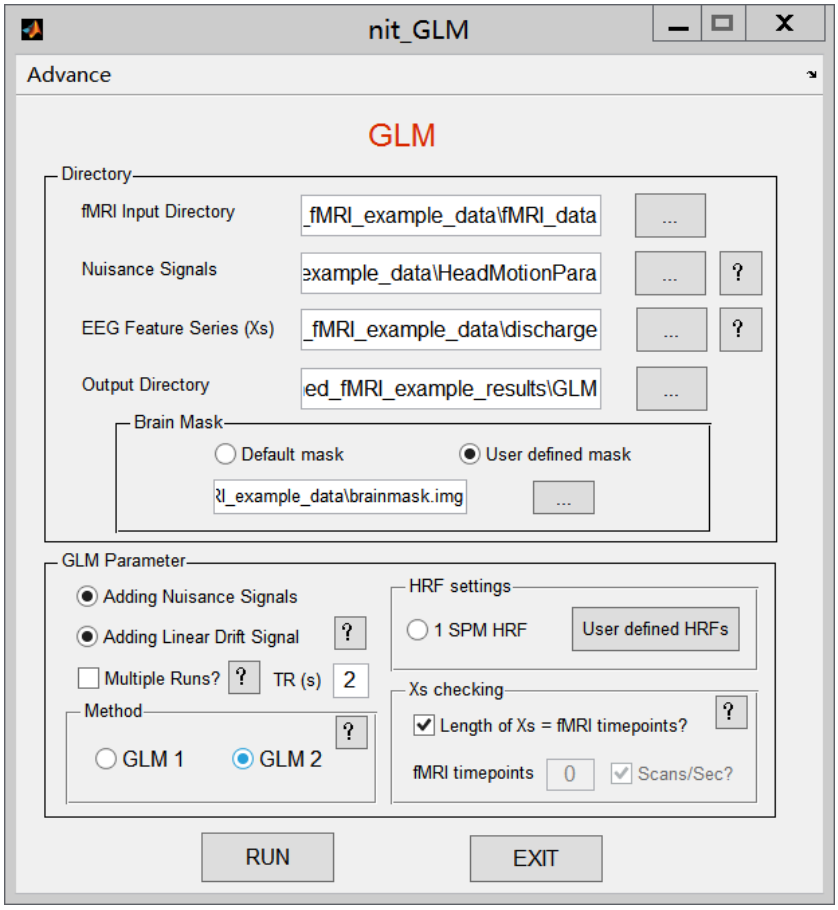


Fig. 4.3.11: GLM parameter settings.

2. Press ‘RUN’ button.
3. The outputs are:

   GLM_log.txt: Log file.

   GLM1:

   beta_*.nii: regression coefficients.

   GLM_results.mat: results file.

   ResMS*.nii: error variance.

   GLM2:

   Con_*.nii: contrast map for each EEG features.

   ConTval*.nii: T map for each contrast.

   GLM_results.mat: results file.

   ResMS*.nii: error variance.

The activation map of sub_01 is showed in Fig. 4.3.12.

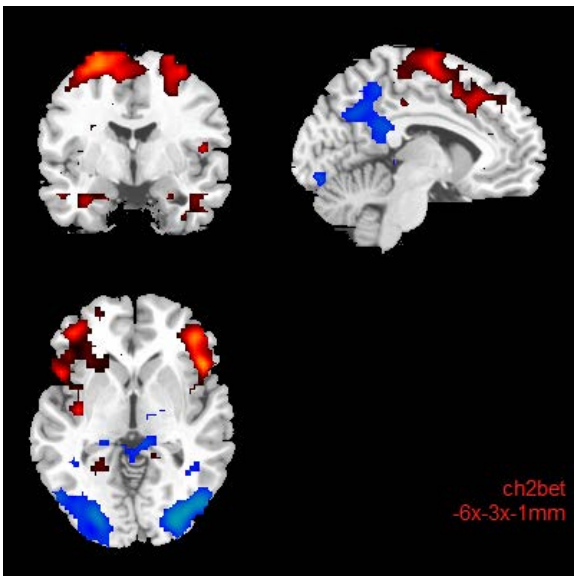


Fig. 4.3.12: The result of patient 1 in FCMTE data (GLM2). The threshold of T value is 3.

B. Note:

1. The fMRI time points of each subject can be unequal, only while the length of Xs (for each subject) is equal to the number of fMRI time points (i.e. must check 'Length of Xs = fMRI timepoints?').
2. The definition of design matrix in the GLM is showed in Fig. 4.3.13. The order of EEG features in each run must be consistent. If one feature is not included in one run, please input zeros to instead of them. After calculating, you can click 'DesignMatrix' in Advance, select GLM_results.mat file to show the design matrix (Fig. 4.3.14).
3. If you select GLM1, you can click 'SHOW' button to show the contrast, and click 'DONE' to save the T map corresponding to the contrast. If you select GLM2, you can only show the design matrix.
4. For each subject, time points of EEG features (Xs), nuisance signals and fMRI data must be consistent. If the Xs is the same for each subject, you can select a subject Xs file (e.g. event or block design task).
5. If you want to use different HRFs, please click 'SAVE' button in HRF interface before calculating. You can see the variable 'HRF' in Matlab work space after saving the HRFs.
6. Before GLM calculating, high-pass filter is used to remove low frequency fMRI noise (cut-off period in seconds is 128s), and global mean normalization is also conducted (i.e. data = 100*data/global mean). These settings are consistent with SPM8.

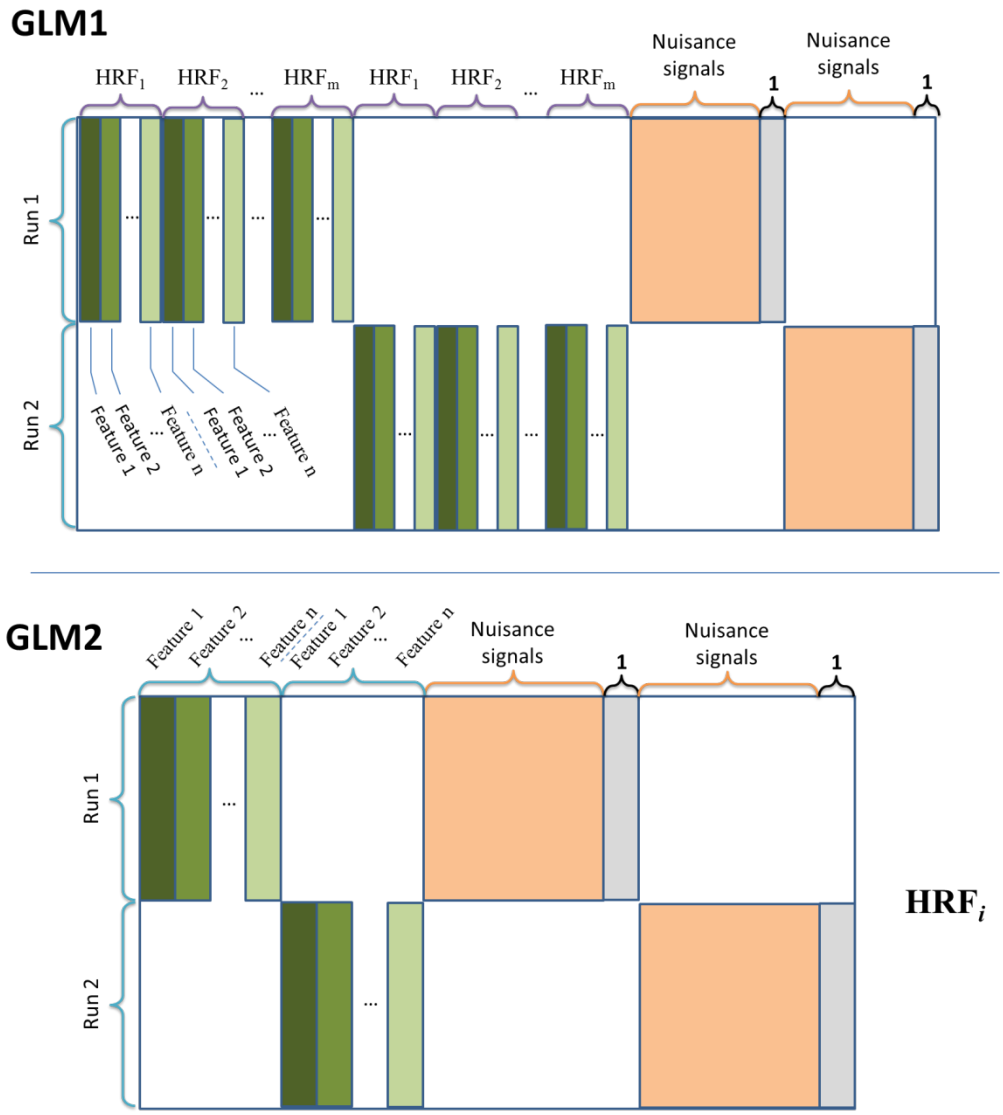


Fig. 4.3.13: Design matrix in GLM for one subject (2 runs, n EEG features and m HRFs). The design matrix of GLM1 is defined in the upper, and design matrix of GLM2 for each HRF is defined in the lower. Row in the design matrix is time points.

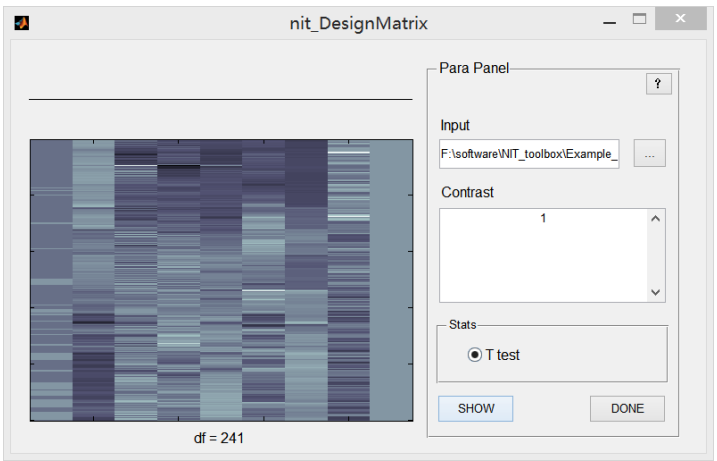


Fig. 4.3.14: Design matrix interface. From left to right, 1st column is Xs, 2nd-7th columns are 6 head motion parameters, 8th column is linear trend signal and the last

column is 1.

4.3.3 EEG-informed fMRI analysis based on LMSA

A. Step by step:

1. Press ‘LMSA’, then the LMSA GUI will popup (Fig. 4.3.15).

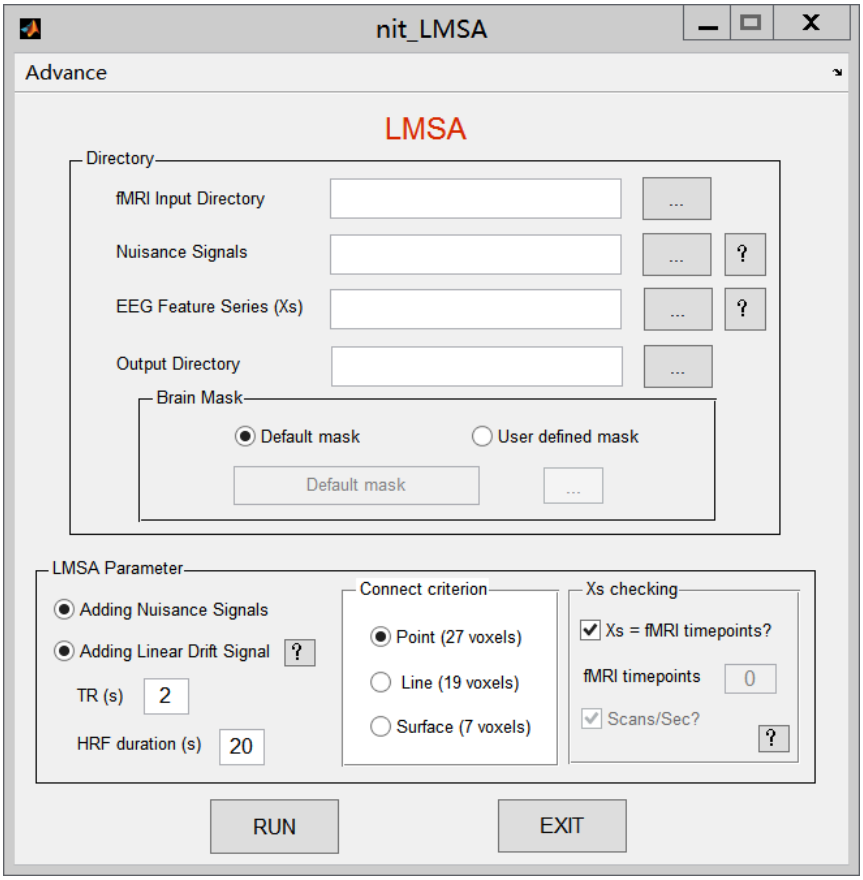


Fig. 4.3.15: LMSA interface.

fMRI Input Directory: Directory of input data. The data can be images files such as *.img and *.nii (NIFTI format). Support subfolders (multiple subjects) of a directory. The example directory is ‘*\EEG_informed_fMRI_example_data\fMRI_data’.

Nuisance Signals: Covariables in the linear regression model. For example, 6 head motion parameters obtained from Alignment step (E.g.‘*\EEG_informed_fMRI_example_data\HeadMotionPara’).

EEG Feature Series (Xs): The EEG feature series, such as epileptic discharge onset times, ERP amplitudes and power in specific band etc., in the regression model (*.txt; or Office *.xls and *.xlsx file). Row is time points, and column is number of EEG features. As an example, information of EEG discharge time are provided (‘*\EEG_informed_fMRI_example_data\discharge’).

Output Directory: Output directory. E.g. '*\ EEG_informed_fMRI_example _results'.

Brain Mask: Select brain mask. The default is standard brain mask generated from a probabilistic template. Here we use a user-defined brain mask. Select 'define mask', and press the button [...] to select the brain mask (*\EEG_informed_fMRI_example_data \brainmask.img).

Adding Nuisance Signals: Adding the covariables such as head motion parameters in regression model?

Adding Linear Drift Signal: Adding the linear drift signals in regression model?

TR: Repeating time of fMRI (second).

HRF duration: The duration of HRF, default is 20 s.

Connect criterion: The connect criterion is the definition of spatial voxel connection. 'Point': 26-connected neighborhood; 'line': 18-connected neighborhood and 'surface': 6-connected neighborhood. Default is 'point' criterion.

Xs checking: Checking whether Xs is matched to fMRI time courses. If the time points of Xs is equal to fMRI data, check the 'Xs is matched to fMRI?'; otherwise, please input the number of fMRI time points and the unit of Xs (scans or seconds).

As an example, simultaneous EEG-fMRI data of 2 FCMTE patients are provided. The discharges onset times from EEG and preprocessed fMRI data are directly provided. For each subject, 1 type of discharge onset times is included in 1 run. Here, we set TR = 2 s, HRF duration is 20 s and connection criterion is 'Point' (Fig. 4.3.16).

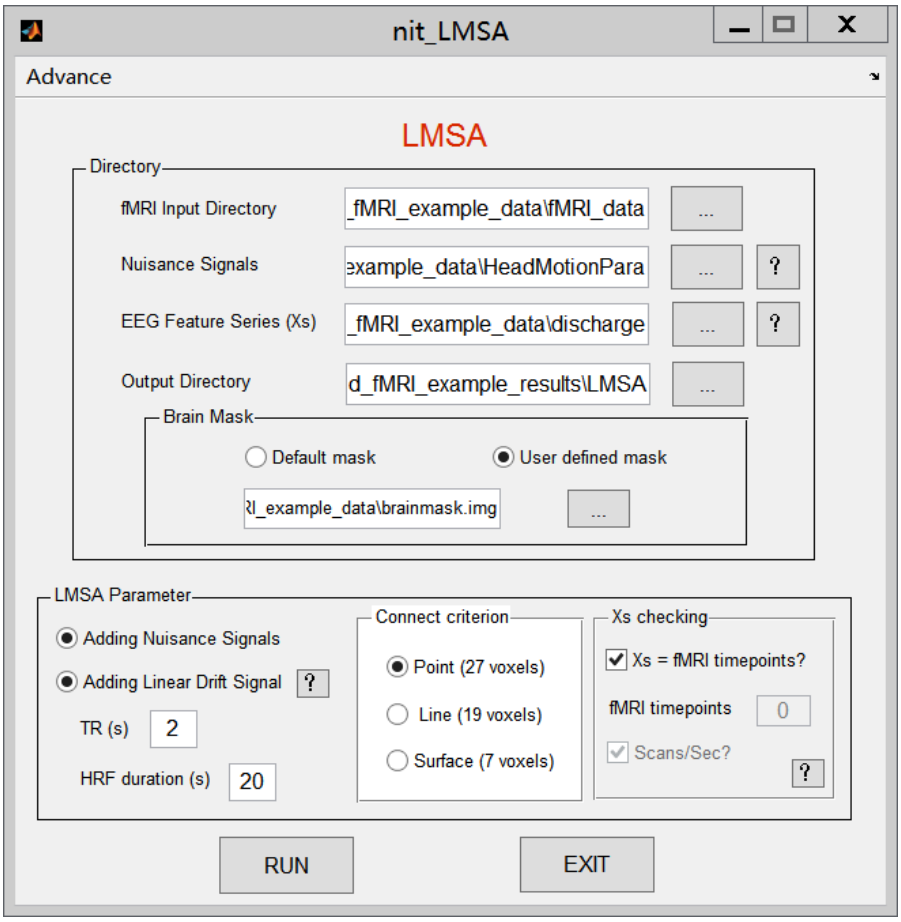


Fig. 4.3.16: LMSA parameter settings.

2. Press ‘RUN’.
3. The results are listed as:

LMSA_log.txt: Log file.

LMSA_results.mat: Results file.

beta*.nii: Regression coefficients of each EEG feature. You can use these files for second-level statistical analysis.

CanonicalCorr*.nii: Canonical correlation coefficients estimated by LMSA for each EEG feature.

F*.nii: F values corresponding to each canonical correlation coefficients.

Pval_F*.nii: P values of F values.

T*.nii：T values of regression coefficients estimated by LMSAfor each EEG feature.

The activation map of sub_01 is showed in Fig. 4.3.17.

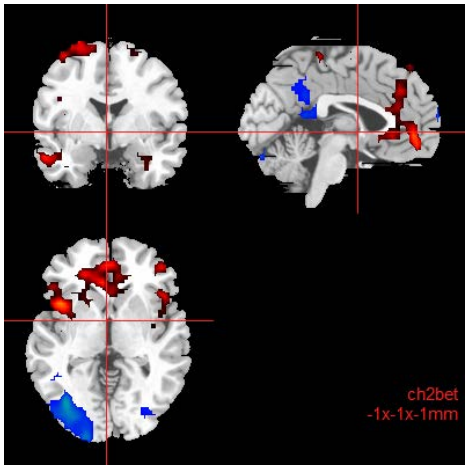


Fig. 4.3.17: The result of patient 1 in FCMTE data (LMSA). The threshold of T value is 3.

B. Note：

1. The fMRI time points of each subject can be unequal, only while the length of Xs (for each subject) is equal to the number of fMRI time points (i.e. must check 'Xs = fMRI timepoints?').
2. For each subject, time points of EEG features (Xs), nuisance signals and fMRI data must be consistent. If Xs is the same for each subject, you can select only one subject Xs file (e.g. event or block design task). One subject should contain only one run!
3. If you want to show the HRF of one voxel, you can click 'Plot HRF' button in 'Advance' option. Then, input MNI XYZ coordinates, LMSA_results.mat file, label of EEG feature and a image file (*.nii or *.img file used to read rigid transform matrix in header info). Finally, press 'PLOT' to show the HRF. The HRF of sub_01 in one voxel (MNI: [15, 30, 30]) is showed in Fig. 4.3.18.
4. Before LMSA calculating, global mean normalization is conducted (i.e. data = 100*data/global mean). This setting is consistent with SPM8.

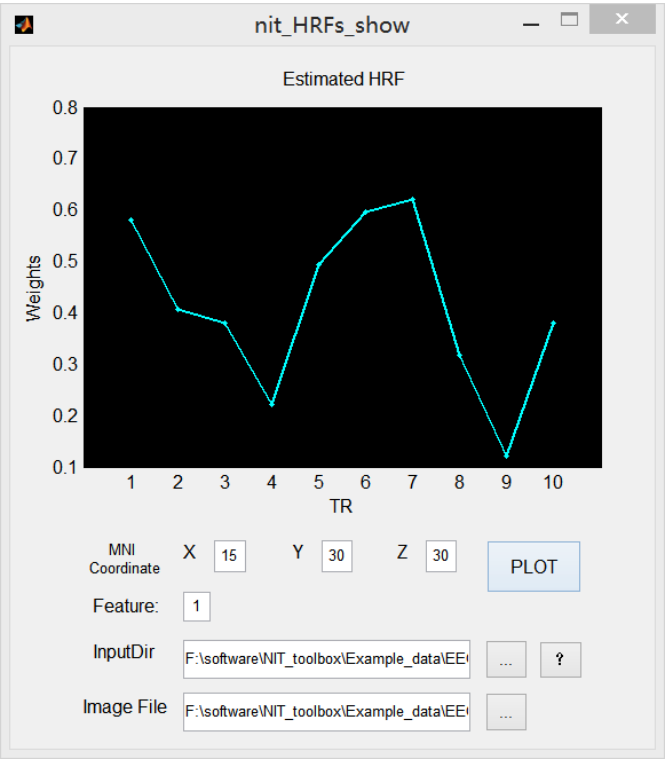


Fig. 4.3.18: The HRF of sub_01 in one voxel (MNI: [15, 30, 30]) estimated by LMSA.

4.4 Utilities

Click the pull-down menu ‘Utilities’ in NIT main interface, the utilities will popup (Fig. 4.4.1).

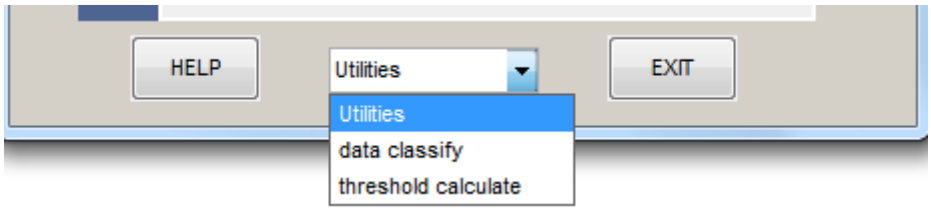


Fig. 4.4.1: Utilities interface.

4.4.1 DICOM data Classification

This toolkit will identify and classify the original DICOM files. NIT DO NOT make any change or move the original data, all operations (such as copy, move etc.) are only performed on copy data.

1. Press ‘data classify’, the interface will popup (Fig. 4.4.2-4.4.3).

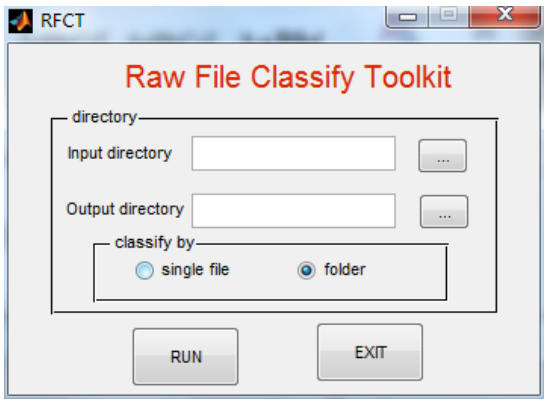


Fig. 4.4.2: Classification interface.

Input directory: Select directory of original DICOM files.

Output directory: Select output directory.

Option button: Select '**single file**' if one folder contains different types of DICOM files (e.g. DTI and fMRI data are in one folder). Select '**folder**' if one folder only contains one type of DICOM files (e.g. All images are fMRI data in one folder).

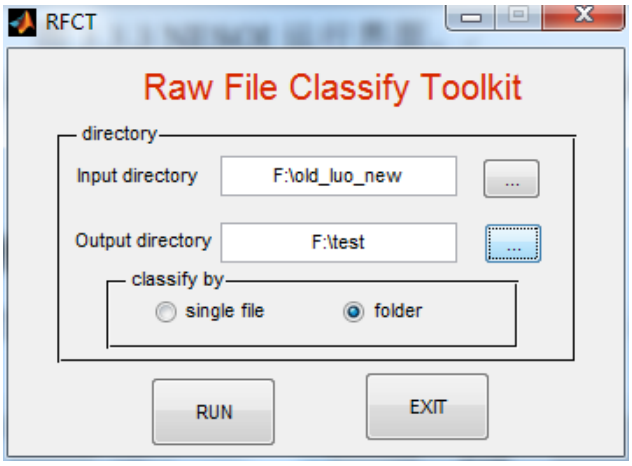


Fig. 4.4.3: The classification settings.

2. Press RUN button (Fig. 4.4.4).

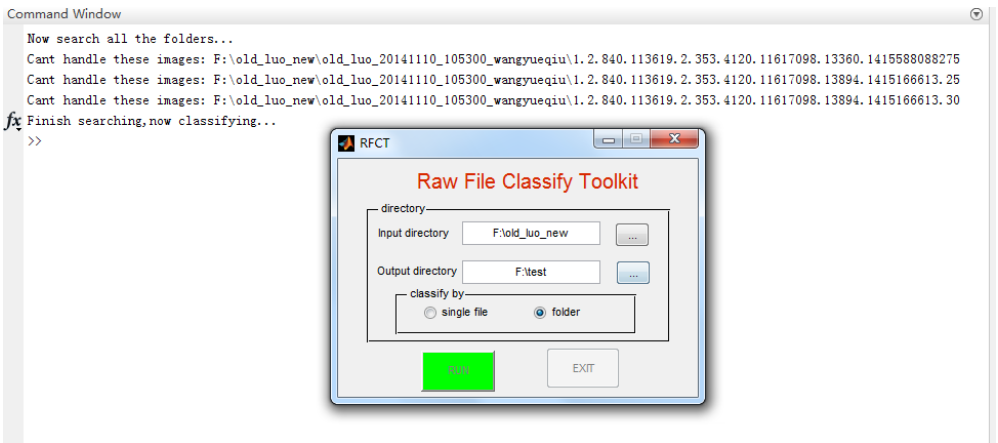


Fig. 4.4.4: Running interface.

4.4.2 Threshold calculation

Show the threshold of T maps corresponding to a P-value.

1. Press the ‘threshold calculate’ (Fig. 4.4.5).

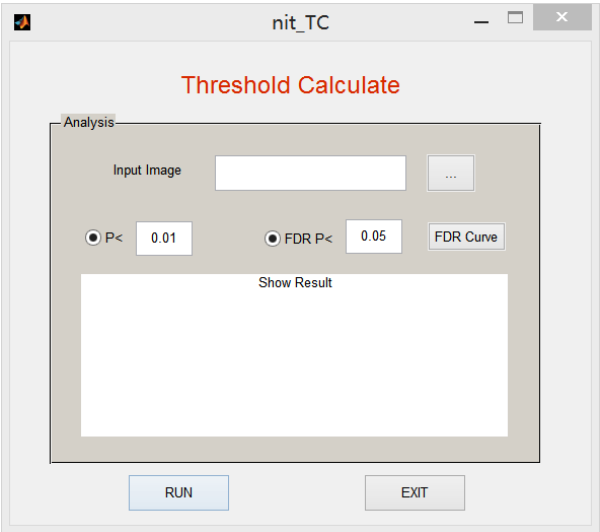


Fig. 4.4.5: The threshold calculation interface.

2. Select the T-map image in ‘Input Image’ box and press RUN button.
3. The one tail and two tails thresholds of T values (uncorrected and false discovery rate corrected) are showed. Click ‘FDR curve’ button will show the P-value curve (Fig. 4.4.6).

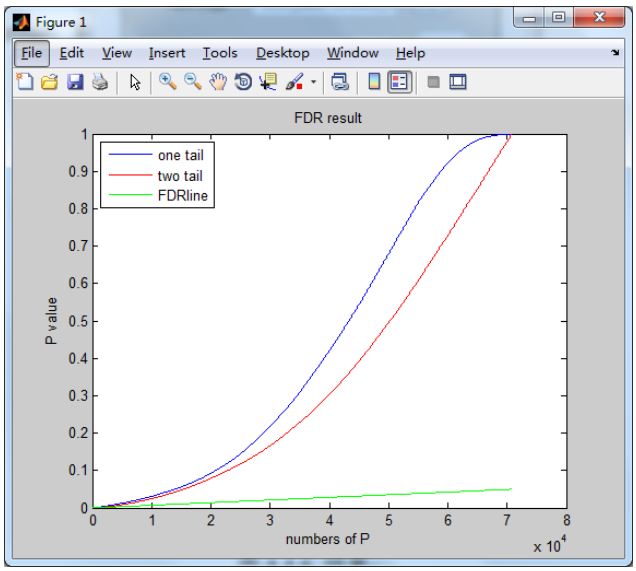


Fig. 4.4.6: The illustration of FDR curve. The horizontal axis is the number of P-values, and the vertical axis is P-values.

5. Appendix

5.1 Theories of main methods

5.1.1 NESOI

For the topography of each EEG IC, *Y*, we employ an Empirical Bayesian (EB) model (Lei et al., 2011; Phillips et al., 2005) for its underlying source distribution,

$$Y = L\theta + \varepsilon_1 \qquad \varepsilon_1 \sim N(0, T, C_1)$$

$$\theta = 0 + \varepsilon_2 \qquad \varepsilon_2 \sim N(0, T, C_2) \tag{5-1}$$

where $Y \in R^{n\times s}$ is the EEG topographies with *n* electrodes and *s* sampling points. $L \in R^{n\times d}$ is the known lead-field matrix calculated for the selected head model, and $\theta \in R^{d\times s}$ is the unknown distribution of *d* dipoles. $N(\mu, \mathrm{T}, \mathbf{C})$ denotes a multivariate Gaussian distribution with mean μ and covariance **C**. The terms ε_1 and ε_2 represent random fluctuations in channel and source spaces, respectively. These spatial covariances $\mathbf{C}_1$ and $\mathbf{C}_2$ are mixtures of covariance components at the corresponding levels. At the electrode space level, we assume $C_1 = \alpha^{-1} I_n$ to encode the covariance of electrode noise, where I_n is an $n\times n$ identity matrix. At the source space level, we express $\mathbf{C}_2$ as the covariance components,

$$C_2 = \sum_{i=1}^{k} \gamma_i V_i \tag{5-2}$$

where $\gamma \equiv [\gamma_1, \gamma_2, \ldots, \gamma_k]^T$ is a vector of *k* non-negative hyperparameters that control the relative contribution of each covariance basis matrix, $\mathbf{V}_i$. The Green function **G**, encodes the neighboring relationships among nodes of the cortical mesh defining the solution space. The *j*th column of the Green function matrix **G** is G_j, encoding neighboring patches weighted by their surface proximity (Friston et al., 2008).

NESOI employs two different kinds of covariance matrices: $\mathbf{V}_i^f$ and $\mathbf{V}_i^e$. $\mathbf{V}_i^f$ encodes the prior coherence pattern information derived from fMRI (Lei et al., 2011) and $\mathbf{V}_i^e$ encodes multiple sparse priors (Friston et al., 2008) that are sparsely sampled from a subspace of EEG source space that does not contribute to fMRI measurements. To derive $\mathbf{V}_i^f$, the intensity values in each fMRI IC are scaled to z scores. Voxels with absolute z scores >3 are considered to be activated. Negative z scores indicate that the BOLD signals are modulated oppositely to the IC waveform. A node in the EEG source space is assigned according to the z score of its nearest-neighbor fMRI voxel after spatial registration. All the activated nodes (absolute z scores >3) in each IC show similar temporal dynamics of the BOLD signal, thus we assume they have

similar properties for EEG signal generation. The simplest way to construct a covariance component from an IC is to set diagonal terms corresponding to activated nodes to 1, and set the rest to 0. NESOI takes into account the local coherence in source space and introduces the covariance component $\mathbf{V}_i^f$ as,

$$\mathbf{V}_i^f = \frac{1}{n_i}\sum_{j\in W(i)} G_j G_j^T \tag{5-3}$$

where W(i) is a set of activated nodes for ith IC, n_i is the cardinality of W(i), and G_j is the jth column of the Green function matrix **G**.
For the remaining source space outside the subspace generated by fMRI IC, multiple sparse priors (Friston et al., 2008) are employed:

$$\mathbf{V}_i^e = G_j G_j^T \tag{5-4}$$

where G_j is evenly sampled from the remaining subspace. In light of its location, this approach can denote right hemisphere components as G_j^{right}, and left ones as G_j^{left}. Furthermore, homologues are added to form a bilateral component, $G_j^{both} = G_j^{right} + G_j^{left}$, which models correlated sources in the two hemispheres.

In summary, the spatial priors for NESOI consist of two parts: fMRI IC and multiple sparse priors (Friston et al., 2008). The effective number of fMRI ICs is automatically selected using an EB model optimization procedure. After the optimization convergence, the conditional source estimate $\dot{\theta}$ is the Maximum a Posteriori (MAP) estimate, or equivalently, the weighted minimum norm, the Tikhonov solution, and is given by:

$$\theta = \alpha \mathbf{C}_2 \mathbf{L}^T \left(\alpha \mathbf{L}\mathbf{C}_2\mathbf{L}^T + \mathbf{I}_n\right)^{-1} Y \tag{5-5}$$

Finally, above problem is solved by ReML (restricted maximum likelihood) method, and the obtained hyperparameter γ_i encodes the link between W(i) (the i^{th} fMRI IC) and Y (the topography of an EEG IC). The flowchart can be seen in Fig. 5.1.1:

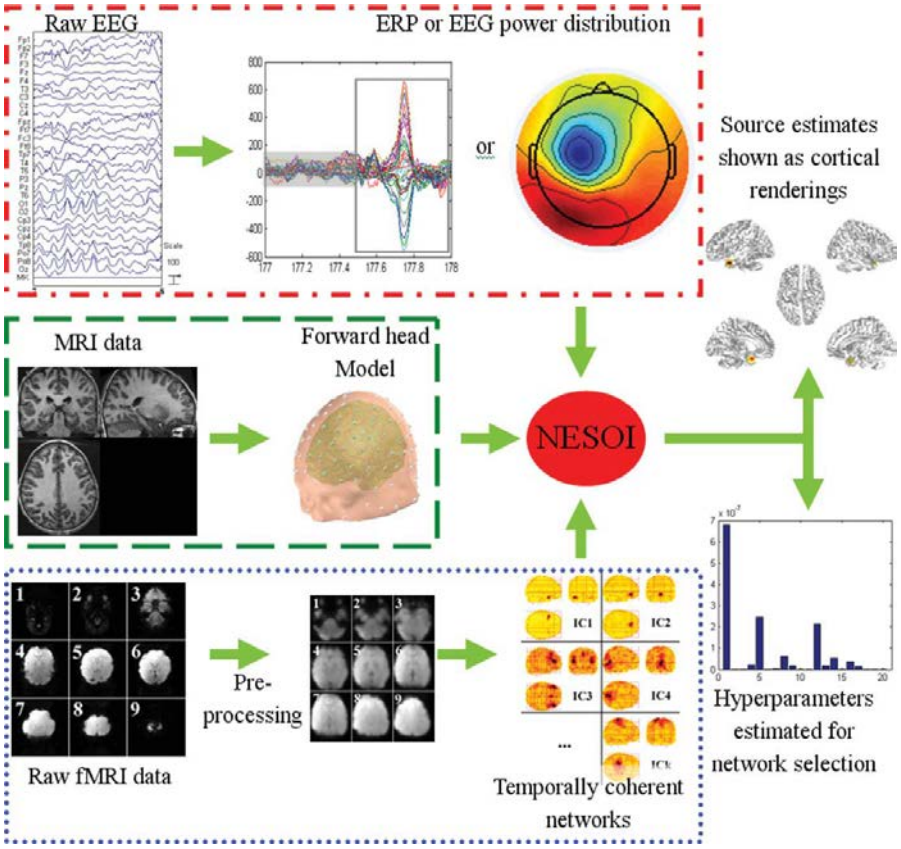


Fig. 5.1.1: Schematic representation of NESOI. The raw EEG data is processed for artifact-rejection and the amplitude and/or other features of interest are extracted. The corresponding fMRI data are pre-processed and separated into spatially independent components. The structural MRI is segmented to provide a forward model for EEG imaging. The intensity of the neural electric sources and the hyperparameters are iteratively estimated by NESOI.

5.1.2 FOCA

For image data, a time series of a given voxel with those of its nearest neighbors (26 voxels) can be obtained (Fig. 5.1.2a), and a FOCA value assigned to the given voxel can be calculated by the following procedure (Fig. 5.1.2b). In the temporal correlation aspect, C_t is defined as the mean of the cross-correlation coefficients of the local voxels and is given in the equation below

$$C_t = \left| \frac{\sum_{i<j}^{N} r_{ij}^t}{N} \right|; N = \frac{k(k-1)}{2} \tag{5-6}$$

where r_{ij}^t is Pearson's correlation coefficient between voxel *i* and voxel *j*, and *k* is the number of voxels in the local region (27 voxels). On the other hand, for the local spatial distribution in the *m*-th time point, a spatial correlation between distributions in the neighboring time point is defined as following equation

$$\overline{r}_m^s = \frac{r_{m,m-1}^s + r_{m,m+1}^s}{2} \tag{5-7}$$

where r is Pearson's correlation coefficient and m is the m-th time point. The mean spatial correlation (C_s) across all time points is given in the equation below

$$C_s = \left| \frac{\sum_{m=1}^{N_t} \overline{r}_m^s}{N_t} \right| \tag{5-8}$$

where N_t is the number of time points. Then (Fig. 5.1.2c), the FOCA value is defined as

$$FOCA = C_t * C_s \tag{5-9}$$

Finally, the FOCA value for every voxel can be calculated by equation (5-9) to form FOCA maps. In order to reduce the effect of individual variability, we also normalized the FOCA value of each voxel by dividing it by the mean FOCA of the whole brain for each subject, that is

$$FOCA_{norm} = \frac{FOCA}{mean\left(FOCA\right)} \tag{5-10}$$

In brief, there are several advantages for FOCA measure. 1), FOCA measure integrates both temporal and spatial information in a local brain region; therefore, it is more flexible to characterize the local spontaneous activity. It emphasizes temporal homogeneity of local adjacent voxels, and regional stability of brain activity states (local functional states) between neighboring time points. The larger the FOCA value (value from 0 to 1) is, the higher the consistency of local spontaneous activity. 2), it is a data-driven method without prior knowledge and practical choices of the key parameter settings. 3), it has a good reproducibility and reliability.

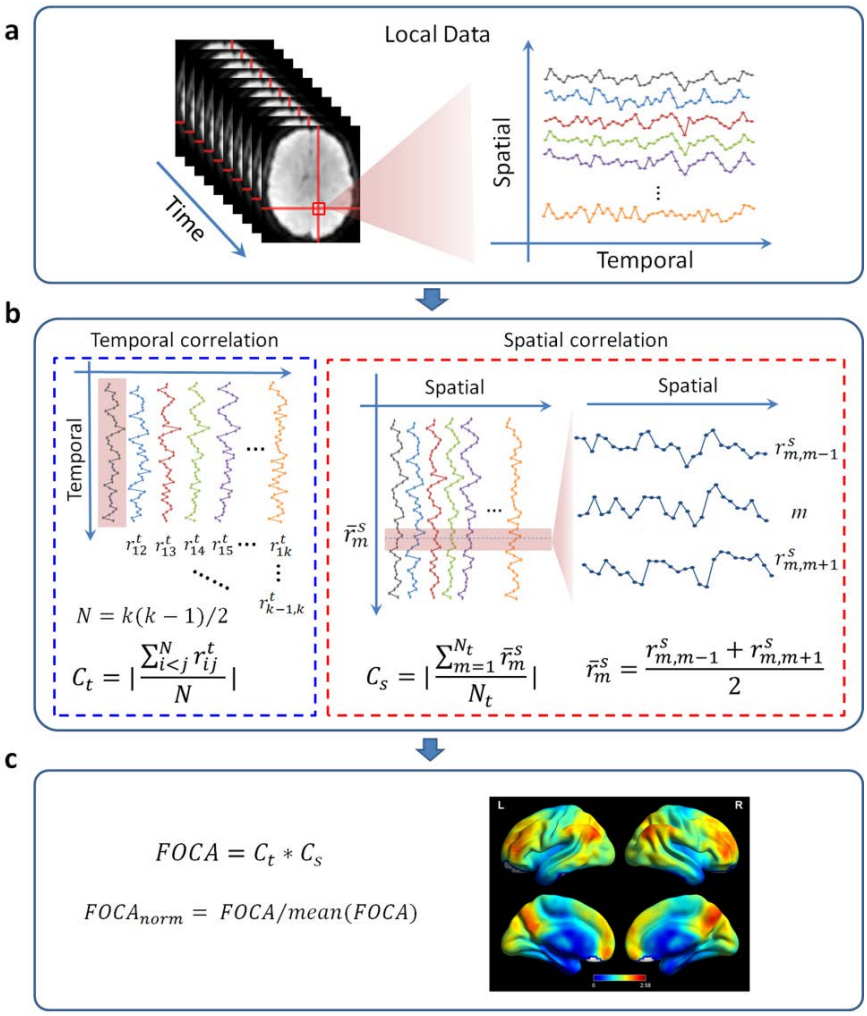


Fig. 5.1.2: Framework of FOCA. **a**: spatial and temporal series of a given voxel with those of its nearest neighbors (26 voxels in general) were obtained from fMRI data. **b**: temporal correlation (C_t) and spatial correlation (C_s) are calculated in parallel. For C_s (though here we just show window with ± 1 TR (m - 1, m, m + 1)), various durations of neighboring time could be considered (for example, from ± 1 TR to ± 8 TR in the following test). **c**: FOCA is defined as $C_s \cdot C_t$ and normalized.

5.1.3 LMSA

Here, we demonstrate a new method that is serially fusing EEG and fMRI in the local region to efficiently capture the potential brain functional activities. This method is called the local multimodal serial analysis (LMSA).

As an example, we are formally considering the two following multimodal data, EEG and fMRI data (Fig. 5.1.3). For fMRI data, $\mathbf{Y} \in R^{M \times N}$ where M is the number of time points and N is the number of voxels, time courses of i-th voxel $y_i \in R^{M \times 1}$ and its neighboring voxels (26 voxels) can be defined as matrix $\mathbf{Y}_i$. For EEG data,

the lagged discharge function matrix, $\mathbf{X}$ (also named lagged matrix which contains the onset times related to the epileptic discharges and downsampled to fMRI time scale), can be given as:

$$\mathbf{X}=\begin{bmatrix} x_1 & 0 & \cdots & 0 \\ x_2 & x_1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ x_k & x_{k-1} & \dots & x_1 \\ \vdots & \vdots & \vdots & \vdots \\ x_M & x_{M-1} & \dots & x_{M-k+1} \end{bmatrix} \tag{5-11}$$

where M is the number of time points which is matched to fMRI data, and *k* is the number of the lagged time points. First, the maximal correlations between these two data sets, $\mathbf{Y}_i$ and $\mathbf{X}$, can be solved by canonical correlation analysis, which finds the matrices of weights $\mathbf{a}$ and $\mathbf{b}$ such that the linear combinations $\mathbf{Y}_i * \mathbf{a}$ and $\mathbf{X} * \mathbf{b}$ maximize the pair-wise correaltions across the two data sets, that is:

$$\begin{aligned} &\underset{\mathbf{a},\mathbf{b}}{maximize}\ \ \mathrm{Corr}_{\mathbf{Y}_i*\mathbf{a},\mathbf{X}*\mathbf{b}} \\ &subject\ to\ \ \mathrm{var}\left(\mathbf{Y}_i * \mathbf{a}\right) = \mathrm{var}\left(\mathbf{X} * \mathbf{b}\right) = \mathbf{1} \end{aligned} \tag{5-12}$$

where var (.) is the variance and $\mathrm{Corr}_{(.,.)}$ is Pearson correlation. Then, the significant canonical variate, $v_i = \mathbf{X} * \pm\mathbf{b}_1$ (v_i and $\mathbf{b}_1$ is column vector, and the sign, $\pm$, is determined by sign of maximal absolute value in $\mathbf{b}_1$) which is corresponding to the maximal canonical correlation coefficient, is obtained. The HRF in the local region is also estimated by weight $\pm\mathbf{b}_1$. Next, a multiple linear regress model is utilized to estimate the activity of the voxel *i*, that is,

$$y_i = [v_i\ \mathbf{v}_{\mathrm{cov}}] * [\beta_i\ \beta_{\mathrm{cov}}] + \varepsilon \tag{5-13}$$

where β_i (*i*-th element) and β_{cov} (column vector) are the regression coefficients, v_i is canonical variate related to the maximal correlation between EEG and fMRI data sets, $\mathbf{v}_{\mathrm{cov}}$ is nuisance covariate matrix contained headmotion and linear trend signals during fMRI recording, and ε is residual error. And, the regression coefficient β_i which represents the activity intensity of voxel *i* can be estimated by the following formula,

$$[\hat{\beta}_i\ \hat{\beta}_{\mathrm{cov}}] = [v_i\ \mathbf{v}_{\mathrm{cov}}]^{+} * y_i \tag{5-14}$$

where $[.]^{+}$ is the pseudoinverse operator. Finally, above-mentioned procedure is performed for all voxels, and the T-map of all estimated regression coefficients, $\hat{\beta} \in R^{N\times 1}$, can be calculated by following formula,

$$T = \frac{\hat{\beta}}{SE(\hat{\beta})} \tag{5-15}$$

where $SE(\cdot)$ is standard error corresponding to $\hat{\beta}$.

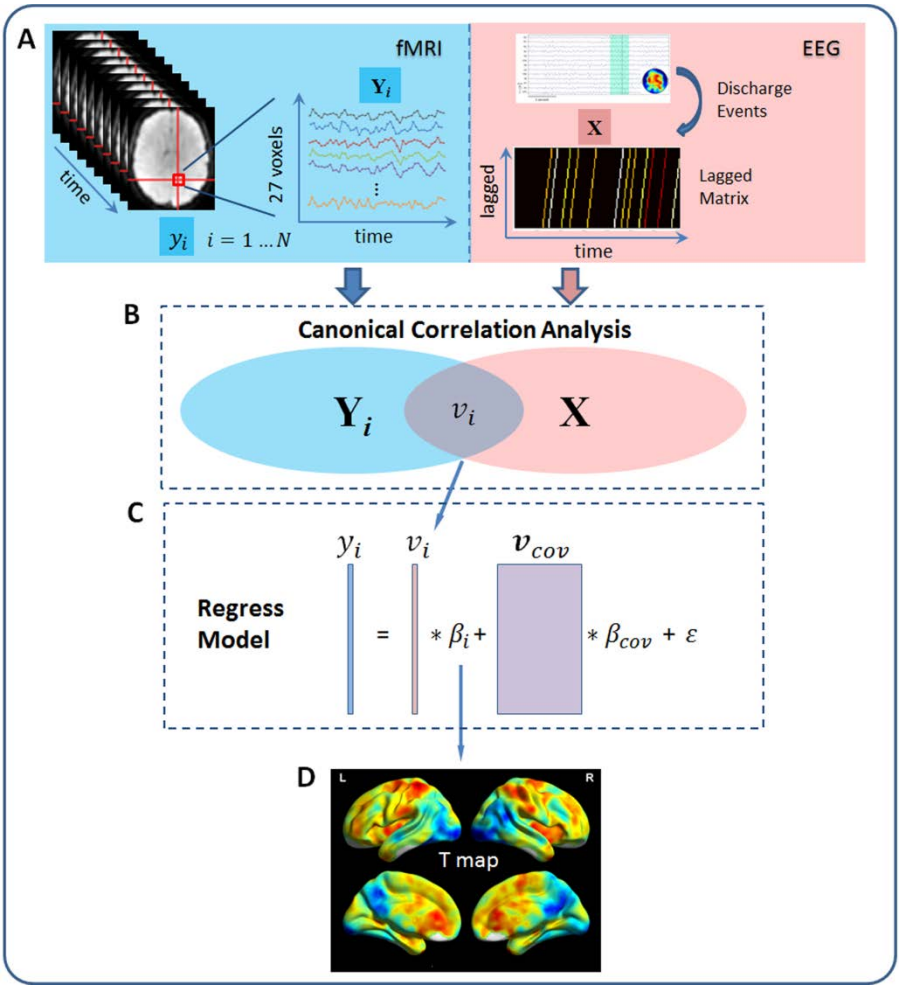


Fig. 5.1.3: The framework of local multimodal serial analysis. A: Time courses of *i*-th voxel and its neighboring 26 voxels, Y_i, are obtained from fMRI data, and the lagged function matrix of discharge onsets, X, is also obtained from EEG data. B: Canonical correlation analysis is utilized to obtain the canonical variate (v_i) which is corresponding to the maximal correlation between EEG and fMRI data sets. C: the activity intensity (β_i) is estimated by the multiple linear regress model where v_{cov} are nuisance covariates such as headmotion and linear trend signals during fMRI recording. D: The above-mentioned procedure is performed for the whole brain, and

the T-map of estimated β_i can be finally obtained.

5.2 Copyright:

All copyrights of the NIT software are reserved by the Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China. This software is for non-commercial use only. It is freeware but not in the public domain.

5.3 Version release

NIT v1.1 (20160512):

- ✓ Can load 4D functional images (.img/.nii).
- ✓ Parallel computing for fMRI preprocessing, FOCA calculating and nuisance signals removing.
- ✓ NOT require to add SPM8 toolbox in MATLAB for fMRI preprocessing. The preprocessing functions of SPM8 are extracted and integrated in NIT toolbox;
- ✓ Print details of fMRI preprocessing parameters in the log file.
- ✓ Add a preprocessing: 'realignment -> EPI normalise -> smooth';
- ✓ Debug the program of smooth. Debug the program of preprocess 2 (sliece timing -> Alignment -> T1Seg Normalise -> smooth);
- ✓ If fMRI preprocessing is interrupted at a certain step, you can re-calculate data from interrupted step;
- ✓ Save the HRFs in MATLAB work space, while using the GLM in NIT;
- ✓ Normalize (global mean normalization, data = 100*data/global mean) fMRI data before conducting LMSA/GLM analysis. The mean is estimated after discounting voxels outside the object using a criteria of greater than > (global mean)/8 (SPM8 criteria).
- ✓ Use high-pass filter to removes low frequency confounds for fMRI data before conducting GLM analysis. The cut-off period in seconds is fixed at 128s (SPM8 default).
- ✓ Debug the output images of GLM (fix the pinfo = [1;0;0] and dt = [16,0]).
- ✓ Parallel computing is realized for parallel computing command in MATLAB 2010-2015 ('matlabpool' for MATLAB 2010-2014; 'parpool' for MATLAB 2015).
- ✓ Add EEG toolbox for extracting features from cleaned EEG data, including event onsets, power and ERP amplitudes, marking interested events (e.g. epileptic discharges) in EEG data and displaying EEG data etc;
- ✓ Revise the English and Chinese manual of NIT;
- ✓ Debug and optimize the codes.

NIT v1.0 (20150604):

- ✓ Batch processing of the fMRI data analysis;
- ✓ Data preprocessing based on SPM8; Need to add path of SPM8 toolbox to Matlab

first.

- ✓ Removing nuisance signals from fMRI data such as linear trend, head motion, white, CSF and global signals, and band-pass filtering;
- ✓ Calculating functional connectivity density (FCD);
- ✓ Calculating FOur dimensional (spatio-temporal) Consistency of local neural Activities (FOCA);
- ✓ EEG-fMRI fusion: 1) fMRI-informed EEG analysis (NEtwork-based SOurce Imaging, NESOI); 2) EEG-informed fMRI analysis.
- ✓ Identify and classify original DICOM data;
- ✓ Viewing threshold of T-map.

5.4 Websites:

NIT download:
http://www.neuro.uestc.edu.cn/NIT.html

The Key Laboratory for NeuroInformation of Ministry of Education:
http://www.neuro.uestc.edu.cn/index.html

The download page in the Key Laboratory for NeuroInformation of Ministry of Education:
http://www.neuro.uestc.edu.cn/neuro/html/achievements/achievements.html

SPM main page:
http://www.fil.ion.ucl.ac.uk/spm/

SPM8 download page:
http://www.fil.ion.ucl.ac.uk/spm/software/spm8/

EELAB main page:
http://sccn.ucsd.edu/eeglab/index.html

MRIcromain page:
http://www.mccauslandcenter.sc.edu/mricro/

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2. Thanks the SPM, EEGLAB, MRIcro and DPARSF software.

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