

# WMFPrep Manual

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*A toolbox for brain white-matter function preprocessing*

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## Contents

1 Overview .....	3
2 Installation .....	5
3 Preprocessing.....	6
3.1 Path and Repetition time (TR) .....	6
3.2 DICOM to NIFTI.....	8
3.3 Remove first n time points .....	9
3.4 Slice timing .....	10
3.5 Realign.....	11
3.5 T1 preprocessing.....	12
3.6 Nuisance covariates regression .....	14
3.7 Apply white mask to EPI.....	16
3.8 Normalize .....	17
3.9 Group white matter region .....	18
3.10 Smooth .....	20
3.11 Detrend .....	21
3.12 Filter.....	22
3.13 Run.....	23

# 1 Overview

Recent studies have explored white-matter functional information during resting-state functional magnetic resonance imaging (rs-fMRI). However, user-friendly toolbox for “pipeline” data analysis of white-matter function based on rs-fMRI is still lacking. WMFPrep is a MATLAB toolbox, with an easy, flexible and quick manner, for functional preprocessing within brain white-matter (WM).

WMFPrep is openly available at <https://github.com/weiliao81/WMFPrep>.

WMFPrep is developed in MATLAB (The MathWorks Inc., Natick, MA, US), based on some functions in Statistical Parametric Mapping 12 (SPM, <http://www.fil.ion.ucl.ac.uk/spm/>) and Resting-State fMRI Data Analysis Toolkit (RESTplus, <http://www.restfMRI.net/forum/restplus>), under a 64-bit Windows (Microsoft Corp., Redmond, WA, US) environment. This toolbox runs in MATLAB 2014a or higher, including Windows (8, 10 and Server versions), and Linux (Ubuntu and CentOS) in 64-bit versions.

Please cite WMFPrep as these papers (Li et al., 2019, 2020a, 2020b; Ji et al., 2017) while using the toolbox to preprocess WM functional data based on rs-fMRI.

References:

- Ji, G.-J., Liao, W., Chen, F.-F., Zhang, L., Wang, K., 2017. Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise. *Science Bulletin* 62, 656–657. <https://doi.org/10.1016/j.scib.2017.03.021>
- Li, J., Biswal, B.B., Wang, P., Duan, X., Cui, Q., Chen, H., Liao, W., 2019. Exploring the functional connectome in white matter. *Hum Brain Mapp* 40, 4331–4344. <https://doi.org/10.1002/hbm.24705>
- Li, J., Biswal, B.B., Meng, Y., Yang, S., Duan, X., Cui, Q., Chen, H., Liao, W., 2020a. A neuromarker of individual general fluid intelligence from the white-matter functional connectome. *Transl Psychiatry* 10(1): 147. <https://doi.org/10.1038/s41398-020-0829-3>
- Li, J., Chen, Heng, Fan, F., Qiu, J., Du, L., Xiao, J., Duan, X., Chen, Huaifu, Liao, W., 2020b. White-matter functional topology: a neuromarker for classification and prediction in unmedicated depression. *Transl Psychiatry* 10(1): 365. <https://doi.org/10.1038/s41398-020-01053-4>

## 2 Installation

1) Run Matlab. (A version of R2014a or above is recommended)

2) Add WMFPrep, SPM12 and RESTplus path to Matlab search path:

Click 'File' in Matlab menu --> Click 'Set Path' --> Click 'Add with Subfolders...'

button in the popup dialog --> Select the 'WMFPrep', 'SPM12' and 'RESTplus' folders on the machine --> Click 'OK' button --> Click 'Save' Button.

3) Run WMFPrep.m

Type 'WMFPrep' in the command window of Matlab. You can find the interface below (Fig. 1) after successfully running the WMFPrep.

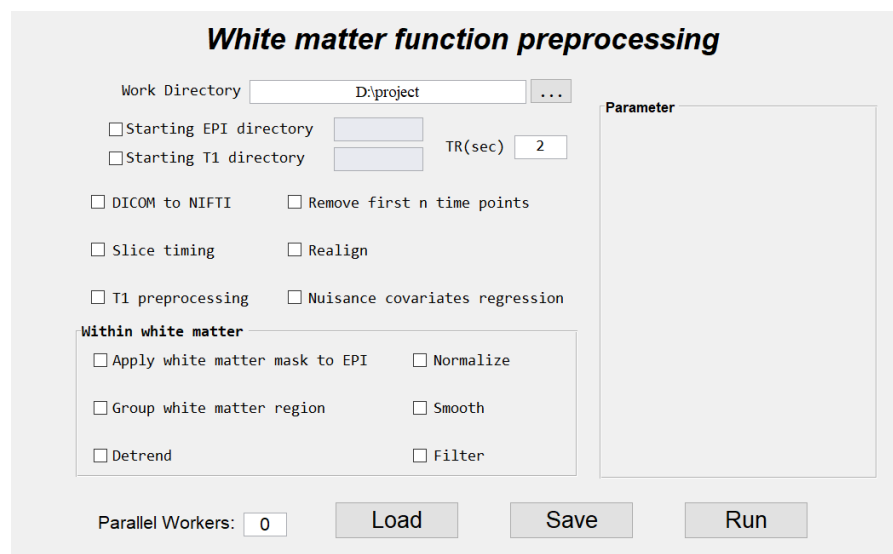


Fig. 1 The main window of WMFPrep.

## 3 Preprocessing

### 3.1 Path and Repetition time (TR)

**White matter function preprocessing**

Work Directory: D:\project

☐ Starting EPI directory

☐ Starting T1 directory

TR(sec): 2

☐ DICOM to NIFTI

☐ Remove first n time points

☐ Slice timing

☐ Realign

☐ T1 preprocessing

☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI

☐ Normalize

☐ Group white matter region

☐ Smooth

☐ Detrend

☐ Filter

Parallel Workers: 0

Load Save Run

Parameter

Fig. 2 The Path and TR settings of WMFPrep.

#### Input:

- (1) Work Directory: Set the path of the project, which contains the fMRI and MRI data.
- (2) Starting EPI directory: Check the check box and enter the folder name of the fMRI data in the text box. The directory includes N (i.e., the number of subjects) subfolders, and each subfolder includes the functional data of the subject.
- (3) Starting T1 directory: Check the check box and enter the folder name of the MRI data in the text box. The directory includes N (i.e., the number of subjects) subfolders, and each subfolder includes the anatomical data of the

subject. Notably, the name of the subfolders should be consistent with EPI directory.

- (4) TR: TR is the amount of time that passes between consecutive acquired brain volumes. The value (in seconds) is used for slice timing correction and filtering. A specific TR value should be set in the text box.

## 3.2 DICOM to NIFTI

**White matter function preprocessing**

Work Directory  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ **DICOM to NIFTI** ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

**DICOM to NIFTI**

☐ EPI DIOCM to NIFTI

☐ T1 DIOCM to NIFTI

Parallel Workers:

Fig. 3 The settings of DICOM to NIFTI.

Convert DICOM format to NIFTI format.

### Input:

- (1) EPI DICOM to NIFTI: Convert fMRI DICOM data format to NIFTI data format.
- (2) T1 DICOM to NIFTI: Convert MRI DICOM data format to NIFTI data format.

### Output folder:

- (1) FunName (The name of the fMRI folder) '**H**';
- (2) T1Name (The name of the MRI folder) '**H**'.



### 3.3 Remove first n time points

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☒ Remove first n time points

☒ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

Parallel Workers:

**Remove first n time points**

Remove time points number:

Fig. 4 The setting of Remove first n time points.

Remove first n (i.e., 1 to n) time points of fMRI data.

#### Input:

Remove time points number: set the number of time points that will be removed.

#### Output folder:

FunName 'T'.

### 3.4 Slice timing

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☒ **Slice timing** ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

**Slice timing**

Slice number

Slice order

Reference slice

Parallel Workers:

Fig. 5 The settings of Slice timing.

Most fMRI data are acquired using two-dimensional pulse sequences that acquire images one slice at a time, thus all slices are acquired at different time within a TR. Acquisition time differences are especially problematic for longer TR. Hence, the differences in image acquisition time across slices need to be corrected.

#### Input:

- (1) Slice number: The number of slices.
- (2) Slice order: Set the scanning of the slices such as [1:2:32 2:2:31].
- (3) Reference Slice: select a slice as reference.

#### Output folder:

FunName 'A'.

### 3.5 Realign

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☒ **Realign**

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

Parallel Workers:

**Parameter**

Fig. 6 The setting of Realign.

Realign is used to adjust the time series of images acquired from the same subject over time, aiming to possibly ensure the brain in the same position across images. Six parameters for transformation were estimated between the source images and a reference image (1st image). Then the transformation matrix was applied to the functional images.

#### Output folder:

FunName '**R**'; RealignParameter.

### 3.5 T1 preprocessing

**White matter function preprocessing**

Work Directory: D:\project

☐ Starting EPI directory

☐ Starting T1 directory

TR(sec): 2

☐ DICOM to NIFTI

☐ Remove first n time points

☐ Slice timing

☐ Realign

☒ T1 preprocessing

☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI

☐ Normalize

☐ Group white matter region

☐ Smooth

☐ Detrend

☐ Filter

**T1 Preprocessing**

☐ Reorient T1 Image

☐ Bet

☐ T1 Coregister to EPI

☐ New Segment

☐ East Asian

☒ European

Parallel Workers: 0

Load Save Run

Fig. 7 The settings of T1 preprocessing.

#### Input:

Reorient T1 Image: Reorient the image manually (seek screenshot).

#### Output folder:

ReoientsMats.

#### Input:

Bet: BET (Brain Extraction Tool) deletes non-brain tissue from an image of the whole head. If the operating system is Linux, you should install FSL (FMRIB Software Library).

#### Output folder:

T1Name '\_Bet'.

**Input:**

T1 Coregister to EPI: Linear transformation is used to coregister anatomical images to functional images for the same subject.

**Output folder:**

T1Name '**C**'.

**Input:**

New Segment: Segment the MRI data into six probability maps.

**Output folder:**

T1Name '**E**'.

### 3.6 Nuisance covariates regression

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☒ **Nuisance covariates regression**

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

**Nuisance covariates regression**

Polynomial trend

☐ Friston 24

☐ Global mean signal

☐ Grey matter signal  
segment mask thre.

☐ Cerebrospinal fluid signal  
segment mask thre.

☐ Add mean back

☐ Other covariates

Other covariates

Parallel Workers:

Fig. 8 The settings of Nuisance covariates regression.

Remove the nuisance signals and noise.

#### Input:

- (1) Friston 24: Remove 24 motion parameters through linear regression.
- (2) Global mean signal: Remove Global signal through linear regression.
- (3) Grey matter signal: Remove grey matter signal through linear regression and set the probability threshold of the grey matter probability map.
- (4) Cerebrospinal fluid signal: Remove cerebrospinal fluid signal through linear regression and set the probability threshold of the cerebrospinal fluid probability map.
- (5) Add mean back: The mean will be added back to the residual after nuisance regression.

(6) Other covariates: Add other covariates to be remove.

**Output folder:**

FunName 'C'.

### 3.7 Apply white mask to EPI

**White matter function preprocessing**

Work Directory: D:\project

☐ Starting EPI directory

☐ Starting T1 directory

TR(sec): 2

☐ DICOM to NIFTI

☐ Remove first n time points

☐ Slice timing

☐ Realign

☐ T1 preprocessing

☐ Nuisance covariates regression

**Within white matter**

☒ Apply white matter mask to EPI

☐ Normalize

☐ Group white matter region

☐ Smooth

☐ Detrend

☐ Filter

**Apply white matter mask to EPI**

Individual WM thre. (probability 0~1): 0.9

Parallel Workers: 0

Load Save Run

Fig. 9 The setting of Apply white matter mask to EPI.

Subsequent fMRI data was preprocessed within white matter mask.

#### Input:

Individual WM thre.: Set the probability threshold of the individual white matter probability map.

#### Output folder:

T1Name 'WM'; FunName 'M'.



### 3.8 Normalize

**White matter function preprocessing**

Work Directory: D:\project

☐ Starting EPI directory ☐ Starting T1 directory TR(sec): 2

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☒ **Normalize**

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

**Normalize**

Bounding box: [-90,-126,-72;90,90,108]

Voxel size: [3 3 3]

☒ Normalize by DARTEL using T1 image new segment

☐ East Asian ☒ European

Parallel Workers: 0

Load Save Run

Fig. 10 The settings of Normalize.

Normalize the individual functional image to MNI template by DARTEL using T1 image new segment.

#### Input:

- (1) Bounding box: Set the size of box.
- (2) Voxel size: Set the size of voxel (in mm).

#### Output folder:

FunName 'W'.

### 3.9 Group white matter region

**White matter function preprocessing**

Work Directory: D:\project

☐ Starting EPI directory ☐ Starting T1 directory TR(sec): 2

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☒ Normalize

☒ **Group white matter region** ☐ Smooth

☐ Detrend ☐ Filter

**Group white matter region**

Group WM thre. (subjects %): 0.9

☐ Remove other regions

☐ Uniform parcellate number of regions: n = 7 (number = 2<sup>n</sup>)

☐ Use white matter atlas

Parallel Workers: 0 [Load] [Save] [Run]

Fig. 11 The settings of Group white matter region

Identifying voxels in  $> n\%$  of subject (i.e., threshold) as white-matter were used for group white-matter mask creation

#### Input:

- (1) Group WM thre.: The percentage of the number of subjects.
- (2) Remove other region: Remove the regions that you enter from the group white-matter mask, such as deep brain structures.
- (3) Uniform parcellate: Parcellate the group white-matter mask into  $2^n$  regions.  
The size of the regions was almost equal. The code is obtained from previous study by Zalesky, A., et al., Neuroimage, 2010, 50: 970-983.
- (4) Use white matter atlas: Add the white matter atlas on Group WM mask.

**Output folder:**

FunName 'group\_WMMask'. Individual white-matter mask was in subfolder of 'SubMasks'.

### 3.10 Smooth

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☒ Smooth

☐ Detrend ☐ Filter

Parallel Workers:

**Smooth**

FWHM

Fig. 12 The setting of Smooth

The Full width at half maximum (FWHM) of the Gaussian smoothing kernel (mm) was applied to the functional images.

#### Input:

FWHM: The size of full width at half maximum.

#### Output folder:

FunName 'S'.

### 3.11 Detrend

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☒ Detrend ☐ Filter

Parameter:

Parallel Workers:

Fig. 13 The setting of Detrend.

Remove the linear trend.

**Output folder:**

FunName 'D'.

### 3.12 Filter

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☒ **Filter**

Band (Hz):  ~

Parallel Workers:

Fig. 14 The setting of Filter.

Use band pass filter to filter the signal.

#### Input:

Band (Hz): Set the range of the band.

#### Output folder:

FunName 'F'.

### 3.13 Run

**White matter function preprocessing**

Work Directory:  ...

☐ Starting EPI directory

☐ Starting T1 directory  TR(sec)

☐ DICOM to NIFTI ☐ Remove first n time points

☐ Slice timing ☐ Realign

☐ T1 preprocessing ☐ Nuisance covariates regression

**Within white matter**

☐ Apply white matter mask to EPI ☐ Normalize

☐ Group white matter region ☐ Smooth

☐ Detrend ☐ Filter

Parameter

Parallel Workers:  Load Save Run

Fig. 15 The setting of Run.

Parallel workers: Start the parallel pool of the Matlab and set the number of parallel.

Load: Load the parameter of the settings.

Save: Save the parameter of the current settings.

Run: Save the current settings and run with it.