



## News &amp; Views

## RESTplus: an improved toolkit for resting-state functional magnetic resonance imaging data processing

Xi-Ze Jia<sup>a,b</sup>, Jue Wang<sup>a,b</sup>, Hai-Yang Sun<sup>a,b</sup>, Han Zhang<sup>a,b,c</sup>, Wei Liao<sup>d</sup>, Ze Wang<sup>a,b</sup>, Chao-Gan Yan<sup>e,f</sup>, Xiao-Wei Song<sup>g</sup>, Yu-Feng Zang<sup>a,b,\*</sup>

<sup>a</sup> Center for Cognition and Brain Disorders, Institutes of Psychological Sciences, Hangzhou Normal University, Hangzhou 311121, China

<sup>b</sup> Zhejiang Key Laboratory for Research in Assessment of Cognitive Impairments, Hangzhou 311121, China

<sup>c</sup> Department of Radiology and Biomedical Research Imaging Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27517, USA

<sup>d</sup> School of Life Science and Technology, Center for Information in BioMedicine, University of Electronic Science and Technology of China, Chengdu 610054, China

<sup>e</sup> CAS Key Laboratory of Behavioral Science, Institute of Psychology, Beijing 100101, China

<sup>f</sup> Department of Psychology, University of Chinese Academy of Sciences, Beijing 100101, China

<sup>g</sup> Preclinical Pharmacology Section, National Institute on Drug Abuse, Baltimore 21224, USA

Resting-state functional magnetic resonance imaging (RS-fMRI) [1,2] provides relatively high spatial and temporal resolution for mapping spontaneous brain activity non-invasively. It has been widely used in cognitive neuroscience and clinical studies. A number of comprehensive software packages have been developed for RS-fMRI data analysis, among which a MATLAB package named REST (RESing-state fMRI data analysis Toolkit, released in October 2008 at <http://www.restfmri.net>) [3] is the earliest one dedicated to RS-fMRI analysis. REST focuses on RS-fMRI postprocessing metrics. Combining preprocessing procedures in a famous software toolkit named Statistical Parametric Mapping (SPM) [4] and the postprocessing toolkit REST, a pipeline software named DPARSF (Data Analysis of Resting-State fMRI) was developed [5]. Based DPARSF and SPM, a new version named DPABI was developed [6] with several new features added.

REST, as a user-friendly toolbox, has been widely used in RS-fMRI studies. However it has not been updated for a long time. We here introduced a new version of REST, named RESTplus (Fig. 1). RESTplus was derived from REST [3], DPARSF [5], and SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). It was written in MATLAB m-scripts. The toolkit, the codes, as well as a detailed usage of RESTplus are freely available at <http://www.restfmri.net>. An exemplar dataset and manual were also shared. For validation purpose, we compared the results of a few metrics and found that the results were the same between RESTplus and existing analytic tool DPARSF V2.3 (<http://www.restfmri.net/forum/DPARSF>). The detailed information could be found in <http://www.restfmri.net/forum/RESTplusV1.2>. RESTplus supports Windows, MacOS, and Linux operating systems. Compared with REST, RESTplus has the following new features.

- (1) Graphical user interface (GUI) flexible pipeline for both pre-processing and postprocessing steps. This flexible pipeline consists of all processing steps used in the mainstream RS-fMRI data analysis, including image reorientation, slice timing correction, motion correction, spatial normalization, spatial smoothing, bandpass filtering, detrending, nuisance covariate regression, and RS-fMRI metric calculation (i.e., postprocessing).
- (2) A new RS-fMRI metric named percent amplitude of fluctuation (PerAF) [7]. For standardization purpose, the widely used RS-fMRI metric amplitude of low-frequency fluctuation (ALFF) must be divided by the global mean ALFF and hence a mALFF map is generated. PerAF is an analog to the percent signal change that has been widely used in the task fMRI studies. PerAF is standardized at the single voxel level, and could be further standardized by the global mean PerAF, i.e., mPerAF. Both PerAF and mPerAF can be used for group-level statistical analysis [7,8].
- (3) A flexible batch script “pipeline\_batch.m” for both preprocessing and postprocessing steps. This batch script is executed in MATLAB command line and more flexible than the GUI panel. Its parameters can be easily modified for users who are skilled in programming. In order to create a robust batch script, we refactored some REST V1.8 code.
- (4) A GUI-based wrapper for Arterial Spin Labeling Perfusion MRI Signal Processing Toolbox (ASLtbx) [9]. This plug-in provides a user-friendly environment for using ASLtbx. Users can toggle up each of the processing step in the entire pipeline, such as image re-orientation, realignment, bandpass filtering, spatial smoothing. Both 3D and 4D Nifti format are acceptable. The output includes the mean cerebral blood flow (CBF) map and the CBF map at each acquisition time. The 4D CBF-weighted images can be used to calculate metrics like those generated from RS-fMRI data.

\* Corresponding author.

E-mail address: [zangyufengrest@foxmail.com](mailto:zangyufengrest@foxmail.com) (Y.-F. Zang).

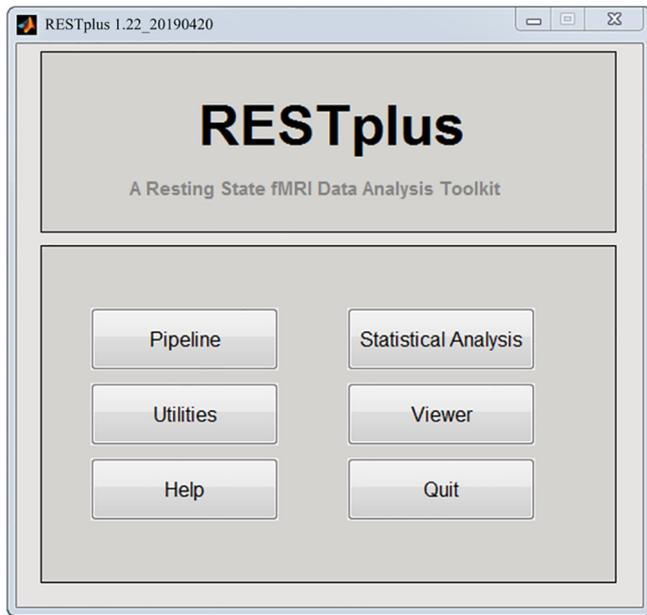


Fig. 1. The main interface of pipeline module.

- (5) A module for positron emission tomography (PET) analysis. This module includes spatial normalization, the standard uptake value (SUV) calculation, and the global mean normalization or standardization. The SUV calculation formula was adopted from [10]. The spatial normalization of the PET image is based on SPM [4].
- (6) A quality assurance module for calculating spatial signal to noise ratio (SNR) and temporal SNR (tSNR) [11].
- (7) A module of inverse transformation to transform an image from the standard space back to its original space. The inversion is based on the inverting deformation field generated from spatial normalization.
- (8) A module for converting coordinate from original space to the standard space, and vice versa. The conversion is based on the inverting deformation field generated from spatial normalization.
- (9) A module for calculating intraclass correlation (ICC). It can be used for reliability analysis or similarity analysis of twin study.
- (10) A module for calculating standardized effect size (Cohen's  $d$ ) for between-group design and within-group design.
- (11) A fixed pipeline module towards multi-center data analysis in which the parameters were fixed. Meta-analysis on raw data is absolutely better than coordinate-based meta-analysis. However, many research centers are not willing to share the raw data. We recently carried out a meta-analysis on RS-fMRI raw data of Parkinson's disease (PD) from 20 research centers worldwide (please see preprint from <https://www.biorxiv.org/content/10.1101/285171v1>). We compiled a pipeline and sent to research centers who wanted to perform data analysis themselves. The analytic parameters were fixed, therefore, the data analyses are completely the same for all research centers. After data analysis, the pipeline automatically packed all intermediate results of each subject, including a few RS-fMRI metrics, the head motion parameters, the spatial normalization images, detailed log files, and so on. Each research center sent the package to

us for quality assessment and then meta-analysis. We implemented this fixed pipeline into RESTplus. It will be helpful for other meta-analyses on raw RS-fMRI data.

### Conflict of interest

The authors declare that they have no conflict of interest.

### Acknowledgments

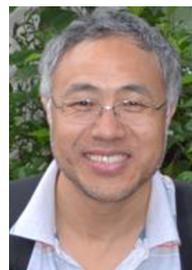
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Xi-Ze Jia is a research assistant at the Institutes of Psychological Sciences, Hangzhou Normal University. His research focuses on cognitive neuroscience, especially on resting-state fMRI data analysis, meta-analysis on resting state fMRI data and resting-state fMRI methods research.



Yu-Feng Zang, M.D., is a professor at Institutes of Psychological Sciences, Hangzhou Normal University. His research is focused on resting-state fMRI computational methodology and application to brain disorders.