LoCoS-R Manual

Local Correspondence Spatial Correlation Toolbox

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2. Introduction.

The advent of multimodal neuroimaging has empowered the scientific community with a window on structure, molecular processes, and function of the human brain. Recently, investigating the relationship between distinct modalities has gained enormous interest among the community. Distinct neuroimaging modalities can complement each other, inform us on how structure, function and metabolic processes are related to each other in the human brain, eventually leading to a deeper understanding of brain organization in the healthy and diseased brain. However, most approaches relating distinct modalities to each other rely on region-of-interest analyses at the across-subjects level.

The **Local Correspondence Spatial Correlation Toolbox** (**LoCoS-R**) offers a novel procedure, by using a searchlight approach in order to build spatial maps of local correspondence between two modalities at the within subject level (see References 1 and 2 for more information).

2.1 What is LoCoS-R doing?

LoCoS-R is using a searchlight approach in order to generate a map of local correspondence between two modalities. Searchlight approaches are multivariate analysis methods that step through all voxels of interest in sequence (for example, all voxels in a given intrinsic brain network). The correlation between both modalities is assessed by using the voxel's values in a 'searchlight' region of interest surrounding the current voxel. The measure of interest is then recorded in the central voxel. This procedure is repeated for every voxel, resulting in a spatial map of local correspondence between both modalities. See the Example section, figures 2-3, and the relevant references for more information.

2.2. Citing.

If you use LoCoS-R, please cite the two papers listed under the section 'Relevant references' at the end of the manual, and refer to the GitHub webpage (https://github.com/TUMnicMuenchen/LocosR).

3. Installing LoCoS-R.

LoCoS-R is an application developed in MATLAB that uses a searchlight approach in order to build spatial maps of local correspondence between two modalities at the within subject level. LoCoS-R is thoroughly tested and works on MATLAB R2012 and higher and requires SPM5 or higher (http://www.fil.ion.ucl.ac.uk/spm/). In order to install LoCoS-R, download the toolbox from GitHub (https://github.com/TUMnicMuenchen/LocosR). Unzip the file LoCoS_Rv1.1.zip and copy the folder LoCoS_Rv1.1 onto your local machine. Start the LoCoS-R GUI by typing SearchLightOrthGUI in MATLAB (figure 1).

Note:

- The LoCoS-R folder contains a folder called private, containing important MATLAB scripts that support the analysis. These files will be automatically included and do not have to be added to the MATLAB path.

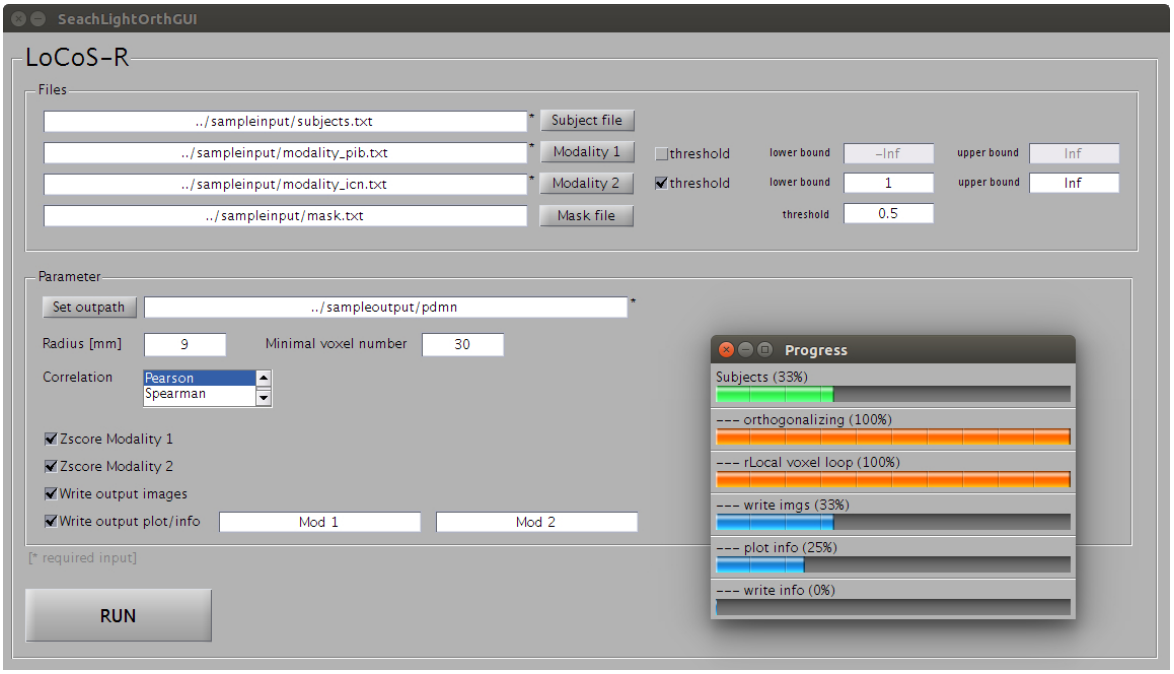

Figure 1. Graphical user interface (GUI) of LoCoS-R.

4. Setting up the analysis.

4.1. What neuroimaging data can be used as input in LoCoS-R?

You can use virtually any type of neuroimaging data, as soon as you have two distinct modalities/neuroimaging measures for each participant of your study.

Note:

- The data of each subject should have the same dimensions, the same voxels size, and should be coregistered in the same space.

4.2. Set input and output.

In order to define you input data, create three distinct text files starting with column title followed by a line with at least one '%' separating title from subject content.

1. One text file just listing your subjects vertically with an addition column whether to include this subject in the current analysis. In turn, you can setup one global input-file and easily perform multiple analyses on group-level.

   1.1. Example file.

```
NAME        INCLUDE
%%%%%%%%%%%%
Sub_001     1
Sub_002     0
Sub_003     1
```

2. A second text file listing the directories and the names of the first modality.

   2.1. Example file.

```
FILE
%%%%%%%%%%%%%%%%%%
/myfolder/subject1/mod1/mod1.nii
/myfolder/subject2/mod1/mod1.nii
/myfolder/subject3/mod1/mod1.nii
```

3. A last text file listing the directories and the names of the second modality.

3.1. Example file.

```
FILE
%%%%%%%%%%%%%%%%%
/myfolder/subject1/mod2/mod2.nii
/myfolder/subject2/mod2/mod2.nii
/myfolder/subject3/mod2/mod2.nii
```

Browse and load the text files to the toolbox. Finally, select an output path were the generated maps and plots will be stored.

Note:

- **Important:** For the distinct text files, list the data for each subject in the same order. Otherwise it will result in a wrong correspondence of modalities across individuals.

4.3. Thresholds and masking.

Depending on the data used, it is advisable that you apply thresholds on your data, by applying upper and lower boundaries. For example, you can apply a lower bound of 1 on z-values of intrinsic functional connectivity (iFC) coming from an intrinsic brain network map, derived from and independent component analysis on resting-state fMRI data. In this case, only voxels with a z-value of iFC bigger than 1 will be considered.
By selecting the box 'use as mask', the same voxels that survive the threshold in the first modality, will be selected for the second modality. All other voxels will be ignored.

You can also mask your data by using individual images from a third modality with a threshold at a certain value. In this case, in analogy of the previous text files, build a fourth text file listing the directories and the names of the third modality and select a threshold. This option is particularly useful if you want to include only voxels with grey matter values above a certain probability threshold. You can load the individually segmented grey matter probability maps from a voxel-based morphometry map and define a threshold, only voxels surviving this threshold will be considered in your analysis.

4.3.1. Example file.

```
FILE
%%%%%%%%%%%%%%%%%
/myfolder/subject1/gm/gm1.nii
/myfolder/subject2/gm/ gm1.nii
/myfolder/subject3/gm/ gm1.nii
```

Note:

- It makes sense to apply thresholds if your data is normally distributed around 0, and you want to include only positive values above a certain threshold in your analysis — this is often the case for iFC measures. It makes sense to use an individual mask based on grey matter if one of your modalities shows non-specific binding — as in the case of the amyloid-ß PET tracer AV-45 (Florbetapir).

4.4. Set parameters for the searchlight analysis.

Following parameters need to be set in order to perform the searchlight analysis. First, you need to define the radius of the sphere (in mm), which is used in the searchlight approach in order to generate maps of local correspondence between the two modalities of interest. To avoid unreliable estimates of local correspondence at network boundaries, you will also need to define a minimal number of voxels having 'real values' to be included in the analysis.

Note:

- The length of the radius and the minimal number of voxels is depending on the data type, data size, and research question. It is advisable that at least 25% of the voxels included in the analysis have real numbers. For orientation see the relevant references at the end of the manual.

You then need to select whether the local correspondence should be computed using Pearson's correlation coefficients or Spearman's rank correlation coefficients. You also can select whether your modalities should be z-transformed prior to the searchlight analysis.

Note:

- The choice of correlation type is depending on the distribution of the data. If the applied thresholds are resulting in a right skewed distribution, it is advisable to use Spearman's rank correlation coefficient. If Pearson's correlation is used in order to derive the local correspondence between both modalities, it is advisable to transform the skewed distribution via log transformation, and to z-transform the data first.

5. Output.

Select the relevant boxes whether you want LoCoS-R to save the generated output images and related plots. Optionally, you can add descriptive names for the two modalities that will be applied labeling the plots. In the output folder defined at the beginning of the analysis, you will find a folder containing a text file with the parameters used in the analysis (params.txt), the raw local correspondence map (R_images), the r to Fisher's z transformed local correspondence map (Z_images), and the corresponding plots which are useful to check the quality and distribution of the used data (Info_plots).

Note:

- Second level analysis: The generated maps can be subsequently evaluated for group differences using neuroimaging toolboxes as SPM. Importantly, when using SPM, under the 'Implicit Mask' option select 'No', given that the thresholding approach usually results in a high number of voxels having a representation of NaN.

6. Example.

In this particular example, we want to assess the individual, local correspondence between amyloid-ß uptake (Aß) and intrinsic functional connectivity (iFC) of the posterior default mode network (pDMN) — this local correspondence will from now on be called r_{LOCAL} (Aß, iFC).

In order to do so, we assessed and preprocessed structural MRI, AV-45 PET, and resting-state fMRI data (details on assessment and preprocessing can be found in the relevant references). In a nutshell, data was projected into MNI space ensuring same dimensionality for both PET

structural MRI, and resting-state fMRI data. PET uptake values were normalized to the cerebellar vermis. Voxel-based morphometry was used on structural MRI data to derive grey matter segmentations. Independent component analysis was applied on resting-state fMRI data to derive individual maps of the pDMN.

The searchlight approach implemented in LoCoS-R was subsequently used to derive local spatial correspondence maps between AV-45 uptake and z-values of iFC within the pDMN, using following parameters: sphere radius = 9 mm; number of voxels = 25; Spearman's rank correlation coefficient (see figure 2).

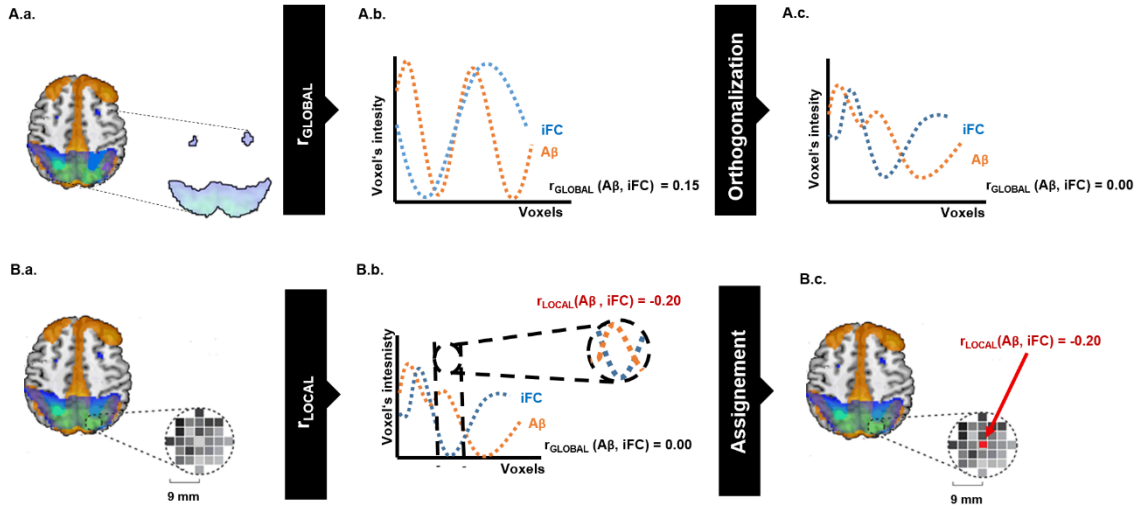

Figure 2. Procedure of LoCoS-R. (A.a) Within a subject, voxels where iFC of an intrinsic brain network and Aß overlap are identified. (A.b) The correlation between both modalities is performed at the global network level, resulting in a global network measure of correspondence — r_{GLOBAL} (Aß, iFC). (A.c) Orthogonalization of both modalities, results in a global correspondence of 0. (B.a) After orthogonalization, a sphere of 9 mm radius is used to scan the whole brain. (B.b) The correlation between both modalities is computed within the sphere. (B.c) The derived local correlation coefficient is assigned to the central voxel in the sphere. The procedure is repeated for all brain voxels, resulting in an individual map of local correspondence.

A z-value of 1 was applied on iFC of the pDMN, no threshold was applied on PET data, only voxels with a grey matter probability bigger than 0.5 where included in the analysis (see figure 3).

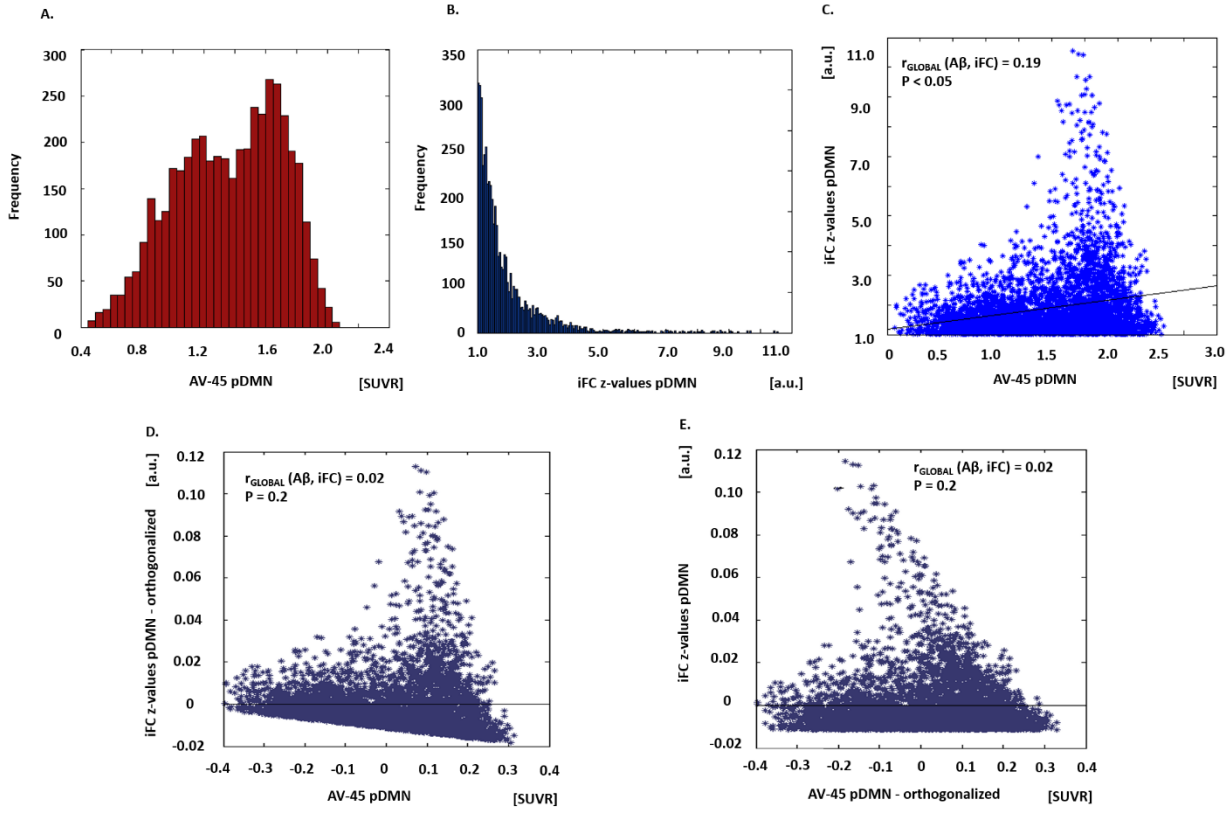

Figure 3. Individual data distributions after application of iFC z-values (>1) and grey matter thresholds (>0.5). (A) AV-45 data distribution within the thresholded pDMN. (B) iFC z-values within the pDMN, thresholded at a z-value of 1. Note the skewed distribution. (C) r_{GLOBAL} (Aß, iFC): Global correlation between AV-45 uptake and thresholded iFC z-values within the pDMN — note the significant positive correlation. (D) Global correlation between AV-45 uptake and iFC z-values after orthogonalization (iFC orthogonalized, AV-45 unchanged) — note the absence of significant correlation. (E) Global correlation between AV-45 uptake and iFC z-values after orthogonalization (iFC unchanged, AV-45 orthogonalized) — note the absence of significant correlation.

The global correspondence between both modalities was assessed at the whole network level — r_{GLOBAL} (Aß, iFC). In order to account for such aforementioned global correspondence, AV-45 uptake and iFC z-values were orthogonalized across the whole network at a voxel-wise level, ensuring a global correlation of about 0. As orthogonalization is an asymmetric operation (modifying one vector while leaving the other unchanged), the orthogonalization and subsequent searchlight analysis were repeated, but this time decorrelating connectivity z-values with respect to AV-45 uptake (see figure 3). The searchlight results of the two analyses were then averaged, resulting in an individual spatial map reflecting the local correspondence of Aß and iFC within the pDMN (see figure 4).

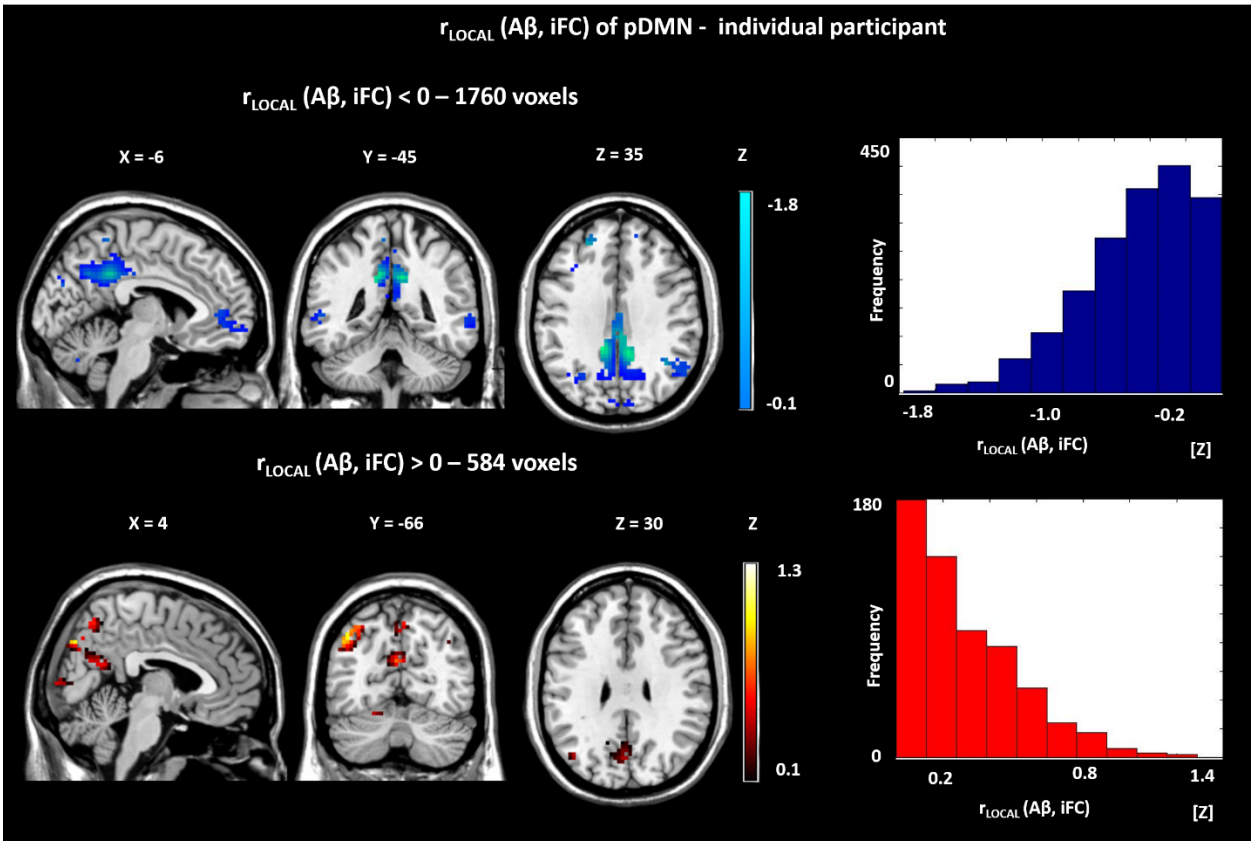

Figure 4. Individual r_{LOCAL} (Aß, iFC) map, reflecting the local correspondence between Aß and iFC of the pDMN; r_{LOCAL} (Aß, iFC) values were r to Fisher z transformed. The upper row shows the vast majority of voxels, having negative values (in blue) and located around medial parietal regions of the pDMN. The lower row shows a minority of voxels with positive values (in red).

Relevant references

1. Myers NE, Pasquini L, Gottler J, Grimmer T, Koch K, Ortner M, Neitzel J, Muhlau M, Forster S, Kurz A, Forstl H, Zimmer C, Wohlschlager AM, Riedl V, Drzezga A, Sorg C (2014) Within-patient correspondence of amyloid-beta and intrinsic network connectivity in Alzheimer's disease. Brain 137, 2052-2064.

2. Pasquini L, Benson G, Grothe MJ, Utz L, Myers NE, Yakushev I, Grimmer T, Scherr M, Sorg C (2017) Individual correspondence of amyloid-β and intrinsic connectivity in the posterior default mode network across stages of Alzheimer’s disease. Journal of Alzheimer’s Disease.