BCBtoolkit (v4.0.0)

In Summary

Brain Connectivity and Behaviour toolkit is a free and open-source software package based on open source libraries which aims to provide the scientific community with the several tools to indirectly assess brain disconnections. Subscribe to the mailing list to receive updates.

BCBtoolkit includes:

Tractotron (standalone version): For a given lesion, Tractotron provides a probability (but not the severity) of disconnection for almost all known tracts.

Disconnectome maps (standalone version): For a given lesion, disconnectome map provides a map indicating a probability to be disconnected for every voxel of the MNI152

Normalisation (standalone version) based on ANTs scripts, normalisation is adapted to use a mask to register patients with lesions to the MNI152. This is a long but very strong registration based on diffeomorphic algorithms.

Cortical Thickness (standalone version) based on ANTs scripts. Cortical Thickness will produce a map indicating the thickness of the cortex.

AnaCOM2 (requires R language) AnaCOM2 aims at establishing structure–function relationships by comparing neuropsychological scores between patients and healthy controls.

Funcon-Preprocessing (requires FSL) Removing of the head motion and other artifacts on fMRI raw data.

Funcon-Connectivity (requires FSL) Calculation of the functional connectivity on fMRI data from seeds regions to a target area.

If you are on OSX :

To launch the BCBtoolkit, double-click on the script : BCBToolKit.command

If you are on Linux :

To launch the BCBtoolkit, double-click on the script : BCBToolKit.sh (Or launch it in terminal if .sh scripts are not directly executable by double-click on your OS)

You can access to the entire file tree of the BCBtoolkit in tree.txt and a summary here :

BCBToolKit
the root of the toolkit with readme, licence and information files etc ...
├── **BCBToolKit.sh**
the launching script
├── **sources.jar**
the compiled java executable
├── **Sources**
the folder containing the uncompiled java sources
├── **Tools**
│ ├── **binaries**
│ │ ├── **ANTs**
the ANTs software
│ │ ├── **bin**
binaries used for the standalone modules
│ │ ├── **data**
data imported from the FSL library, templates, gray matter masks etc ...
│ │ └── **ICA-AROMA-master**
the ICA-AROMA software
│ ├── **extraFiles**
configuration file, templates, priors etc ...
│ │ ├── **Hypertron**
healthy control tractographies used for disconnectome maps
│ ├── **libraries**
required libraries for binaries from fsl
│ ├── **scripts**
sources of the bash and R scripts of the BCBtoolkit
├── **Tracts**
atlas of white matter tracts from Rojkova et al., BSF 2015

TRACTOTRON: HOW DOES IT WORK?

In Summary

Tractotron is a software using FMRIB software library (FSL) as well as recently published white matter tract atlases (Rojkova et al., BSF 2015) in the MNI152 referential to determine the pattern of disconnection induced by a lesion at the individual level. For a given lesion, Tractotron provides a probability and the severity of disconnection for almost all known tracts. Results are exported as excel files ready to be analysed with any statistical software distribution.

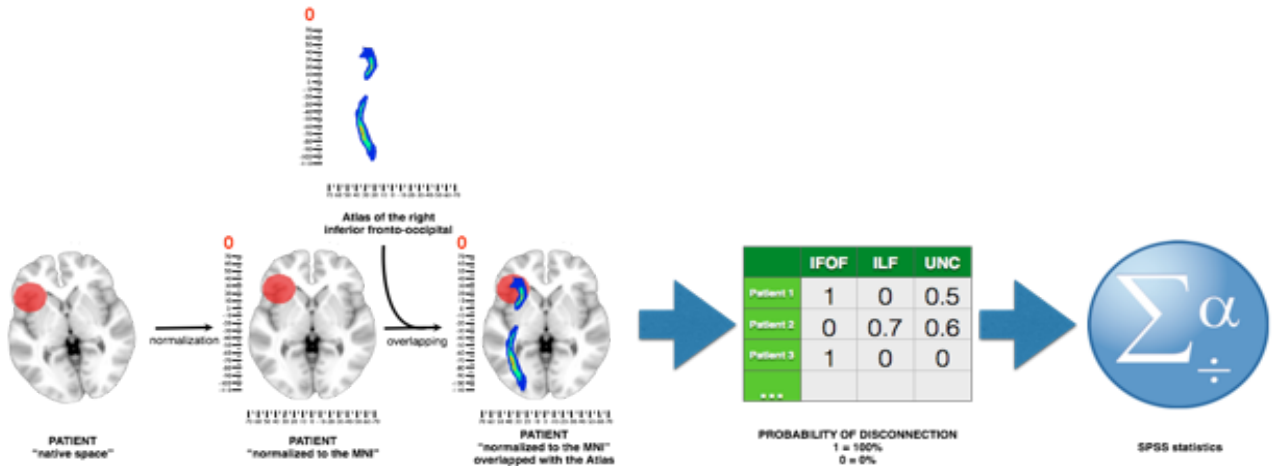
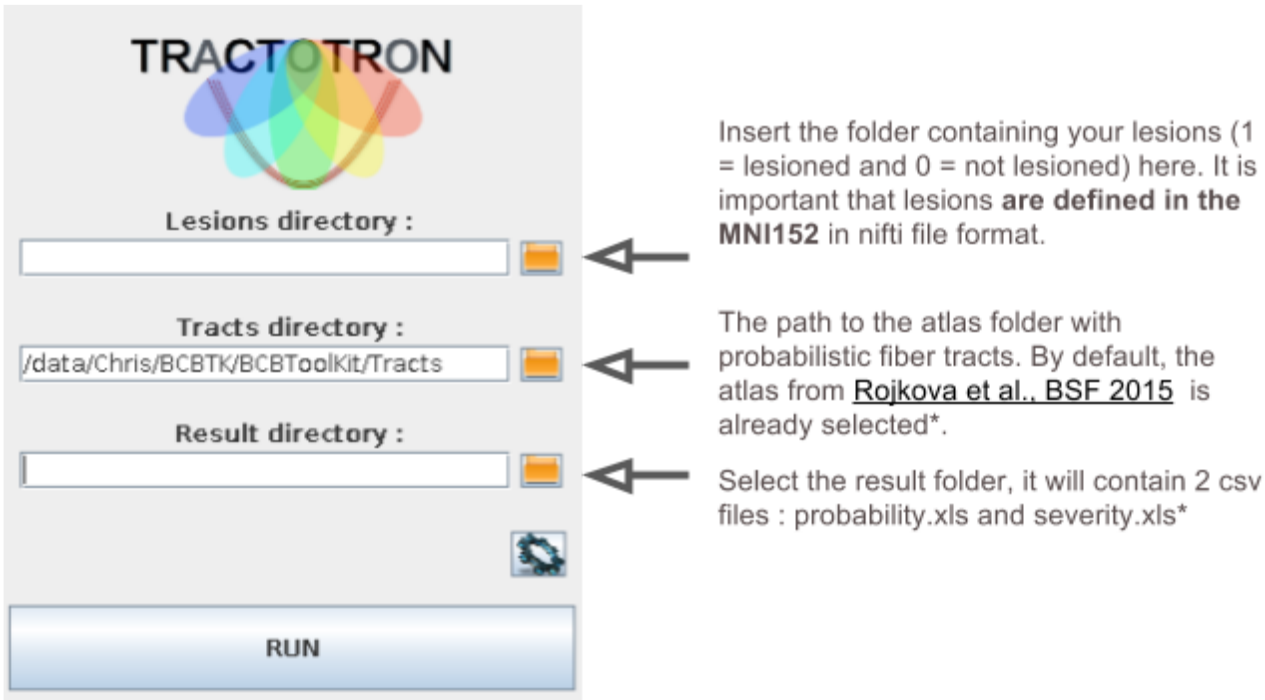


Figure 1: Tractotron step by step



*probability.xls is the chance to have fibers disconnected in the tract.

proportion.xls is the proportion of overlap between the lesion's volume and the tract's volume.
** By using the setting button, you can reset this field to the default folder.

PAPER METHOD SECTION (feel free to edit or copy and paste)

We mapped the lesion from each patient onto tractography reconstructions of white matter pathways obtained from a group of healthy controls (Rojkova et al., BSF 2015). We quantified the severity of the disconnection by measuring the probability of the tract to be disconnected (Thiebaut de Schotten et al. 2014) using Tractotron software as part of the BCBtoolkit (http://www.brainconnectivitybehaviour.eu).

DISCONNECTOME MAPS: HOW DOES IT WORK?

In Summary

Disconnectome maps will track in 10 healthy controls the connections passing by the lesion and will create for every lesion loaded in the software a map of the tracks which pass through the lesion as follows:

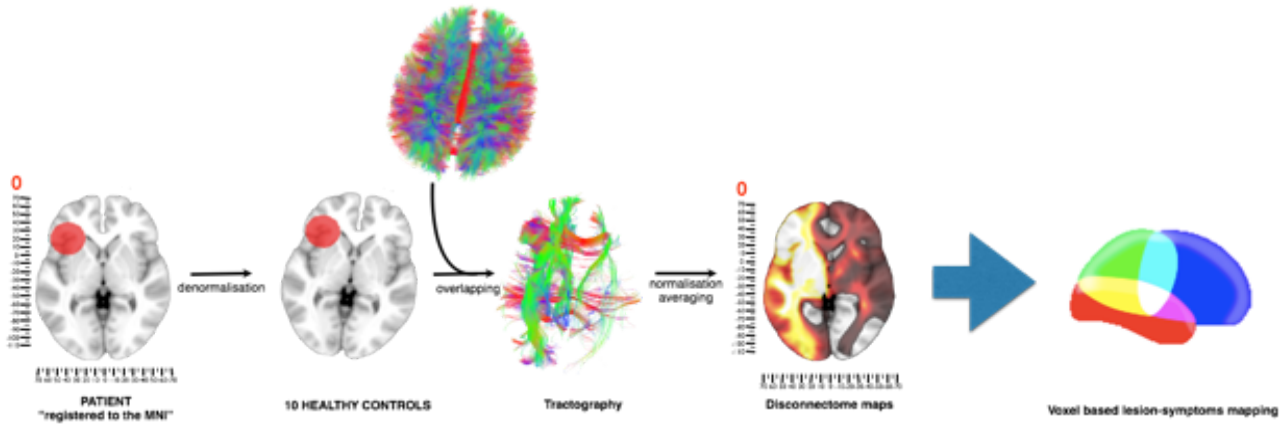
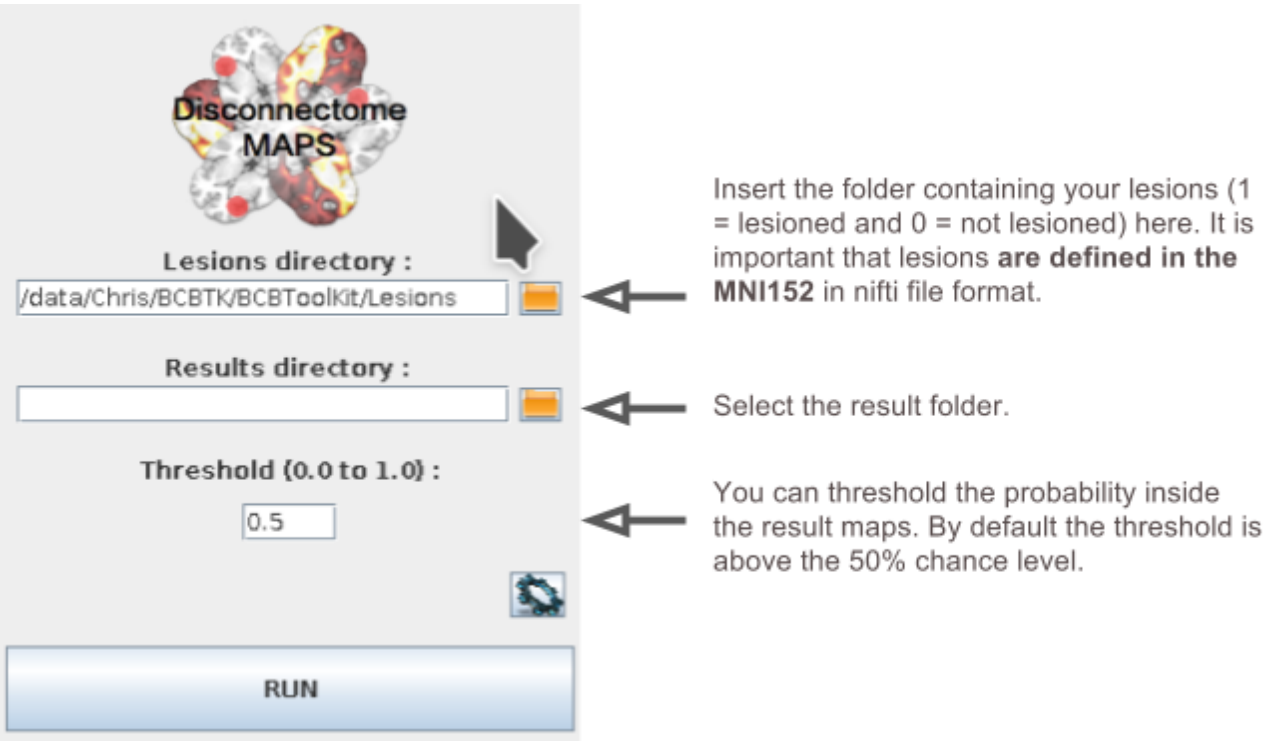


Figure 1: Disconnectome maps step by step



PAPER METHOD SECTION (feel free to edit or copy and paste)

This approach uses a set of 10 healthy controls (Rojkova et al., BSF 2015) diffusion weighted imaging datasets to track fibers passing through each lesion. For each participant tractography was estimated as indicated in (Thiebaut de Schotten *et al.*, 2011).
Patients' lesions in the MNI152 space are registered to each control native space using affine and diffeomorphic deformations (Klein *et al.*, 2009; Avants *et al.*, 2011) and subsequently used as seed for the tractography in Trackvis (Wang *et al.*, 2007). Tractographies from the lesions are transformed in visitation maps (Thiebaut de Schotten et al. 2011), binarised and brought to the MNI152 using the inverse of precedent deformations. Finally, we produce a percentage overlap map by summing at each point in MNI space the normalized visitation map of each healthy subject. Hence, in the resulting disconnectome map, the value in each voxel take into account the interindividual variability of tract reconstructions in controls, and indicate a probability of disconnection from 0 to 100% for a given lesion.

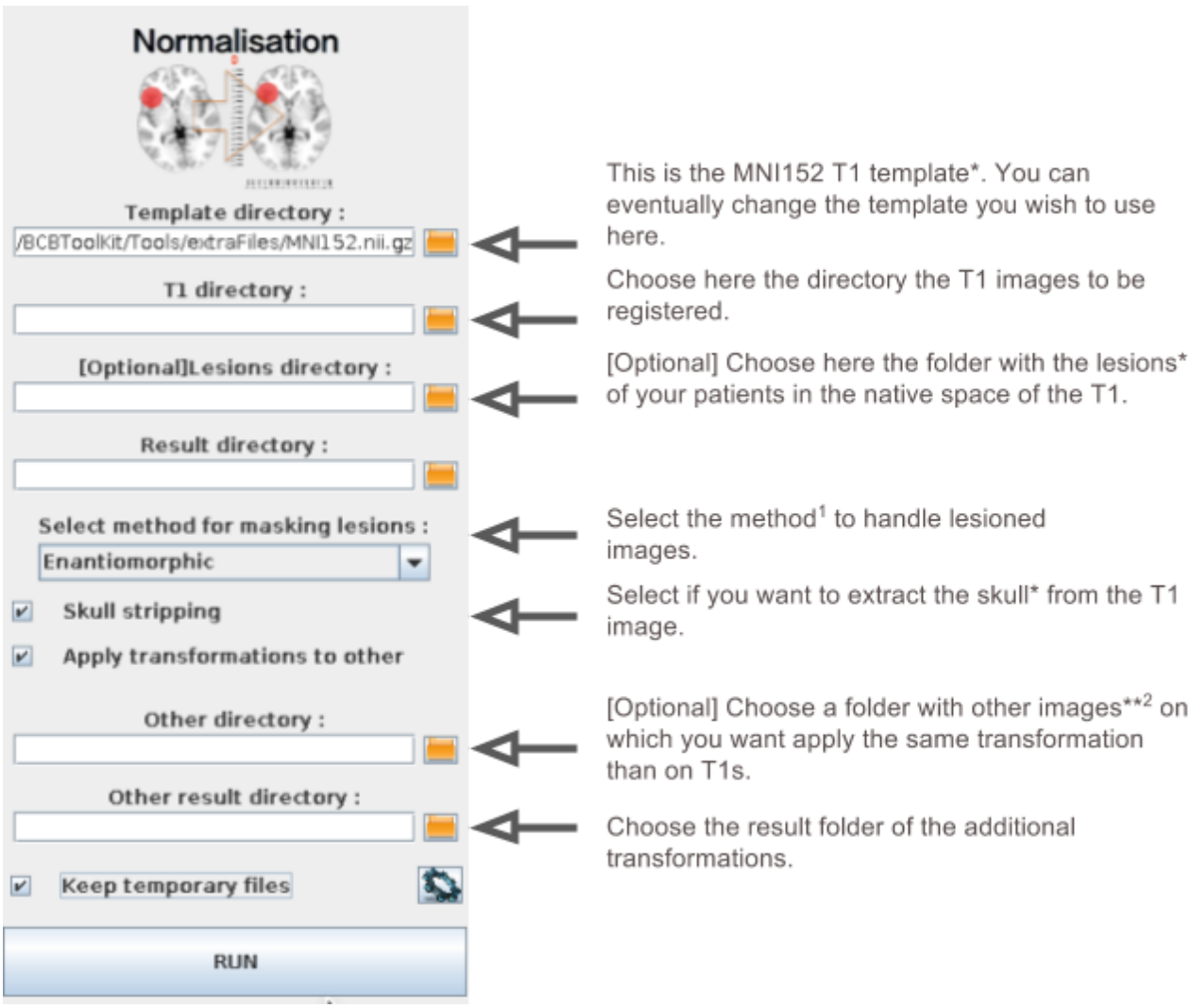
NORMALISATION: HOW DOES IT WORK?

In Summary

Normalisation is based on ANTs software package. Please visit http://stnava.github.io/ANTs/ for a detailed description of their great work.

A good registration of your T1 to the MNI template is key if you wish to have optimal results. Therefore we added the new tool “normalisation” to our software package, which combined what we think being the best way to “*normalise*” your brain images.

Normalisation will calculate affine and diffeormorphic deformation to register your T1 to the MNI152 space. Adding an optional lesion directory will limit diffeormorphic deformation to areas located outside the lesioned tissue. This is important as the result might be biased by the presence of abnormal tissue.



[1]With the Classic way, the lesioned area will only be masked, but with the enantiomorphic (Nachev et al. 2008), the software will take the healthy tissue of the spared hemisphere to fill the damaged area and calculate a better transformation on an entirely "spared" image to apply it to your T1. **Be careful, the enantiomorphic transformation cannot be used in case of a lesion in the left and the right hemispheres.**

[2]You can apply transformations on 4D images, the 4D images will be splitted across the 4th dimension and transformations will be apply on each 3D images and then merged again.

***be careful to be consistent between your images and the template, for instance : if you choose to not use the skull stripping on T1 images with skull you have to select a template with skull (You can find a MNI152 with skull in BCBToolKit/Tools/extraFiles/MNI152_wskull.nii.gz). If you want to normalise lesioned T1 without the skull, you may want to use classic lesion masking.**

****exact same name as the T1 images used above**

PAPER METHOD SECTION (feel free to edit or copy and paste)

As spatial normalization can be affected by the presence of a brain lesion, each lesion or signal abnormalities due to the lesion (manually segmented) can be used as a mask during the normalization procedure to optimize the brain normalisation (Ripoles et al., 2012; Volle et al. 2012) :
- In the case of the classic approach (choose this one if you have bilateral lesions or if you want to normalise images without skull), this masking procedure was used to weight the normalization to brain rather than non-brain tissue or lesions (Brett et al., 2001).
- **In the case of the enantiomorphic approach** (Nachev et al. 2008): Each patient lesions or signal abnormalities due to the lesion is replaced symmetrically by the healthy tissue of the contralateral hemisphere.

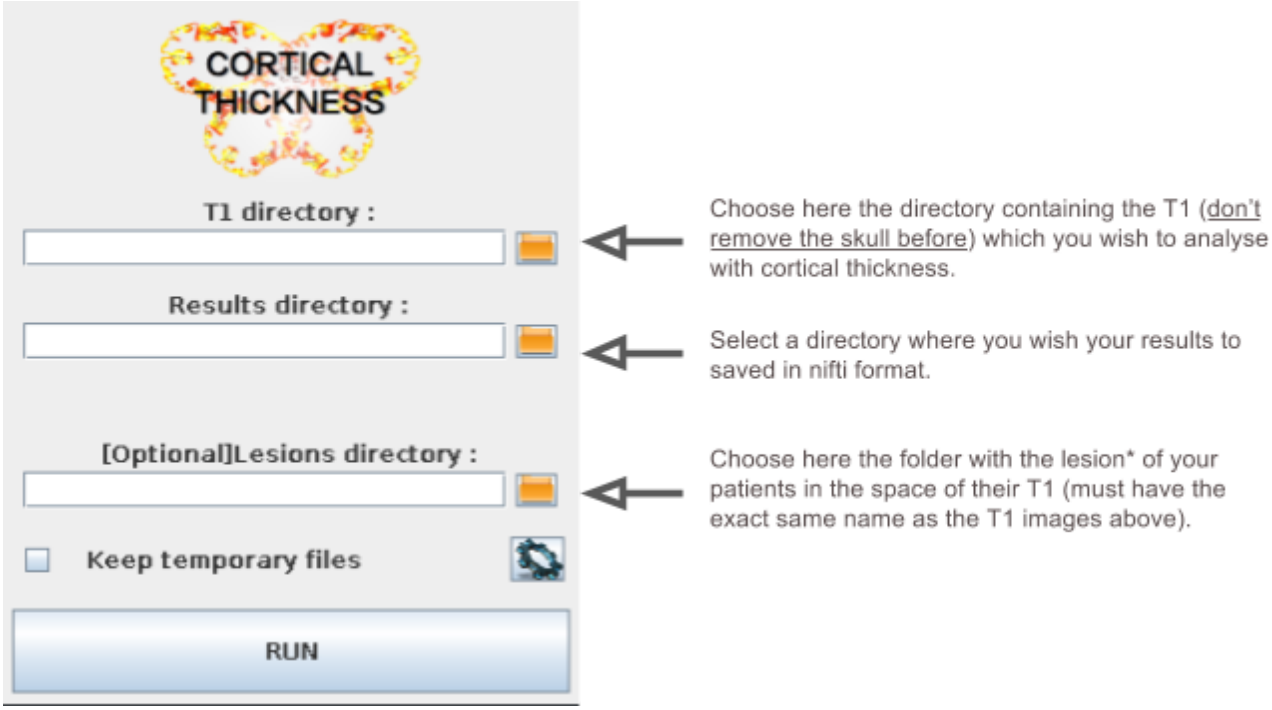
The skull stripping (if selected) is performed using the ANTs brain extraction algorithm (http://stnava.github.io/ANTs/)

T1 images are registered to the template (MNI152) using affine and diffeomorphic deformations (Klein et al., 2009; Avants et al., 2011).

CORTICAL THICKNESS: HOW DOES IT WORK?

In Summary

Cortical Thickness is based on ANTs software package. Please visit http://stnava.github.io/ANTs/ for a detailed description of their great work.



***If you add lesion masks, the cortical thickness will be calculated on the enantiomorphic (Nachev et al. 2008) transformation of the T1 (We replace the lesioned area by the healthy tissue of the spared hemisphere) to avoid artifacts during the calculation and then the lesioned region is removed (because the measure of the cortical thickness inside a damaged area is not relevant). Be careful, the enantiomorphic transformation cannot be used in case of lesions in the left and right hemispheres.**

PAPER METHOD SECTION (feel free to edit or copy and paste)

Before the calculation, in case of lesioned image, we create the enantiomorphic transformation (Nachev et al. 2008): Each patient lesions or signal abnormalities due to the lesion is replaced symmetrically by the healthy tissue of the contralateral hemisphere. The estimation of the cortical thickness is then performed on the enantiomorphic image to avoid abnormal values and then the lesion is masked (indeed, the cortical thickness value inside the damaged area is irrelevant).
A registration-based method (Diffeomorphic Registration based Cortical Thickness, DiReCT) is employed to estimate the cortical thickness (Das et al., 2009) from the T1-weighted imaging dataset.

The first step of this method consists in creating a two voxel thick sheet, one which lies just between the grey matter and the white matter and a second lying between the grey matter and the cerebrospinal fluid. Then, the grey/white interface is expanded to the grey/cerebrospinal fluid interface using diffeomorphic deformation estimated with ANTs (Avants et al., 2007; Klein et al., 2009; Tustison & Avants, 2013). The registration produces a correspondence field that allows an estimate the distance between the grey/white and the grey/cerebrospinal fluid interfaces, and thus cortical thickness. This approach has good scan-rescan repeatability and good neurobiological validity as it can predict, with high statistical power the age and gender of the participants (Tustison et al., 2014).

ANACOM2: HOW DOES IT WORK?

In Summary

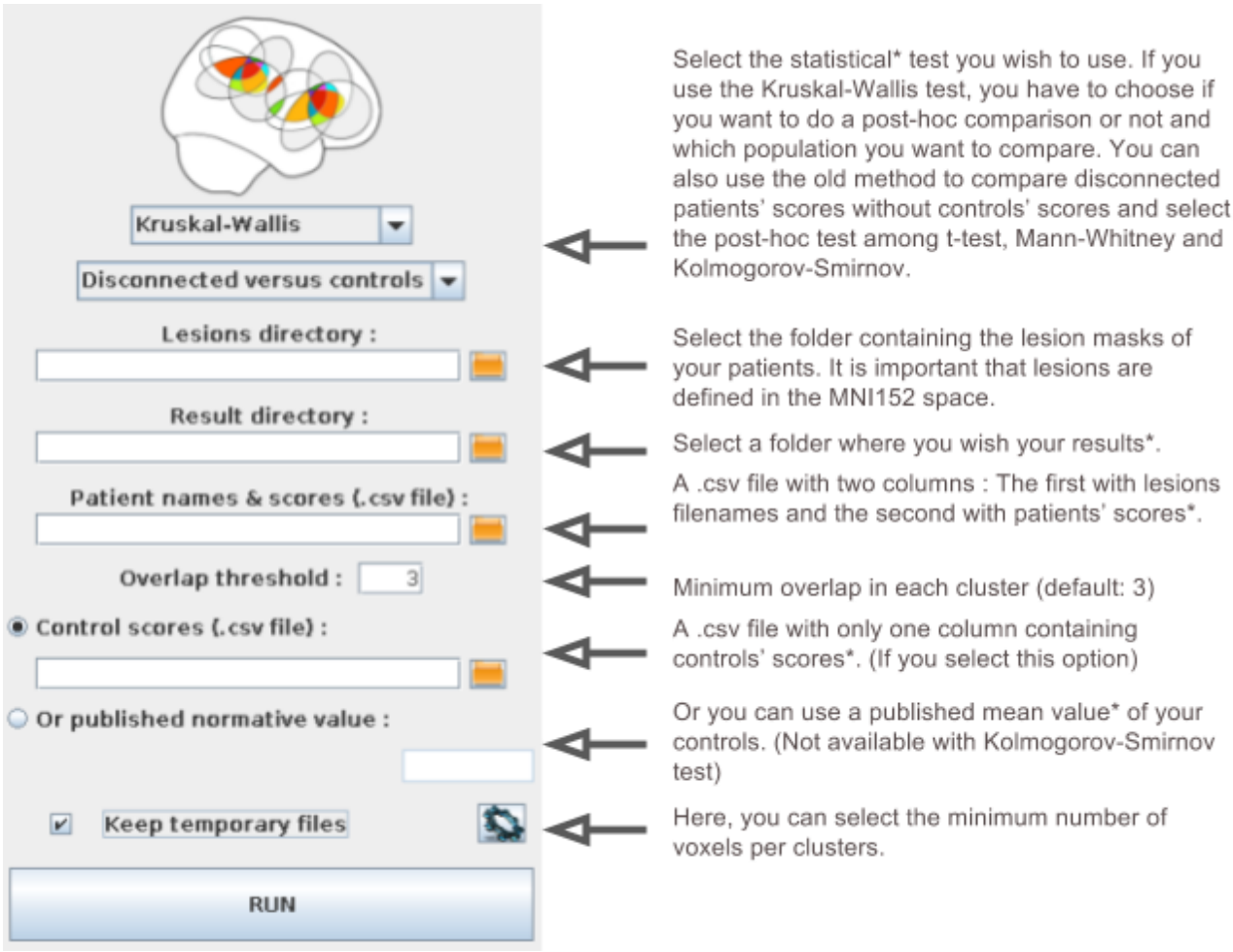
AnaCOM2 is based on a previously published methods (Kinkingnéhun et al. 2007) and aims at establishing structure–function relationships. AnaCOM2 is using FMRIB software library (FSL) to interact with R software package.

Typically, the software compare neuropsychological scores between lesioned patients and controls to determine which brain area critically affect the performance.

!!! IMPORTANT !!!

You need to have R installed if you want to run this module.

To install R please visit : https://www.r-project.org/ click on « CRAN » at the top left, choose your preferred mirror and download the R version corresponding to your system.



***Please don't use values lower or equal to zero in scores.**

RESULTS

clusters.csv: For each given cluster of voxels, *nb_disco(nb_spared if you compare only spared patients and controls)* is the number of patients whose disconnectome involves that cluster of voxels. (kw_)pval is the pvalue of the test, (kw_)stat is the value of the statistical test (H for Kruskal-Wallis, U for Mann-Whitney, T for T-test, D for Kolmogorov-Smirnov) and (kw_)holm is the column containing the pvalues corrected for multiple comparison by the Bonferroni-Holm algorithm.
With Kruskal-Wallis option :

	kw_pval	kw_stat	kw_holm	nb_disco	pval	stat	holm
cluster3	0.00139401	13.15113594	0.01607283	4	0.00182220	6	0.02186645
cluster2	0.00152658	12.96945030	0.01607283	4	0.00288715	10.5	0.03175862
cluster0	0.00152893	12.96637088	0.01607283	4	0.00303479	11	0.03175862

cluster1	0.00133940	13.23106393	0.01607283	3	0.00471027	1.5	0.04239240
cluster11	0.00146002	13.05861654	0.01607283	3	0.00691230	5	0.05529840
cluster10	0.00148785	13.02084235	0.01607283	3	0.00729412	5.5	0.05529840

Without :

	nb_disco	pval	stat	holm
cluster3	4	0.00182220	6	0.02186645
cluster2	4	0.00288715	10.5	0.03175862
cluster0	4	0.00303479	11	0.03175862
cluster1	3	0.00471027	1.5	0.04239240
cluster11	3	0.00691230	5	0.05529840
cluster10	3	0.00729412	5.5	0.05529840

In the example above, the uncorrected pvalues are lower than 0.05 but the BH correction, at some point, is higher than 0.05, hence these clusters did not survive BH correction for multiple comparison.
Note that optimising the overlap of lesions (and the number of voxels per clusters will reduce the total number of comparison and decrease the severity of the correction.

warnings.csv: Statistical assumptions are not always respected in every cluster. warning.cvs will report the cluster for which statistical assumptions were violated. For instance, the wilcoxon test will not be able to compute an exact value when a patient has the same score as the published normative value.

patients_info.csv: contains the name of patient's files and the scores of patients who have disconnections within clusters.

cluster0	patient03.nii.gz	patient04.nii.gz	patient07.nii.gz	patient08.nii.gz
cluster0	27	26	22	21
cluster10	patient04.nii.gz	patient07.nii.gz	patient10.nii.gz	
cluster10	26	22	20	
cluster11	patient04.nii.gz	patient08.nii.gz	patient10.nii.gz	
cluster11	26	21	20	

cluster1	patient07.nii.gz	patient08.nii.gz	patient10.nii.gz	
cluster1	22	21	20	

clusters_holm.nii.gz is a nifti map in the MNI152 indicating Bonferroni-Holm (BH) corrected pvalues after the post_hoc test.

clusters.nii.gz is a nifti map in the MNI152 indicating uncorrected pvalues (If you chose the Kruskal Wallis test, the values are only for clusters that passed the Kruskal Wallis test).

kruskal_holm_clusters.nii.gz is a nifti map in the MNI152 indicating Bonferroni-Holm corrected pvalues after the Kruskal-Wallis test.

kruskal_clusters.nii.gz is a nifti map in the MNI152 indicating the pvalue in the Kruskal-Wallis test before Bonferroni-Holm correction.

When activating the 'keep temporary files' option, the following files will be saved in anacomTemporaryFiles :

the folder anacomClustersDir contains all binary « cluster » images.
maskedMeanValMap.nii.gz is a nifti map in the MNI152 indicating the average score.
maskedStd.nii.gz is a nifti map in the MNI152 indicating standard deviations.

PAPER METHOD SECTION (feel free to edit or copy and paste)

AnaCOM2 is a cluster-based lesion approach allowing to identify the brain lesions locations that are associated with a given deficit, i.e. the regions that are critical for a given function. Compared to standard VLSM (Bates et al. 2003), AnaCOM2 regroup voxels with the same distribution of neuropsychological scores into clusters of voxels. Additionally, AnaCOM2 performs comparisons between patients and controls as a first step in order to avoid drastic reduction of statistical power when two or more non-overlapping areas are responsible for patients reduced performance (Kinkingnéhun *et al.*, 2007). AnaCOM2 resulted in a statistical map revealing for each cluster the significance of a deficit of patients at a given task, compared to controls. P-values are Bonferroni-Holm corrected for multiple comparisons.

Funcon-Preprocessing

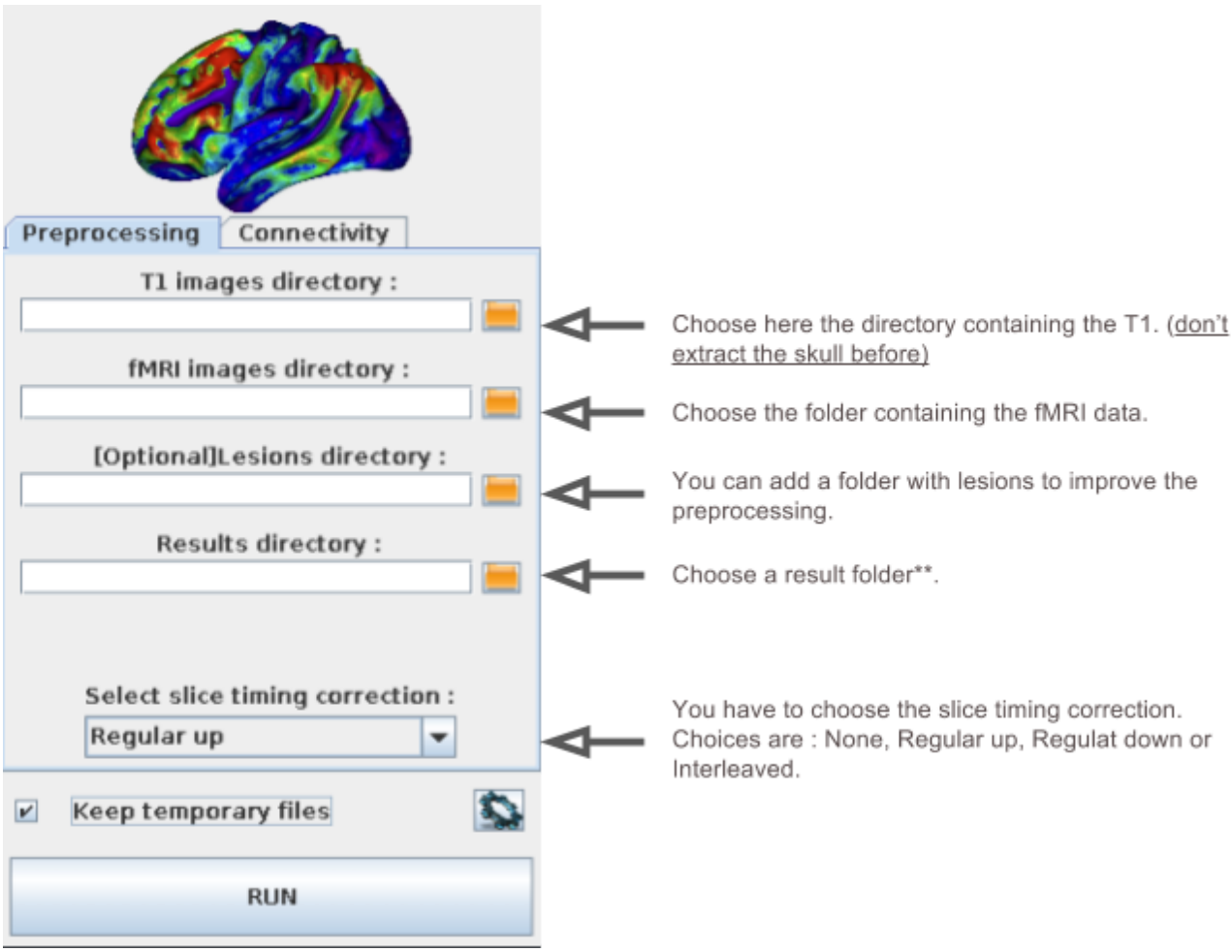
In summary

The preprocessing module of Funcon aims to correct the head-motion and artifacts from fMRI data using features from FSL library.

!!! IMPORTANT !!!

You need to have FSL installed if you want to run this module.

To install FSL please visit : https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation and follow instructions.



***If you choose to add lesion masks, the cortical thickness will be calculated on the enantiomorphic (Nachev et al. 2008) transformation of the T1 (We replace the lesioned area by the healthy tissue of the spared hemisphere) to avoid artifacts during the calculation and then the lesioned region is removed (because the measure of the cortical thickness inside a damaged area is not relevant). Be**

careful, the enantiomorphic transformation cannot be used in case of lesions in the left and the right hemispheres.

PAPER METHOD SECTION (feel free to edit or copy and paste)

fMRI images are first motion corrected using MCFLIRT (Jenkinson et al., 2002), then corrected for slice timing, smoothed with a full half width maximum equal to 1.5 times the largest voxel dimension and finally filtered for low temporal frequencies using a gaussian-weighted local fit to a straight line. These steps are available in Feat as part of FSL package (Woolrich et al., 2009).
In case of lesioned image, we create the enantiomorphic transformation (Nachev et al. 2008): Each patient lesions or signal abnormalities due to the lesion is replaced symmetrically by the healthy tissue of the contralateral hemisphere.
*f*MRI images are linearly registered to the (enantiomorphic in case of lesioned images) T1 images, and subsequently to the MNI152 template (2mm) using affine transformation. Confounding signals are discarded from *f*MRI by regressing out a confound matrix from the functional data. The confound matrix included the estimated motion parameters obtained from the previously performed motion correction, the first eigenvariate of the white matter and cerebrospinal fluid as well as their first derivative. Eigenvariates can easily be extracted using fslmeants combined with the --eig option. White matter and cerebrospinal fluid eigenvariates are extracted using masks based on the T1 derived 3-classes segmentation thresholded to a probability value of 0.9, registered to the Rs-fMRI images and binarized. Finally, the first derivative of the motion parameters, white matter and cerebrospinal fluid signal is calculated by linear convolution between their time course and a [-1 0 1] vector.

Funcon-Connectivity

Correlation between the average of seed's time-courses and every time course of the target's voxels.

!!! IMPORTANT !!!

You need to have FSL installed if you want to run this module.

To install FSL please visit : https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation and follow the instructions for you system.