Normalisation pipeline

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2024-01-08

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Preface

The book was intended as documentation on a suggested pipeline for normalising brain and lesion masks from chronic stroke T1 weighted imaging. To make it a bid more widely useful, the pipeline documented here will register T1 weighted images to either 1 or 2 mm MNI standard space and include a lesion mask in that process, if any is present.

The pipeline was comprised as part of my exchange stay at the Brain Behaviour Lab at UBC, Vancouver, Canada during August-October 2023. It is my hope that the notes and scripts may be of help to others, myself being a new learner to FSL and everything around it.

Motivation

The reason for creating this tool is to use 1mm MNI normalised (registration) lesion masks for the NeMo tool.

Most of the hard working scripts in this pipeline are based on the work by Dr. Dianne Patterson, PhD, which in turn is also based on others work. I have tried my best at modifying the original scripts as little as possible for clarity, and instead created a few new scripts to work as wrappers.

And then, the frustration. I found that documentation that is easy to understand is highly lacking in the field (or I just didn't manage to find it). Also, the documentation on fsl-functions is difficult to always follow. As an example, this is the best overview of `fslmaths -help`. And please notice, that to get help for `fslmaths`or `flirt`, type the command followed by `-help`. If you want the same from `fnirt`, then type `-h` or `--help` as is the case for most other command-line programs.

I have tried to lower the bar to get started working on MRI registration. Feedback is very welcome on GitHub.

License

term	definition
fsleyes	Thes picture viewing tool from the fsl-package. https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes
MNI	Montreal Neurological Institute. https://nist.mni.mcgill.ca/atlases/
MRI	Magnetic Resonance Imaging
NeMo	Network Modification tool. https://github.com/kjamison/nemo
pipeline	A set of tools working together as chain links being dependent on one-another. Just a fancy ter
registration	I this context, registration denotes to art of registrering to normal space. In this case to the MI

Glossary

1 Contents

The pipeline provides a set of handy tools listed below, which I will also go through:

- Bash pipeline to process multiple subject folders to do cropping, bias correction and skull stripping before registering brain and possibly lesion mask to 1 or 2 mm MNI space (this is the primary content). The registration can be performed with fsl or ANTs.
- A few other Bash-scripts to register brain and lesion mask after manual correction of brain mask (no, even using optiBET is not perfect), and to do other things.
- A few *R*-scripts to organise files and to package lesion masks to supply to the NeMo tool in Chapter 5.
- In a separate folder (`nemo/`) I've included a few scripts to collect data from the NeMo-output and do basic visualisation based on the NeMo output data.
- Finally, three Python scripts from the NeMo-repository: `nemo_save_average_glassbrain.py`, `nemo_save_average_graphbrain.py` and `nemo_save_average_matrix_figure.py`. These are used for data visualisation in the included pipeline use case example in Chapter 5. The NeMo-project project, however is shared without a license. The files can be downloaded from the NeMo-repository or directly with the following lines of code:

```
download.file("https://raw.githubusercontent.com/kjamison/nemo/master/nemo_save_avera
download.file("https://raw.githubusercontent.com/kjamison/nemo/master/nemo_save_avera
download.file("https://raw.githubusercontent.com/kjamison/nemo/master/nemo_save_avera
```

1.1 Glossary

term	definition
ANTs	Advanced Normalization Tools. https://github.com/ANTsX/ANTs
Bash	Short version: The language of the terminal console in Windows, Linux and MacOS.
fsleyes	Thes picture viewing tool from the fsl-package. https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes
MNI	Montreal Neurological Institute. https://nist.mni.mcgill.ca/atlases/
MRI	
NeMo	Network Modification tool. https://github.com/kjamison/nemo
optiBET	A four step optimization of the fsl BET tool from the Monti lab at UCLA. https://montilab.ps
pipeline	A set of tools working together as chain links being dependent on one-another. Just a fancy ter
Python	A snake, or in this case refers to the free and open source programming language Python. https
R	
regex	
registration	

2 Getting started

```
source("glossary_setup.R")
```

You need to have the following programs installed:

- fsl as well as
- *R* and RStudio (or similar) installed.
- I also highly recommend the package ITK-SNAP, which can be used for some (semi-)manual mask modifications.
- You may want to use the powerful ANTs package (or the underlying `ANTsR` package) for registration. The included script, to is provided by Dr. Dianne Patterson, PhD.

2.1 Let's get to it

> **Keep a backup**
>
> Before starting, be warned. The script might override original data with modified data without warning. Please keep a backup of original files. Now you have been warned.

Script files are located in the `codes` folder like below.

```
${normalisation-pipeline}
   ...
   codes
      00norm_prep_pipeline.sh
      T1_2_MNI152_1mm.cnf
      ant_reg3_bbl.sh
      file-structure.R
      fsl_anat_alt_bbl.sh
      fsl_norm_bbl.sh
      modified_brain_mask_bbl.sh
      multi_punch.sh
```

```
   nemo-packing.R
   optiBET.sh
   prep_T1w_bbl.sh
...
```

1. Download or clone the repository to your computer and extract the folder if necessary. Move the contents of the `codes` folder to whereever you find appropriate (or just leave them for now). This is now the "codes folder" and will be referenced as `/codes/folder/` in the script examples. Edit this to run on your computer.

   Now, open a terminal window and navigate to in the parent directory of your data folder, which we will now refer to as the "root directory".

   This pipeline assumes, that your files are organised in the following way. This is not completely according to the BIDS-format, but that might be coming in the future. For now, this is the way:

   ```
   ${ROOT}
      sub01
          sub01_T1w.nii.gz (T1 weighted base image)
          sub01_lesion.nii.gz (lesion mask, optional)
      subNN
          subNN_T1w.nii.gz
          subNN_lesion.nii.gz
   ```

   If, your files are like this, just jump ahead. If your files are all on one folder, but named as above, you can use the `file-prep.R` script to organise subject files into subfolders. Open the script and edit the first three variables. Save it and then, run the following in the terminal window:

   ```
   Rscript file-prep.R
   ```

   Now the files and folders should be structured as expected.

2. *Optional*: If you want to do registration to 1mm MNI space, you need to add a new config file to fsl. If not, skip ahead. The config file is the `.cnf` file in your codes folder, and it can be copied to the correct location using the following command:

   ```
   imcp /codes/folder/T1_2_MNI152_1mm.cnf $FSLDIR/etc/flirtsch/T1_2_MNI152_1mm.cnf
   ```

   Depending on what you are doing, you'll probably be fine doing 2mm registration, but for some use cases, the 1mm registration is necessary. Here is a discussion, I found useful on doing 1 or 2 mm.

term	definition
ANTs	Advanced Normalization Tools. https://github.com/ANTsX/ANTs
BIDS	Brain Imaging Data Structure. https://bids-standard.github.io/bids-starter-kit/index.html
fsleyes	Thes picture viewing tool from the fsl-package. https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes
registration	I this context, registration denotes to art of registrering to normal space. In this case to the MI

3. Now you are ready for start data processing. The script has a few assumptions. It will look for a file with the file name pattern '*[Ll]esion*.nii.gz', and assume this is a lesion mask for the T1 weighted image (which should be named '*T1w.nii.gz'). You may optionally specify the lesion mask file name pattern used, eg: `sh 00norm_prep_pipeline.sh 1mm 'lesion.nii.gz'`. If no lesion mask is in the folder, the script will just perform skull stripping and registration of the head/brain. The script will also assume you want 2mm registration and do so with fsl. To view the documentation and see a few examples run this:

   ```
   sh /codes/folder/00norm_prep_pipeline.sh -h
   ```

   Then, when ready run the main script with your desired settings. Now processing starts, and it will take some time. Sit back and relax while your computer hums away. Or do something else in the meantime. You'll get time stamps along the way to have an idea of the progress and the time needed. The output files are written along the way, so you can manually check the output while the script works. Note that your original T1 and lesion mask will have "_orig" appended as suffix and be substituted with corrected files. If the script gets interrupted, you can just restart it, and it will skip subjects already processed. Make sure you delete the output files, if you want the script to rerun on a specific subject.

4. Now it is time for quality control. Please refer to the separate Chapter 3 on this. Then, you are done and can use these normalised files however you like.

2.2 Glossary

3 Quality control

```
source("glossary_setup.R")
```

As quality control goes, this is not exhaustive, but here is my suggestion as to a minimum approach.

On paper, everything is now done. But of course, you should go through all subjects manually to check that, the masking went well, as that is the real key step in this process.

Sticking to the broader lines, the problems may be of either auto-cropping or masking. As masking goes, the script may have included too much or too little in the brain mask. I'll go through suggested solutions to all these below.

3.1 Inspection

I have come to like the ITK-SNAP tool, but fsleyes is good as well.

I would open the new "SubNN_T1w.nii.gz" in fsleyes or ITK-SNAP and overlay the "SubNN_T1w_brain_mask.nii.gz" and go through to check the masking and cropping. Check the cropping and the masking. Happy? Carry on to the next subject. Not so much? See below.

3.2 Cropping

Do not skip this step. Take a good look at the cropping, as the algorithm might have cropped out part of cerebellum (typically the issue, if any).

1. Delete all the output-files (remembering that the original files were preserved with "_orig" suffix) and renaming the original files removing the suffix.
2. Open the original T1 image and lesion mask in fsleyes, and manually crop the two with the same mask when cropping, you can save the crop mask from the T1 and load it for the lesion mask). If the two files are not cropped to the same dimensions, they won't align, and you'll be in trouble.

3. After cropping, run the `00nemo_prep_pipeline.sh` script again. It will only run in folders with the *.anat folder not present.

3.3 Masking

In ITK-SNAP, you can correct the brain mask manually. Overall, open the "SubNN_T1w.nii.gz" with `Control-G` (linux), `Control-G` (windows), `Command-G` (mac) and the "SubNN_T1w_brain_mask.nii.gz" with `Control-O` (linux), `Control-O` (windows), `Command-O` (mac). You can manually edit the brain mask by using the interpolate tool to apply changes to all layers in all three planes. Please have a look at this demonstration of the tool. Make sure that changes are made in a different label to the main label of the brain mask segmentation.

Here, I'll just go through an order of work for the two different cases:

3.3.1 Too little

This is simple. You just add the missing:

1. Using the drawing tool, include the missing parts of the brain/infarct in the new label. You can get by by just drawing on each 5-7 layers in the axial plane. Then do interpolate along the axial axis. Check that you are satisfied. If not, then `Control-Z` (linux), `Control-Z` (windows), `Command-Z` (mac). Add a few other layers of manual drawing. Interpolate again. When done, save as a new file.

3.3.2 Too much

This is also relatively simple, but has an extra step:

1. Invert the lesion mask:

```
fslmaths SubNN/SubNN_T1w_brain_mask.nii.gz -binv SubNN/SubNN_T1w_brain_mask_INV.nii.g
```

2. Follow the same steps as above to add non-brain area to exclude from the brain mask. Save the new brain mask and then invert the modified inverted brain mask again:

```
fslmaths SubNN/SubNN_T1w_brain_mask_INV.nii.gz -binv SubNN/SubNN_T1w_brain_mask_MODIF
```

3. Check that you are satisfied with the result.

3.3.3 Register to MNI space again

1. Having a new, modified brain mask, go to the terminal window again and write the following:

   ```
   sh modified_brain_mask_bbl.sh SubNN/SubNN_T1w.nii.gz SubNN/SubNN_T1w_brain_mask_MODIF
   ```

   Please notice that the naming of the modified brain mask doesn't matter.

3.4 Final quality control steps

After registering the lesion mask to standard space, please make sure, that you are satisfied with the result. You might have to correct to masking, especially if its a large lesion. In my experience, the common problem is that the algorithm have left out some of the infarcted area towards cortex. In ITK-SNAP you can add this area. If the lesion is all the way to the surface of the cortex, then make sure to overfill towards the surface (into the non-brain area). Afterwards, you can perform a three step approach to "punch" out the lesion only to the surface of the brain.

1. The following will create an inverted MNI brain mask in you source directory. Make sure that the fsl directory is correct.

   ```
   fslmaths /usr/local/fsl/data/standard/MNI152_T1_1mm_brain_mask.nii.gz -binv mni_1mm_b
   ```

2. The next is the short version of a three-step operation to 1) make sure the lesion mask is binary, 2) subtract the inverted MNI brain mask as an inverted hole-puncher, and finally 3) using the threshold function to isolate the lesion mask. Please correct the subfolder and file names.

   ```
   fslmaths subNN/subNN_T1w_MNI-1mm_lesion.nii.gz -bin -sub mni_1mm_brain_mask_inv.nii.g
   ```

3. Now please rename the old MNI lesion mask and remove the "_punch" suffix from the new lesion mask name to follow the standard naming.

If you are performing several of the "punch-out" actions, I have created a small script `other/multi-punch.sh`, that will automate this process a bit. To run it, you provide a folder name to search and a common regex pattern to search for within the folder (it includes with sub-folders). The syntax would be like this:

```
sh multi-punch.sh /sourcefolder "*_lesion.nii.gz"
```

term	definition
fsleyes	Thes picture viewing tool from the fsl-package. https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes
regex	Short of Regular Expression. Provides a very powerful character search interface. There are various

3.5 Glossary

Part I

Use case #1: Finding NeMo

4 Preparations

Following the steps laid out in Chapter 2, we got all lesions normalised to standard 1mm MNI space, and they are all located in the individual subject folders, som we just need a few steps to offload work to the NeMo-tool. This was the command used to perform fsl based registration to 1 mm MNI standard space:

```
sh /codes/folder/00norm_pipeline.sh --do1mm
```

1. Now you should be ready to package for the NeMo tool. The web interface has an upload limit of 10 lesion masks. Open and edit the source-folder in the `nemo-packing.R` script. It will collect all 1mm MNI lesion masks and package in zip-files of max 10 lesion masks each and put them in the provided folder. Save and then run the following:

   ```
   Rscript nemo-packing.R
   ```

Then files were uploaded and sent to the NeMo tool server.

4.1 Glossary

```
data frame with 0 columns and 0 rows
```

5 Using the NeMo tool

This section will exists as documentation on how we have worked with the NeMo tool. Coding is very much inspired and copied from other sources. I will try to write sources and inspiration.

5.1 Package and upload

First step is to get the normalised lesion masks processed by the NeMo tool to get a "disconnectome".

The online instance of the tool offers to freely process lesion masks in batches of 10. You can use the bundled *R*-script to package lesion masks into compressed zip-batches of maximum 10.

1. Open the `nemo_packing.R` file and edit the variables in the first section, then run the script, from either RStudio or the command terminal window:

   ```
   Rscript nemo-packing.R
   ```

2. Then head over to the NeMo processing website and upload the zip-files, one at a time with your desired settings and atlas for parcellation.

5.2 Glossary

term	definition
connectome	Term used to denote the collection of connections in the brain.
NeMo	Network Modification tool. https://github.com/kjamison/nemo

6 ZIP to data set

So, here I'll show how we went from compressed zip file, from the NeMo tool, and to having a data set for further analyses.

I am fairly new to Python, but have worked in R for many years. This means, that I have written just enough in Python, and everything else in R. Small python functions will be wrapped in R scripts. Just a word of warning.

First, extract the compressed file and put it where you like. I'll denote this location as the `source.folder`.

```
# source.folder <- "/full/path/NeMo_output"
source.folder <- "/Users/au301842/NeMo_output"
```

Then we want to extract the `chacovol` data. This is extracted by unpikling `.pkl` files using a short python script wrapped in R:

```
source("nemo/unpkl-sparse.R")
unpkl_sparse(data.folder = source.folder,
             "chacovol_yeo17_mean.pkl")
```

The unpikled files are then collected and merged in a wide format.

But first, we need to handle the provided atlas `.txt` files to get ROI names:

```
atlas <- readLines("/Users/au301842/NeMo_output/Yeo2011_17Networks_NetworkNames_ColorLUT.t
rois <- do.call(c,lapply(atlas[-1],function(i){
  s1 <- strsplit(i,"_[0-9]{1,3}_")[[1]][2]
  strsplit(s1," ")[[1]][1]
  }
  ))
```

```
source("nemo/nemo-collect.R")
df <- nemo_collect(
  data.folder = source.folder,
  id.pattern = "W[0-9]{2}",
```

```
  file.pattern = "chacovol_yeo17_mean.tsv",
  roi.names = rois
)
```

I very much prefer writing function to do the data handling, but I just have to note, that these functions are very primitive due to lack of time on my end. But they are working and will provide a good foundation for further worker.

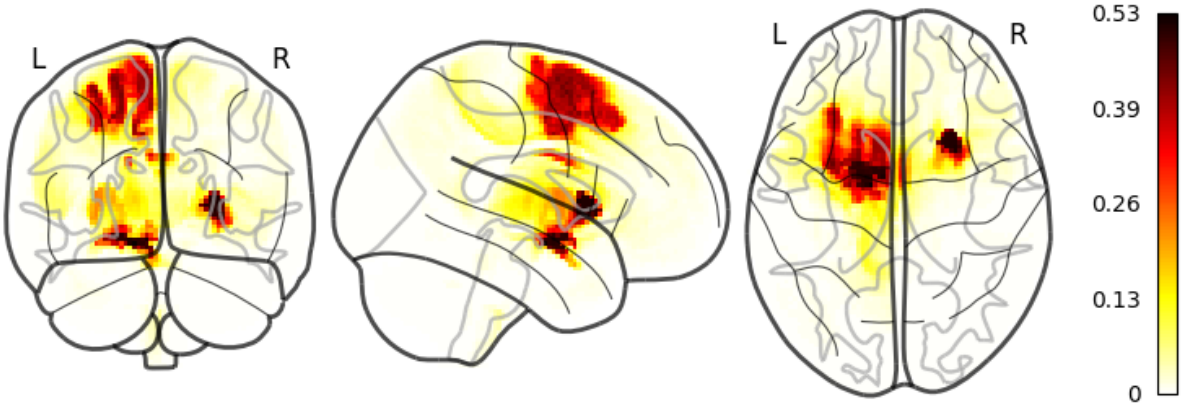
6.1 Visualisation

> ! Please note that the NeMo-repository is shared without a license
>
> This means it is technically not allowed to modify or redistribute the code. Please refer to {#contents}.

We also want those nice glass brains. These following R scripts are all simple wrappers for the scripts from the NeMo tool, which uses the `nibabel` Python package for plotting. All the examples below are created based on a small sample of two subjects and the Yeo17 atlas which is also shared in the NeMo tool source.

First we do the simpel voxel based heatmap.

```
source("nemo/glass-brain.R")
glass_brain(
  data.folder = source.folder,
  file.pattern = "chacovol_res2mm_mean.nii.gz",
  out.name = "images/glass_chacovol.png"
)
```



Next we can do the parcellation or atlas based chacovol plotting:

```
source("nemo/glass-brain.R")
glass_brain(
  data.folder = source.folder,
  file.pattern = "chacovol_yeo17_mean.pkl",
  out.name = "images/glass_chacovol_parc.png",
  parcellation = "/Users/atlas/folder/Yeo2011_17Networks_MNI152_182x218x182_LiberalMask.ni
)
```

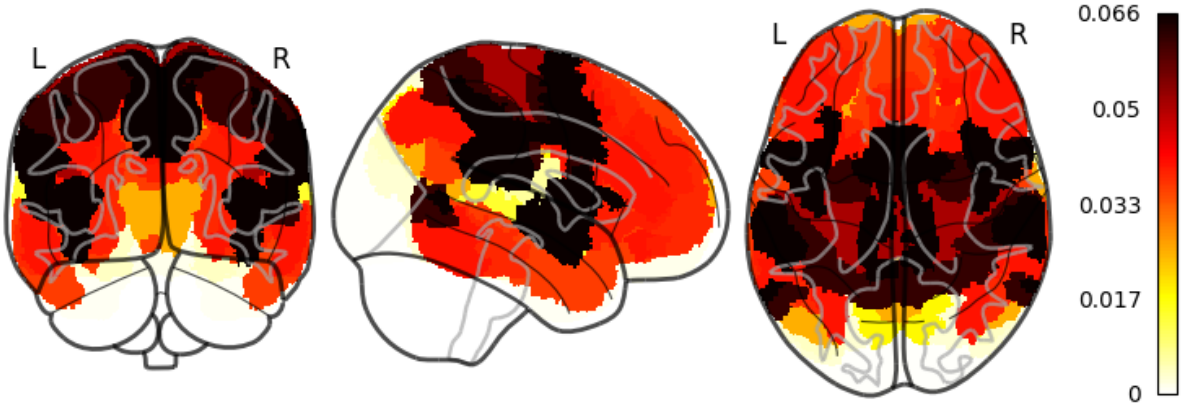


Figure 6.1: Averaged parcellation based chacovol glassbrain plot

The same scirpt can also be used for lesion plotting:

```
glass_brain(
  data.folder = "/Users/folder/with/lesions/",
  file.pattern = "lesion.nii.gz",
  id.pattern = "W(50|49)", # This id.pattern is used to only include specified ids
  out.name = "images/glass_lesion.png"
)
```

And finally the change in connections between areas in the brain can be visualised as a graph-brain:

```
source("nemo/graph-brain.R")
graph_brain(
  data.folder = source.folder,
  file.pattern = "chacoconn_yeo17_mean.pkl",
  out.name = "images/glass_chacoconn.png",
  node.file="/Users/atlas/folder/Yeo2011_17Networks_MNI152_182x218x182_LiberalMask.nii.gz"
```

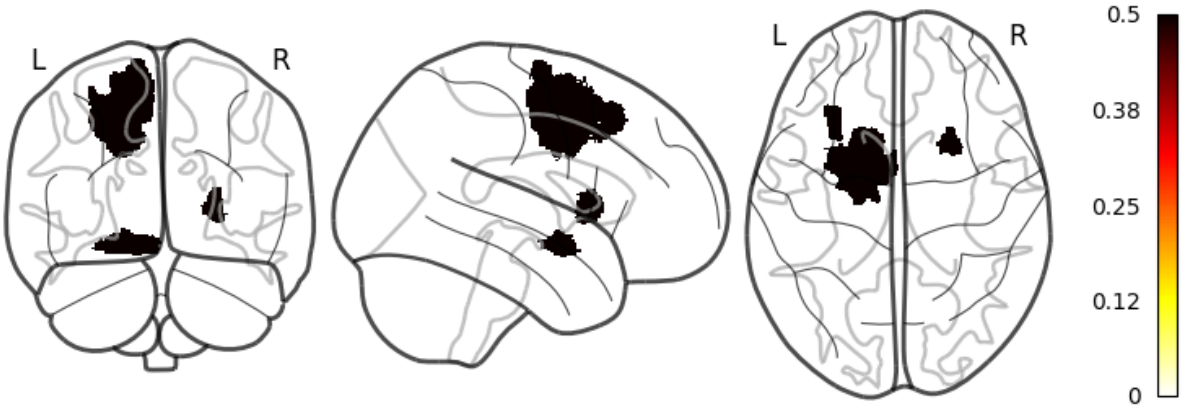


Figure 6.2: Combined lesion plot

```
)
```

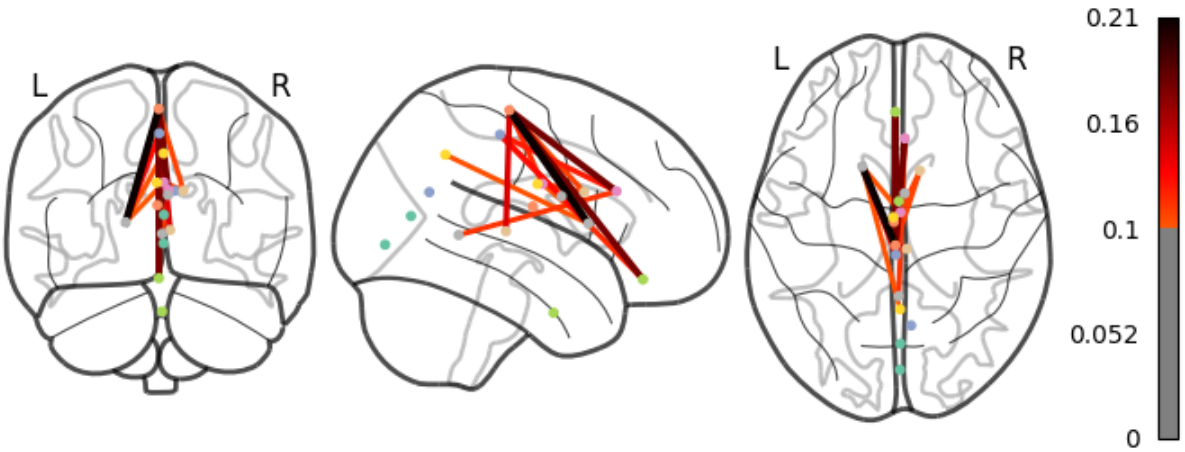


Figure 6.3: Graph brain plot of lost connections between atlas based ROIs

6.2 Glossary

```
data frame with 0 columns and 0 rows
```

A Changelog

A.1 2024.1.1

Changed versioning scheme.

As the NeMo-tool is published without a license, the package or parts of it cannot be redistributed, and should instead be downloaded directly from the NeMo repository. This pipeline-project is shared under the FOSS-license A-GPL-v3.

This version will be the first released on Zenodo and have a DOI.

DESCRIPTION file added for easier cloning of the project. Initialise `renv` with `renv::init(bare=TRUE)`.

A.2 2023.10.06

This is the final version before leaving the Brain Behavior Lab for now. I have been working hard on maturing the script to better handle different use cases.

The script will run without any specifications passed to it and default to 2 mm fsl registration with or without a lesion mask. It also 1 mm registration if you follow the instructions to supply a modified `.cnf` config file to fsl, see Chapter 2. It also does ANTs registration, but only if a lesion mask is supplied. The script also allows for lesion mask regex specification as well as regex subfolder specification. It will stopp processing if there are several lesion masks in a subfolder. The scripts in `codes/` can be located anywhere, but has to be launched from a terminal window in the parent folder of subject-wise data folder. See the Section 2.1 regarding expected file structure.

Comments and questions are welcome on GitHub Discussions.

A.3 2023.10.05

A.3.1 Notes

Restructuring of the initial book to better emphasize the more general usability of the pipeline. This will prevent renaming the repository and widen the usability. The pipeline was recently tweaked to run 1-level subfolders with or without lesion masks, and final registration space (1/2 mm) is specified on first run. The script are still a little primitive, in that they don't have a ton of control steps built in, so please stick to documentation or start modifying yourself. I'll be very happy to receive comments and PRs here on GitHub.

A few other checks has been added to make the script working a little more robustly. It will give error if several lesion masks are detected. Append data+time as suffix to original files to avoid overwriting on script re-runs.

A.3.2 Changes (non-extensive)

- 00norm_pipeline.sh: everything should now have comments. Handles missing lesion masks more elegantly. Input with named flags and help section. Runs with defaults. ANTs registration option included. Renamed.
- fsl-norm-bbl.sh: now actually does registration of lesion masks, and binarises the lesion normalised lesion mask, if it is there.
- ant_reg3.sh: script included to provide optional ANTs registration. See https://github.com/ANTsX/ANTs for installation instructions. If ANTs is installed in a virtual environment, everything should be run from within this.

B Session info

```
sessionInfo()
```

```
R version 4.3.1 (2023-06-16)
Platform: aarch64-apple-darwin20 (64-bit)
Running under: macOS Sonoma 14.1.2

Matrix products: default
BLAS:   /Library/Frameworks/R.framework/Versions/4.3-arm64/Resources/lib/libRblas.0.dylib
LAPACK: /Library/Frameworks/R.framework/Versions/4.3-arm64/Resources/lib/libRlapack.dylib;  L

locale:
[1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8

time zone: Europe/Copenhagen
tzcode source: internal

attached base packages:
[1] stats     graphics  grDevices datasets  utils     methods   base

loaded via a namespace (and not attached):
 [1] compiler_4.3.1    fastmap_1.1.1     cli_3.6.2         htmltools_0.5.7
 [5] tools_4.3.1       rstudioapi_0.15.0 yaml_2.3.8        rmarkdown_2.25
 [9] knitr_1.45        jsonlite_1.8.8    xfun_0.41         digest_0.6.33
[13] rlang_1.1.2       renv_1.0.3        evaluate_0.23
```

B.1 Libraries used in the project

These are the projects listed with `renv::dependencies()`

```
renv::dependencies()$Package |> unique()
```

```
Finding R package dependencies ... Done!
```

```
[1] "glossary"  "rmarkdown" "stRoke"    "zip"       "here"      "styler"
[7] "usethis"   "renv"
```

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