

brainGraph User Guide

Version 2.0.2

Christopher G. Watson, Ph.D.

*Dept. of Pediatrics, Children's Learning Institute
University of Texas Health Science Center at Houston*

February 24, 2018

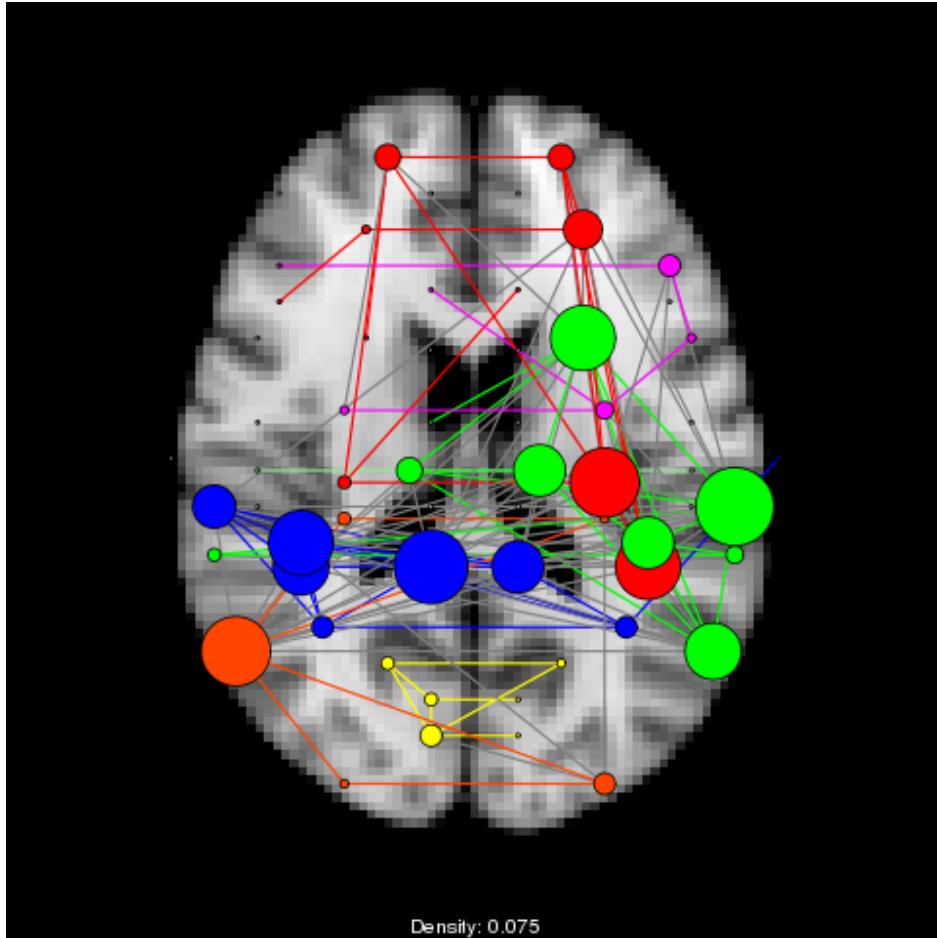


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Preface

`brainGraph` is an R package for performing graph theory analysis of brain MRI data. It started out essentially as one long script I wrote while taking a course in Fall 2013 on the statistical analysis of network data. Initially, the functionality was specific to cortical thickness data only (from `Freesurfer`), but I have since extended it to include functionality for DTI tractography (e.g., `fdt_network_matrix` from FSL’s `probtrackx2`, and matrices from `PANDA` (18)) and resting-state fMRI (e.g., DPABI (91) and AFNI (14)). It should work for any data that can be represented as a connectivity matrix. There is some plotting functionality, but it doesn’t look as “polished” as other software. (However, it looks comparable to figures I have seen in publications; see [Plotting](#) for some example plots and a function to export the network data, and [The GUI](#) for a few screenshots of the GUI).

Organization of this Manual

At the highest level of organization, there are several *Parts*. The general contents of each part are:

Introductory material contains installation information, validity of graph metrics calculated by `igraph` and `brainGraph`, neuroimaging software and brain atlas compatibility, how to get help, other R packages that may be of interest to neuroimaging researchers, and some code examples for getting data from `Freesurfer` and `FSL`.

brainGraph basics contains information for starting to use the package. This includes a general overview of the package, a brief introduction to R notation/conventions, a recommended workflow/script organization, and an introduction to the package’s features and most basic operations.

Graph creation covers the necessary steps for creating graphs from your neuroimaging data. There are separate chapters for *structural covariance networks* and data for which single-subject networks can be created (e.g., DTI tractography or resting-state fMRI). The code blocks in these chapters start with importing your data and end with some example operations you can perform on the graphs.

Group analyses detail the available methods for comparing groups (or performing within-group analyses). These include the standard GLM, the *Network-Based Statistic (NBS)*, and statistical mediation analysis for single-subject graphs. For covariance networks, this includes bootstrapping, permutation/randomization tests, and *individual contributions*. And for both types of network, *random graph* generation, *small world* calculations, and *rich club* analysis.

Visualization describes the components of the `brainGraph` GUI, in addition to other functions for visualizing different aspects of your data, such as adjacency matrix plots, plotting global (graph-level) metrics by density, boxplots of vertex-level metrics, creating three-panel plots of the networks overlaid on a brain MRI slice, and saving a list of graph plots. The chapter closes with description of a function for exporting your data to work with the `BrainNet Viewer` tool.

Appendices list the attributes set by the function `set_brainGraph_attr`, several benchmarks (i.e., runtimes) for various functions/analyses, and the computing environment used in creating this document.

Intended Audience

This User Guide is appropriate for researchers who use brain MRI to study *connectivity*. `brainGraph` is not strictly limited to human MRI data, but it does not contain atlases for animal brains (but these can be provided by the user). It is expected that the user has *some* experience with R (and/or other programming languages), but this document should be appropriate for beginners. The user should have some understanding of network/graph theoretical concepts. This User Guide is quite long, but I have attempted to be comprehensive in documenting the functions in the package and the types of analysis that are common in neuroimaging, with extensive code examples and figures. To learn more about the relevant topics (i.e., the mathematics of networks, R programming), see some of my suggestions at [Getting Help and Other Resources](#).

Rationale

“The nice thing about standards is that you have so many to choose from.”

— Andrew S. Tanenbaum

Other tools for performing graph theory analysis of brain MRI data already exist. So why create a new one, and why do it in R?

R is Free Software

Using R does not require an expensive license (like Matlab), and does not involve any “red tape” (such as the need to upgrade annually, having to deal with a licensing office, etc.). You can simply download and install it. R is also open source, so you can add features, fix bugs, etc. Finally, you can write your own packages, either for personal or public use. **This package is, and will remain to be, free and open source**, in line with the recent push for sharing your code along with publications (see Eglen et al. (24) for discussion).

R was made to do statistics

The designers of R were statisticians (as are most/all of the R `core` members). Many statisticians use R in their work. Additionally, there are currently more than 10,000 packages in the *CRAN* repository (as of Feb. 2018), many of which are created and maintained by experts in statistics. If there is a statistical analysis you would like to perform, there’s a good chance it is available in R. The R community is very extensive, with multiple e-mail lists, blogs, and forums (such as [Stack Overflow](#)) available for help.

Package management

Package management is very well done in R; downloading and updating packages is nearly trivial. I have had a much easier time with R compared to dealing with dependencies for e.g., some Python-based software (I know there is `pip`, but I had some issues; see this [Stack Overflow question](#), which I’m sure is now out-of-date). I consider myself tech-savvy, so I imagine it would be even more frustrating for beginners. Downloading and installing `brainGraph` and its dependencies should be very simple, so the user can focus on learning graph theory and how to interact with their data.

Documentation

I have found the documentation for other tools/software specializing in graph theory analysis of MRI data to be lacking (and in some cases non-existent), particularly in terms of the first step: getting your data (cortical thickness/volumes, tractography, etc.) into a format that will *just work*. It has been said that software is “only as good as its documentation”; I appreciate that many users just want a tutorial to walk them through the steps, and I hope I have succeeded in that aspect.

Good support for reproducible research

It is very easy to generate reproducible reports (or documents such as this one) on-the-fly. For this User Guide, I used `knitr` (90) with L^AT_EX, and all the code is in a `git` repository for *version control*. This system allows for easy documentation of analysis workflow and any changes in output resulting from parameter changes; (re-)running all the code is essentially automatic (I simply press `\kp` using

Nvim-R with *tmux* to knit the pdf). I use the same process for generating results from other analyses I do in R, such as reporting summary statistics from DTI analyses of FA/MD/RD.¹ Furthermore, Tables are generated automatically, so I don't have to type all entries by hand, or copy-paste things and worry about formatting (reducing user error). In fact, my dissertation was written with `knitr` and L^AT_EX because of these features.

Why isn't there a “main” GUI?

Although GUI's can be helpful to beginners, I chose not to create a “point-and-click” GUI for all of the processing/analysis steps (except for exploring the results visually with `plotBrainGraph_gui`) because I think it is of paramount importance to be “closer” to your data, instead of expecting a software package to do all of the work. That said, this User Guide will provide examples for data organization and example code to be placed in scripts that you can then run from the R console. So technically, you could “copy-paste” the code from this User Guide and complete your analyses without paying attention, but I don't recommend it. *Inspect your data at every step.* I believe I have provided enough code to do that easily.

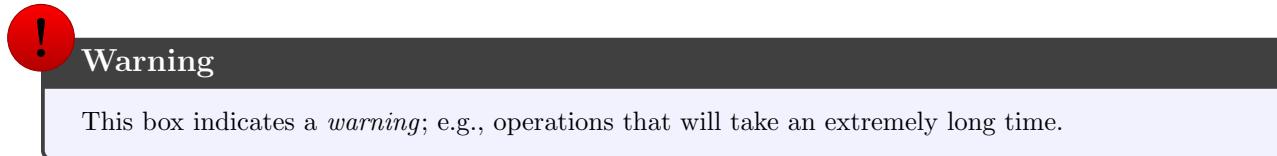
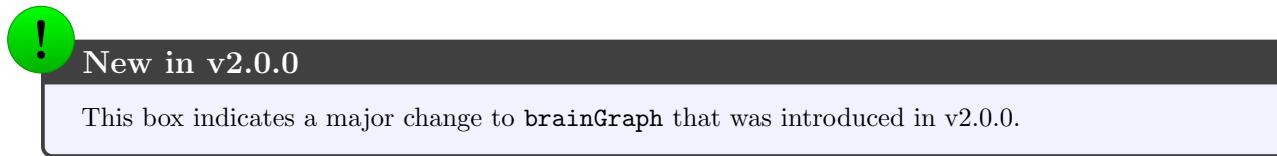
Typographical conventions

I use different font styles to indicate different types of objects:

- Software tools/packages, R functions/objects (not in `brainGraph`), inline code, data objects (e.g., function arguments or data column names), and filenames are printed in `monospace font`.
- Functions in the `brainGraph` package are highlighted and in monospace font.
- R code is printed in `monospace font in a box with light gray background`, with syntax highlighting applied.
- Linux command-line code is printed in a separate text box (also with some syntax highlighting).
- Graph metrics are printed in *italicized font*.
- Links to chapters/sections, figures, tables, and footnotes are printed with `red font`.
- External links (i.e., URL's) are printed with `blue font`.
- Citations are printed with `green font`.

Icons and text boxes used

There are several places where you will see a colored text box (occasionally with an exclamation mark):



¹There are other solutions in R that are similar to the Jupyter notebook, see for example `rNotebook` and `editR`

Note

This box replaces a footnote if the note is long.

Release Notes

Including all release notes would extend this document unnecessarily. You can always find the `NEWS.md` file at the `brainGraph` repository: <https://github.com/cwatson/brainGraph/blob/master/NEWS.md>

Citing brainGraph

First, please cite Ref. Csardi and Nepusz (17) and any other relevant references for calculating certain graph theory measures (see function documentation for some references). `brainGraph` is very reliant on `igraph`, and they should be cited for their work.

I do not currently have a manuscript that specifically describes/introduces the package, but you may cite Watson et al. (84). You also can get some citation information with the following code:

```
citation('brainGraph')

##
## To cite package 'brainGraph' in publications use:
##
##   Christopher G. Watson (2018). brainGraph: Graph Theory Analysis
##   of Brain MRI Data. R package version 2.0.2.
##   https://github.com/cwatson/brainGraph
##
## A BibTeX entry for LaTeX users is
##
##   @Manual{,
##     title = {brainGraph: Graph Theory Analysis of Brain MRI Data},
##     author = {Christopher G. Watson},
##     year = {2018},
##     note = {R package version 2.0.2},
##     url = {https://github.com/cwatson/brainGraph},
##   }
##
## ATTENTION: This citation information has been auto-generated from
## the package DESCRIPTION file and may need manual editing, see
## 'help("citation")'.
```

Publications using brainGraph

- Caligiuri et al. (10)
- Barbagallo et al. (3)
- Tanimizu et al. (74)
- Cinelli et al. (12)
- Watson et al. (84)

Part I

Introductory Material

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1

Installation and Requirements

1.1 System Requirements

There aren't any, specifically. But I have some recommendations:

- *Hardware* - you should have a multi-core CPU and lots of RAM (the more, the better; probably at least 4 GB). Having a large number of cores is very important, particularly if you want to do permutation testing or bootstrapping (or if you are working with very large graphs). Note that you will need a lot of RAM with more CPU cores.
- *Operating System* - I 100% recommend using Linux (my personal preference is CentOS; RHEL and Scientific Linux are the same, and Fedora is similar). If you have been using Freesurfer and/or FSL, then you likely have access to a Linux machine. It may be worthwhile to spin up a virtual machine running some flavor of Linux. Almost all testing and developing of this package was done on 64-bit CentOS 6 and CentOS 7. Some was also done on 64-bit Windows 7.
- *Packages* - there are several packages that are required/recommended:
 - `igraph` (current version is v1.1.2)
 - `RGtk2` and `cairoDevice` (for the GUI)
 - `Hmisc` (just for the function `rcorr`, but it's useful in its own right)
 - `foreach` (for parallel processing)
 - `doMC/doSNOW` (multicore package for Linux/Windows)
 - `oro.nifti` (a general *NIfTI* library)
 - `data.table` (excellent general-purpose package)
 - `ggplot2` (excellent for plotting)
 - `scales` (for some plotting functionality)
 - `boot` (for bootstrapping)
 - `abind` (for multi-dimensional arrays)
 - `ade4` (for `loo` and `aop`)
 - `permute` (to generate random permutations)
 - `RcppEigen` (for fast linear model calculations)
 - `MASS` (supports the Venables & Ripley textbook *Modern Applied Statistics with S*([80](#))
 - `Matrix` (provides a number of classes and methods for matrices)
 - `mediation` (causal mediation analysis)
 - `gridExtra` (helpful for plotting)

- `expm` (calculates matrix exponentials)
- *R interface* For users not comfortable with a full command line interface, I recommend using [RStudio](#). It is a full desktop environment (free), that is *very* similar in look and concept to the [Matlab](#) desktop.

1.2 OS-specific instructions

Regardless of the operating system, to install the latest stable version, you can download it from *CRAN* by simply typing:

```
install.packages('brainGraph')
```

For the latest development version, use `devtools` to install it from *Github*. It should install all dependencies for you.

```
install.packages(devtools)
devtools::install_github('cwatson/brainGraph')
```

1.2.1 Linux

You may [download the tarball](#) and on the command line, type:

```
R CMD INSTALL brainGraph_${VERSION}.tar.gz
```

1.2.2 Mac

I haven't tested on Mac yet, but here are the versions that it should work on:

- *macOS 10.13 High Sierra*: see [this GitHub Gist](#). Of note, look at the comments for more information.
- *macOS 10.12 Sierra*: passed *CRAN* checks.
- *OS X 10.11 El Capitan*: *has not* passed recent *CRAN* checks (specifically, version *10.11.6*), but I have had previous confirmation from a user that it works.
- *OS X 10.10.5 Yosemite*: it may be necessary to download the binary GTK package (`.pkg` file) from <https://r.research.att.com/>.
- *OS X 10.9.2 (13C64)*: passed *CRAN* checks.

As I mention above (under *macOS 10.13*), see the following link if you run into an issue with installing `RGtk2`: <https://gist.github.com/sebkopf/9405675#macos>. The comments section may contain helpful information as well.

1.2.3 Windows

You should first try to download directly from *CRAN*. If that causes any problems, I recommend using `devtools` and installing directly from *Github*. See also the URL listed under the *Mac* section for some instructions when it comes to installing `RGtk2`. You may end up needing to add/edit a couple *environment variables*.

- Packages that *may* need to be installed manually are: `gWidgets`, `gWidgetsRGtk2`, `RGtk2Extras`
- To install *from source* on Windows, you first have to download and install [Rtools](#)

- You may have to install either the 32- or 64-bit version *only*, in case there is a problem with GTK+ (required for the plotting GUI). To install the package for just one architecture, add `INSTALL_opts='--no-multiarch'` to the above call to `install.packages`.

1.3 Compatible neuroimaging software

The functions in `brainGraph` should work for any software that returns a text file containing connectivity matrices (unless you are creating covariance/correlation networks). Here is a list of software that I know to work (either first-hand or from a `brainGraph` user):

- [Freesurfer](#) (for structural covariance networks)
- [FSL](#) (specifically DTI tractography using `probtrackx2`)
- [DPARSF](#) (seed-based connectivity from resting-state fMRI; see Ref. (91))
- [PANDA](#) (for DTI analyses; see Ref. (18))
- [TrackVis](#) (for DTI analyses; see Ref. (83))

1.4 Compatible atlases

There are a handful of atlases that will work “out-of-the-box”. These are:

- *Desikan-Killiany*: called `dk` in the package (20)
- *Desikan-Killiany-Tourville*: called `dkt` (47)
- *Destrieux*: called `destrieux` (21)
- *FS atlases w/ scgm*: called `dk.scgm`, `dkt.scgm`, `destrieux.scgm`
- *AAL*: called `aal90` (only cortical and subcortical ROI’s) and `aal116` (includes the 26 cerebellar ROI’s); see Tzourio-Mazoyer et al. (77)
- *AAL2*: called `aal2.94` (only cortical and subcortical) or `aal2.120` (with cerebellar ROI’s); see Rolls et al. (65)
- *Dosenbach*: called `dosenbach160` (22)
- *Craddock-200*: called `craddock200` (15)
- *Harvard-Oxford*: called `hoa112` (53)
- *LONI probabilistic brain atlas*: called `lpba40` (71)
- *Brainsuite*: called `brainsuite` (59, 70)

Here are several lines of the `dk` atlas (this object is a `data.table`). The `name.full` column is provided so you can create a table for publication (although not all atlases have this column).

```
dk [4:9]
```

```

##   name x.mni y.mni z.mni      lobe hemi index          name.full
## 1: 1CUN    -1   -82    20 Occipital     L     4           L cuneus
## 2: 1ENT   -16   -10   -29 Temporal     L     5        L entorhinal
## 3: 1FUS   -24   -54   -16 Temporal     L     6         L fusiform
## 4: 1IPL   -47   -70    31 Parietal     L     7 L inferior parietal lobule
## 5: 1ITG   -56   -32   -24 Temporal     L     8 L inferior temporal gyrus
## 6: liCC    -1   -48    25 Cingulate    L     9 L isthmus cingulate cortex

str(dk, strict.width='cut')

## Classes 'data.table' and 'data.frame': 68 obs. of  8 variables:
## $ name    : chr "1BSTS" "lcACC" "lcMFG" "1CUN" ...
## $ x.mni   : num -56 -2 -45 -1 -16 -24 -47 -56 -1 -43 ...
## $ y.mni   : num -44 21 18 -82 -10 -54 -70 -32 -48 -87 ...
## $ z.mni   : num 5 27 46 20 -29 -16 31 -24 25 1 ...
## $ lobe    : Factor w/ 6 levels "Frontal","Parietal",...: 3 6 1 4 3 3 2 3...
## $ hemi    : Factor w/ 2 levels "L","R": 1 1 1 1 1 1 1 1 1 ...
## $ index   : int 1 2 3 4 5 6 7 8 9 10 ...
## $ name.full: chr "L bank of the superior temporal sulcus" "L caudal an"...
## - attr(*, ".internal.selfref")=<externalptr>
## - attr(*, "index")= atomic
## ..- attr(*, "_index")= int
## ..- attr(*, "_lobe")= int 3 11 13 16 17 18 19 23 26 27 ...

```

1.4.1 Custom atlas format

If you have an atlas you would like to use, then just follow the data structure shown above, and it *should* work without issue. The requirements are: ¹

- The object must be a `data.table`
- The `lobe` and `hemi` columns should be *factor* variables.
- The `index` column is simply an integer sequence from 1 to the number of rows (regions).
- You can also include additional columns if you wish. For example, `dosenbach160` is the only atlas to contain a `network` column, seen in the code block below. I calculate *assortativity* based on these values, and you can calculate other graph measures based on these network delineations as well.

```

dosenbach160[, table(network)]

## network
##           default    fronto-parietal cingulo-opercular      sensorimotor
##             34                  21                   32                   33
## cerebellum          occipital
##             18                  22

```

I recommend writing the data object as a `rda` file (using `save`); then it can be re-loaded with `load`.

1.4.2 Atlases to be added

I intend on adding more atlases in the future. The following list is a work-in-progress.

¹See the structure of other atlases by typing e.g. `str(dosenbach160)`.

- *Power-264* ([60](#))
- *Gordon-333* ([32](#))
- *Shen-268* ([72](#))

2

Getting Help and Other Resources

2.1 Getting help

The main *CRAN* page for `brainGraph` is <https://cran.r-project.org/web/packages/brainGraph/>; there you will find the R reference manual. The *Github* repository page is <https://github.com/cwatson/brainGraph>; this contains the package source code for the latest development version.

For general questions, complaints, bug reports, feature requests, criticisms, etc., you have 2 options:

1. Join the *Google Group*, `brainGraph-help`, by going to the [Google Group page](#) and clicking *Apply to join group*. The email address for the group is brainGraph-help@googlegroups.com.
2. Open an *issue* on the [Github issues page](#). This requires that you have a *Github* username already. I am emailed any time an issue is opened.

2.2 Learning resources

2.2.1 Graph theory

M.E.J. Newman's text is perhaps the best comprehensive textbook on networks, and is appropriate for beginners and experts alike (55). In the literature, there are many extensive/classic review articles on graph theory. For an incomplete list, see the [Wiki](#) on my *Github* page. If you want to learn more about network statistics (in general, not domain-specific), I recommend Kolaczyk's text, which requires at least an intermediate level of statistical knowledge (48). To learn more about network statistics using `igraph` specifically, I recommend Kolaczyk & Csardi (2014) (part of the *Use R!* series) (49).

2.2.2 R programming

For help with learning R itself, there are a multitude of tutorials (freely) available, and I can help with code issues specific to `brainGraph`. Some websites that might be of use:

- [R-tutor](#)
- [Quick-R](#)
- [R for Matlab users cheat sheet](#)
- [Stack Overflow](#): questions tagged with R

2.3 Other R packages

2.3.1 Other network-related packages

Besides `igraph`, there are several R packages that deal with networks. First, you can see the graphical models Task View, which lists packages with functionality specific to graphs.

network General network tools; [CRAN page](#)

intergraph Package for converting between `igraph` and `network` packages; [CRAN page](#)

statnet An integrated suite of packages; [CRAN page](#)

tnet Tools for analyzing weighted networks; [CRAN page](#) and [Tore Opsahl's personal page](#)

sna Tools for social network analysis; [CRAN page](#)

Rgraphviz Interface for the `graphviz` library for visualization; [Bioconductor page](#)

2.3.2 Medical Imaging Task View

There are quite a few R packages for working with MRI data. First, there is a “CRAN Task View”, *Medical Imaging*, that is a collection of medical image analysis packages. The website is [here](#).

2.3.3 Neuroconductor

Neuroconductor is a repository of medical image analysis packages as well. The name calls to mind the *Bioconductor* project for molecular biology. More information can be found [here](#).

2.3.4 Implementations of popular MRI software

There are several packages that are re-implementations of other popular tools.

fslr Port to FSL tools

spm12r Port to SPM tools

freesurfer Port to Freesurfer

ANTsR Implementation of ANTs tools

rcamino Port of Camino

hcp Connects to the Human Connectome Project

2.3.5 Other

Finally, there are still more packages for working with MRI data:

RNifti Read and write NIfTI images

tractor Tools for tractography in R

dti DTI processing in R

RAVEL Processing and analysis of MRI data

2.4 Validation of graph metrics

Since I don't expect potential users to blindly trust that my code will do what they want it to do, I have compared results using `brainGraph` with results from Brain Connectivity Toolbox (BCT). There are a few minor differences that appear to be off by just a scalar:

	Measure	
No differences	Degree	Strength (weighted networks)
	Edge betweenness	K-coreness centrality
	Subgraph centrality	Within-module degree z-score
	Participation coefficient	Clustering coefficient
	Transitivity (graph-wise)	Assortativity (graph-wise)
	Global efficiency	Local efficiency
	Connected components	Motif frequency (# of triangles)

Betweenness centrality

Results obtained from BCT are exactly 2x that of `igraph`.

Eigenvector centrality

Results obtained from BCT are ≈ 3.6 x that of `igraph` (for unknown reasons)

Leverage centrality

Doesn't exist in BCT

Characteristic path length

To get the same answer as in BCT, use:

```
mean(shortest.paths(g)[!is.infinite(shortest.paths(g))])
```

However, the 2 correlate perfectly, and the largest absolute difference I have seen is ≈ 0.03 (which is less than 1%)

Rich club

Number of edges is exactly 2x in BCT compared to `brainGraph` (and is incorrect in BCT)

Modularity (Louvain)

There are differences, but minor. I don't know if they are systematic or not.

If you still would like to convince yourself, or do your own testing (please do so!), download the `R.matlab` package and use the following code. To understand what these variables are, see Chapter 5 (and later). To use these variables in Matlab, simply type (in Matlab) `load g1.mat`.

```
A <- corrs[[1]][[N]]$r.thresh # Unweighted (binary) adjacency matrix
diag(A) <- 0
W <- corrs[[1]][[N]]$R # Weighted adjacency matrix
diag(W) <- 0
C <- V(g[[1]][[N]])$comm
writeMat('g1_N.mat', A=A, W=W, C=C)
```

Beyond checking just network-related measures, I also (painfully) imported my cortical thickness data and covariates into Matlab, and used `glmfit` to get the residuals. The results were nearly identical; the only reason they weren't a perfect match is because Matlab returns the *Pearson* residuals, whereas I use the *studentized* residuals (and I couldn't be bothered to figure out how to calculate those in Matlab).

And, as a further sanity check, I asked a colleague who is a biostatistician to confirm my results. Even though he used `SAS`, and did partial correlations (as opposed to linear models), the results were nearly identical. The median difference in correlation thresholds across all densities tested was 0.003, and the maximum was 0.007.

3

Getting data from Freesurfer and FSL

This chapter describes how to get data that can easily be imported into R for use with `brainGraph`. Specifically, I will use cortical thickness data from `Freesurfer` in the first section, and will explain how to use Freesurfer ROI's as seed regions for tractography in the second section.

Note

The code in this chapter is specific to `Bash`; there should be a similar solution for other shells.

3.1 Cortical thickness

Here, I assume there are 2 subject groups. The atlas being used in this section of the manual is the *Desikan-Killiany (DK)* atlas (20).

3.1.1 aparcstats2table

First, use `aparcstats2table` to get mean cortical thickness for each region and each subject into a single file. Replace the `SUBJECTS` variable definition with something that makes sense for your data. I have a script that wraps this step among others which makes it easy to change the parcellation or the measure (thickness, area, lgi, volume) on the command line.

```
aparcstats2table  
1 parc='aparc'      # Or 'aparc.DKTatlas40', or 'aparc.a2009s'  
2 subjects=$(ls -d [[:lower:]]*[a-z0-9]* | grep -v fsaverage)  
3 for h in 'lh rh'; do  
4     aparcstats2table --subjects ${subjects} --hemi ${h}  
5         --meas thickness -p ${parc}  
6         --delimiter=comma  
7         --tablefile ${parc}_${h}_thick.csv  
8 done
```

3.1.2 sed

Next, use `sed` to abbreviate the brain regions' names, and to remove the final column (which, if present, is the mean thickness across the hemisphere; this is optional). This will need to be repeated for the RH thickness file, and these arguments should work for the DK, DKT, and `destrieux` atlases. It is probably a good

idea to copy the following into a text file and use with the `-e` option to `sed`. I have it all in a script that also can accept the `asegstats.csv` file, if you wish to include subcortical volumes.¹

Abbreviate region names

```

1 SED_ARGS='
2 s/lh_/.l/g
3 s/rh_/.r/g
4 s/_thickness//g
5 s/_volume//g
6 s/_area//g
7 s/\///
8 s/bankssts/BSTS/g
9 s/caudalanteriorcingulate/cACC/g
10 s/caudalmiddlefrontal/cMFG/g
11 s/precuneus/PCUN/g
12 s/cuneus/CUN/g
13 s/entorhinal/ENT/g
14 s/fusiform/FUS/g
15 s/inferiorparietal/IPL/g
16 s/inferiortemporal/ITG/g
17 s/isthmuscingulate/iCC/g
18 s/lateraloccipital/LOG/g
19 s/lateralorbitofrontal/LOF/g
20 s/lingual/LING/g
21 s/medialorbitofrontal/MOF/g
22 s/middletemporal/MTG/g
23 s/parahippocampal/PARH/g
24 s/paracentral/paraC/g
25 s/parsopercularis/pOPER/g
26 s/parsorbitalis/pORB/g
27 s/parstriangularis/pTRI/g
28 s/pericalcarine/periCAL/g
29 s/postcentral/postC/g
30 s/posteriorcingulate/PCC/g
31 s/precentral/preC/g
32 s/rostralanteriorcingulate/rACC/g
33 s/rostralmiddlefrontal/rMFG/g
34 s/superiorfrontal/SFG/g
35 s/superiorparietal/SPL/g
36 s/superiortemporal/STG/g
37 s/supramarginal/SMAR/g
38 s/frontalpole/FP/g
39 s/temporalpole/TP/g
40 s/transversetemporal/TT/g
41 s/insula/INS/g
42 s/_div//g
43 s/L\./.l/g
44 s/R\./.r/g
45 s/Thalamus.Proper/THAL/g
46 s/Putamen/PUT/g
47 s/Pallidum/PALL/g

```

¹Script available on request.

```

48 s/Caudate/CAUD/g
49 s/Hippocampus/HIPP/g
50 s/Amygdala/AMYG/g
51 s/Accumbens.area/ACCU/g
52 '
53
54 awk -F, 'NR == 1 { $1="Study.ID"}1' OFS=, aparc_lh_thick.csv >> tmp1.csv
55 sed -i -e "${SED_ARGS}" tmp1.csv
56
57 # Remove the last column (if the mean thickness column is still there):
58 cat tmp1.csv | cut -d',' -f1-35 >> lh.csv
59 rm tmp1.csv

```

The `-f1-35` above is specific to the *DK* atlas; for *DKT* it should be 32, and for *Destrieux* it should be 75. These steps then need to be repeated for the second group (and if you have more groups). However, running the code a single time is sufficient if all subjects are in a single directory.

Now combine group files. If you have 2 groups: (repeat for the RH file as well)

```
tail -n +2 lhThick_group2.csv >> lh_dk_thickness.csv
```

3.2 Tractography

In this section, I describe the steps for using one of the **Freesurfer** atlases (along with subcortical gray matter) as seed regions for `probtrackx2` in **FSL**. I have a script for automation, but the code in this section is a good start. It is assumed that `recon-all` has been completed for the current subject (because I use the transformation matrices that are calculated by `TRACULA`). I use the *Desikan-Killiany* atlas for cortical regions, and the subcortical regions are included.

3.2.1 Create/convert parcellated volume

First, the parcellation volume must be created if it doesn't exist, and converted to **NIfTI**.² The DWI volume is called `dwi.nii.gz`. If you need to create the file for the *DKT* atlas, the following code will do so.

Parcellation volume

```

1 # Replace {subj} with your Subject's ID
2 if [ ! -e "aparc.DKTatlas40+aseg.mgz" ]; then
3     mri_aparc2aseg --s ${subj} --annot aparc.DKTatlas40
4     mri_convert aparc.DKTatlas40+aseg.{mgz,nii.gz}
5 fi

```

3.2.2 Get individual seed ROI's

I created a text file with the names and (**Freesurfer**-specific) indices of each ROI; in this example, it is called `dk.scgm.txt`. The lines of this file look like:

²The `mgz` volumes for the *DK* and *Destrieux* atlases are created automatically by `recon-all`.

ROI label file

```
1001 1001_1BSTS
1002 1002_lcACC
1003 1003_lcMFG
...
```

The existence of the file `anatorig2diff.bbr.mat` is from TRACULA; if you want to use this file, you must run the first step of `trac-all`.

Get individual ROI's

```

1  if [ ! -e "${SUBJECTS_DIR}/${subj}/dmri/xfms/anatorig2diff.bbr.mat" ]; then
2      trac-all -c ${subj}.dmrirc -intra -masks
3  fi
4
5  labelfile='dk.scgm.txt'
6  mkdir -p seeds/dk.scgm && cd seeds/dk.scgm
7  while read line; do
8      roiID=$(echo ${line} | awk '{print $1}' -)
9      roiNAME=$(echo ${line} | awk '{print $2}' -)
10     fslmaths
11         ${SUBJECTS_DIR}/${subj}/dlabel/diff/aparc+aseg.bbr
12         -thr ${roiID} -uthr ${roiID}
13         -bin ${roiNAME}
14     fslstats ${roiNAME} -V | awk '{print $1}' >> sizes.txt
15 done < ${labelfile}
16
17 echo ${PWD}/*.nii.gz | tr " " "\n" >> seeds.txt
18 paste sizes.txt seeds.txt | sort -k1 -nr - | awk '{print $2}' - >> seeds_srt.txt
19
20 # Ventricle mask; for use with ``--avoid'' flag
21 mri_binarize --i ${SUBJECTS_DIR}/${subj}/dlabel/diff/aparc+aseg.bbr.nii.gz
22     --ventricles -o ventricles.nii.gz

```

The final step of the `for` loop calculates the ROI sizes, which you may wish to use when normalizing the connectivity matrices; see [Tractography and fMRI](#). The final lines of the code create a text list of the seed region files and sorts them by size; this is used as input to `probtrackx2` (specifically, the `-x` option).

Part II

brainGraph Basics

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4

Overview of the brainGraph Package

This chapter provides an overview of `brainGraph` both in terms of concepts/workflow and the functions themselves. This package relies almost entirely on the `igraph` package (17) (hence the creative name for my package), so all operations/functions require this package. A complete list of the functions and their help sections is in the [package manual](#).

4.1 Concepts/workflow

There are a handful of conceptual/workflow-related categories (or “levels”) under which functionality in `brainGraph` falls. By “workflow”, I mean this is more or less the order of operations for your user scripts.

4.1.1 “Step 0”: Setting up data and scripts

This needs to be done before using `brainGraph`, and is not specific to the package (i.e., is common to all data analysis projects). I give some advice in [Setting up files for your project](#). Throughout the User Guide, there are code blocks that can be placed into your scripts, or adapted to work with your specific analysis needs.

4.1.2 Import data and create connectivity matrices

The operations/functions for this step differ depending on the type of networks you have: for covariance networks, you import the region-wise brain metrics (e.g., cortical thickness; see [Initialize variables](#)) and create matrices from partial correlations, linear model residuals, etc. (see [Correlation Matrix and Graph Creation](#)). The same function that performs the correlations will also threshold the matrices. For single-subject networks (DTI tractography or resting state fMRI), you load the connectivity matrices from your neuroimaging software-of-choice (see [Setting up](#)); typically those software tools can generate the matrix for you (e.g., `fdt_network_matrix` from FSL’s `probtrackx2`). Next, you threshold these matrices based on criteria of your choosing (see [Import, normalize, and filter matrices for all subjects](#)).

4.1.3 Create graphs and calculate metrics

These operations are slightly different for covariance networks ([Graph creation](#)) and single-subject networks ([Graph creation](#)), as the nested `list` object will have a third “level” in the case of single-subject networks (group, threshold/density, and subject). In those same sections, I show how to calculate graph metrics of interest.

4.1.4 Perform group analyses

There are several types of analysis, all of which require more in-depth description. See [Part IV](#) and [Part V](#).

4.1.5 Visualize results

There is a GUI for quick manipulation and inspection of graphs, as well as several functions for plotting results from specific analyses. See Part VI and the group analysis chapters.

4.2 Functions

4.2.1 Graph creation

Several functions can create graphs for various analyses; the names begin with `make_`, following the naming convention for graph constructors in the `igraph` package. The creation functions and the respective classes/analyses are described in more detail in [Box 4.1](#)

`make_brainGraph` Creates a `brainGraph` graph object, given an `igraph` graph object. This assigns several attributes that are specific to brain MRI data (mostly related to the brain atlas in use).

`make_empty_brainGraph` Creates an *empty* graph (i.e., one with no edges); typically the end user will not need to call this. This is analogous to `make_empty_graph`.

`make_ego_brainGraph` Creates a graph of the union of multiple vertex neighborhoods. This is analogous to `make_ego_graph`.

`make_glm_brainGraph` Creates a graph specific to a GLM (or MTPC) analysis. See [Vertex-wise group analysis \(GLM\)](#) (or [Multi-threshold permutation correction](#)).

`make_nbs_brainGraph` Creates a graph specific to NBS analysis. See [Network-based statistic \(NBS\)](#).

`make_mEDIATE_brainGraph` Creates a graph specific to mediation analysis. See [Graph- and vertex-level mediation analysis](#).

4.2.2 Graph metrics

`igraph` already contains functions for the most common graph metrics (e.g., degree, betweenness, etc.). Functions that I wrote and the graph metrics they calculate include:

- leverage centrality; `centr_lev` ([45](#))
- global, local, and nodal efficiency; `efficiency`
- *Vertex roles*; `gateway_coeff` ([79](#)), `part_coeff` and `within_module_degree_z_score` ([33](#))
- Rich club calculations; `rich_club_coeff`, `rich_club_norm`, and `rich_core` ([52](#))
- The *s-core* of vertices; `s_core` ([25](#))
- Euclidean distances; `edge_spatial_dist` and `vertex_spatial_dist`
- Communicability; `communicability` ([16](#), [26](#)) and `centr_betw_comm` ([27](#))
- Vertex vulnerability; `vulnerability` ([1](#), [36](#))
- Edge counts; `count_homologous` (counts the number of edges between homologous brain regions) and `count_interlobar` (counts the number of edges from one lobe to all others)

One function in the package, `set_brainGraph_attr`, calculates most of these metrics and more for a given graph (e.g., global efficiency, clustering coefficient, characteristic path length, and many more), and for its vertices (e.g., degree, nodal efficiency, etc.) and edges (e.g., edge betweenness). This is very useful because it removes the nuisance of having to type a separate command for every measure of interest. To see exactly what it calculates, see [Attributes created by set_brainGraph_attr](#) or check the function help (accessible by typing `?set_brainGraph_attr`) under the heading *Value*.

Class name	Creation function	Description
<code>brainGraph</code>	<code>make_brainGraph</code>	Any graph with certain attributes (see text)
<code>brainGraph_GLM</code>	<code>make_glm_brainGraph</code>	Graphs from GLM analysis
<code>brainGraph_NBS</code>	<code>make_nbs_brainGraph</code>	Graphs from NBS analysis
<code>brainGraph_mtpc</code>	<code>make_glm_brainGraph</code>	Graphs from MTPC analysis
<code>brainGraph_mediate</code>	<code>make_mediate_brainGraph</code>	Graphs from mediation analysis
<code>brainGraph_boot</code>	<code>brainGraph_boot</code>	Bootstrapping analysis (non-graph)
<code>brainGraph_permute</code>	<code>brainGraph_permute</code>	Permutation analysis (non-graph)
<code>brainGraph_resids</code>	<code>get.resid</code>	Residuals for covariance networks (non-graph)

Table 4.1: Class names and graph creation functions.

4.2.3 Group comparison

There are several methods for comparing groups:

- Between-group vertex-wise analysis of graph metrics with the *General Linear Model (GLM)*: `brainGraph_GLM`. See [Vertex-wise group analysis \(GLM\)](#) for details.
- The *network-based statistic (NBS)* (93): `NBS`. See [Network-based statistic \(NBS\)](#) for details.
- *Multi-threshold permutation correction (MTPC)* (23) method for inference: `mtpc`. See [Multi-threshold permutation correction](#) for details.
- *Mediation analysis*: `brainGraph_mediate`. See [Graph- and vertex-level mediation analysis](#) for details.
- Bootstrapping and permutation testing (for structural covariance networks): `brainGraph_boot` and `brainGraph_permute`. Details can be found in [Further analysis](#).
- “Individual contributions” for data in which single-subject graphs are not available (e.g., structural covariance networks); `loo` and `aop`. See [Individual contributions](#) for details. (68)
- Targeted attack and failure analyses: `robustness`. See the “Robustness” section in [Further analysis](#) for implementation and plotting.

4.2.4 Visualization

There is a GUI for plotting the graphs overlaid on a slice of the MNI152 brain; the function is `plot_brainGraph_gui`. You can visualize up to two brains (single orientation; e.g., axial) at once. The GUI controls vertex/edge color and size, labels, inclusion/exclusion, and more. See [The GUI](#) for more details. In addition, there are some functions for plotting various graph metrics; see [Other plotting](#).

4.2.5 Random graphs, small world, and rich club

`sim.rand.graph.par` will create a number of random graphs in parallel, based on the “standard” method of random graph generation (54). An additional option is to generate random graphs with the same degree distribution *and* transitivity (clustering) as the observed graph. This is based on the algorithm from Bansal et al. (2), and is particularly important for partial correlation networks (e.g., cortical thickness correlations; see Refs. Hosseini and Kesler (37), Zalesky et al. (93)). Finally, `analysis_random_graphs` is really a wrapper that will perform all of the steps for getting small-world and rich-club coefficients for all group data. See [Random graph generation](#) for more information.

BOX 4.1 CLASSES AND METHODS



New in v2.0.0

I have introduced some simple *classes* and *methods* corresponding to different functions/analyses for `brainGraph`.

Having classes and methods should simplify package usage in several areas. For example, in `base R`, if you use the `lm` function, the object returned has class `lm`; to view a summary and to plot some results, you simply call `summary` and `plot`, respectively. These “invisibly” run the functions `summary.lm` and `plot.lm` which are specialized for that type of data.

Second, each of the objects with a special class will also contain the important input parameters that the user supplies (for example, the significance level `alpha`). This is helpful for bookkeeping purposes and facilitates reproducible research or comparing results with varying inputs.

Here, I list the classes in `brainGraph` and in later chapters give example usage and output. *NOTE:* you do not need to remember the full names of these classes; you can simply type the base method name and `R` will take care of the rest.

brainGraph This class is essentially the same as an `igraph` graph object, but adds several graph-level (atlas, modality, Group, etc.) and vertex-level (lobe, hemi, spatial coordinates, etc.) specific to brain MRI analysis. These are created directly by `make_brainGraph` and indirectly by `set_brainGraph_attr`.

bg_GLM This class contains results from `brainGraph_GLM` (see [Vertex-wise group analysis \(GLM\)](#)).

brainGraph_GLM This class is the graph associated with `bg_GLM` objects. It has GLM-specific attributes (for plotting), created by the function `make_glm_brainGraph`.

NBS This class contains results from `NBS` (see [Network-based statistic \(NBS\)](#)).

brainGraph_NBS This class is the graph associated with `NBS` objects. It has NBS-specific attributes (for plotting), created by the function `make_nbs_brainGraph`.

mtpc This class contains results from `mtpc` (see [Multi-threshold permutation correction](#)).

brainGraph_mtpc This class is the graph associated with `mtpc` objects. It is also created by `make_glm_brainGraph`.

bg_mEDIATE This class contains results from `brainGraph_mEDIATE` (see [Graph- and vertex-level mediation analysis](#)).

brainGraph_mEDIATE This class is the graph associated with `bg_mEDIATE` objects. It has mediation-specific attributes (for plotting), created by the function `make_mEDIATE_brainGraph`.

brainGraph_boot This class is specific to objects returned by `brainGraph_boot` (formerly `boot_global`). See [Bootstrapping](#) for details.

brainGraph_permute This class is specific to objects returned by `brainGraph_permute` (formerly `permute.group`). See [Permutation testing](#) for details.

brainGraph_resids This class is specific to objects returned from `get.resid` for structural covariance networks (see [Structural covariance networks](#)). The new `plot` method replaces the old function `check.resid`.

5

Getting started

In this Chapter, I describe the most basic aspects of using `brainGraph`. I begin by suggesting some script/code organization. Then I show the other R packages that I load. Next, I show the structure of my *covariates* data. Finally, I introduce graph, vertex, and edge attributes and show how to plot from the terminal. For some information about R notation, see [Box 5.1](#).

5.1 Setting up files for your project

5.1.1 Project scripts

I have several scripts, each of which carries out a separate “task”; they are numbered sequentially in a manner that may depend on the imaging modality, project, etc. For example: (incomplete list)

00_packages.R loads required packages

01_load_myProject.R loads/imports the [thickness/tractography/rs-fMRI] data and creates some initial variables. I have a different script for each modality and for each project/study.

02_create_graphs.R creates the graphs, etc. I have a different script for volumetric (covariance networks) data and for tractography/rs-fMRI.

03_random_graphs.R runs `analysis_random_graphs`, and does extra processing if, for example, I create random graphs controlled for clustering.

main.R sources all of the other scripts. I can comment out specific lines if I don’t want to re-do a step.¹

This is similar in philosophy to the top response to [this Stack Overflow question](#)). I also recommend that you read Noble ([57](#)) which is specific to computational biology but has very good recommendations for project organization. In the future, I would like to move to using *Makefiles* for this kind of data processing workflow.

I keep my `code`, `data`, and `results` in separate directories. Within the `results`, I have sub-directories for different modalities and the date the analysis was performed.

¹I actually haven’t done analyses this way lately because it seems to be slower overall (possibly due to how R handles memory, does garbage collection, or something else).

BOX 5.1 BASIC R NOTATION

Here, I *briefly* explain some of the R notation. In sections with R code, any line beginning with a double hashtag/pound sign (i.e., `##`) signifies code output. Lines beginning with a single hashtag/pound sign are comments written by me, and are ignored by the R interpreter.

Assignment

Unlike Matlab, assignment is usually done with the symbol `<-`. Reasons for this are beyond the scope of this document. However, argument specification within a function call will always use the equals sign.

Lists

The variable `g` is a *list*; this type of object is very similar to a *cell array* in Matlab. To access list elements in R, you must use double square brackets (whereas in Matlab you would use curly braces). For the variable `g`, for example, to access the graphs for group 1, you would type `g[[1]]`.

Dollar sign

The dollar sign `$` is used to access list or *data frame* elements if they are *named*. In the section on covariates, if I want to access the column for subject `Age`, I would just type `covars$Age`.

data.table assignment

In some code using `data tables`, I use the assignment operator `:=`. This allows you to insert/change a column *in-place*, and is very fast and memory efficient.

The *apply functions

These functions (`sapply`, `lapply`, `mapply`, `Map`, `llply`, etc.) all operate on lists/vectors. They are equivalent to a `for` loop in other languages, but require less typing.

Object names

Following the [Google style guide](#), I name my *constants* beginning with a `k`, e.g., `kNumDensities` refers to the number of densities. Object names should be as informative as possible; however, some of the ones I use are stupid/bad and were done out of laziness. Most of the `data.table`'s I create begin with `dt` and the graphs I create begin with `g`. I *usually* include a dot/period in object names, which differs from [Hadley Wickham's style guide](#), and also differs from dot notation in Object-Oriented Programming.

5.1.2 Loading required packages

This step will be the same regardless of the imaging modality. See [System Requirements](#) for a list of required/recommended packages. The `if-else` part of the OS check below is unnecessary if you will be using the same OS every time. I load the most useful packages (e.g., `data.table`) at the start of every R session by including the relevant commands in my [.Rprofile](#).

```
library(brainGraph)
# Check OS version for parallel processing
OS <- .Platform$OS.type
if (OS == 'windows') {
  pacman::p_load(snow, doSNOW)
  num.cores <- as.numeric(Sys.getenv('NUMBER_OF_PROCESSORS'))
  cl <- makeCluster(num.cores, type='SOCK')
  clusterExport(cl, 'sim.rand.graph.par')
  registerDoSNOW(cl)
} else {
```

```

library(doMC)
num.cores <- detectCores()
registerDoMC(num.cores)
}
# Load some other packages
pacman::p_load(plyr, ggplot2, gridExtra)

```

Once `brainGraph` is loaded, you can quickly see all its functions and the package help section:

```

ls('package:brainGraph')
help(package='brainGraph')

```

5.1.3 Project data

You will almost certainly want to include covariates for your analyses (e.g., adjust for *age*, *sex*, etc.). Additionally, you may be interested in testing for associations between graph metrics and demographic or neuropsychological variables. I show a portion of my covariates below. The *Study ID*'s have been changed and will possibly/probably be character strings in your project.

```

covars

##      Study.ID   Group Sex   Age Scanner
## 1:          1 Control   F 14.17 Site 1
## 2:          2 Control   F 14.58 Site 1
## 3:          3 Control   F 16.42 Site 1
## 4:          4 Control   M 14.17 Site 1
## 5:          5 Control   F 16.33 Site 1
## ---
## 137:       137 Patient   M 16.50 Site 1
## 138:       138 Patient   M 16.33 Site 1
## 139:       139 Patient   M 16.42 Site 1
## 140:       140 Patient   M 15.58 Site 2
## 141:       141 Patient   M 15.42 Site 1

str(covars)

## Classes 'data.table' and 'data.frame': 141 obs. of  5 variables:
## $ Study.ID: chr  "1" "2" "3" "4" ...
## $ Group    : Factor w/ 2 levels "Control","Patient": 1 1 1 1 1 1 1 1 1 ...
## $ Sex      : Factor w/ 2 levels "F","M": 1 1 1 2 1 1 2 2 2 1 ...
## $ Age      : num  14.2 14.6 16.4 14.2 16.3 ...
## $ Scanner  : Factor w/ 2 levels "Site 1","Site 2": 1 1 1 1 1 1 1 1 1 ...
## - attr(*, ".internal.selfref")=<externalptr>

```

One of the nice things about R is that you don't need to change a variable such as *sex* to 0's and 1's; it considers the M and F as *factors* and can handle them easily. The same goes for subject group names (and pretty much any other non-numeric variable).

What I consider to be a smart thing to do (regarding covariates files) is to include some kind of “indicator variable” in your spreadsheet/database of *all* study subjects, where a 1 means the subject has acceptable data for that [MRI sequence, neuropsychological test, experiment, etc.], and a 0 otherwise. You can see this in the first code block of [Tractography and fMRI](#), in which I subset the `covars.all` data table using `tract == 1`. I then only select the first 5 columns, as those contain the only relevant covariates I wanted for that application. Later, if I choose to, for example, test for correlation between vertex betweenness and *full-scale IQ (FSIQ)*, I can access that variable easily:

```
cor.test(btwn, covars.all[tract == 1, FSIQ])
```

5.1.4 Compatibility

The only real requirements for your non-MRI data are that they be in a `csv` file and that they share a `Study.ID` column with the MRI data. If you keep your patient data in an `Excel` file, then it is simple enough to save it as a `csv`. If you use a database, it also should be simple; I know that `REDcap` has an option to output files for use in `R` and there are packages for working with `SQL`.

5.2 Graph object attributes

There are three types of *attributes* that an `igraph` graph object can have: graph-, vertex-, and edge-level.

5.2.1 Graph-level attributes

Graph-level attributes can be of any data type (e.g., a character string specifying the atlas used, or a numeric specifying the global efficiency, etc.). They are visible when you print the graph (by typing the object name), or with the following command:

```
graph_attr_names(g.ex)

## [1] "Cp"                      "Lp"
## [3] "rich"                     "E.global"
## [5] "mod"                      "density"
## [7] "conn.comp"                 "max.comp"
## [9] "num.tri"                  "diameter"
## [11] "transitivity"              "assortativity"
## [13] "atlas"                     "version"
## [15] "modality"                  "Group"
## [17] "assortativity.lobe"        "assortativity.lobe.hemi"
## [19] "asymm"                     "spatial.dist"
## [21] "num.hubs"                  "E.local"
## [23] "vulnerability"
```

Using the `$` operator, you can access these graph-level attributes; the following example will display the size and count of the graph's connected components.²

```
g.ex$conn.comp

##   size number
## 1    68      1
```

Also of interest may be the *rich club coefficient* of a graph (see Colizza et al. (13), Zhou and Mondragón (94)). Briefly, the rich club coefficient is the ratio of edges present to total possible edges in a subgraph with minimum degree k .³ The following example returns a `data.frame` for (in this specific example) $k = 1, 2, \dots, 19$; R is the rich club coefficient, N_k is the number of vertices present, and E_k is the number of edges present:

```
g.ex$rich
```

²Calculated by the `igraph` function `components`, and set by `set_brainGraph_attr`

³See [Rich-club Analysis](#) for more details.

```
##      phi Nk  Ek
## 1  0.1681 68 383
## 2  0.1681 68 383
## 3  0.1681 68 383
## 4  0.1714 67 379
## 5  0.1779 65 370
## 6  0.1806 64 364
## 7  0.1940 59 332
## 8  0.2006 56 309
## 9  0.2239 47 242
## 10 0.2423 40 189
## 11 0.2710 31 126
## 12 0.3083 23 78
## 13 0.3309 17 45
## 14 0.3182 12 21
## 15 0.4762 7 10
## 16 0.3333 3 1
## 17 0.0000 2 0
## 18    NaN  1  0
## 19    NaN  0  0
```

If you're working with single-subject graphs, you can use the `subject` argument to `setBrainGraphAttr`. This will give the graph a `name` attribute, which is displayed when you print the graph; the name is on the first line of the output:⁴

```
print(g.tmp, full=FALSE)

## IGRAPH e2ef81a U--- 68 359 -- Watson, Christopher
## + attr: name (g/c)

g.tmp$name

## [1] "Watson, Christopher"
```

5.2.2 Vertex-level attributes

You can also access vertex-level attributes, using both the `V()` function and the `$` operator (the following example will display each vertex's degree).

```
vertex_attr_names(g.ex)

##  [1] "degree"          "name"           "lobe"
##  [4] "lobe.hemi"       "hemi"           "x.mni"
##  [7] "x"               "y.mni"          "y"
## [10] "z.mni"          "z"               "color.lobe"
## [13] "circle.layout"   "asymm"          "dist"
## [16] "dist.strength"  "knn"            "Lp"
## [19] "btwn.cent"      "hubs"           "ev.cent"
## [22] "lev.cent"       "k.core"         "transitivity"
## [25] "E.local"         "E.nodal"        "vulnerability"
## [28] "eccentricity"   "comm"           "color.comm"
## [31] "comp"            "color.comp"     "circle.layout.comm"
## [34] "GC"              "PC"             "z.score"
```

⁴You will most likely want to use subject ID's, not real names.

```
V(g.ex)$degree

## [1] 7 10 17 5 14 12 15 11 11 6 15 13 13 10 13 16 15 11 12 9 9 11 14
## [24] 12 13 10 7 4 11 9 12 14 9 12 19 8 10 5 11 8 9 9 11 7 18 14
## [47] 16 15 7 12 16 8 14 10 7 11 12 10 9 11 16 10 13 9 13 12 15 9
```

5.2.3 Edge-level attributes

Finally, you can access edge-level attributes, using both the `E()` function and the `$` operator. First, I show a sample of the edges; as you can see, the vertex names are joined by double dashes. Then I display edge betweenness the first several edges (to save space).

```
E(g.ex)[2:6]

## + 5/383 edges from 4621e19 (vertex names):
## [1] 1BSTS--lITG 1BSTS--lLING 1BSTS--lpOPER 1BSTS--rMOF 1BSTS--rMTG

edge_attr_names(g.ex)

## [1] "color.lobe" "dist"      "btwn"      "color.comm" "color.comp"

head(E(g.ex)$btwn)

## [1] 13.155 6.954 13.978 12.470 16.911 11.428
```

5.3 Community detection

There are multiple community detection algorithms available in `igraph`. The default (which is called in my function `set_brainGraph_attr`) I have chosen for `brainGraph` is the *Louvain* algorithm (see Ref. Blondel et al. (9)), mainly because it seems to be the most popular one for neuroscience studies. The function is `cluster_louvain`. For general help with communities, type `?communities`. For a great demo on community detection (from which you can get useful code) is accessed by typing `demo(community)`. A description of some of the algorithms can be found in [this Stack Overflow answer](#).

To plot the communities with a specific layout, use the following code.⁵ Here, the function `layout_with_fr` uses the *Fruchterman-Reingold* method, which is a force-directed layout algorithm (30). This is shown in Figure 5.1.⁶

```
class(g.ex) <- 'igraph'
plot(cluster_louvain(g.ex), g.ex, layout=layout_with_fr, vertex.label=NA,
     vertex.size=5, edge.width=0.5)
class(g.ex) <- c('brainGraph', class(g.ex))
```

5.4 Plotting

Plotting graphs is much simpler when using the GUI `plot_brainGraph_gui`; however, you can achieve almost all of its functionality on the command line. For example, the `subgraph` argument allows you to specify a

⁵To avoid seeing the polygons that highlight each group, include the argument `mark.groups=NULL`.

⁶For more layouts, type the command `?layout_` (include the trailing underscore).

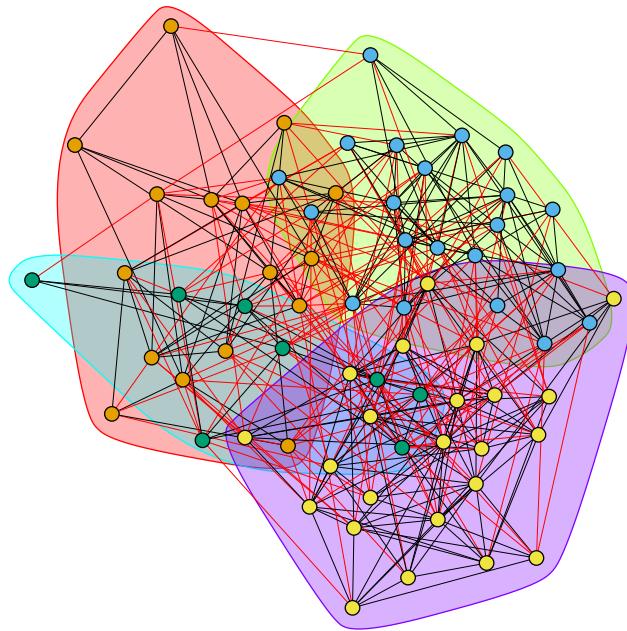


Figure 5.1: Communities plot, Fruchterman-Reingold layout.

condition for which vertices to *keep*; if you wanted to plot only vertices with degree greater than 10, this would be `subgraph='degree >10'`. You can combine multiple conditions, using either `&` (AND) or `|` (OR), e.g., `subgraph='degree >10 & btwn.cent >50'`. Plotting a single hemisphere is a “special” subgraph and can be chosen using the `hemi` argument. Additionally, you may choose to show a legend for vertex colors, using the `show.legend` argument.



New in v2.0.0

The `plot_brainGraph_mni` function has been removed; its functionality is now the default behavior in the `plot` method. You can specify `mni=FALSE` to omit showing the brain slice.

5.4.1 Axial

Figure 5.2 shows an example plot of an axial view⁷; here, vertex size is proportional to vertex degree. The vertex color is based on community (module) membership.

```
plot(g.ex, vertex.label=NA, vertex.size='degree',
      vertex.color='color.comm', edge.color='color.comm', main='Toy graph')
```

⁷Axial images are always in neurological orientation

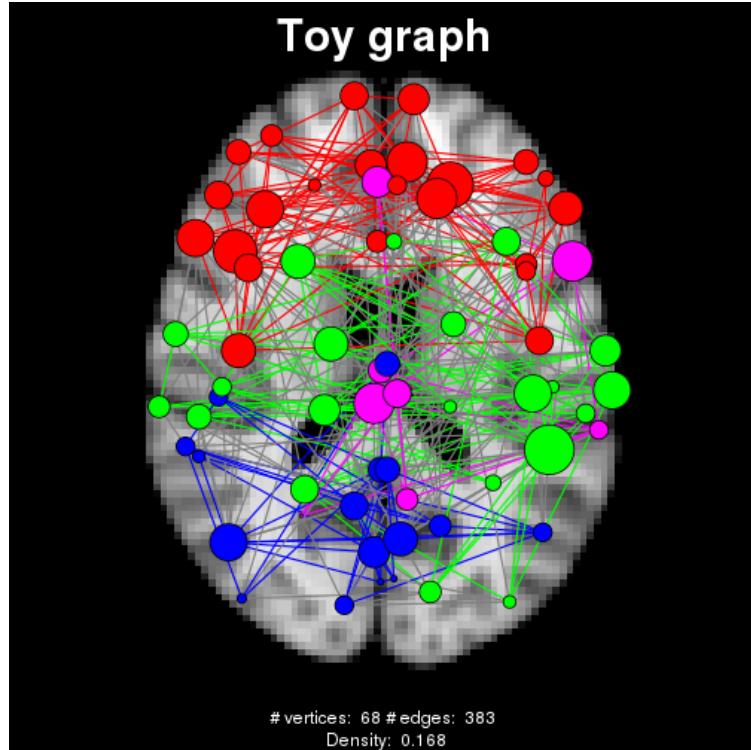


Figure 5.2: Axial view; vertex colors signify community membership.

5.4.2 Sagittal

Figure 5.3 shows an example of left and right sagittal views. These only show the *intra-hemispheric* connections. Here, lobe colors are based on *lobe* membership.

```
plot(g.ex, plane='sagittal', hemi='L',
      vertex.label=NA, vertex.size=10, vertex.color='color.lobe',
      edge.color='color.lobe', edge.width=1, main='Toy graph (L)')

plot(g.ex, plane='sagittal', hemi='R',
      vertex.label=NA, vertex.size=10, vertex.color='color.lobe',
      edge.color='color.lobe', edge.width=1, main='Toy graph (R)')
```

5.4.3 Circular

Figure 5.4 shows a circular plot. As the legend indicates, vertex color indicates lobe membership. Vertices of the left hemisphere are located on the left half of the plot, frontal lobe vertices at the front, etc.

```
plot(g.ex, plane='circular', vertex.label=NA, vertex.size=5,
      vertex.color='color.lobe', edge.color='color.lobe',
      edge.width=1, show.legend=TRUE)
```

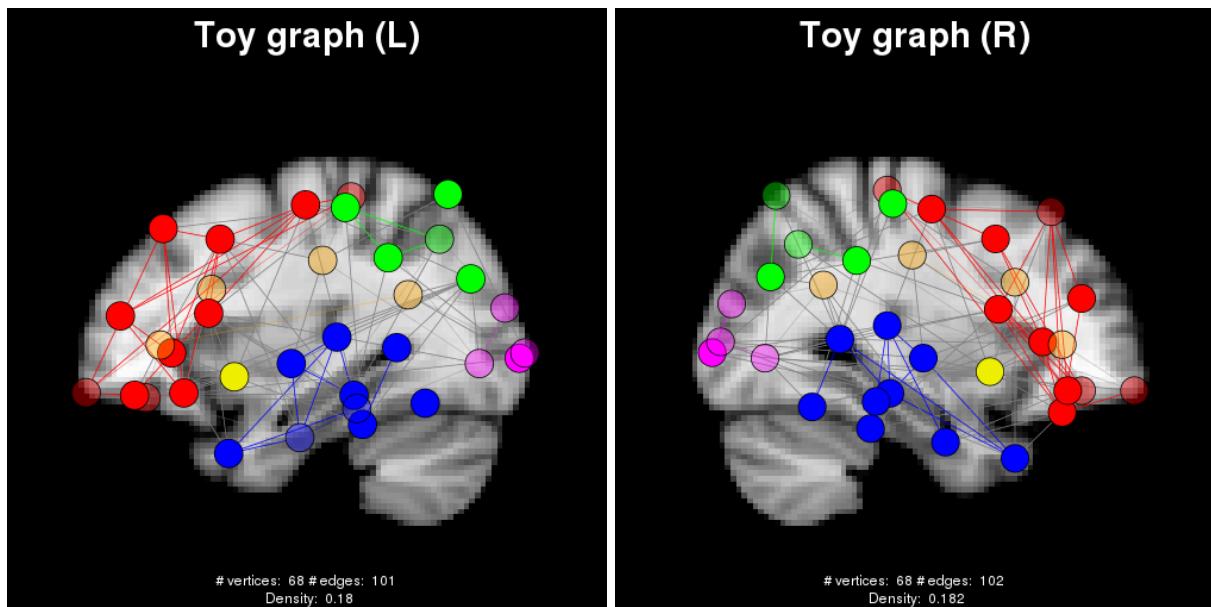


Figure 5.3: Sagittal view; vertex colors signify lobe membership.

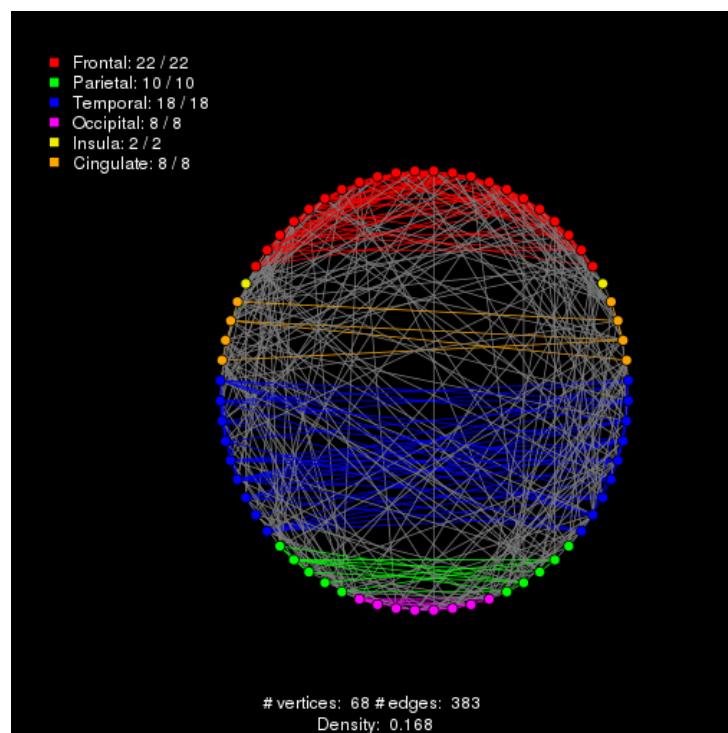


Figure 5.4: Circular view; vertex colors signify lobe membership.

Part III

Graph Creation

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6

Structural covariance networks

This chapter shows how to create graphs of *structural covariance networks*. The code is specific to **Freesurfer** and cortical *thickness*, but will also work with *volume*, *surface area*, and *local gyration index (LGI)*.

6.1 Overview

The following is the sequence of steps for completing the first steps of structural covariance network analysis. Each of these are discussed in subsequent sections of this chapter.

1. Load data and covariates
2. Generate model residuals (and check the QQ plots) (this is optional; you may also correlate the *raw volumetric data*)
3. Create correlation matrices (of residuals or raw volumetric data) for a number of densities/thresholds
4. Create a set of graphs for each group and density/threshold
5. Put the data into tables for easy exploration of graph- and vertex-level metrics (e.g., global efficiency, vertex degree, etc.)

6.2 Initialize variables

The following code block is what I put in my `01_load_project.R` script, and likely will be project-specific. There is a call to an “initialization function”, `brainGraph.init`, that will create and return the variables needed for later steps.

You will need to have several files in the `datadir`:

- `covars.csv` (with a field called `Study.ID`; required unless you supply a data table yourself)
- `lh_{atlas}_{modality}.csv` (and the RH file)
- `scgm.csv` (if you are including e.g., subcortical volumes)
- `covars.scgm.csv` (if you have additional covariates, e.g., *Total Intracranial Volume*)

```
datadir <- paste0('~/Dropbox/packages/brainGraph.other/data/Patient')

# If you need to exclude subjects, specify here
# Best to use their Study.ID's for record-keeping
```

```

exclude.subs <- NULL #c(2, 25, 30)

use.mean <- FALSE # I won't include mean thickness as a covariate

init.vars <- brainGraph_init(atlas='dk', densities=seq(0.05, 0.20, 0.01),
                             datadir=datadir, modality='thickness',
                             exclude.subs=exclude.subs)

# Hack to place list elements in the global environment
lapply(seq_along(init.vars), function(x)
  assign(names(init.vars)[x], eval(init.vars[[x]]), envir=.GlobalEnv))

# In case one density in particular is of interest, here 10%
N <- which(abs(densities - 0.10) < 0.001)

```

6.2.1 Custom atlas

To use a custom atlas, you must:

- Specify `atlas='custom'` as the first argument
- Supply the name of the R object (the `data.table`) for the custom atlas you would like to use.
- Make sure the `data.table` is loaded in your R environment and matches the structure of the atlases in `brainGraph`

6.3 Model residuals

Now you get the model residuals. In this example, I use the entire `covars` object. I have chosen to use the *studentized* residuals (sometimes called *leave-one-out residuals*).¹

To get the residuals, I use the function `get.resid`. This uses the combined dataset, `lhrh`, that was output by `brainGraph_init`. You may optionally provide a character vector of variables you would like to exclude from the models. Finally, you may change `use.mean` to `TRUE` here if you would like to adjust for hemispheric mean values. It returns an object of class `brainGraph_resids`, which has three elements:

X The design matrix

all.dat.tidy The “tidied” data

resids.all A `data.table` of residuals for each vertex

```

# Exclude the 'Group' column
all.dat.resids <- get.resid(lhrh, covars=covars, use.mean=use.mean, exclude='Group')
all.dat.tidy <- all.dat.resids$all.dat.tidy
resids.all <- all.dat.resids$resids.all
head(all.dat.resids$X)

```

¹In my data, the correlation between these and the *standardized* residuals (for all regions/models), was no lower than 0.9993.

6.3.1 Excluding covariates

If, for example, you import a file with covariates that you aren't interested in for this analysis, you may exclude them (e.g., `Age`).

```
all.dat.resids <- get.resid(lhrh, covars=covars, exclude='Age')
```

6.3.2 Adjust for hemispheric mean

You may want to adjust for mean thickness. The earlier function, `brainGraph_init`, will calculate for you both LH and RH mean thickness, separately (set `use.mean` to `TRUE`).

```
all.dat.resids <- get.resid(lhrh, covars=covars, use.mean=TRUE)
```

6.3.3 Separate linear models for each group

If you would like to get the residuals for each group separately:

```
all.dat.resids <- lapply(groups, function(x)
                           get.resid(lhrh[Group == x], covars=covars, exclude='Group'))
all.dat.tidy <- rbindlist(lapply(all.dat.resids, with, all.dat.tidy))
resids.all <- rbindlist(lapply(all.dat.resids, with, resids.all))
```

6.4 Data checking

It is always useful to check the quality of your data (which *should* have been done at a previous step). I wrote a function that will show a *qqplot* for each region (see the [Wikipedia page](#) if you are unfamiliar with qqplots).



New in v2.0.0

The `plot` method replaces the old function `check.resid`. The `summary` method is new.

```
plot(all.dat.resids)
```

And I see that, for *rSMAR* (right supramarginal gyrus), there is one sample quantile that is ≈ -3 . To check which subject this is, the following will work (it was subject #81). When I looked at the subject's brain MRI, it turns out he/she had a stroke in the right supramarginal/inferior parietal lobe.

```
all.dat.tidy[region == 'rSMAR', .SD[which.min(resids)]]
##   Study.ID  Group Sex Age Scanner region value resids
## 1:       81 Patient    M  16 Site 1  rSMAR  2.37 -3.348
```

This subject is also listed as an outlier in the `summary` method output for this object:

```
summary(all.dat.resids, region='rSMAR')
```

```
## 
## Structural covariance residuals
## -----
## Number of outliers per region: (sorted in descending order)
## rSMAR
##      6
## 
## 
## Number of times each subject was an outlier: (sorted in descending order)
## 81  5 49 47 65 41
## 1  1  1  1  1  1
```

As an example of the plotting output, Figure 6.1 shows the qqplot for one region; one panel is the “standard” output, and the second shows points colored by group, and “outliers” (those further than 2 SD’s from the mean) are asterisks. The outliers are also marked with their number in the `data.table` of residuals (zoom into the plot to see).

```
plot(all.dat.resids, regions='rSMAR')[[1]]
plot(all.dat.resids, regions='rSMAR', cols=TRUE)[[1]]
```

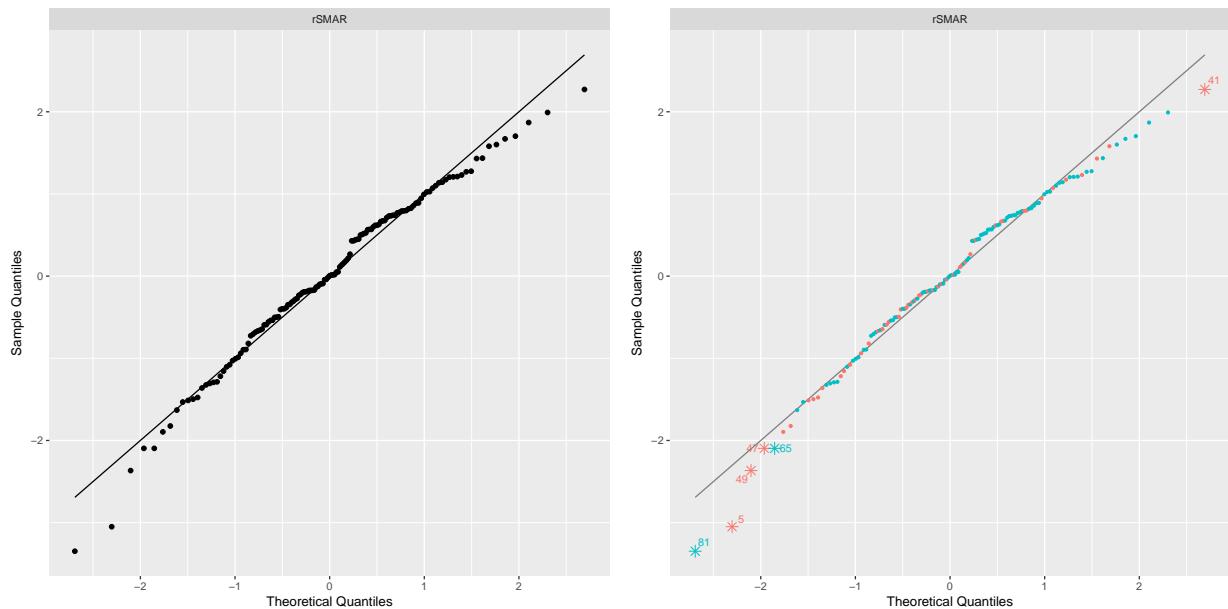


Figure 6.1: QQ plot of model residuals.

To see the plots for all regions, you can either use `lapply` and open a new plot device for each set of 9 regions, or save them to a multi-page PDF using the function `marrangeGrob` from the `gridExtra` package. Both methods are shown in the next code block.

```
p.resids <- plot(all.dat.resids)

# Method 1
lapply(p.resids, function(x) {dev.new(); print(x)})

# Method 2
```

```
ml <- gridExtra::marrangeGrob(p.resids, nrow=1, ncol=1)
ggsave('residuals.pdf', ml)
```

6.5 Correlation Matrix and Graph Creation

Next, correlate between pairs of regions for each group, and create the graphs.

The function `corr.matrix` has an argument, `density`, which indicates the density of the desired graph. So, if you want a graph with 10% of all possible connections, this value should be 0.1. To access the (correlation) threshold used, see code below.

```
# Correlate residuals for each group separately
corrs <- lapply(groups, function(x)
                 corr.matrix(resids.all[x], densities=densities))

corrs[[1]]$thresholds
## [1] 0.5342 0.5199 0.5109 0.4981 0.4858 0.4752 0.4649 0.4542 0.4482 0.4388
## [11] 0.4346 0.4276 0.4190 0.4102 0.4016 0.3941
```

Alternatively, you can skip the step above and just correlate the raw cortical thickness values. I don't recommend this, though, as variables like age and sex have known effects on cortical thickness.

```
# Correlate raw thickness
corrs <- lapply(groups, function(x)
                 corr.matrix(lhrh[which(covars$Group == x)], densities=densities))
```

6.5.1 Excluding regions

If you wanted to exclude some regions from your analysis (e.g., if you weren't interested in the L and R *transverse temporal*), use the following code:

```
exclude <- eval(parse(text=atlas))[name %in% c('lTT', 'rTT'), index]
corrs <- lapply(groups, function(x)
                 corr.matrix(resids.all[x], densities=densities, exclusions=exclude))
```

If you were interested in e.g., only the right hemisphere, you could set the following:²

```
exclude <- eval(parse(text=atlas))[hemi == 'L', index]
```

6.5.2 Graph creation

Then create the graphs:

```
# Create simple, undirected graphs for each group
g <- lapply(corrs, function(x)
            apply(x$r.thresh, 3,
                  graph_from_adjacency_matrix, mode='undirected', diag=F))
```

²See the next section for an alternate method

If you prefer that your graphs are weighted by the correlation coefficient, then a slight adjustment is needed:

```
g <- lapply(corrss, function(x)
  apply(x$r.thresh, 3, function(y)
    graph_from_adjacency_matrix(x$R * y, mode='undirected', diag=F, weighted=T)))
```

Finally, set the relevant graph-, vertex-, and edge-level attributes. This should only take a few seconds per graph, depending on the number of vertices.

```
g <- Map(function(x, y) llply(x, set_brainGraph_attr, atlas=atlas,
  modality=modality, group=y, .progress='text'),
  g, as.list(groups))
```

ASIDE: An alternate method of getting a subgraph of e.g., the left hemisphere only:

```
g.lh <- lapply(g, lapply, function(x) induced.subgraph(x, V(x)$hemi == 'L'))
```

6.6 Getting measures of interest

There are a number of graph measures that may be of interest to you, so there are a couple of helper functions to make plotting and exploring easier. `graph_attr_dt` will get graph-level (global) attributes into a `data.table`, ordered by graph density. Similarly, `vertex_attr_dt` will get vertex-level attributes; for multiple densities, they are combined (by row) into a single `data.table`.

```
dt.G <- rbindlist(lapply(g, graph_attr_dt))
dt.V <- rbindlist(lapply(g, function(x) rbindlist(lapply(x, vertex_attr_dt))))
setkey(dt.V, density, Group)

# Maximum degree for each Group & density
dt.V[density < 0.1, .SD[which.max(degree), .(region, degree)],
  by=.(Group, density)]

##      Group density region degree
## 1: Control    0.05   rIPL     11
## 2: Patient    0.05   rSPL     13
## 3: Control    0.06   rIPL     15
## 4: Patient    0.06   rSPL     15
## 5: Control    0.07   rIPL     16
## 6: Patient    0.07   rSPL     16
## 7: Control    0.08   rIPL     18
## 8: Patient    0.08   lSFG     16
## 9: Control    0.09   rIPL     18
## 10: Patient   0.09   lSFG     18

# List the regions with the highest participation coefficient at one density
dt.V[density == densities[N], .SD[order(-PC, -degree)[1:5],
  .(density, region, lobe, hemi, degree, PC)], by=Group]

##      Group density region    lobe hemi degree      PC
## 1: Control    0.1   rLOF Frontal     R     11 0.6446
## 2: Control    0.1   rpTRI Frontal     R     14 0.6429
```

```

## 3: Control    0.1 rrMFG Frontal    R    14 0.6224
## 4: Control    0.1 rparaC Frontal    R    10 0.6200
## 5: Control    0.1 rpORB Frontal    R    10 0.6200
## 6: Patient    0.1 rpOPER Frontal    R    3 0.6667
## 7: Patient    0.1 lSFG Frontal    L    20 0.5450
## 8: Patient    0.1 lpreC Frontal    L    4 0.5000
## 9: Patient    0.1 rcMFG Frontal    R    17 0.4983
## 10: Patient   0.1 rSFG Frontal    R    17 0.4983

# Count vertices with betweenness > mean + sd (i.e. 'hub' regions)
dt.V[density == round(densities[N], 2) & hubs > 0, .N, by=Group]

##      Group N
## 1: Control 12
## 2: Patient  7

# Mean degree by 'Group' and 'lobe', for one density
dt.V[density == densities[N], .(mean.deg=mean(degree)), by=.(Group, lobe)]

##      Group      lobe mean.deg
## 1: Control Temporal  6.944
## 2: Control Cingulate 0.250
## 3: Control Frontal   6.273
## 4: Control Occipital 6.375
## 5: Control Parietal  12.400
## 6: Control Insula   8.000
## 7: Patient Temporal  5.611
## 8: Patient Cingulate 1.000
## 9: Patient Frontal   8.273
## 10: Patient Occipital 5.875
## 11: Patient Parietal 10.800
## 12: Patient Insula  5.000

```

6.7 Tidying Data

To make some plotting functions easier, it's important to "tidy" the data (see Wickham (86)). This is an example of *reshaping* your data. Here is the required code:

```

# For a given density, vertex-wise network measures
dt.V.tidy <- melt(dt.V,
  id.vars=c('density',
            dt.V[, names(which(lapply(.SD, class) == 'character'))])))

# Number of rows = (number of vertices) * (number of variables)
dt.V.tidy[seq(1, nrow(dt.V.tidy), kNumVertices)]
```

	density	region	lobe	hemi	modality	atlas	Group	variable	value
## 1:	0.05	LBSTS	Temporal	L	thickness	dk	Control	degree	2.000
## 2:	0.05	LBSTS	Temporal	L	thickness	dk	Patient	degree	1.000
## 3:	0.06	LBSTS	Temporal	L	thickness	dk	Control	degree	2.000
## 4:	0.06	LBSTS	Temporal	L	thickness	dk	Patient	degree	1.000
## 5:	0.07	LBSTS	Temporal	L	thickness	dk	Control	degree	2.000

```

## ---
## 604: 0.18 LBSTS Temporal L thickness dk Patient z.score -1.229
## 605: 0.19 LBSTS Temporal L thickness dk Control z.score -1.472
## 606: 0.19 LBSTS Temporal L thickness dk Patient z.score -1.247
## 607: 0.20 LBSTS Temporal L thickness dk Control z.score -1.555
## 608: 0.20 LBSTS Temporal L thickness dk Patient z.score -1.281

# Example tidying global network measure data frame
dt.G.tidy <- melt(dt.G,
  c('density', dt.G[, names(which(lapply(.SD, class) == 'character'))])))

# Number of rows = (number of densities) * (number of global measures)
dt.G.tidy[seq(1, nrow(dt.G.tidy) / 2, 16)]

##      density atlas modality Group      variable    value
## 1: 0.05     dk thickness Control      Cp 0.5468
## 2: 0.05     dk thickness Patient      Cp 0.4842
## 3: 0.05     dk thickness Control      Lp 3.2575
## 4: 0.05     dk thickness Patient      Lp 2.9870
## 5: 0.05     dk thickness Control E.global 0.1783
## 6: 0.05     dk thickness Patient E.global 0.1599
## 7: 0.05     dk thickness Control      mod 0.5741
## 8: 0.05     dk thickness Patient      mod 0.5659
## 9: 0.05     dk thickness Control max.comp 46.0000
## 10: 0.05     dk thickness Patient max.comp 39.0000
## 11: 0.05     dk thickness Control num.tri 103.0000
## 12: 0.05     dk thickness Patient num.tri 90.0000
## 13: 0.05     dk thickness Control diameter 7.0000
## 14: 0.05     dk thickness Patient diameter 8.0000
## 15: 0.05     dk thickness Control transitivity 0.4866
## 16: 0.05     dk thickness Patient transitivity 0.4355

```

7

Tractography and fMRI

This section will list the code needed to get *fdt_network_matrix* and *waytotal* into R so you can create and work with graphs. This example code uses the *dkt.scgm* atlas and 2 subject groups. I used FSL for DTI-related processing; see relevant references (5, 6, 43, 44).

Note

The information in this chapter is not specific to FSL, nor to DTI tractography. The code is applicable to any set of single-subject graphs. If you use different software with different outputs, just adjust the code (e.g., filenames) accordingly. I call the covariates object *covars.dti* simply because I don't want it to be over-written if I am loading data from multiple modalities concurrently and the covariates set is different for each. In my fMRI scripts, I call it *covars.fmri*.

7.1 Setting up

First, as mentioned in [Setting up files for your project](#), you will need to load the required packages. Then, you set some initial variables that will depend on your project, data, directory structure, etc.

7.1.1 Tractography

The files containing connectivity matrices must contain the *Study.ID*'s for your study. For example, the directory structure might look like: (where *con01* is an example Study ID)

```
./Control/con01-fdt_network_matrix  
./Control/con01-sizes.txt  
./Control/con01-waytotal  
etc.  
./Patient/pat01-fdt_network_matrix  
./Patient/pat01-sizes.txt  
./Patient/pat01-waytotal
```

The **-sizes.txt* files contain the ROI volume (in # of voxels) for each of the 76 ROI's (i.e., it contains a single column vector with 76 elements). The *waytotal* files have the same format. The *fdt_network_matrix* files are output by *probtrackx2* and are 76×76 matrices (in this example).

You can place the following code in a script, e.g., *01_load_DTI.R*. Note again that these files are *not* required; if you use a different software for tractography (or for fMRI), just change the relevant lines in the following code block.

```

#=====
# These variables need to be set correctly before any data analysis is done
#=====

groups <- c('Control', 'Patient')
atlas <- 'dkt.scgm'
modality <- 'dti'

# Get all relevant filenames
datadir <- '/home/cwatson/probtrackx_results/'
covars.all <- fread(paste0(datadir, 'covars.all.csv'))
covars.dti <- covars.all[tract == 1, 1:5, with=F]
covars.dti[, Group := as.factor(Group)]
covars.dti[, Scanner := as.factor(Scanner)]
setkey(covars.dti, Group, Study.ID)

# If your files aren't in separate directories, you don't need ``list.dirs''
matfiles <-
  list(A=list.files(list.dirs(datadir, recursive=F), 'fdt_network_matrix', full.names=T),
       way=list.files(list.dirs(datadir, recursive=F), 'waytotal', full.names=T),
       size=list.files(list.dirs(datadir, recursive=F), 'sizes.txt', full.names=T))
inds <- lapply(seq_along(groups), function(x)
  covars.dti[, which(Group == groups[x])])

# Output directory to save the data I generate
today <- format(Sys.Date(), '%Y-%m-%d')
savedir <- paste0('/home/cwatson/brainGraph/', today)

```

7.1.2 fMRI

The code for resting-state fMRI is almost exactly the same, except the matrix files are different. The following code example is using the outputs of DPABI:

```

matfiles$A <- list.files(list.dirs(datadir, recursive=T),
                         'ROICorrelation_[a-z]+.*.txt', full.names=T)

```

7.2 Import, normalize, and filter matrices for all subjects

Now we will load all the relevant data from the files provided, and normalize the connection matrices based on what you want (e.g., divide every entry by the corresponding *waytotal*). For resting-state fMRI, the thresholds will likely be different (e.g., correlation coefficients), or you may choose to threshold in such a way that the graphs have a specific density (but see (78)). Either way, the same function is used. In this section, I describe the inputs and outputs of `create_mats`.

7.2.1 Function arguments

A.files A character vector of the filenames containing the connectivity matrices.

modality A character string; either `dti` (default) or `fmri`. (new since v1.0.0)

divisor A character string specifying how to normalize the matrices. Either `none` (default), `waytotal`, `size` (normalize by average size of ROI pairs), or `rowSums` (normalize by the row sums of the connection matrix). Ignored if `modality='fmri'`.

div.files Character vector of the filenames of the files containing the normalization factor (e.g., the *waytotal* files from FSL’s *probtrackX2*). Ignored if `divisor='none'`.

threshold.by Character string with 4 possible options. The 3rd and 4th options will enforce the same connections across all study subjects. (new since v1.1.0)

consensus Perform “consensus-based” thresholding; i.e., keep connections that are above a given threshold for a certain percentage of subjects *in each group*. The default value for `sub.thresh` of 0.5 means it will keep connections if they are present in at least 50% of subjects.

density Threshold the matrices such that they result in a specific graph density. The values given to `mat.thresh` must be between 0 and 1.

mean You may choose to specify a set of thresholds τ (which you would supply to `mat.thresh`) and keep connections only if

$$\text{mean}(A_{ijk}) + 2 \times \text{SD}(A_{ijk}) > \tau$$

where A_{ijk} is a connectivity matrix, and k indexes *Subject*. See for example (11, 31).

consistency Perform “consistency-based” thresholding (63). Similar to specifying **density**, you supply the desired graph densities to `mat.thresh`, and the matrices are thresholded to keep the most consistent connections across all study subjects (as determined by the *coefficient of variation*).

mat.thresh Numeric vector of the thresholds to apply. See the description for **threshold.by** for how this is applied. Default: `0`. These values may end up being arbitrary, but with *deterministic tractography* you may choose *streamline counts*; for *probabilistic tractography*, this may be some measure of *streamline density* or *connectivity probability*; and with *resting-state fMRI* you may choose to threshold based on *correlation coefficients*.

sub.thresh Numeric (between 0 and 1); only valid if `threshold.by='consensus'`. Default: `0.5`

inds List (number of elements equal to the number of groups) containing integer vectors; the integers should represent the indexes for each group, and the length of each individual vector should equal the number of subjects per group. For example, if you have 3 groups of 12 subjects each, this would be: `inds=list(1:12, 13:24, 25:36)`.

algo Character string specifying the tractography algorithm used; either **probabilistic** (the default) or **deterministic**. Ignored if `modality='fmri'`.

P Integer; the number of samples per voxel for probabilistic tractography (default: `5000`). Only valid if `algo='probabilistic'`.

... Other arguments passed to `symmetrize.mats`. Here you can pass the argument `symm.by` which tells the function how to symmetrize the matrices. The default in `igraph` is to take the *maximum* of $\{A_{ij}, A_{ji}\}$, so the default option is `symm.by='max'`. You may also specify `min` or `avg`.

7.2.2 Return value

`create.mats` returns a list (of lists) of arrays. I use the following abbreviations:

Nvert The # of vertices in the graph

Nsub The # of subjects (total, across all groups)

Nthr The # of thresholds applied

Most of the elements in the return object are *lists*; otherwise, they are 3D (numeric) *arrays*.



Warning

As of v2.0.2, the element `A.norm.sub` returns lists of 3D arrays in which the order along the 3rd dimension matches that of the input matrix files (i.e., the input argument `A.files`), and therefore the raw matrices and normalized matrices in `A` and `A.norm`, respectively. This would not affect you unless you chose `threshold.by='consensus'` or `threshold.by='consistency'`. Furthermore, this would not affect you if your *Study ID*'s (and therefore the matrix files) were already in the correct order, alphanumerically by `Study.ID` and by `Group`. Nevertheless, you should be aware of the change in behavior. Thanks to @seantma for pointing out the bug!

A The raw connection matrices (from e.g., `fdt_network_matrix`). Dimensions of this array are e.g., $N_{vert} \times N_{vert} \times N_{sub}$.

A.norm The normalized connection matrices (e.g., $A \div \text{waytotal}$). Dimensions are the same as for `A`. This is different from `A` only if `modality='dti'`; further, for *deterministic* tractography only if `divisor='size'`.

A.bin List of binarized matrices based on some *threshold*. The number of elements in the list equals the number of thresholds, e.g., N_{thr} arrays of size $N_{vert} \times N_{vert} \times N_{sub}$. Only valid if `threshold.by='consistency'`.

A.bin.sums A list of 2-d matrices, in which each entry represents the total number of subjects with that connection present (from `A.bin`). This will be used to threshold by % of subjects. The number of elements in this list equals the number of thresholds; each of those list elements is itself a list (if you have more than 1 group), e.g., 2. And finally each of those matrices is just $N_{vert} \times N_{vert}$. Only valid if `threshold.by='consistency'`.

A.ind A list of 2-d binary matrices, in which a 1 indicates that a connection is present *for that group*. The dimensions are the same as for `A.bin.sums`. Only valid for *consensus*- and *consistency-based* thresholding.

A.norm.sub A list of 3-d arrays; the number of list elements equals the number of *thresholds*. Each of the list elements is of the same dimension as `A.norm` (e.g., $N_{vert} \times N_{vert} \times N_{sub}$); however, the connections which were deemed absent (e.g., if too few subjects have the connection) have been replaced by 0. All of these matrices will be *symmetrized* based on the value given to `symm.by`.

A.norm.mean A list of matrices; there is one for each group and each threshold. Each matrix in this list is the corresponding group average (based on `A.norm.sub`).

7.2.3 Code example

First, I set the *subject threshold* to 0.5, meaning I will only accept connections which are present in at least 50% of the subjects of a given group. If you do not want to impose any subject constraint, set equal to 0. The *matrix threshold* is determined by the variable `thresholds`, which may end up being arbitrary (i.e., it will depend on the tractography algorithm and the actual values of the matrices, and would be different if you used correlations for fMRI). For *deterministic* tractography, this could be equal to the number of streamlines connecting two ROI's (e.g., an integer between 1 and 10, or higher).

```
thresholds <- rev(seq(0.001, 0.01, 0.001))
sub.thresh <- 0.5
divisor <- 'waytotal'
```

```
my.mats <- create_mats(matfiles$A, modality=modality, divisor=divisor,
                        div.files=matfiles$way, mat.thresh=thresholds,
                        sub.thresh=sub.thresh, inds=inds)
A.norm.sub <- my.mats$A.norm.sub
A.norm.mean <- my.mats$A.norm.mean
```

7.2.4 Applying the same thresholds to other matrices

In the case where you have connectivity matrices in which the entries are from the same subjects but are a different metric (e.g., in DTI tractography *streamline count* and *mean FA*), you can use the function `apply_thresholds` to threshold the second set by the first. See the following code block and Ref. (50).

```
matfiles$W <- list.files(dirs$data, pattern='.*W.txt', full.names=T)
if (length(matfiles$W) > 0) {
  W.mats <- apply_thresholds(A.norm.sub, A.norm.mean, matfiles$W, inds)
  W.norm.sub <- W.mats$W.norm.sub
  W.norm.mean <- W.mats$W.norm.mean
}
```

7.3 Graph creation

We now create graphs based on the matrices from the previous section, and calculate the relevant attributes for these graphs. I use a similar “hack” as that in [Random graph generation](#) to generate the lists of graphs, save them to disk, and then later load them into one large list object (it seems to be faster, perhaps due to R’s handling of memory). This actually gave me a speed increase of 1.85x, and seems to improve with increasing numbers of subjects and/or thresholds/densities.

In this case, I will use the list of arrays stored in `A.norm.sub` (which contains the arrays thresholded by both the % of subjects with a connection, and by a series of thresholds). The list `g` will have 3 “levels”:

- `g[[X]]` The first index is for *subject group*
- `g[[X]][[Y]]` The second index is for *threshold*
- `g[[X]][[Y]][[Z]]` The third index is for *subject*

You may want to place the following code in its own script, e.g., `02_create_graphs_DTI.R`. The code for a *progress bar* is not necessary and simply lets you track how far along the processing is.

As of v1.0.0, I include the weighted adjacency matrix in the call to `setBrainGraphAttr`; this is not required but it does improve the speed (particularly when calculating weighted local efficiency; see [Benchmarks](#) for benchmarking). I also recommend using `foreach` for the subject-level graphs; on my machine this results in a speed-up of $\approx 3.4x$.

```
g.group <- g <- fnames <- vector('list', length=length(groups))

for (i in seq_along(groups)) {
  for (j in seq_along(thresholds)) {
    print(paste0('Threshold ', j, '/', length(thresholds), '; group ', i, '; ',
                format(Sys.time(), '%H:%M:%S')))
```

```

foreach (k=seq_along(inds[[i]])) %dopar% {
  g.tmp <- graph_from_adjacency_matrix(A.norm.sub[[j]][, , inds[[i]][k]],
                                         mode='undirected', diag=F, weighted=T)
  g.tmp <- set_graph_attr(g.tmp, atlas, modality='dti',
                           weighting='sld', threshold=thresholds[j],
                           subject=covars.dti(groups[i], Study.ID[k]), group=groups[i],
                           use.parallel=FALSE, A=A.norm.sub[[j]][, , inds[[i]][k]])
  saveRDS(g.tmp, file=paste0(savedir,
                             sprintf('g%02i_subj%03i.s', i, j, k, '.rds')))
}

# Group mean weighted graphs
print(paste0('Group', i, '; ', format(Sys.time(), '%H:%M:%S')))
g.group[[i]] <- lapply(seq_along(thresholds), function(x)
  graph_from_adjacency_matrix(A.norm.mean[[x]][[i]],
                               mode='undirected', diag=F,
                               weighted=T))
g.group[[i]] <-
  llply(seq_along(thresholds), function(x)
    set_graph_attr(g.group[[i]][[x]], atlas,
                  modality='dti', weighting='sld',
                  threshold=thresholds[x], group=groups[i],
                  A=A.norm.mean[[x]][[i]], use.parallel=FALSE),
    .parallel=TRUE)
}

```

And now we combine the list objects saved to disk in one list, for further processing. I perform a check to make sure the `name` graph attribute matches the `Study.ID` of the study subjects, and then remove all of the individual files that were created in the previous step.

```

for (i in seq_along(groups)) {
  g[[i]] <- fnames[[i]] <- vector('list', length=length(thresholds))
  for (j in seq_along(thresholds)) {
    fnames[[i]][[j]] <- list.files(savedir,
                                   sprintf('g%02i.*', i, j), full.names=T)
    g[[i]][[j]] <- lapply(fnames[[i]][[j]], readRDS)
  }
  x <- all.equal(sapply(g[[i]][[1]], graph_attr, 'name'),
                 covars.dti(groups[i], Study.ID))
  if (isTRUE(x)) lapply(fnames[[i]], file.remove)
}
saveRDS(g, file=paste0(savedir, 'g.rds'))
saveRDS(g.group, file=paste0(savedir, 'g.group.rds'))

```

7.4 Graph- and vertex-level measures

Just as we did in [Getting measures of interest](#), we will create `data.table`'s of graph- and vertex-level measures for further analysis. The line beginning `setcolorder` is optional; it changes the column ordering to whatever you specify.

```

# GROUP-LEVEL
#=====
dt.V.group <- rbindlist(lapply(g.group, function(x)
                                rbindlist(lapply(x, vertex_attr_dt))))
dt.G.group <- rbindlist(Map(graph_attr_dt, g.group, as.list(groups)))

# SUBJECT-LEVEL
#=====
dt.V <- vector('list', length=length(groups))
for (i in seq_along(groups)) {
  dt.V[[i]] <- lapply(g[[i]], llply, vertex_attr_dt, groups[i])
  dt.V[[i]] <- rbindlist(lapply(dt.V[[i]], rbindlist))
}
dt.V <- rbindlist(dt.V)

dt.G <- rbindlist(Map(function(x, y)
                        rbindlist(lapply(x, graph_attr_dt, y)),
                        g, as.list(groups)))

dt.V.group$sub.thresh <- dt.G.group$sub.thresh <- dt.G$sub.thresh <-
  dt.V$sub.thresh <- sub.thresh
setorderv(dt.V, 'threshold', -1)
setorderv(dt.G, 'threshold', -1)
setcolorder(dt.V.group, c('modality', 'atlas', 'weighting', 'sub.thresh',
                          'threshold', 'Group', names(dt.V.group)[1:33]))
setcolorder(dt.G.group, c('modality', 'atlas', 'weighting', 'sub.thresh',
                          'threshold', 'Group', names(dt.G.group)[c(1:4, 6:23)]))
setcolorder(dt.G, c('modality', 'atlas', 'weighting', 'sub.thresh', 'threshold',
                    'Group', 'Study.ID', names(dt.G)[c(1:4, 6:23)]))
setcolorder(dt.V, c('modality', 'atlas', 'weighting', 'sub.thresh', 'threshold',
                    'Group', 'Study.ID', names(dt.V)[1:33]))

dt.G.group.tidy <- melt(dt.G.group, names(dt.G)[1:6])
dt.G.tidy <- melt(dt.G, c(names(dt.G)[1:7], 'density'))

```

7.5 Example commands

Similar to [Getting measures of interest](#), here are some example commands for looking at your data.

```

# Mean degree for the group-averaged graphs
env.dti$dt.V.group[, .(mean.deg=mean(degree)), by=.(Group, threshold, lobe)]

##          Group threshold      lobe mean.deg
## 1: Control    0.005   SCGM    16.71
## 2: Control    0.005 Occipital  10.88
## 3: Control    0.005 Temporal  11.14
## 4: Control    0.005  Insula   22.00
## 5: Control    0.005 Parietal  10.70
##   --
## 206: Patient   0.004 Temporal  10.93
## 207: Patient   0.004  Insula   22.00

```

```

## 208: Patient      0.004  Parietal     10.40
## 209: Patient      0.004  Frontal      11.50
## 210: Patient      0.004  Cingulate    13.25

# t-test of nodal efficiency for Frontal lobe vertices
env.dti$dt.V.group[lobe == 'Frontal',
  .(p=t.test(E.nodal ~ Group)$p.value),
  by=threshold]

##      threshold      p
## 1:      0.005 2.482e-01
## 2:      0.015 2.373e-01
## 3:      0.025 1.735e-01
## 4:      0.035 9.670e-02
## 5:      0.045 1.577e-01
## 6:      0.055 3.196e-02
## 7:      0.065 1.824e-05
## 8:      0.075 8.523e-03
## 9:      0.085 5.396e-02
## 10:     0.095 2.816e-03
## 11:     0.105 2.775e-01
## 12:     0.001 3.575e-01
## 13:     0.002 2.985e-01
## 14:     0.003 3.049e-01
## 15:     0.004 4.160e-01

```

We can also create a plot of the global graph measures across the thresholds we applied, shown in [Figure 7.1](#). Here I use my function `plot_global`, specifying that I want to plot across `threshold` instead of `density`. This uses the `stat_smooth` function, which creates a line plot along with a smoother.

```

exclude.vars <- c('assortativity.lobe.hemi', 'max.comp', 'diameter.wt',
                 'clique.num', 'num.tri')
plot_global(env.dti$dt.G.tidy, xvar='threshold', exclude=exclude.vars)

```

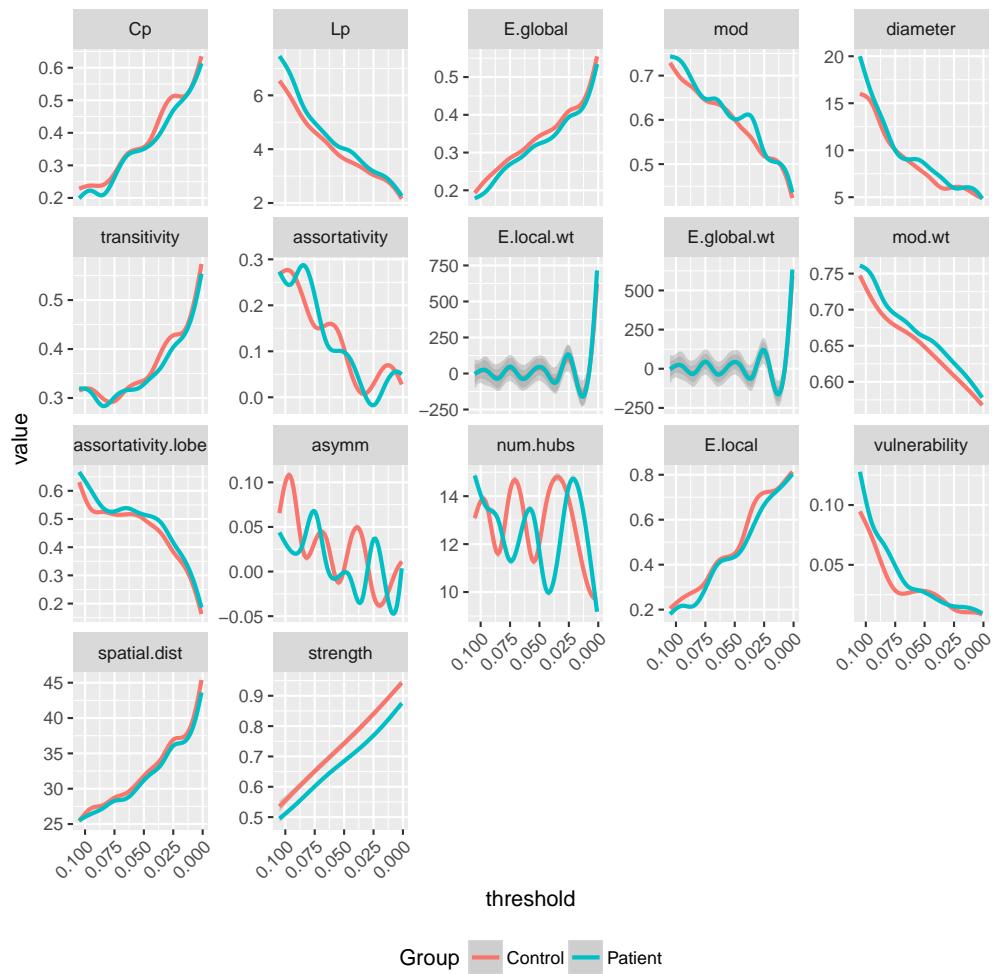


Figure 7.1: Global graph measures vs. density, DTI data.

Part IV

Group Analyses: GLM-based

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8

Vertex-wise group analysis (GLM)

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Analysis of between-group differences in a given vertex measure (e.g., *degree*, *betweenness centrality*, etc.) is described in this chapter (equivalent to a voxel-wise analysis common in fMRI, DTI, VBM, etc. analyses). This is only possible if you have a graph for each subject (at a given density/threshold). In this chapter, I describe the inputs and outputs of the function `brainGraph_GLM`. Next, I provide a “mini-tutorial” on design matrix coding and provide several examples of common experimental designs. Finally, I show an example using *permutations* (as in FSL’s *randomise*).[\(29, 56, 88\)](#)

8.1 Function arguments

```
args(brainGraph_GLM)

## function (g.list, covars, measure, con.mat, con.type = c("t",
##           "f"), X = NULL, con.name = NULL, alternative = c("two.sided",
##           "less", "greater"), alpha = 0.05, level = c("vertex", "graph"),
##           permute = FALSE, N = 5000, perms = NULL, long = FALSE, ...)
## NULL
```

8.1.1 Mandatory

The following list details the *mandatory* function arguments:

g.list A list of `igraph` graph objects. You can include graphs from one or more subject groups. If you have multiple groups, you must *concatenate* the lists using the `c()` function (see Examples later).

covars A `data.table` of covariates. It should have as its first column `Study.ID`; the data in this column must match the `name` graph-level attribute of the graphs in `g.list` (or at least a subset of them). ¹ You may include any additional columns of your choosing (e.g., age, sex, etc.). This data object will be used to create the *design matrix*.

measure The vertex- or graph-level measure of interest (e.g., `E.nodal.wt`).

con.mat A numeric matrix specifying the contrast(s) of interest. It can be multiple rows, and you can specify row names.

con.type Either `t` or `f`, if you want to calculate t- or F-statistics. F-statistics are only “two-sided”. Otherwise, this choice only affects whether statistics are calculated for each row of the contrast matrix (`t`) or a single set for the whole matrix (`f`).

8.1.2 Optional

The following are *optional* function arguments:

X If you wish to provide your own design matrix, you can specify it with this argument. Note that, if you do this, you still need to provide the `covars` data table; this is used for making sure the covariates and the graph metrics are in the same order, and to remove the appropriate data if some are missing for certain subjects. However, the function will assume that you have correctly created your own design matrix, and doesn’t do any checking.

con.name A character string of the name of the contrast (e.g., `'Control > Patient'`). If this argument is not provided, the function first checks if `con.mat` has row names (which you would create yourself); otherwise they will be generic (i.e., `'Contrast 1'`).

alternative Either `two.sided` (the default), `less`, or `greater` corresponding to (respectively)

$$H_A : \hat{\gamma} \neq 0$$

$$H_A : \hat{\gamma} \leq 0$$

$$H_A : \hat{\gamma} \geq 0$$

alpha The significance level (default: 0.05)

level Either `vertex` or `graph`, depending on if the measure of interest is vertex- or graph-level.

The following optional arguments pertain to *permutation/randomization* tests (see [Permutation testing](#)):

permute A *logical* indicating whether or not to do a permutation test (default: FALSE).

N An *integer* indicating the number of permutations to create; only relevant if `permute` is TRUE (default: 5,000).

perms A numeric matrix of the permutation order, if you would like to provide your own.

long A *logical* specifying whether or not to return the null distribution of the maximum statistics across permutations (default: FALSE)

¹If you are creating a design matrix for a different application, e.g., TBSS, this is not required.

8.1.3 Unnamed

The ellipsis (i.e., the `...`) in a function call specifies unnamed arguments that are passed to other functions. In `brainGraph_GLM`, they are passed to `brainGraph_GLM_design`, a function that simply creates a design matrix \mathbf{X} . Here I list the arguments that you may specify in your function call.

coding A character string, either `dummy` (default), `effects`, or `cell.means`. This determines how your factor variables will be coded in the design matrix. See [Tutorial: design matrix coding](#) for more.

mean.center A *logical* specifying whether or not to mean-center your non-factor variables (default: `FALSE`). Mean-centering will be done for all subjects, not within groups. Note that any factor variables that are binarized (see next bullet point) will also be mean-centered.

binarize A *character* vector of the column name(s) of `covars` to convert from *factor* to *numeric* (binary) vector. If the factor has $k > 2$ levels, it will not be binarized but instead will be changed to $0, 1, \dots, k - 1$.

int A *character* vector of the column names of `covars` to test for an interaction. The resulting columns will be appended to the *end* of the design matrix. If you provide only one column, nothing will happen. If you provide 3, then the 3-way *and all 2-way interactions* will be added to the design.

Note

It is recommended that, if you include interaction terms, you should also mean-center the other variables to partially reduce multicollinearity (e.g., see Chapter 8.2 of Kutner et al. (51)).

So, to summarize, columns in the design matrix \mathbf{X} will likely be in a different order than the input `covars`. The first column will be the *Intercept* (a column of all 1's), if `coding` is not set to `cell.means`. The next column(s) will by any numeric variables, followed by *Group* column(s), and finally *interaction* columns (if applicable). You may wish to inspect the design matrix before specifying your contrast vector by typing, e.g., `head(brainGraph_GLM_design(covars, ...))`.

8.2 Return value

This function returns an object of class `bg_GLM` with several of the input arguments in addition to a `data.table` of the statistics of interest. First, I describe the statistics that are calculated, and then the return object itself.

8.2.1 Statistics

For all analyses, the following statistics are calculated (C is the contrast matrix):

Gamma (if `con.type='t'`) The *contrast of parameter estimates*:

$$\hat{\gamma} = C^T \hat{\beta}$$

This is equivalent to the `cope?` images from FSL, the `con_?????` images from SPM, and `gamma.mgh` from Freesurfer.

ESS (if `con.type='f'`) The *extra sum of squares* due to the full model, compared to the reduced model. This is specific to the contrast matrix, and is equivalent to the `ess_?????` images from SPM.

Standard error (if `con.type='t'`) The standard error of the contrast, SE , is

$$SE = \sqrt{C \Sigma C^T}$$

where Σ , the *variance-covariance matrix*, is calculated as

$$\Sigma = s^2 \mathbf{X}^T \mathbf{X}$$

Standard error (if `con.type='f'`) The *sum of squared errors* of the full model.

stat The *t-statistic* for the contrast of interest is

$$T = \frac{\hat{\gamma}}{SE}$$

The *F-statistic* is

$$F = \frac{ESS/rank(C)}{SSEF/df}$$

CI (if `con.type='t'`) The lower and upper confidence limits:

$$\hat{\gamma} \pm t_{\alpha/2, df} \times SE$$

8.2.2 The `bg_GLM` object

The elements of the return object are:

level Either `vertex` or `graph`

X The *design matrix*

y The *outcome variable*. If `level='graph'`, this is a *numeric vector*; If `level='vertex'`, this is a numeric matrix. The number of rows equals the number of subjects, and the number of columns equals the number of vertices.

outcome The name of the *outcome variable* (the graph metric chosen by the `measure` function argument).

con.type Either '`t`' or '`f`'.

con.mat The *contrast matrix*.

con.name The contrast name(s).

alt The *alternative hypothesis*.

alpha The significance level.

DT A `data.table` containing statistics of interest; see the next section for details.

removed A character vector of the subjects removed from the analyses (due to incomplete data). If none were removed, this will be `NULL`.

permute A *logical* indicating whether or not permutations were calculated.

N The number of permutations (if applicable).

perm A *list* containing two `data.table` objects:

null.dist The null distribution of the maximum statistic for each permutation.

thresh The $(1 - \alpha)$ th percentile of the null distribution.

`DT`

The `data.table` object that is returned contains all statistics of interest. Each row is a different vertex (brain region) or a single row for graph-level metrics. Additionally, statistics are listed for each contrast (if more than one is specified).

For *t*-contrasts, the columns are:

- region** The region name (abbreviated)
- gamma** The contrast(s) of parameter estimates
- se** The standard error of the contrast(s)
- stat** The *t-statistic(s)* associated with the contrast(s)
- p** The *p-value* associated with the contrast(s)
- ci.low** The lower confidence limit
- ci.high** The upper confidence limit
- p.fdr** The FDR-adjusted p-value
- p.perm** The permutation p-value (if `permute=TRUE`)
- Outcome** The name of the outcome variable (e.g., `E.nodal.wt`)
- Contrast** The name of the contrast(s)
- contrast** Integer indicating the contrast number

For *F*-contrasts, the columns are:

- region**
- ESS** The *extra sum-of-squares*
- se**
- stat** The *F-statistic* of the contrast(s)
- p**
- p.fdr**
- p.perm**
- Outcome**
- Contrast**
- contrast**

8.3 Tutorial: design matrix coding

8.3.1 Suggested reading

A very good website with MRI-focused information on design matrices in the GLM is [FSL's GLM site](#). For more information regarding coding schemes in linear models, see ([46](#), [58](#), [69](#), [87](#)). For a complete treatment of this topic, see Kutner et al. ([51](#)); they usually use *dummy* coding, but see Chapter 8.4 where they introduce *effects* and *cell means* coding (see the sub-section [Other codings for indicator variables](#)). For some information regarding how coding is handled in R, see [this UCLA page](#). Finally, Anderson Winkler's blog has a great post of [common GLM formulas](#).

8.3.2 Dummy coding

The default parameterization of factors in R is known as *reference*, or *dummy*, coding. Let's say we have a simple one-way ANOVA (a factor named *Group*) with two levels (*Control* and *Patient*). In this scheme, instead of having a column in the design matrix X for each level, there is only a column for the second level (*Patient*) in addition to the *Intercept*. You can use this type of coding by setting `coding='dummy'` in the call to `brainGraph_GLM`. There is more on dummy coding at [this UCLA page](#).

The parameter estimate for the intercept represents the mean of the first (alphabetically, by default) group, and the second parameter estimate is the mean of the second group *relative to the first group*. In equation form (generalized to a $1 \times k$ ANOVA):

$$\begin{aligned}\hat{\beta}_0 &= \mu_1 \\ \hat{\beta}_1 &= \mu_2 - \mu_1 \\ &\vdots \\ \hat{\beta}_{k-1} &= \mu_k - \mu_1\end{aligned}$$

To compare group means, assume there are $k = 3$ factor levels. Group 1 (the reference group) is coded +1 for the intercept and 0 for the other parameters; group 2 is coded +1 for the intercept and second parameter, and 0 for the third:

$$\begin{aligned}H_A : \mu_1 - \mu_2 &> 0 \\ \Rightarrow (\hat{\beta}_0) - (\hat{\beta}_0 + \hat{\beta}_1) &> 0 \\ \Rightarrow -\hat{\beta}_1 &> 0 \\ \Rightarrow C &= (0, -1, 0)\end{aligned}$$

$$\begin{aligned}H_A : \mu_1 - \mu_3 &> 0 \\ \Rightarrow (\hat{\beta}_0) - (\hat{\beta}_0 + \hat{\beta}_2) &> 0 \\ \Rightarrow -\hat{\beta}_2 &> 0 \\ \Rightarrow C &= (0, 0, -1)\end{aligned}$$

For a general between-group comparison (that does not involve the reference group), the contrast has a +1 in the i^{th} entry and a -1 in the j^{th} entry:

$$\begin{aligned}H_A : \mu_i - \mu_j &> 0 \\ \Rightarrow (\hat{\beta}_{i-1} + \hat{\beta}_0) - (\hat{\beta}_{j-1} + \hat{\beta}_0) &> 0 \\ \Rightarrow \hat{\beta}_{i-1} - \hat{\beta}_{j-1} &> 0 \\ \Rightarrow C &= (0, 0, \dots, 1, 0, \dots, -1, 0, 0, \dots, 0)\end{aligned}$$

```
# Create a data.table with just Study.ID and Group
X <- env.glm$covars.dti[, 1:2]
setkey(X, Group, Study.ID)
print(X, 4)

##      Study.ID   Group
## 1: 02-115-0 Control
## 2: 02-126-1 Control
## 3: 02-127-2 Control
## 4: 02-128-9 Control
```

```

## ---
## 153: 02-629-8 Patient
## 154: 02-630-6 Patient
## 155: 02-631-5 Patient
## 156: 02-632-2 Patient

# The Control group is chosen to be the reference group
X[, levels(Group)]
```

```

## [1] "Control" "Patient"

# There are only 2 columns, with the second indicating membership in Group 2
model.matrix(~ Group, data=X)[c(1:4, 153:156), ]
```

```

##      (Intercept) GroupPatient
## 1              1          0
## 2              1          0
## 3              1          0
## 4              1          0
## 153            1          1
## 154            1          1
## 155            1          1
## 156            1          1
```

```

# Example outcome variable, nodal efficiency for one vertex
y <- sapply(g.glm, function(x) V(x)$E.nodal.wt[1])
Xy <- cbind(X, y)

# Simple linear regression
summary(lm(y ~ Group, data=Xy))$coefficients
```

```

##                   Estimate Std. Error t value Pr(>|t|)
## (Intercept)  0.045358  0.0009747   46.53 1.338e-92
## GroupPatient -0.003256  0.0011504    -2.83 5.274e-03
```

```

# beta_0 equals the mean of Group 1, and beta_1 equals the difference in Group
# means (Group 2 - Group 1)
Xy[, mean(y), by=Group]
```

```

##      Group      V1
## 1: Control 0.04536
## 2: Patient 0.04210
```

```

Xy[, mean(y), by=Group][, diff(V1)]
```

```

## [1] -0.003256
```

8.3.3 Cell means coding

The values in the second row of the summary in the previous code block would be equivalent to setting a contrast of `c(-1, 1)` in a 2nd-level SPM analysis if the coding scheme were *cell means* coding. Here, the parameters represent the factor level means:

$$\begin{aligned}\hat{\beta}_1 &= \mu_1 \\ \hat{\beta}_2 &= \mu_2 \\ &\vdots \\ \hat{\beta}_k &= \mu_k\end{aligned}$$

If you prefer this kind of parameterization, you can exclude the intercept with the following code. This is the same matrix that results from setting `coding='cell.means'` in a call to `brainGraph.GLM`.

```
# You can manually exclude the intercept to get group means:
model.matrix(~ Group + 0, data=X)[c(1:4, 153:156), ]

##      GroupControl GroupPatient
## 1             1          0
## 2             1          0
## 3             1          0
## 4             1          0
## 153           0          1
## 154           0          1
## 155           0          1
## 156           0          1

summary(lm(y ~ Group + 0, data=Xy))$coefficients

##              Estimate Std. Error t value  Pr(>|t|)
## GroupControl  0.04536  0.0009747   46.53 1.338e-92
## GroupPatient  0.04210  0.0006109   68.91 1.221e-117
```

8.3.4 Effects coding

As detailed in the FSL GLM page, *effects* coding is a better choice for more complicated designs. The coding is almost the same as *dummy* coding except that the reference group is indicated by -1 in the design matrix instead of 0 . You can use this type of coding by setting `coding='effects'` in a call to `brainGraph.GLM`. There is more on effects coding on [this UCLA page](#).

The parameter estimate for the intercept represents the *mean of factor level means* ($\mu.$ in the equations below). The remaining parameter estimates represent the difference between the overall mean and the factor level mean.

Note

This value will not equal the mean of all observations if there are an unequal number of observations in each level.

$$\begin{aligned}\hat{\beta}_0 &= \mu. \\ \hat{\beta}_1 &= \mu_2 - \mu. \\ &\vdots \\ \hat{\beta}_{k-1} &= \mu_k - \mu.\end{aligned}$$

If you are interested in comparing group means under this coding scheme, first assume that there are $k = 3$ factor levels. Then, since group 1 (the reference group) is coded +1 for the intercept and -1 for the other parameters, and group 2 is coded +1 for the intercept and the second parameter, and 0 for the third:

$$\begin{aligned} H_A : \mu_1 - \mu_2 &> 0 \\ \Rightarrow (\hat{\beta}_0 - \hat{\beta}_1 - \hat{\beta}_2) - (\hat{\beta}_0 + \hat{\beta}_1) &> 0 \\ \Rightarrow -2\hat{\beta}_1 - \hat{\beta}_2 &> 0 \\ \Rightarrow C &= (0, -2, -1) \end{aligned}$$

The contrast for a difference in groups i and j (where $i \neq j \neq 1$), i.e., $H_0 : \mu_i - \mu_j \neq 0$, is the same as in the dummy coding example.

```
Xdes <- brainGraph_GLM_design(X, coding='effects')
Xdes[c(1:3, 10:11, 102:105), ]

##      Intercept GroupPatient
## [1,]         1        -1
## [2,]         1        -1
## [3,]         1        -1
## [4,]         1        -1
## [5,]         1        -1
## [6,]         1         1
## [7,]         1         1
## [8,]         1         1
## [9,]         1         1

# Contrasts
Cmat <- matrix(c(1, -1, 1, 1, 0, -2, 0, 2), nrow=4, ncol=2, byrow=TRUE)
rownames(Cmat) <- c(paste('Mean', groups),
                     'Control > Patient', 'Patient > Control')
Cmat

##      [,1] [,2]
## Mean Control     1   -1
## Mean Patient     1    1
## Control > Patient  0   -2
## Patient > Control  0    2

# Some variables to make the LM fit faster across repetitions
XtX <- solve(crossprod(Xdes))
dfR <- nrow(Xdes) - ncol(Xdes)
CXtX <- apply(Cmat, 1, function(x) solve(t(x) %*% XtX %*% x))
options(digits=2)
fits <- vector('list', nrow(Cmat))
for (i in seq_along(fits)) {
  fits[[i]] <- brainGraph:::brainGraph_GLM_fit_t(Xdes, y, XtX, Cmat[i, , drop=FALSE])
  fits[[i]] <- as.data.table(fits[[i]])
}
fits <- rbindlist(fits)
cbind(rownames(Cmat), fits)[, !'contrast']

##      V1    gamma      se
## 1: Mean Control 0.0454 0.00097
## 2: Mean Patient 0.0421 0.00061
## 3: Control > Patient 0.0033 0.00115
## 4: Patient > Control -0.0033 0.00115
```

8.4 Examples

This section contains examples of common analysis scenarios. This is the first demonstration of the `summary` method for `brainGraph_GLM` results. See [Box 8.1](#).

In all examples, the `list` object `g.glm` contains all the graphs for both groups at a single threshold. The covariates table used in each example (varying the inclusion of certain columns) is:

```
env.glm$covars.dti

##      Study.ID   Group Age.MRI Sex Scanner
## 1: 02-001-4 Patient     16   M     3T
## 2: 02-003-2 Patient     17   M     3T
## 3: 02-006-8 Patient     17   M     3T
## 4: 02-008-7 Patient     18   F    1.5T
## 5: 02-013-1 Patient     17   M    1.5T
## ---
## 152: 02-639-2 Control    11   F     3T
## 153: 02-643-9 Control    11   M    1.5T
## 154: 02-644-0 Control    13   M    1.5T
## 155: 02-646-5 Control    12   F    1.5T
## 156: 02-652-9 Control    11   M    1.5T
```

BOX 8.1 THE SUMMARY METHOD FOR RESULTS

In the *Examples* section, you see a printed summary of the results from `brainGraph_GLM`. First, the output in this document is not how it will appear in your terminal. I use the excellent `colorout` package for “colorizing” different aspects of the text.

In my terminal, the lines you see with two leading pound signs and black text are displayed in blue; these are printed using R’s `message` function. Next are the input parameters supplied to the function. Finally, the statistics are displayed; if there are multiple contrasts, there will be a separate section for each. You may also choose to show results for a single contrast using the `contrast` argument. The `summary` function displays only significant results (based on the supplied α level). You may choose to use the actual P-value or the FDR-adjusted P-value for significance (via the function argument `p.sig`). The argument `digits` adjusts the number of significant digits displayed. Finally, the `print.head` argument controls how many rows to display; by default, at most 10 rows will be printed.

8.4.1 Two-group difference

The following code block tests for between-group difference in weighted nodal efficiency. The `summary` method will be shown for a later example.

```
# Simple between-group comparison, Group 1 > Group 2
con.mat <- matrix(c(0, -2), nrow=1, dimnames=list('Control > Patient'))
summary(with(env.glm,
  brainGraph_GLM(g.glm, measure='E.nodal.wt', covars=covars.dti[, 1:2],
  coding='effects', con.mat=con.mat, alt='greater')))
```

8.4.2 Two-group difference adjusted for covariate

In the following code block, I adjust for *age at MRI*. I also mean-center the covariate (but it does not change the statistics). It must be noted that the function adds the factor variables *after* any covariates, so you will need to adjust your contrast vectors accordingly.

```
# Between-group comparison adjusted for age, Group 1 > Group 2
con.mat <- matrix(c(0, 0, -2), nrow=1, dimnames=list('Control > Patient'))
summary(with(env.glm,
  brainGraph_GLM(g.glm, measure='E.nodal.wt', covars=covars.dti[, 1:3],
  coding='effects', mean.center=TRUE, con.mat=con.mat,
  alt='greater')))
```

8.4.3 Two-group difference with continuous covariate interaction

This is essentially the same as the previous model, except now the covariate *Age.MRI* will be mean-centered and then split into two columns in the design matrix (one for each subject group). This is achieved by including `int='Age.MRI'` in your function call. I only show the results for the `cell.means` approach.

```
# A few rows of the design matrix
X <- brainGraph_GLM_design(env.glm$covars.dti[, 1:3], coding='cell.means',
                           mean.center=TRUE, int=c('Group', 'Age.MRI'))
X[c(1:4, 153:156), ]

##      GroupControl GroupPatient GroupControl:Age.MRI GroupPatient:Age.MRI
## [1,]          0          1           0.0            1.2
## [2,]          0          1           0.0            1.6
## [3,]          0          1           0.0            1.6
## [4,]          0          1           0.0            3.1
## [5,]          1          0          -3.8            0.0
## [6,]          1          0          -1.8            0.0
## [7,]          1          0          -3.4            0.0
## [8,]          1          0          -4.2            0.0
```

```
# Between-group comparison with Age interaction, Group 1 > Group 2
con.mat <- matrix(c(0, 0, 1, -1), nrow=1, dimnames=list('Group X Age'))
summary(with(env.glm,
  brainGraph_GLM(g.glm, measure='E.nodal.wt', covars=covars.dti[, 1:3],
  X=X, con.mat=con.mat, alt='greater')))
```

8.4.4 Two-way between subjects ANOVA: 2x2

Here is an example of a 2x2 ANOVA. The two factors are **Group** and **Sex**, and the levels for each are **Control**, **Patient** and **Male**, **Female**. The first example shows *effects* coding, and the second is *cell-means* coding. Note in the second code block that with *cell-means* coding, the order of the columns is A1B1, A2B1, A1B2, A2B2, so that for example the contrast for a main effect of **Group** would be `c(1, -1, 1, -1)` and for main effect of **Sex** would be `c(1, 1, -1, -1)`. I divide the contrast vector by 4 to match the results of *effects* coding.²

²The t-statistics and p-values would be unchanged if you did not divide by 4.

```

# A few rows of the design matrix
X <- brainGraph_GLM_design(env.glm$covars.dti[, c(1:2, 4)], coding='effects',
                           int=c('Group', 'Sex'))
X[c(1:4, 153:156), ]

##          Intercept GroupPatient SexM GroupPatient:SexM
## [1,]           1         1     1             1
## [2,]           1         1     1             1
## [3,]           1         1     1             1
## [4,]           1         1    -1            -1
## [5,]           1        -1     1            -1
## [6,]           1        -1     1            -1
## [7,]           1        -1    -1             1
## [8,]           1        -1     1            -1

con.mat <- matrix(c(0, 0, 0, 1), nrow=1, dimnames=list('Group x Sex interaction'))
summary(with(env.glm,
             brainGraph_GLM(g.glm, measure='E.nodal.wt', covars=covars.dti[, c(1:2, 4)],
                             X=X, con.mat=con.mat, alt='greater')))

##
## brainGraph GLM results
## -----
## Level: vertex
## Graph metric of interest: E.nodal.wt
## 
## Contrast type: T contrast
## Alternative hypothesis: C > 0
## Contrast matrix:
##                   Intercept GroupPatient SexM GroupPatient:SexM
## Group x Sex interaction          0         0     0             1

##
## Statistics
## -----
## Group x Sex interaction

##      Region Estimate 95% CI low 95% CI high Std. error t value p-value
## 1:   lENT 0.001186  1.12e-04    0.00226  0.000543   2.18 0.01533
## 2:   lFUS 0.000767 -9.32e-05   0.00163  0.000435   1.76 0.04007
## 3:   lpORB 0.000865 -8.88e-05  0.00182  0.000483   1.79 0.03758
## 4:    lTT 0.000963  2.67e-04   0.00166  0.000353   2.73 0.00351
## 5:   lTHAL 0.001186  1.85e-04   0.00219  0.000506   2.34 0.01024
## --- 
## 9:   rENT 0.000962 -6.32e-05   0.00199  0.000519   1.85 0.03284
## 10:  rPARH 0.001011  1.70e-05   0.00201  0.000503   2.01 0.02313
## 11:  rTHAL 0.000887 -1.52e-04  0.00193  0.000526   1.69 0.04682
## 12:  rHIPP 0.001186 -2.63e-05  0.00240  0.000614   1.93 0.02756
## 13:  rAMYG 0.001195  2.72e-04   0.00212  0.000467   2.56 0.00577

##      p-value (FDR)
## 1:       0.254
## 2:       0.254
## 3:       0.254
## 4:       0.219

```

```
## 5:      0.254
## ---
## 9:      0.254
## 10:     0.254
## 11:     0.259
## 12:     0.254
## 13:     0.219
```

For *cell-means* coding, I show part of the design matrix, but omit the `summary`, as it is identical to that for *effects* coding. Note that the contrast matrix is divided by 4 to give equivalent results.

```
X <- brainGraph_GLM_design(env.glm$covars.dti[, c(1:2, 4)],
                           coding='cell.means', int=c('Group', 'Sex'))
X[1:4, ]

##      GroupControl:SexF GroupControl:SexM GroupPatient:SexF
## [1,]          0          0          0
## [2,]          0          0          0
## [3,]          0          0          0
## [4,]          0          0          1
##      GroupPatient:SexM
## [1,]          1
## [2,]          1
## [3,]          1
## [4,]

con.mat <- matrix(c(1, -1, -1, 1) / 4, nrow=1, dimnames=list('Group X Sex'))
```

8.4.5 Two-way between subjects ANOVA: 2x3

Here is an example of a 2x3 ANOVA. The first example shows *effects* coding, and the second shows *cell-means* coding. Note that in the second code block, the order of the columns is A1B1, A1B2, A1B3, A2B1, A2B2, A2B3. I show all of the standard ANOVA contrasts.

```
# A few rows of the design matrix; get rid of 'NA' values first
incomp <- covars2x3[!complete.cases(covars2x3), Study.ID]
X <- brainGraph_GLM_design(covars2x3[!Study.ID %in% incomp],
                           coding='effects', int=c('A', 'B'))
head(X)

##      Intercept A2 B2 B3 A2:B2 A2:B3
## [1,]          1 -1 -1 -1      1      1
## [2,]          1  1  0  1      0      1
## [3,]          1 -1 -1 -1      1      1
## [4,]          1  1 -1 -1     -1     -1
## [5,]          1  1  0  1      0      1
## [6,]          1 -1 -1 -1      1      1

con.mat <- cbind(rep(0, 5), diag(5))
rownames(con.mat) <- c('Main A', 'Main B (1st)', 'Main B (2nd)',
                       'A X B (1st)', 'A X B (2nd)')
anova2x3 <- brainGraph_GLM(g.glm[45:156], measure='E.nodal.wt', covars=covars2x3,
                            X=X, con.mat=con.mat, alt='greater')
summary(anova2x3)
```

```

## 
## brainGraph GLM results
## -----
## Level: vertex
## Graph metric of interest: E.nodal.wt
##
## Contrast type: T contrast
## Alternative hypothesis: C > 0
## Contrast matrix:
##              Intercept A2 B2 B3 A2:B2 A2:B3
## Main A          0  1  0  0     0     0
## Main B (1st)   0  0  1  0     0     0
## Main B (2nd)   0  0  0  1     0     0
## A X B (1st)    0  0  0  0     1     0
## A X B (2nd)    0  0  0  0     0     1
##
## Subjects removed due to incomplete data:
## 02-006-8 02-123-7 02-161-8 02-170-3 02-203-8 02-287-7 02-521-5

## 
## Statistics
## -----
## Main A
## No significant results!
## Main B (1st)
## No significant results!
## Main B (2nd)

##      Region Estimate 95% CI low 95% CI high Std. error t value p-value
## 1:   1FUS  0.00123 -1.70e-04   0.00262  0.000703   1.74  0.0423
## 2:   1PARH 0.00173 -3.60e-05   0.00350  0.000892   1.94  0.0274
## 3:   1pORB 0.00139 -1.62e-04   0.00294  0.000781   1.78  0.0394
## 4:   lrMFG 0.00140 -1.80e-04   0.00297  0.000794   1.76  0.0410
## 5:   1PUT  0.00216  2.06e-05   0.00430  0.001079   2.00  0.0239
## 6:   1PALL 0.00181 -5.69e-05   0.00367  0.000940   1.92  0.0286
## 7:   1HIPP 0.00193 -1.34e-04   0.00399  0.001040   1.86  0.0332
## 8:   rparaC 0.00178  8.46e-05   0.00347  0.000854   2.08  0.0199
## 9:   rPALL 0.00171 -1.97e-04   0.00362  0.000963   1.78  0.0391
##      p-value (FDR)
## 1:      0.357
## 2:      0.357
## 3:      0.357
## 4:      0.357
## 5:      0.357
## 6:      0.357
## 7:      0.357
## 8:      0.357
## 9:      0.357

## A X B (1st)
## No significant results!
## A X B (2nd)

##      Region Estimate 95% CI low 95% CI high Std. error t value p-value
## 1:   lcmFG  0.00167  2.92e-04   0.00306  0.000697   2.40  0.00907

```

```

## 2: 1CUN 0.00211 4.48e-04 0.00377 0.000837 2.52 0.00667
## 3: 1ENT 0.00188 8.90e-06 0.00376 0.000945 1.99 0.02447
## 4: liCC 0.00228 3.82e-04 0.00419 0.000959 2.38 0.00956
## 5: 1LOF 0.00263 5.09e-04 0.00475 0.001068 2.46 0.00780
## ---
## 22: rpORB 0.00111 -1.84e-04 0.00240 0.000650 1.70 0.04601
## 23: rpTRI 0.00151 1.37e-04 0.00289 0.000695 2.18 0.01578
## 24: rPCC 0.00156 -1.24e-04 0.00324 0.000847 1.84 0.03456
## 25: rrACC 0.00165 -9.17e-05 0.00339 0.000878 1.88 0.03154
## 26: rSFG 0.00131 -1.53e-04 0.00278 0.000739 1.78 0.03930
##      p-value (FDR)
## 1: 0.0733
## 2: 0.0733
## 3: 0.1123
## 4: 0.0733
## 5: 0.0733
## ---
## 22: 0.1399
## 23: 0.0857
## 24: 0.1194
## 25: 0.1194
## 26: 0.1245

```

For *cell-means* coding, I only show part of the design matrix. I also show how to construct the contrast matrix. Notice that I divide the matrix by 6; this will give equivalent results to the *effects* coding run.

```

X <- brainGraph_GLM_design(covars2x3[!Study.ID %in% incompl,
                                         coding='cell.means', int=c('A', 'B'))
head(X)

##      A1:B1 A1:B2 A1:B3 A2:B1 A2:B2 A2:B3
## [1,]    1    0    0    0    0    0
## [2,]    0    0    0    0    0    1
## [3,]    1    0    0    0    0    0
## [4,]    0    0    0    1    0    0
## [5,]    0    0    0    0    0    1
## [6,]    1    0    0    0    0    0

con.mat <- matrix(c(1, 1, 1, -1, -1, -1,
                    -1, 1, 0, -1, 1, 0,
                    -1, 0, 1, -1, 0, 1,
                    1, 0, -1, -1, 0, 1,
                    0, 1, -1, 0, -1, 1), nrow=5, byrow=TRUE)
con.mat <- con.mat / 6
rownames(con.mat) <- c('Main A', 'B2-B1', 'B3-B1',
                        'A1B1 - A2B1 - A1B3 + A2B3', 'A1B2 - A2B2 - A1B3 + A2B3')

summary(brainGraph_GLM(g.glm[45:156], measure='E.nodal.wt', covars=covars2x3,
                       con.mat=c(1, 1, 1, -1, -1, -1)/6, alt='greater'))

```

8.4.6 Three-way between subjects ANOVA: 2x2x2

Since v2.0.0, three-way interactions are allowed. If the `int` vector has three elements, all two-way interactions will be automatically included. In this example, the three factors and their levels are:

- Group (*Patient* and *Control*)
 - Sex (*M* and *F*)
 - Scanner ($1.5T$ and $3T$)

```
X <- brainGraph_GLM_design(env.glm$covars.dti[, !'Age.MRI'],
                           coding='effects',
                           int=c('Group', 'Sex', 'Scanner'))
head(X)

##      Intercept GroupPatient SexM Scanner3T GroupPatient:SexM
## [1,]           1           1     1           1                   1
## [2,]           1           1     1           1                   1
## [3,]           1           1     1           1                   1
## [4,]           1           1    -1          -1                  -1
## [5,]           1           1     1          -1                   1
## [6,]           1           1     1          -1                   1
##      GroupPatient:Scanner3T SexM:Scanner3T GroupPatient:SexM:Scanner3T
## [1,]           1           1                   1
## [2,]           1           1                   1
## [3,]           1           1                   1
## [4,]          -1           1                   1
## [5,]          -1          -1                  -1
## [6,]          -1          -1                  -1
```

8.5 Permutation testing

If you also would like to get permutation-based p-values, then you can specify `permute=TRUE` to perform the permutations, calculate the maximum test statistic across vertices (or a single statistic if `level='graph'`), and compare this null distribution of maximum statistics to the *observed* statistics. This is essentially the same as the procedure from FSL’s *randomise* and the PALM utility (albeit without as much of the functionality).(29, 56, 88) The default matrix partitioning scheme is (like that of PALM) called `'beckmann'`.(73)

When `long=TRUE` , an additional element called `perm` is returned in the `bg_GLM` object. It is a list with 2 elements:

null.dist A `data.table` containing the null distribution of maximum statistic values for each contrast.

thresh A `data.table` of the $1 - \alpha$ %ile value of the null distribution of maximum statistics for each contrast.

8.5.1 Example

Here, I show the structure of the `perm` element.

```
str(diffs.perm$perm)

## List of 2
## $ null.dist:Classes 'data.table' and 'data.frame': 1000 obs. of  2 variables:
##   ..$ V1      : num [1:1000] 1.8 2.13 1.13 1.87 1.13 ...
##   ..$ contrast: int [1:1000] 1 1 1 1 1 1 1 1 1 1 ...
##   ..- attr(*, ".internal.selfref")=<externalptr>
##   ..- attr(*, "index")= atomic (0)
##   ... ..- attr(*, "_contrast")= int(0)
## $ thresh    :Classes 'data.table' and 'data.frame': 1 obs. of  2 variables:
##   ..$ contrast: int 1
##   ..$ V1      : num 2.96
##   ..- attr(*, ".internal.selfref")=<externalptr>
```

8.6 Plotting LM diagnostics

The `plot` method for `bg_GLM` objects has the same functionality as `plot.lm` in `base R`: it shows linear model “diagnostics”. There are 6 possible plots (for a given region), chosen by the argument `which` :

1. Residuals vs. fitted values
2. QQ plot
3. “Scale-location” plot (standardized residuals vs. fitted values)
4. Cook’s distance
5. Residuals vs. leverage
6. Cook’s distance vs. leverage

The plots are shown in [Figure 8.1](#).

```
grid.arrange(plot(diffs.perm, region='1HIPP', which=1:6)[[1]])
```

If you would like to plot multiple regions, you can supply a character vector, or leave the default (`region=NULL`). The following code block shows how to get the plots for all regions and save each to a page in a PDF. On my system, with 76 regions, it takes 44 seconds for the function call itself, and 38 seconds to save the file to disk. The *list* of plots is 60 MB, and the PDF is 1.1 MB.

```
glmPlots <- plot(diffs.perm, which=1:6)
ml <- marrangeGrob(glmPlots, nrow=1, ncol=1)
ggsave('glmPlots.pdf', ml, width=8.5, height=11)
```

8.7 Create a graph of the results

To create a graph with attributes specific to GLM, use `make_glm_brainGraph`. This will return a list (with length equal to the number of contrasts) of graphs with several additional attributes:

name (graph-level) The contrast name
outcome (graph-level) The network metric tested
alpha (graph-level)
p (graph-level) 1 minus the P-value
p.fdr (graph-level) 1 minus the FDR-adjusted P-value
gamma (graph-level)
se (vertex-level)
size2 (vertex-level) The test statistic
size (vertex-level) The test statistic transformed to a range of 0–20 (for visualization purposes)
p.perm (vertex-level)

```
g.anova2x3 <- make_glm_brainGraph(anova2x3, atlas='dkt.scgm')
# Length equals the # of contrasts
length(g.anova2x3)

## [1] 5
```

8.8 Plotting a graph of the results

If you would like to plot only significant regions, you can simply call the `plot` method on the graph. The `p.sig` lets you choose which P-value determines significance (the standard P-value, FDR-adjusted, or permutation-based).

```
# Plot results for the first contrast only
plot(g.anova2x3[[5]], vertex.color='color.lobe', vertex.size=10)
```

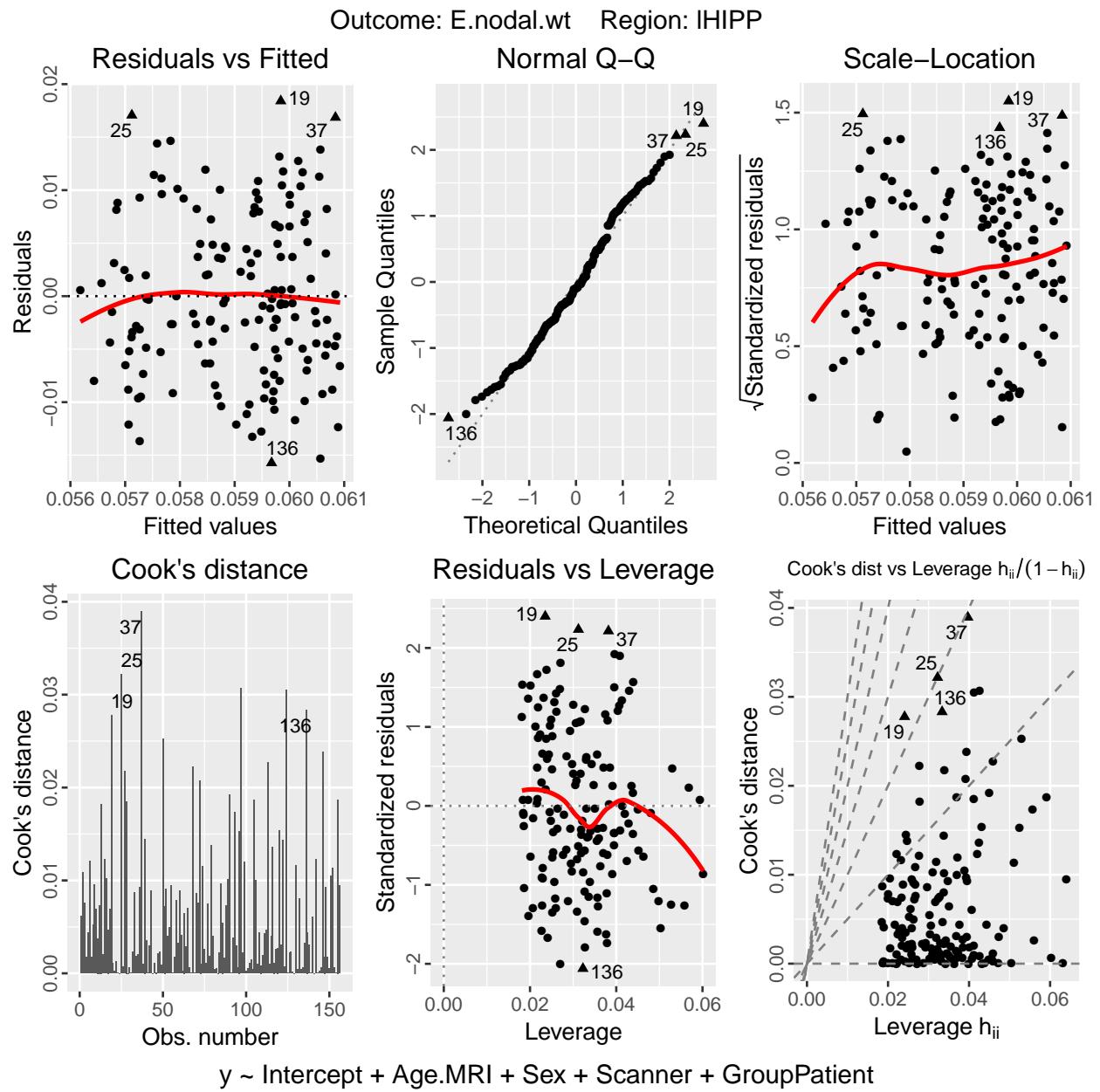


Figure 8.1: GLM diagnostics.

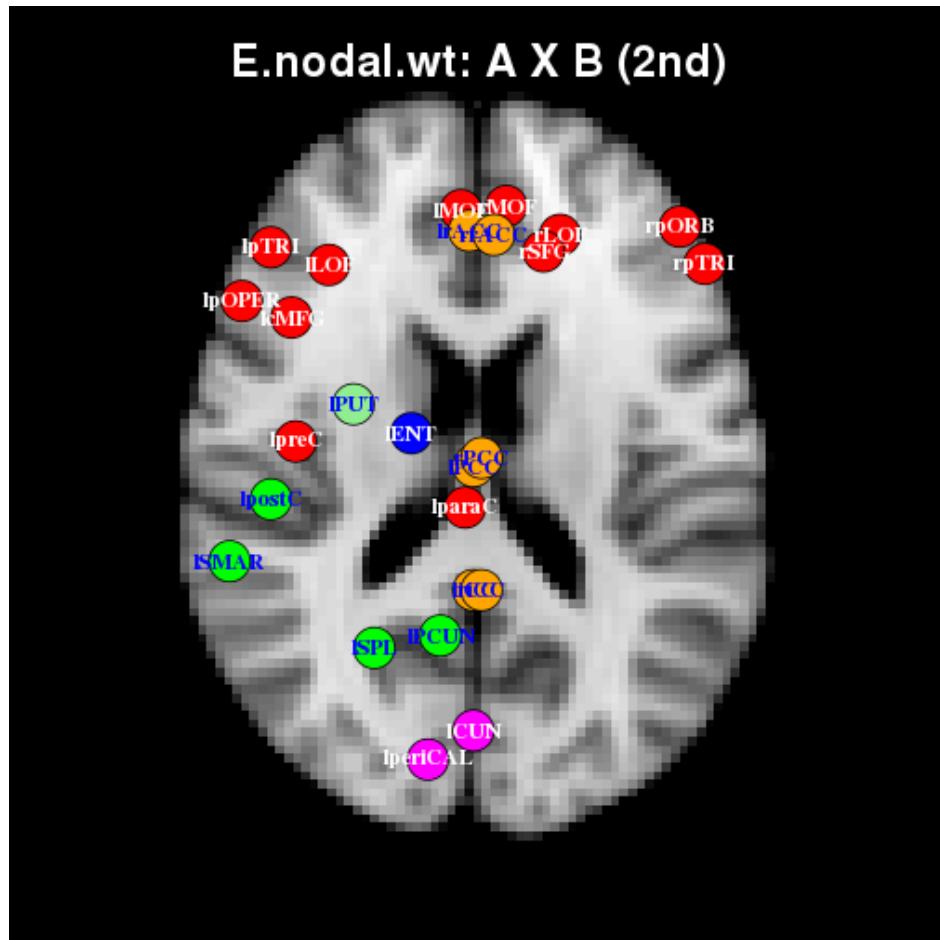


Figure 8.2: GLM results.

9

Multi-threshold permutation correction

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The *multi-threshold permutation correction (MTPC)* method for statistical inference was introduced by Drakesmith et al.(23) Its goal is to reduce the effects of false positives and the use of multiple thresholds in network analyses. This is because network metrics are not stable across thresholds (sometimes even adjacent thresholds), and there is no real standard for choosing a threshold to examine *a priori*. The **brainGraph** function for performing MTPC is **mtpc**.

9.1 Background

As I have described in previous chapters, it is common to generate sets of *thresholded networks* for a given subject or group; this is necessary because most “raw” brain networks have an unrealistically-high *density* (i.e., the proportion of present to possible connections). In structural covariance and resting-state fMRI networks, it is common to threshold the covariance matrix with a range of correlation values; in DTI tractography, the threshold can be a range of *streamline counts*, connectivity probabilities, or average DTI metric for each tract (e.g., FA). However, there is no *principled* way to choose the “correct” threshold to use for your final results.

9.1.1 MTPC procedure

The steps that are applied in MTPC are:

1. Apply a set of thresholds τ to the networks, and compute network metrics and for all subjects/groups and thresholds (we have already done this in **Graph creation** and **Graph creation**).
2. Compute test statistics S_{obs} for all networks and thresholds. This is done from within **mtpc** by calling **brainGraph_GLM** (see **Vertex-wise group analysis (GLM)**).
3. Permute group assignments and compute test statistics for each permutation and threshold (also done by calling **brainGraph_GLM**).
4. Build the null distribution of the *maximum statistic across thresholds* (and across brain regions, if applicable) *for each permutation*.

5. Determine the *critical value* S_{crit} from the null distribution of maximum test statistics (by taking the top α th percentile).
6. Identify *cluster(s)* where $S_{obs} > S_{crit}$ and compute the *area under the curve (AUC)* for the cluster(s); the AUC(s) are denoted A_{MTPC} . Note that these clusters are *across thresholds*; in `brainGraph`, I consider 3 consecutive significant test statistics as a cluster.
7. Compute a *critical AUC* A_{crit} from the *mean* of the supra-critical AUC's for the permuted tests.
8. Reject the null hypothesis H_0 if the AUC of the significant (observed) clusters is greater than the critical AUC; i.e., if $A_{MTPC} > A_{crit}$.

Note that the procedure is nearly identical for graph- and vertex-level metrics; with vertex-level metrics, step 4 (building the null distribution of maximum test statistics) is the only difference in that the maximum is taken across thresholds *and* brain regions.

9.2 Function arguments

Many arguments are the same as those of `brainGraph.GLM`; any listed below without accompanying information are described in [Vertex-wise group analysis \(GLM\)](#).

```
args(mtpc)

## function (g.list, thresholds, covars, measure, con.mat, con.type = c("t",
##   "f"), con.name = NULL, level = c("vertex", "graph"), clust.size = 3L,
##   N = 500, perms = NULL, alpha = 0.05, res.glm = NULL, long = TRUE,
##   ...)
## NULL
```

9.2.1 Mandatory

g.list A *nested* list of `igraph` graph objects. If you followed the code in previous chapters, you can supply your entire `g` (or `g.norm`, or whatever you decide to call it) object. If you would like to isolate only one group (or a subset of all groups), you must “wrap” it in a list; e.g., `g.list=list(g[[2]])` will only look at group 2.

thresholds A numeric vector of the thresholds that were used to create the networks. This can be either the actual threshold values or just an integer vector from 1 to the number of thresholds.

covars

measure

con.mat

9.2.2 Optional

con.type (default: `'t'`).

con.name (default: `NULL`).

level (default: `'vertex'`).

clust.size (default: `3`) The “cluster size” (i.e., the number of consecutive thresholds for which the observed statistic exceeds the null)

N (default: `500`).

perms (default: `NULL`).

alpha (default: `0.05`).

res.glm (default: `NULL`) A list of `bg_GLM` objects, as output by a previous run of `mtpc`. This is useful if you want to asses differences when varying `clust.size`, as it will avoid calculating all of the null statistics over again.

9.2.3 Unnamed

The unnamed arguments are the same as those in `brainGraph_GLM`; please see the relevant section in [Vertex-wise group analysis \(GLM\)](#) for information.

9.3 Return value

The function returns an object of class `mtpc`. Many of the returned elements are the same as those returned by `brainGraph_GLM`; if they have no accompanying information here, see [Vertex-wise group analysis \(GLM\)](#). The elements are: (τ refers to thresholds, and N_τ is the number of thresholds)

res.glm A *list* (with length equal to N_τ) in which each element is the output from `brainGraph_GLM` for a single threshold.

DT A `data.table`, which is combined, for all thresholds, from each run of `brainGraph_GLM`.

stats A `data.table` with the statistics calculated by MTPC: τ_{mtpc} , S_{mtpc} , S_{crit} , and A_{crit} .

null.dist A *list* containing a *numeric matrix* of the maximum statistic for each permutation and threshold. There will be N_{rand} rows and N_τ columns. The number of elements in the list will equal the number of contrasts supplied.

perm.order The *numeric matrix* of permutation orderings.

level

X

outcome

con.type

con.mat

con.name

alt

alpha

N

9.4 Code example

The following code blocks show how to run `mtpc` for a few different network measures, storing all results in a single list. As with some other functions with long runtimes and/or high processing demands, it would be quite a bit faster to run each individually from a fresh R session, but you can let this run without having to repeatedly execute the code while only changing the `measure` argument. There are some benchmarks in [Benchmarks](#).

I have been storing all parameters in a single `data.table`, which makes it easier to loop through without much effort. In the example below, I look at 4 network metrics: 2 graph-level and 2 vertex-level. I show how to change the alternative hypothesis for given metrics. This approach is, of course, optional.

```
mtpcVars <- data.table(level=rep(c('graph', 'vertex'), each=2),
                        outcome=c('E.global.wt', 'Lp', 'E.nodal.wt', 'strength'),
                        alt='greater')

# Change H_A for 'Lp'
mtpcVars[outcome == 'Lp', alt := 'less']
setkey(mtpcVars, level, outcome)

# Different number of permutations based on the level
mtpcVars['graph', N := 1e4]
mtpcVars['vertex', N := 5e3]

# Generate permutation matrices using 'shuffleSet' from the 'permute' package
mtpcPerms <- list(vertex=shuffleSet(n=nrow(covars), nset=mtpcVars['vertex', unique(N)]),
                     graph=shuffleSet(n=nrow(covars), nset=mtpcVars['graph', unique(N)]))

# Create the contrast matrix
mtpcContrast <- matrix(c(0, 0, 0, 0, -2, 0,
                           0, 0, 0, 0, 0, 1),
                           nrow=2, byrow=TRUE,
                           dimnames=list(c('Control vs. Patient', 'Age-squared effect')))

mtpcVars

##      level    outcome    alt      N
## 1:  graph E.global.wt greater 10000
## 2:  graph         Lp    less 10000
## 3: vertex  E.nodal.wt greater  5000
## 4: vertex    strength greater  5000

# Loop through the network metrics
# The 1st-level of the list is for each 'level' (i.e., 'graph' and 'vertex')
mtpc.diffs.list <- sapply(mtpcVars[, unique(level)], function(x) NULL)
for (x in names(mtpc.diffs.list)) { # Loop across 'level'

  # The 2nd-level is for each network metric (for the given level 'x')
  mtpc.diffs.list[[x]] <- sapply(mtpcVars[x, unique(outcome)], function(x) NULL)
  for (y in mtpcVars[x, outcome]) {

    # Print some timing info in the terminal; optional
    print(paste('Level:', x, '; Outcome:', y, ';', format(Sys.time(), '%H:%M:%S')))
```

```

mtpc.diffs.list[[x]][[y]] <-
  mtpc(g, thresholds, covars=covars.dti, measure=y, con.mat=mtpcContrast,
        con.type='t', level=x, N=mtpcVars[.(x, y), N], perms=mtpcPerms[[x]],
        alt=mtpcVars[.(x, y), alt])
}

# Create a single data.table with just the significant regions
mtpc.diffs.sig.dt <-
  rbindlist(lapply(mtpc.diffs.list, function(x)
    rbindlist(lapply(x, function(y)
      y$DT[A.mtpc > A.crit, .SD[1], by=region]))))

# Save the variables created in this script
save(list=ls()[grep('.*mtpc.*', ls())],
     file=paste0(savedir, , groups[2], '_', atlas, '_mtpc.rda'))

```

Here I show what the `summary` method produces. This analysis consisted of 3 groups and 3 t-contrasts. You have the option to choose a single `contrast` (the default is to print results for all contrasts) and to print longer summary tables (the default is to print only the first and last 5 rows).

```

summary(res.mtpc)

##
## MTPC results
## -----
## Level: vertex
## Graph metric of interest: E.nodal.wt
## # of permutations: 5,000
## # of thresholds: 30
##
## Contrast type: T contrast
## Alternative hypothesis: C != 0
## Contrast matrix:
##           Intercept age_mri_6w gender ScannerChange GroupPt1 GroupPt2
## Control > Pt1          0         0         0         0       -2      -1
## Control > Pt2          0         0         0         0       -1      -2
## Pt1 > Pt2              0         0         0         0        1      -1

##
## Statistics
## -----
## tau.mtpc: threshold of the maximum observed statistic
## S.mtpc: maximum observed statistic
## S.crit: the critical (95th percentile) value of the null max. statistic
## A.crit: critical AUC from the supra-critical null AUCs
##
##   contrast tau.mtpc S.mtpc S.crit A.crit
## 1:      1    5555    100    3.3  13757
## 2:      2    5555    119    3.2  14520
## 3:      3    4920     85    3.3  13473

## Control > Pt1

```

```

##      Region S.mtpc S.crit A.mtpc A.crit
## 1:    rLOG  82.65  3.26 151159 13757
## 2:    rLOF  28.17  3.26  39195 13757
## 3:    lLOF  27.72  3.26 19392 13757
## 4:    rFUS  24.85  3.26 32871 13757
## 5:    lCAUD 21.33  3.26 40502 13757
## ---
## 14:   riCC  11.01  3.26 44319 13757
## 15:  lperiCAL  8.73  3.26 21808 13757
## 16:   lpORB  8.10  3.26 19918 13757
## 17:  lparaC  7.56  3.26 14977 13757
## 18:   rSPL  6.74  3.26 16969 13757

## Control > Pt2

##      Region S.mtpc S.crit A.mtpc A.crit
## 1:   rHIPP 119.20  3.19 18235 14520
## 2:    rLOG  98.28  3.19 130618 14520
## 3:    lLOG  72.54  3.19  54591 14520
## 4:    lLOF  43.21  3.19  77614 14520
## 5:   lHIPP  24.36  3.19 15823 14520
## ---
## 44:  lPCUN  8.12  3.19 27565 14520
## 45:  rPCUN  7.86  3.19 15457 14520
## 46:  lparaC  7.80  3.19 33308 14520
## 47:  lrMFG  6.78  3.19 18280 14520
## 48:   rSFG  6.56  3.19 20308 14520

## Pt1 > Pt2

##      Region S.mtpc S.crit A.mtpc A.crit
## 1:  lAMYG  22.67  3.26 36411 13473
## 2:   rBSTS  20.34  3.26 35767 13473
## 3:    lLOF  16.81  3.26 27834 13473
## 4:   lENT  16.31  3.26 18254 13473
## 5:    rFP  13.24  3.26 20976 13473
## ---
## 12:   lCUN  8.54  3.26 15358 13473
## 13:  rrACC  8.14  3.26 22893 13473
## 14:   rMTG  7.87  3.26 13481 13473
## 15:  lcACC  7.03  3.26 17747 13473
## 16:  lrMFG  6.63  3.26 14686 13473

```

9.5 Plotting the statistics

If you would like to see how the (t- or F-) statistic changes with the threshold, in addition to the critical null statistic value, and the null distribution of maximum statistics, you can simply call the `plot` method for your results. This figure is essentially the same as Figure 11 in Drakesmith et al. (23).

The function arguments are:

contrast You can only plot statistics for one contrast.

region You can choose one or multiple regions; if you choose multiple, the function returns a list of `ggplot2` objects.

only.sig.regions The default is `TRUE`. If you do not supply a `region`, then all significant regions will be returned.

show.null Logical indicating whether or not to show points for the maximum null statistics (default: `TRUE`).

caption.stats Logical indicating whether or not to print the statistics values underneath the plot (default: `FALSE`). These are the values in the `stats` `data.table` from the results.

In Figure 9.1 I show the statistics plots for 4 regions. I use the `grid.arrange` function (from the `gridExtra` package) to plot all 4. As you can see, regions determined to be significant can have very different statistics profiles, so you should always check these.

```
mtpcPlots <- plot(res.mtpc, region=c('rCAUD', 'rLOF', 'lSMAR', 'lFUS'),
                     contrast=1, caption.stats=TRUE)
do.call(grid.arrange, mtpcPlots)
```

To save a plot for every region, use (a variant of) the following code. You can also save the PDF with multiple plots per page by changing the `nrow` and `ncol` values.

```
mtpcPlots <- plot(res.mtpc, contrast=1, only.sig.regions=FALSE)
ml <- marrangeGrob(mtpcPlots, nrow=1, ncol=1)
ggsave('mtpcPlots.pdf', ml, width=8.5, height=11)
```

9.6 Create a graph of the results

To create a graph with attributes specific to MTPC, use `make_glm_brainGraph`. This will return a list (with length equal to the number of contrasts) of graphs with several additional attributes:

name (graph-level) The contrast name

outcome (graph-level) The network metric tested

tau.mtpc (graph-level)

S.mtpc (graph-level)

S.crit (graph-level)

A.crit (graph-level)

A.mtpc (vertex-level) The vertex-wise AUC where $S_{obs} > S_{crit}$

sig (vertex-level) Binary value indicating whether the vertex was found to be significantly different

```
g.mtpc <- make_glm_brainGraph(res.mtpc, atlas='dk.scgm')
```

9.7 Plotting a graph of the results

If you would like to plot only significant regions, you can simply call the `plot` method on the graph.

```
# Plot results for the first contrast only  
plot(g.mtpc[[1]], vertex.color='color.lobe', vertex.size=10)
```

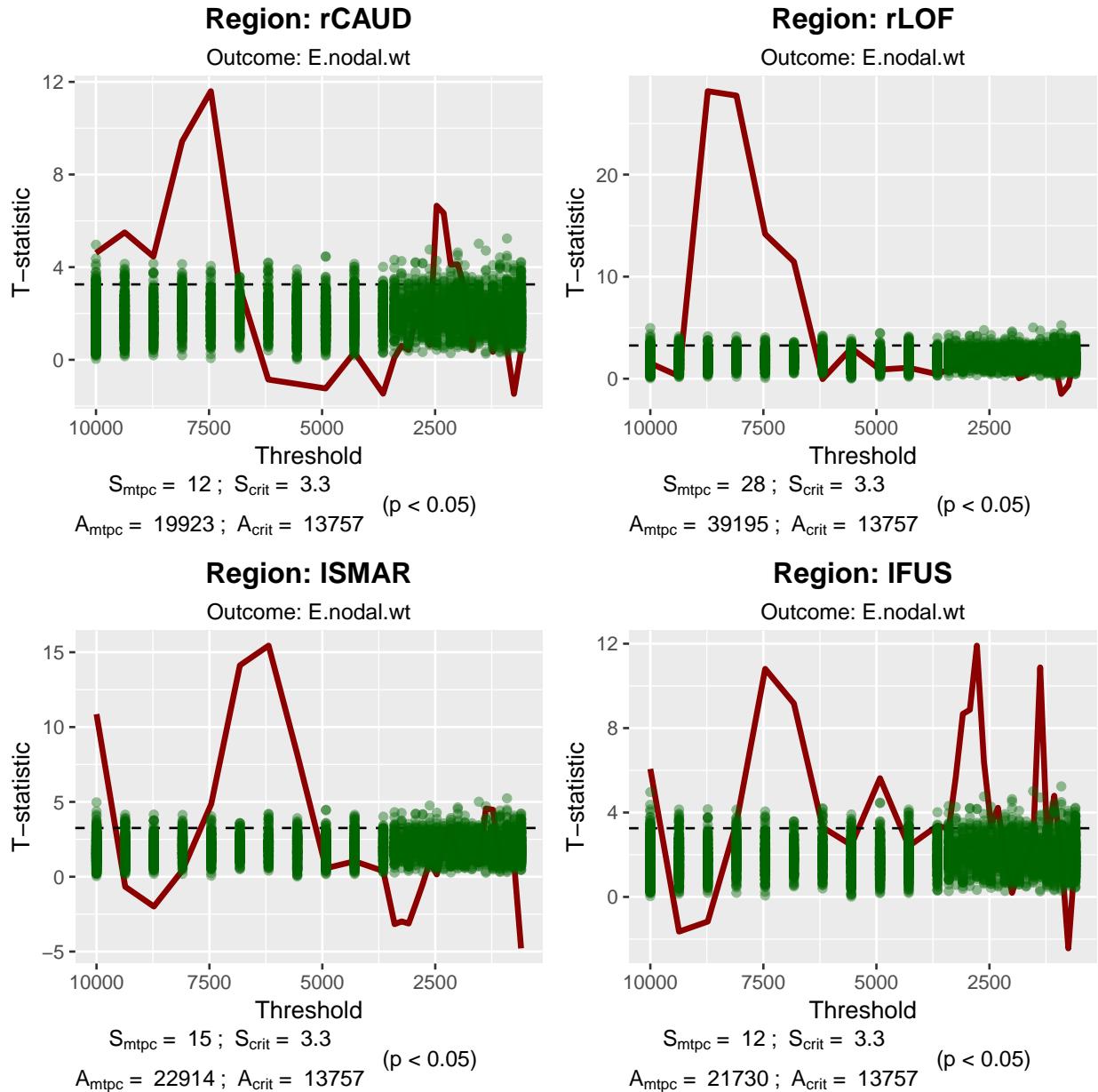


Figure 9.1: **MTPC statistics.** The red shaded areas are those that are above the critical null statistic (dashed line) for at least 3 consecutive thresholds. The green points are the maximum null statistics (per permutation).

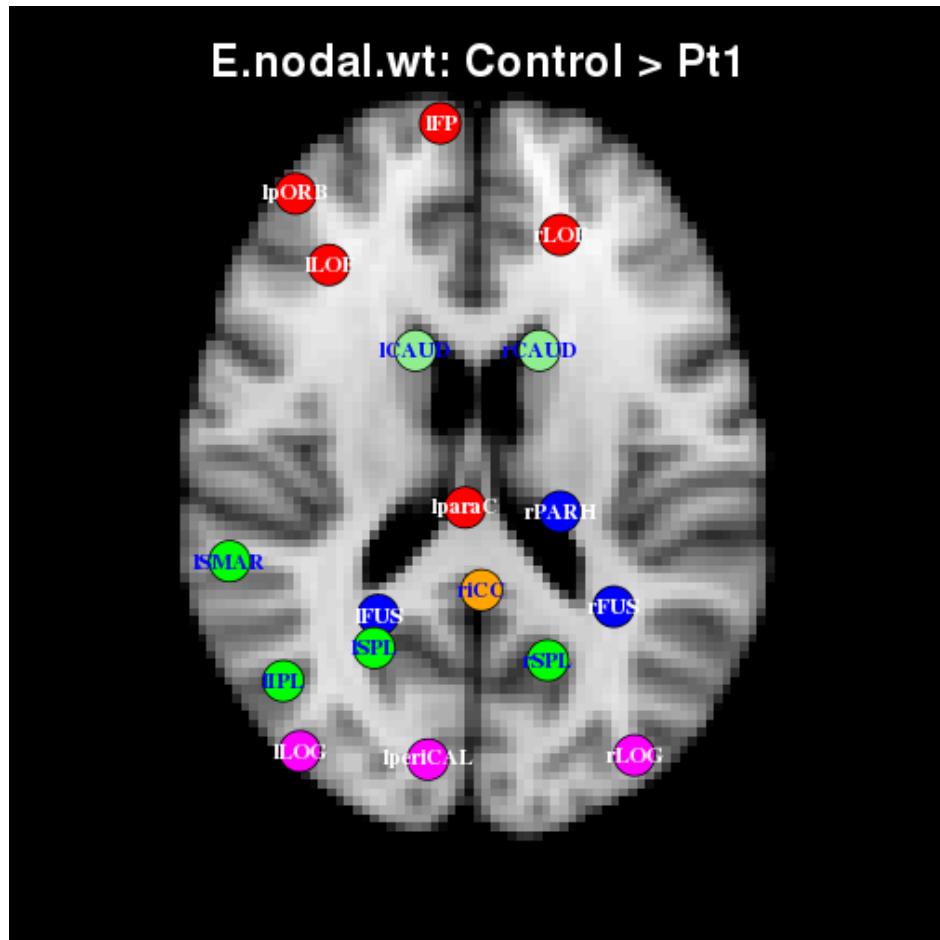


Figure 9.2: MTPC results.

10

Network-based statistic (NBS)

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The *network-based statistic (NBS)* was introduced by Zalesky et al. for performing FWE control of brain network data in a way that is analogous to cluster-based thresholding in fMRI.(92) The `brainGraph` function for performing NBS is `NBS`.

10.1 Background

Most brain networks are relatively large, in terms of the number of possible pairwise connections: even for a brain atlas with 90 regions (the *AAL* atlas), there are $90 \times (90 - 1)/2 = 4005$ possible connections. This is a *multiple comparisons* problem, but a Bonferroni correction is inappropriate because the data are not independent; a *FDR* adjustment is a better alternative. *NBS* provides weak FWE control for “mass univariate” testing of all edges.

This algorithm operates directly on the connectivity matrices. A GLM is specified at every matrix element; the model can be as simple as a two-group difference, or as complex as a three-way ANOVA. All designs that are allowed by `brainGraph_GLM` will also work for this function (see [Examples](#)). An initial p-value threshold is provided by the user, and the *connected component* size(s) of this graph is (are) calculated. The data are then permuted, and for each permutation the *largest connected component* is recorded, creating a null distribution. A p-value is assigned to the observed connected component size(s) based on the location relative to the null distribution. As in `brainGraph_GLM`, randomization is done through the *Freedman-Lane* procedure.(29)

10.2 Function arguments

As with `mtpc`, many of the arguments are the same as those in `brainGraph_GLM`; see [Vertex-wise group analysis \(GLM\)](#) for more information.

```
args(NBS)

## function (A, covars, con.mat, con.type = c("t", "f"), X = NULL,
##   con.name = NULL, p.init = 0.001, N = 1000, perms = NULL,
##   symm.by = c("max", "min", "avg"), alternative = c("two.sided",
##   "less", "greater"), long = FALSE, ...)
## NULL
```

A The 3-d array of (normalized/thresholded) connectivity matrices. This may also be the raw matrices.

covars

con.mat

con.type

X

con.name

p.init An initial p-value threshold for calculating the observed component sizes (default: `P = 0.001`)

N

perms

symm.by Character string indicating how to symmetrize the matrices (see [Import, normalize, and filter matrices for all subjects](#)). Default behavior is to use the maximum of the off-diagonal elements.

alternative

long

... Arguments that are used for creating the design matrix; see [Vertex-wise group analysis \(GLM\)](#) for more information

10.3 Return value

The function returns an object of class `NBS`. Any values not described here can be found in [Vertex-wise group analysis \(GLM\)](#).

X

p.init The initial p-value.

con.type

con.mat

con.name

alt

N

removed

T.mat A *list* of matrices containing the t- or F-statistics. The length of the list will equal the number of contrasts.

- p.mat** A *list* of matrices containing the p-values. The length of the list will equal the number of contrasts.
- components** A list of two **data.tables**: the observed components and p-values, and the null distributions of maximum component sizes.

10.4 Code example

Example usage is in the following code block.

```
X <- brainGraph_GLM_design(env.glm$covars.dti, coding='effects',
                           binarize=c('Sex', 'Scanner'))
con.mat <- matrix(c(rep(0, 4), -2, rep(0, 4), 2), nrow=2, byrow=TRUE)
rownames(con.mat) <- c('Control > Patient', 'Patient > Control')
res.nbs <- NBS(A, env.glm$covars.dti, con.mat, X=X,
                 p.init=0.001, N=1e3, alternative='greater')
```

Here is what the `summary` method for a `NBS` object returns. First are some details on user-specified inputs. Then it prints a table of the significant components and their associated P-values.

```
summary(res.nbs)

##
## Network-based statistic results
## -----
## Number of permutations: 1,000
## Initial p-value: 0.001
##
## Alternative hypothesis: C > 0
## Contrast matrix:
##              Intercept Age.MRI Sex Scanner GroupPatient
## Control > Patient      0      0     0       0        -2
## Patient > Control      0      0     0       0         2

##
## Statistics
## -----
## Control > Patient

##      # vertices # edges p-value
## [1,]       6      0  0.001 ***
## [2,]       4      0  0.002 **
## [3,]       3      0  0.008 **
## [4,]       2      0  0.183
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

##
## Patient > Control

##      # vertices # edges p-value
## [1,]       3      0  0.002 **
## [2,]       2      0  0.069 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

10.5 Creating a graph of the results

To create a graph with attributes specific to NBS, use `make_nbs_brainGraph`. This returns a list (length equal to the number of contrasts) of graphs with several attributes (in addition to those created by `set_brainGraph_attr`):

- stat** (edge-level) The t- or F-statistics for each connection
- p** (edge-level) 1 – the P-value for each connection
- comp** (vertex-level) Integer index of the connected component that each vertex is a member of
- p.nbs** (vertex-level) 1 – the P-value for each connected component

```
g.nbs <- make_nbs_brainGraph(res.nbs, atlas=atlas)
```

10.6 Plotting the results

The default behavior of the plotting method for NBS results will only show the component(s) with a significant effect, given some value α . As you can see in [Figure 10.1](#), it will also plot vertices and edges of the same component with the same color and give the plot a title containing the contrast name (this can be over-ridden by changing the `main` argument). You can adjust various other aspects of the plot, as with any other graph; for example, you could change the edge width to scale with the statistic value (by typing `edge.width='stat'`).

```
plot(g.nbs[[1]], alpha=0.05)
```

10.7 Testing

For some benchmarking info, see [Benchmarks](#). I have done some testing of this function; the t-statistics calculated in my function matched those of the Matlab toolbox NBS; the connected component sizes differed by only 1, and I assume this is due to their toolbox thresholding by *T-statistic*, whereas I threshold by *p-value*. I encourage you to do your own testing if you wish.

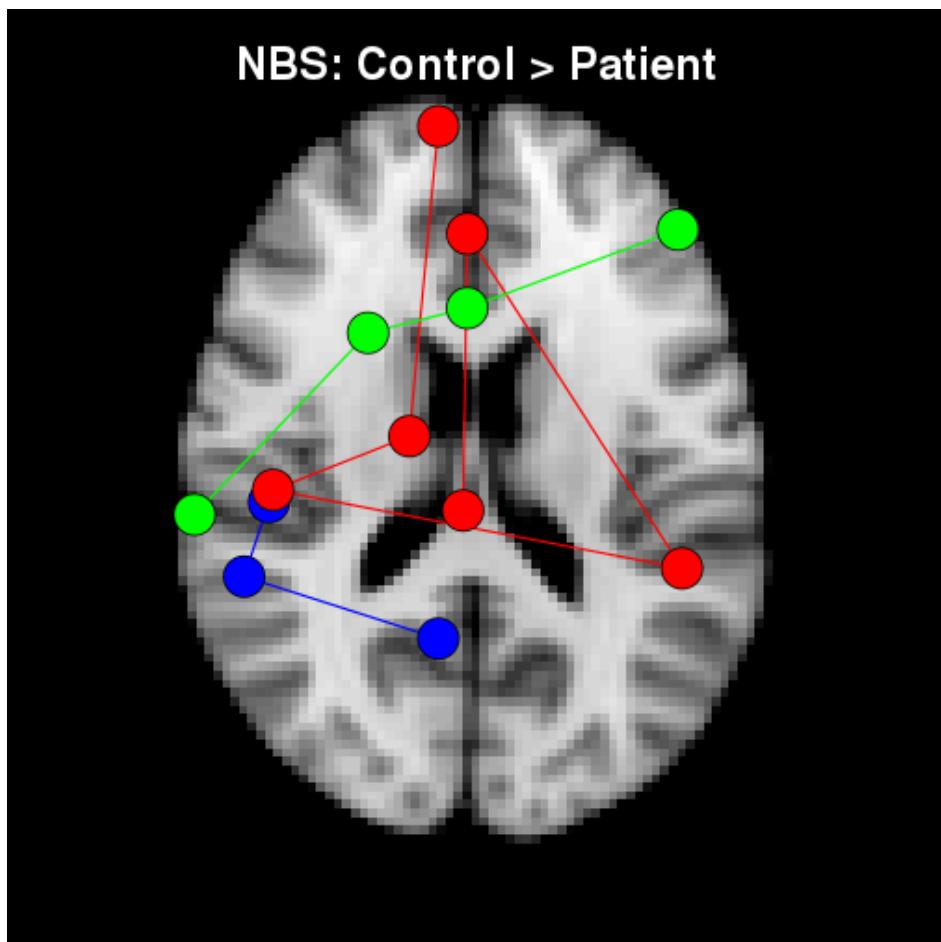


Figure 10.1: **Significant connected components.** Vertices of the same component are plotted in the same color.

11

Graph- and vertex-level mediation analysis

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New in v2.0.0

All of the functionality in this chapter is new to v2.0.0.

Performing mediation analysis in `brainGraph` follows the *potential outcomes* framework that is implemented in the [mediation package](#) (76), as opposed to the more well-known “Baron & Kenny approach” (4). A few advantages of this approach include:

- Allows for mediation-treatment interaction and nonlinearities
- Addresses confounds
- Allows for the decomposition of the total effect into direct and indirect effects

A full treatment of mediation is beyond the scope of this document, but I provide some background here as it can be quite difficult to understand without prior exposure.

11.1 Background

As explained in Preacher (61), the *potential outcomes* framework for causal inference was re-introduced (or popularized) by Donald Rubin in the 1970’s (66, 67).¹ In fact, Holland (35) calls it the *Rubin Causal Model*. To re-iterate, for binary treatment variable X , the effect of X on outcome Y for case/subject i can be defined as the difference between two potential outcomes:

1. $Y_i(1)$ – the outcome that would be realized if $X_i = 1$

¹The notation had previously been used by Jerzy Neyman in 1923 for randomized experiments.

2. $Y_i(0)$ – the outcome that would be realized if $X_i = 0$

We can say that X causes Y if $Y_i(1) \neq Y_i(0)$. However, we can never observe both $X_i = 1$ and $X_i = 0$; Holland (35) calls this the *fundamental problem of causal inference*. Under random assignment, the expected mean between-group difference is equal to the difference in group means; i.e.,

$$E[Y_i(1)] - E[Y_i(0)] = E[Y_i|X_i = 1] - E[Y_i|X_i = 0]$$

There are also potential outcomes for the mediator M , only one of which can be observed for a given unit i (i.e., either $M_i(1)$ or $M_i(0)$). The outcomes for unit i can then be defined using the notation $Y_i(X_i, M_i(X_i))$, and the *indirect effect* δ is defined as the “change that would occur in Y when moving from the value of M if $X_i = 0$ to the value of M if $X_i = 1$ ” (Preacher 2015, p. 834). In equation form,

$$\delta_i(x) = Y_i(x, M_i(1)) - Y_i(x, M_i(0))$$

And under certain assumptions (see below), the average indirect effect $\bar{\delta}(x)$ is simply the difference in expected value: (also known as the *average causal mediation effect (ACME)*)

$$\bar{\delta}(x) = E[Y_i(x, M_i(1)) - Y_i(x, M_i(0))] \quad (11.1)$$

The *average direct effect (ADE)* is the difference in potential outcomes between treatment groups:

$$\bar{\zeta}(x) = E[Y_i(1, M_i(x)) - Y_i(0, M_i(x))] \quad (11.2)$$

And, under the potential outcomes framework, the *total effect* is the sum of the ACME and ADE:

$$\bar{\tau}(x) = \delta_i(x) + \zeta_i(1 - x) \quad (11.3)$$

11.1.1 Suggested reading

An excellent review of mediation analysis can be found in Preacher (61). Specifically, the subsection “Model-Based Tradition” (in the section “Causal Inference for Indirect Effects”) provides some historical background in addition to a set of assumptions and implementations that fit with the approach taken in `mediation`. For the earliest works, see Rubin (66); Holland (35); Robins and Greenland (64). Furthermore, Imai and colleagues, who created the `mediation` package, have several papers that should be considered required reading (40, 41, 42, 76).

11.2 Notation

As I mentioned, it is critical that you read Tingley et al. (76). For convenience, I will include some notation here, including the variable names as seen in the `summary` method.²

?? .acme The *average causal mediation effect* (see [Equation 11.1](#)). This is typically the effect of interest in mediation analysis. Represented by the variables `d0, d1`.

?? .ade The *average direct effect* (see [Equation 11.2](#)). Represented by the variables `z0, z1`.

?? .tot The *total effect* (see [Equation 11.3](#)). Represented by the variable `tau`.

?? .prop The *proportion mediated*. This is the ACME divided by the total effect. Represented by the variables `n0, n1`.

b.* The effect size (e.g., `b.acme` is the ACME estimate).

ci.low.* , ci.high.* The confidence intervals (e.g., `ci.low.acme`).

p.* The P-value (e.g., `p.acme`).

²The `?` is a *wildcard* representing any single character.

11.3 Function arguments

There are a few arguments that are the same as in `brainGraph_GLM`, so their descriptions are omitted here.

```
args(brainGraph_mEDIATE)

## function (g.list, covars, mediator, treat, outcome, covar.names,
##           level = c("graph", "vertex"), boot = TRUE, boot.ci.type = c("perc",
##           "bca"), N = 1000, conf.level = 0.95, control.value = 0,
##           treat.value = 1, long = TRUE, int = FALSE, ...)
## NULL
```

g.list

covars Must have columns `'Study.ID'` and several names you supply in the function call: `treat` , `outcome` , `covar.names` .

mediator The name of the mediator variable; this must be a valid graph- or vertex-level attribute (e.g., `'E.global.wt'` , `'btwn.cent'` , etc.).

treat The name of the *treatment* variable. A common example would be `'Group'` .

outcome The name of the *outcome* variable. This is usually going to be a non-MRI variable you measure in the subject; e.g., IQ some other neuropsychological test/questionnaire score (e.g., WISC processing speed, CVLT immediate recall, etc.)

covar.names Character vector of the nuisance covariates you would like to include in your analyses (e.g., age, sex, etc.)

level

boot Logical indicating whether or not to do bootstrap resampling for estimating confidence intervals (CI) and statistical significance (default: `TRUE`). You should *always* do bootstrap resampling.

boot.ci.type Character string indicating the type of bootstrap confidence intervals. The default is `'perc'` (percentile bootstrap), but you may also choose `'bca'` (bias-corrected and accelerated). However, see Biesanz et al. (8) and Falk and Biesanz (28) which find that the *BCa* approach results in inflated Type I error while the percentile bootstrap performs well.

N Integer; number of bootstrap samples (default: `1000`).

conf.level The confidence level for calculating CI's (default: `0.95`).

control.value The value of `treat` to be used as the *control* condition. If your `treat` variable is a *factor*, then you may wish to use the first level. The default, `0` , essentially has this effect.

treat.value The value of `treat` to be used as the *treatment* condition. If your `treat` variable is a *factor*, then you may wish to use the second (or a higher) level. The default, `1` , essentially has this effect.

long Logical indicating whether or not to also return the statistics for each bootstrap sample (default: `TRUE`).

int Logical indicating whether or not to include a *mediator-treatment* interaction term (default: `FALSE`).

... Arguments that are used for creating the design matrix. See [Vertex-wise group analysis \(GLM\)](#) for more information; you should not specify the `coding` argument (accepting the default coding `'dummy'`).

11.4 Return value

The function returns an object of class `bg_mEDIATE`. You will usually not work with the specific elements of this object yourself, but I list them for completeness. Any elements that are simply input arguments are included without description. For more details, see the help file for the `mediate` function in the `mediation` package.

level

removed

X.m The design matrix of the model in which the *mediator* is the outcome variable

y.m A matrix of the mediator variable; the number of columns equals the number of brain regions

X.y A *named list* (the names will be the vertex/region names) of the design matrices of the models with the mediator is another predictor variable

y.y The outcome variable specified in the function call

res.obs A `data.table` of the *observed* statistics (point estimates)

res.ci A `data.table` of the confidence intervals

res.p A `data.table` of the (two-sided) P-values

boot

boot.ci.type

res.boot A `data.table` of the statistics from all bootstrap samples (if `long=TRUE`)

treat

mediator

outcome

covariates `NULL`

INT The same as input argument `int`

conf.level

control.value

treat.value

nobs The number of observations in the data (i.e., number of rows in the design matrix)

sims The same as input argument `N`

covar.names

11.5 Code example

The following code block shows how to run `brainGraph_mEDIATE` for a few different network measures. This is basically the same approach I used in [Multi-threshold permutation correction](#).

```

medVars <- data.table(level=c(rep('graph', 2), rep('vertex', 2)),
                      outcome='FSIQ',
                      mediator=c('E.global.wt', 'mod.wt', 'E.nodal.wt', 'strength'),
                      treat='Group',
                      interact=FALSE,
                      N=c(rep(1e4, 2), rep(5e3, 2)))
medVars

##      level outcome    mediator treat interact      N
## 1: graph    FSIQ E.global.wt Group FALSE 10000
## 2: graph    FSIQ     mod.wt Group FALSE 10000
## 3: vertex   FSIQ  E.nodal.wt Group FALSE  5000
## 4: vertex   FSIQ     strength Group FALSE  5000

```

Then you can loop through these values to create a list (of lists) of `bg_mEDIATE` objects. I usually separate graph- and vertex-level analyses into different objects.

Below is code to loop across all thresholds for the graph-level measures. Depending on the number of thresholds, this can take a very long time. The list object `med.list.g` will have 3 “levels”:

1. The `outcome` variable(s)
2. The `mediator` variable(s)
3. An element for each threshold

```

med.list.g <- sapply(medVars['graph'], unique(outcome)], function(x) NULL)
for (x in names(med.list.g)) {
  med.list.g[[x]] <- sapply(medVars[.(‘graph’, x), unique(mediator)], function(x) NULL)
  for (y in names(med.list.g[[x]])) {
    print(paste('Outcome:', x, '; Mediator:', y, ';', format(Sys.time(), '%H:%M:%S')))
    med.list.g[[x]][[y]] <- vector('list', length=length(thresholds))
    for (z in seq_along(med.list.g[[x]][[y]])) {
      med.list.g[[x]][[y]][[z]] <-
        brainGraph_mEDIATE(do.call(Map, c(c, g))[[z]], covars.med,
                            mediator=y, treat=medVars[.(‘graph’, x, y), treat],
                            outcome=medVars[.(‘graph’, x, y), outcome],
                            covar.names=c('age', 'gender', 'scanner'),
                            boot=T, boot.ci.type='perc', N=medVars[.(‘graph’, x, y), N],
                            long=TRUE, binarize=c('gender', 'Scanner'))
    }
  }
}

```

11.5.1 Printing a summary

There are 2 ways to use the `summary` method. First, I show the result when setting `mediate=TRUE`, which uses the method from the `mediation` package. For this, you must select a region; if you do not, the first (alphabetically) will be selected.

```

summary(res.med, mediate=TRUE, region='lHIPP')

##
## brainGraph mediation results
## -----

```

```

## # of observations: 71
## Level: vertex
## Mediator: E.nodal.wt
## Treatment: Group
## Control value: Control
## Treatment value: Patient
## Outcome: brief_gec_raw_6m
## Pre-treatment covariates:
##
## 1 age
## 2 gender
## 3 scanner
##
## Treatment-mediator interaction? FALSE
##
## Bootstrapping
## -----
## Bootstrap CI type: Percentile bootstrap
## # of bootstrap replicates: 1,000
## Bootstrap CI level: [2.5% 97.5%]

## Mediation summary for: lHIPP
## -----
## Causal Mediation Analysis
## Nonparametric Bootstrap Confidence Intervals with the Percentile Method
##
##          Estimate % CI Lower % CI Upper p-value
## ACME (control)    1.1049 -10.2795   11.74  0.780
## ACME (treated)    1.1049 -10.2795   11.74  0.780
## ADE (control)     17.4068  -0.5028   33.66  0.062 .
## ADE (treated)     17.4068  -0.5028   33.66  0.062 .
## Total Effect      18.5116   6.5066   29.60  0.006 **
## Prop. Mediated (control) 0.0597 -0.6195   1.03  0.786
## Prop. Mediated (treated)  0.0597 -0.6195   1.03  0.786
## ACME (average)     1.1049 -10.2795   11.74  0.780
## ADE (average)      17.4068  -0.5028   33.66  0.062 .
## Prop. Mediated (average) 0.0597 -0.6195   1.03  0.786
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 71
##
##
## Simulations: 1000

```

The second option will print the entire statistics table (for all regions). Since everything above the “Bootstrapping” section is the same, I only show the summary table.

```

summary(res.med)$DT[]

##       region   Mediator treat        Outcome b0.acme ci.low0.acme

```

```

## 1: 1ACCU E.nodal.wt Group brief_gec_raw_6m 2.149 -5.8
## 2: 1AMYG E.nodal.wt Group brief_gec_raw_6m -0.049 -13.1
## 3: 1BSTS E.nodal.wt Group brief_gec_raw_6m -0.298 -5.0
## 4: 1CAUD E.nodal.wt Group brief_gec_raw_6m 0.619 -4.8
## 5: 1CUN E.nodal.wt Group brief_gec_raw_6m -0.631 -5.5
## ---
## 78: rperiCAL E.nodal.wt Group brief_gec_raw_6m 0.458 -4.2
## 79: rpostC E.nodal.wt Group brief_gec_raw_6m -2.177 -7.7
## 80: rpreC E.nodal.wt Group brief_gec_raw_6m -2.310 -9.1
## 81: rrACC E.nodal.wt Group brief_gec_raw_6m -0.773 -5.9
## 82: rrMFG E.nodal.wt Group brief_gec_raw_6m -0.269 -8.3
## ci.high0.acme p0.acme b0.ade ci.low0.ade ci.high0.ade p0.ade b.tot
## 1: 10.5 0.53 16 1.7 31 0.024 19
## 2: 12.5 0.99 19 2.2 37 0.028 19
## 3: 4.0 0.88 19 7.0 31 0.000 19
## 4: 6.1 0.79 18 5.7 31 0.004 19
## 5: 4.2 0.81 19 6.0 32 0.004 19
## ---
## 78: 5.3 0.84 18 5.9 31 0.010 19
## 79: 1.1 0.23 21 9.4 33 0.000 19
## 80: 1.8 0.31 21 8.4 34 0.004 19
## 81: 4.1 0.75 19 6.2 32 0.008 19
## 82: 8.1 0.97 19 5.6 32 0.010 19
## ci.low.tot ci.high.tot p.tot b0.prop ci.low0.prop ci.high0.prop
## 1: 7.0 31 0.002 0.1161 -0.37 0.811
## 2: 6.8 30 0.004 -0.0027 -0.90 0.815
## 3: 6.3 31 0.002 -0.0161 -0.42 0.250
## 4: 7.4 31 0.004 0.0334 -0.32 0.408
## 5: 6.9 29 0.000 -0.0341 -0.38 0.284
## ---
## 78: 6.6 31 0.002 0.0247 -0.32 0.391
## 79: 7.4 31 0.000 -0.1176 -0.67 0.064
## 80: 6.7 31 0.006 -0.1248 -0.68 0.108
## 81: 6.5 31 0.008 -0.0418 -0.45 0.259
## 82: 6.4 30 0.004 -0.0145 -0.66 0.447
## p0.prop
## 1: 0.53
## 2: 0.99
## 3: 0.88
## 4: 0.78
## 5: 0.81
## ---
## 78: 0.83
## 79: 0.23
## 80: 0.31
## 81: 0.75
## 82: 0.97

```

11.6 Create a graph of the results

To create a graph with attributes specific to mediation analysis, use `make_mediate_brainGraph`. This will return a graph with several additional attributes:

- mediator** (graph-level) The mediator variable
- treat** (graph-level) The treatment variable
- outcome** (graph-level) The outcome variable
- nobs** (graph-level) The number of observations
- b.acme,p.acme** (vertex-level) The point estimates and (two-sided) P-values for the ACME
- b.adc,p.adc** (vertex-level) The point estimates for the ADE
- b.tot,p.tot** (vertex-level) The point estimates for the total effect
- b.prop,p.prop** (vertex-level) The point estimates for the proportion mediated

```
g.med <- make_mediate_brainGraph(res.med, atlas='dkt.scgm')
```

11.7 Plot a graph of the results

If you would like to plot only significant regions, you can simply call the `plot` method on the graph. In this example, however, there were no vertices for which $P_{ACME} < \alpha$, so I relax this for display purposes. Note that I use the form `p0.acme > X`, as the P-values are actually subtracted from 1.³ I also use the default `main` value for printing the plot title (which includes the names of the mediator, treatment, and outcome variables).

```
plot(g.med, subgraph='p0.acme > 0.9', vertex.color='color.lobe', vertex.size=10)
```

11.8 Benchmarks

The `mediate` function in the `mediation` package is quite slow, but very feature-rich (i.e., there are many different types of models you can use in your analyses such as generalized additive models). In `brainGraph_mEDIATE`, only simple linear models are allowed. This is a sacrifice in features but comes with a high speed advantage. Second, `mediate` works with *model objects* (e.g., R objects of type `lm`). These objects are convenient for interactive data analysis, but overall slower to work with. Third, `mediate` does not have a parallel or multi-core option, whereas I take advantage of the `foreach` package. For a multi-region analysis in which the same model is used for every brain region (e.g., 82 regions in the `dk.scgm` atlas), and with 1,000 (or more) bootstrap samples calculated, the speed increase can be large (particularly with a higher number of bootstrap samples). Finally, I use `data.table` for fast calculations.

I have seen speed increases of 10x–30x. You can see the actual numbers in [Benchmarks](#).

³Since there is no mediator-treatment interaction, `p0.acme` equals `p1.acme`.

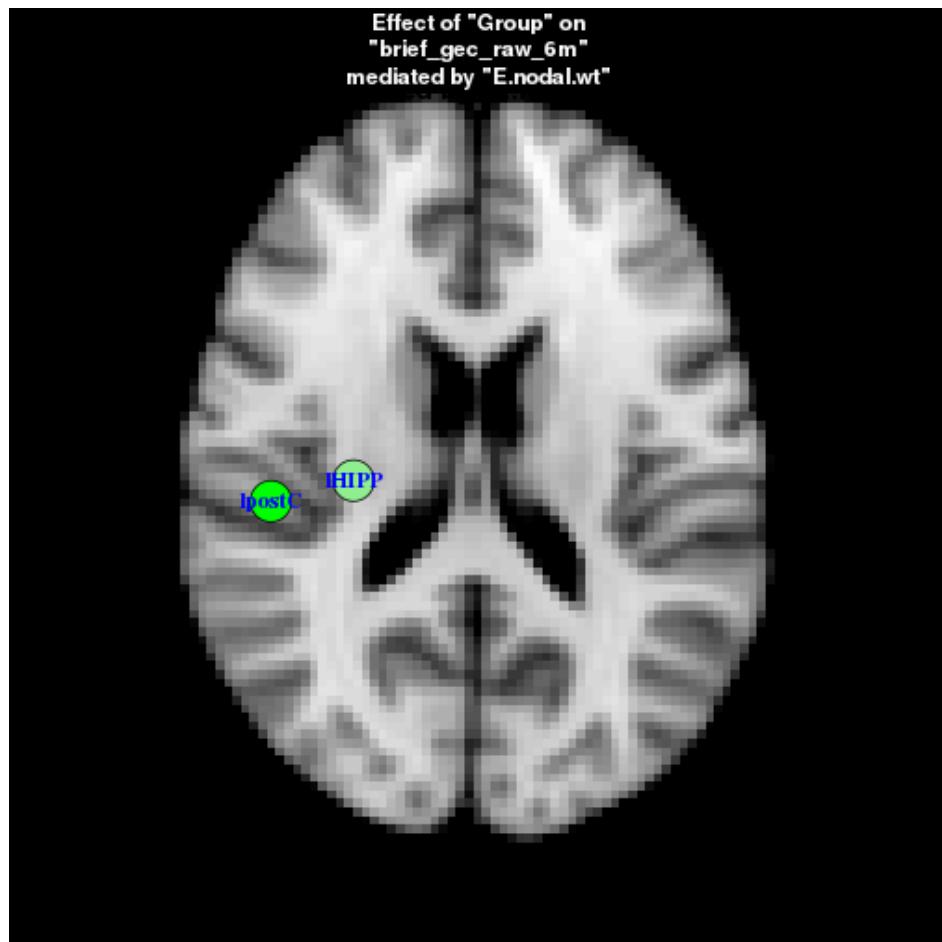


Figure 11.1: Mediation results.

Part V

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12

Random graphs, small world, and rich-club

12.1 Random graph generation

Random graph generation is a necessary step if you want to calculate a graph's small-worldness.(39, 85) However, generating an *appropriate* random graph is not trivial. This is particularly true when working with data generated from correlations (e.g., structural covariance and resting-state fMRI networks), as graphs generated from this kind of data will necessarily have a higher than expected level of clustering.(37, 93) It is true for other data, as well, because random networks have low clustering in general. For more discussion, see Chapter 12 of Newman (55), and also Telesford et al. (75).

12.1.1 Simple random graph generation

This is the “standard” method of creating random graphs, controlling for the observed *degree distribution*. It relies on the `igraph` functions `rewire` along with `keeping_degseq` (see Viger and Latapy (81) for the method used; see also Milo et al. (54)). `sim.rand.graph.par` generates a number of these in parallel, and calculates *modularity*, *clustering coefficient*, *average path length*, *global efficiency*, and *rich club coefficient* for each random graph. The number of rewiring steps is hard-coded to be the larger of either 10,000 or $10 \times$ the graph’s edge count (see Ray et al. (62)).

The function `analysis_random_graphs` is a “helper function” that performs all of the steps that are typically done when you need to create equivalent random graphs. These include:

- `N` random graphs are generated for each group and density/threshold (and subject if you have subject-specific graphs).
- These graphs are all written to disk in `savedir`. All of these are read back into `R` and combined into *lists*; there will be one list object per group and density/threshold combination. These lists are also written to disk (in a sub-directory named `ALL`), so you can delete the individual `.rds` files afterwards.
- *Small world* parameters are calculated, along with values for a few global graph measures that may be of interest.
- *Normalized rich-club coefficients* and associated P-values will be calculated.

The return value is a *list*, with three elements:

1. `rich` : a `data.table` of (normalized) rich-club coefficients
2. `small` : a `data.table` of small-world parameters
3. `rand` : a `data.table` of graph-level measures for the random graphs

```
kNumRand <- 1e2
clustering <- F
outdir <- paste0(getwd(), '/../../rand/')

rand_vars <- analysis_random_graphs(g, kNumRand, savedir=outdir,
                                      clustering=clustering)
rich.dt <- rand_vars$rich
rich.dt <- rich.dt[complete.cases(rich.dt)] # Remove rows w/ NA
small.dt <- rand_vars$small
rand.dt <- rand_vars$rand
```

12.1.2 Control for clustering

`sim.rand.graph.clust` generates equivalent random graphs controlling not only for degree distribution, but also clustering. It uses the algorithm given in Bansal et al. (2). Since you will want to generate a large number of graphs, you should specify `clustering=TRUE` in the call to `sim.rand.graph.par`. Because this step takes quite long, you can limit the number of Markov Chain steps with the `max.iters` argument. The default is 100. Keeping this at 100 is a reasonable limit, but basically defeats the purpose of this step as the observed level of clustering may not be reached with only 100 iterations.

The time required to generate the random graphs with this method can be quite high, and is higher for graphs with high clustering and density. The final line shows how to calculate ω (see next section); this requires that you have already generated simple random graphs and created `small.dt` (done in the previous section).



Warning

This will take a long time. See [Benchmarks](#) for example processing times.

```
kNumRandClust <- 1e2 # Create 100 graphs per group/density combination
g.rand <- small.clust.dt <- vector('list', length=length(groups))
for (i in seq_along(groups)) {
  g.rand[[i]] <- vector('list', length=kNumDensities)
  for (j in seq_along(densities)) {
    g.rand[[i]][[j]] <- sim.rand.graph.par(g[[i]][[j]],
                                              kNumRandClust, clustering=T)
  }
  small.clust.dt[[i]] <- small.world(g[[i]], g.rand[[i]])
}
small.clust.dt <- rbindlist(small.clust.dt)
```

12.2 Small-worldness

The function `small.world` will calculate small world parameters, including normalized clustering coefficient and characteristic path length, as well as the small world coefficient σ .⁽³⁹⁾ It returns a `data.table` with those values. Each row corresponds to a group/density combination.

```
head(small.dt)
```

##	density	N	Lp	Cp	Lp.rand	Cp.rand	Lp.norm	Cp.norm	sigma	Group
## 1:	0.05	100	3.3	0.55	2.7	0.14	1.2	3.8	3.2	Control
## 2:	0.06	100	3.1	0.55	2.6	0.18	1.2	3.1	2.6	Control
## 3:	0.07	100	2.7	0.54	2.5	0.21	1.1	2.6	2.4	Control
## 4:	0.08	100	2.6	0.56	2.4	0.22	1.1	2.6	2.4	Control
## 5:	0.09	100	2.7	0.56	2.3	0.23	1.2	2.5	2.1	Control
## 6:	0.10	100	2.6	0.57	2.3	0.25	1.1	2.3	2.0	Control

To calculate ω (see Telesford et al. (75)), which is a better metric for small-worldness, you will have to:

1. Generate simple random graphs to get the characteristic path length L_{rand} (see previous section).
2. Create random graphs controlling for the level of clustering, and use the clustering coefficient of these random graphs as the value for equivalent *lattice* networks (C_{latt})
3. The values L and C are characteristic path length and clustering coefficient, respectively, for the observed graphs.

The equations for both σ and ω are:

$$\sigma = \frac{C/C_{rand}}{L/L_{rand}} \quad (12.1)$$

$$\omega = \frac{L_{rand}}{L} - \frac{C}{C_{latt}} \quad (12.2)$$

The only downside to this approach is the processing time needed. As I mentioned earlier, a reasonable compromise would be to limit the number of Markov Chain steps (via the `max.iters` function argument), as even with only 100 iterations, the resultant graphs will be much closer to a lattice than a simple random graph controlling only for degree distribution.

The R code for calculating ω is:

```
small.clust.dt[, Group := rep(groups, each=kNumDensities)]
setkey(small.dt, Group, density)
setkeyv(small.clust.dt, key(small.dt))
small.dt[, omega := small.dt[, Lp.rand / Lp] - small.clust.dt[, Cp / Cp.rand]]
small.dt[, Lp.latt := small.clust.dt$Lp.rand]
small.dt[, Cp.latt := small.clust.dt$Cp.rand]
small.tidy <- melt(small.dt, id.vars=c('density', 'Group', 'N'))
```

To show that the random graph generation approach from the last section *does* result in networks with higher clustering, we can plot these values, shown in Figure 12.1. As you can see, the random graphs generated by the Markov Chain process (dotted lines) have a similar clustering level as the observed networks (solid lines). As expected, the “simple” random graphs have much lower clustering. This is also reflected in the much higher normalized clustering coefficients in calculating σ .

If you refer back to Equation 12.1 and Equation 12.2, the normalized path length will roughly equal 1; i.e., $L/L_{rand} \approx L_{rand}/L \approx 1$. It is also the case that $C/C_{rand} \gg 1$ and $C/C_{latt} \approx 1$. So we should see $\sigma \gg 1$ and $\omega \approx 0$, which is confirmed in the next Figure.

```
ggplot(small.dt.m, aes(x=density, y=value, col=interaction(Group, variable),
                        lty=interaction(Group, variable))) +
  geom_line(size=1.25) +
  scale_linetype_manual(name='Group', type',
                        labels=mylabels.sm,
                        values=rep(1:3, each=2)) +
```

```
scale_color_manual(name='Group, type',
                   labels=mylabels.sm,
                   values=rep(c('red', 'cyan3'), 3)) +
labs(x='Density', y='Clustering coefficient')
```

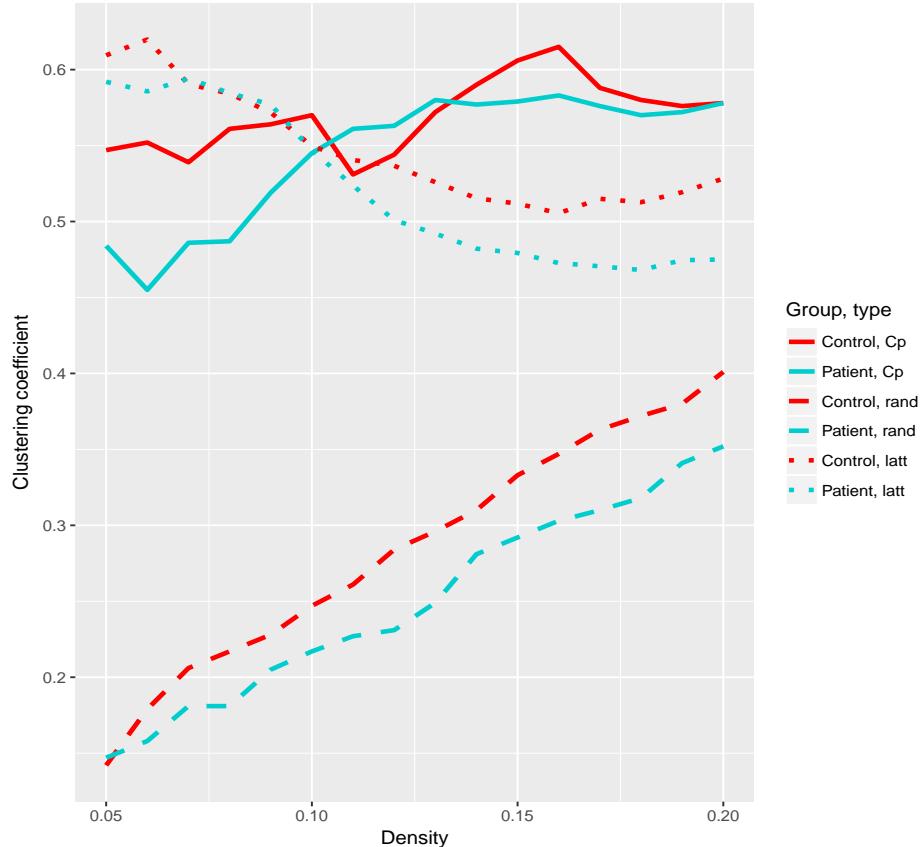


Figure 12.1: **Clustering coefficients for random networks.** The solid lines are clustering for the observed networks. The dotted line are values from networks generated by the Markov Chain approach, and the dashed lines are values from networks generated by the “simple” approach.

We can plot both σ and ω in the same plot, shown in Figure 12.2. As stated in Telesford et al. (75), networks with ω closer to 0 indicate more balance between high clustering and low path length; networks with ω closer to -1 are more similar to a lattice network. The results of this analysis indicate that the Patient group’s networks at higher density are closer to a lattice than the Control networks.

```
small.tidy[variable == 'sigma', yint := 1]
small.tidy[variable == 'omega', yint := 0]
ggplot(small.tidy[variable %in% c('sigma', 'omega')], 
       aes(x=density, y=value, col=Group)) +
  geom_line() +
  geom_hline(aes(yintercept=yint), lty=2) +
  facet_wrap(~ variable, scales='free_y', ncol=1) +
  theme(legend.position=c(1, 1), legend.justification=c(1, 1)) +
  ylab('Small-worldness')
```

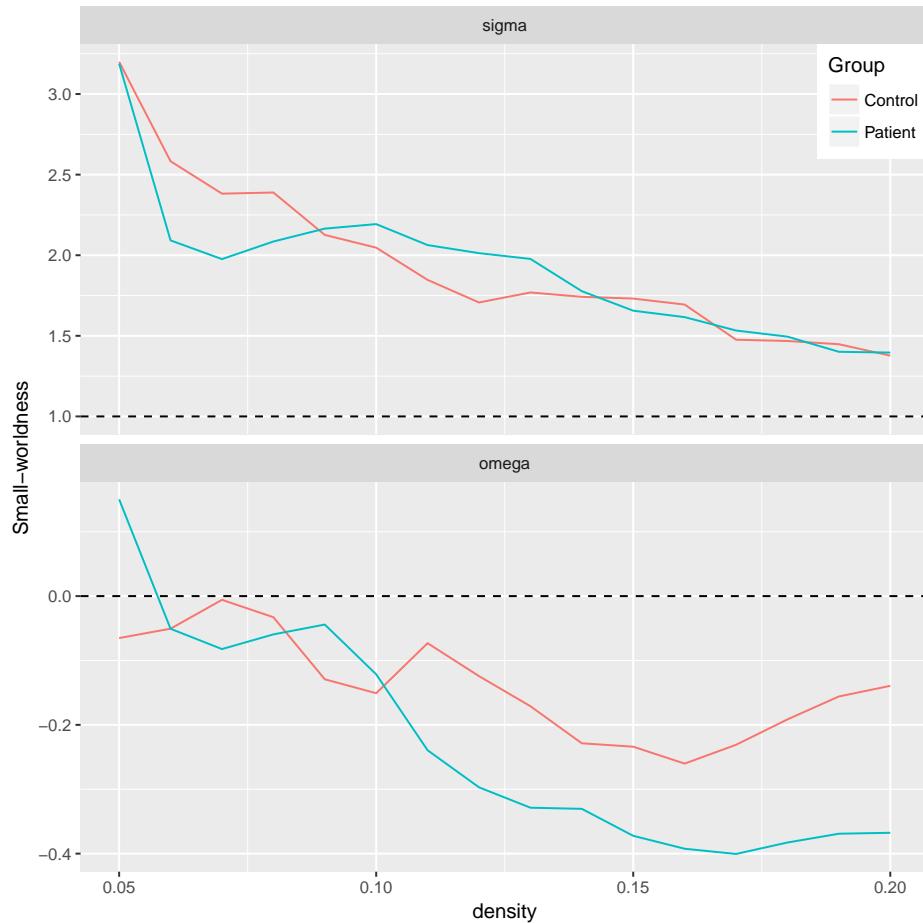


Figure 12.2: **Small-world indexes.** (top) The classic small-world index, σ ; the dashed horizontal line at $y = 1$ is included to show the minimum value for a network to be considered “small-world” (85) (bottom) The small-world index ω introduced by Telesford et al. (75); the dashed horizontal line at $y = 0$ indicates the value at which the network displays a balance between clustering coefficient and characteristic path length.

12.3 Rich-club Analysis

The *rich club* is a set of vertices that have a high degree themselves and which also have a high probability of being connected to one another (see Colizza et al. (13), Zhou and Mondragón (94)).

When creating random graphs with `analysis_random_graphs`, normalized rich-club coefficients and P-values were also calculated (now in `rich.dt`). This will be used later for plotting.

12.3.1 Rich-core

A recent paper provided an algorithm for determining the cut-off degree for inclusion in the rich club (52). The function to calculate this is called `rich.core`. The degree value is given in the output data frame, with column name `k.r` (`k` stands for *degree* and the `r` is for *rank*). In the next code section, I show how to get this value, and then how to plot a shaded region that starts at the maximum cut-off value from 2 groups.

12.3.2 Rich-club plots

Then plot the data using the function `plot_rich_norm`. A plot of the normalized rich club coefficients for each group and 2 example densities is shown in Figure 12.3.¹ The shaded region is based on the *rich-core* calculation; this option is selected if you provide a list of graph objects to the argument `g`. You can also choose to specify significance based on the regular P-values or FDR-adjusted P-values (the default), via the `fdr` function argument).

```
plot_rich_norm(rich.dt, facet.by='density', densities[11:12], g=g)
```

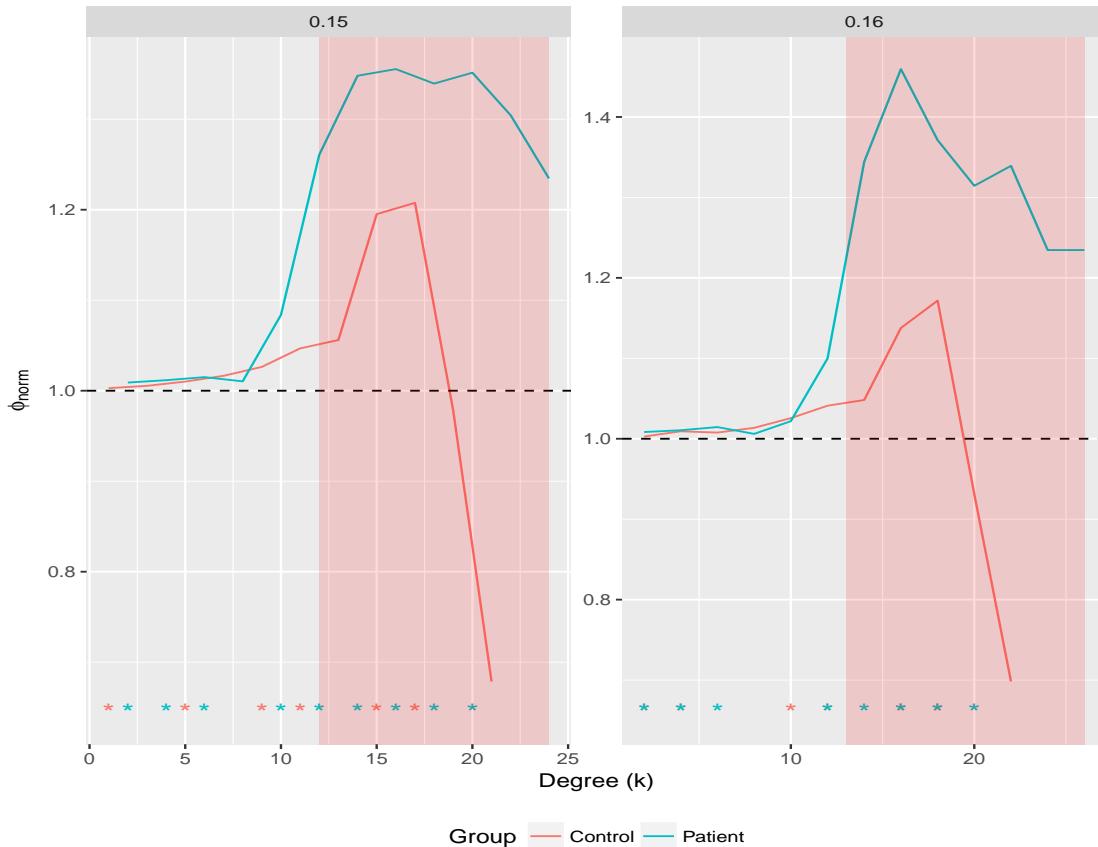


Figure 12.3: Normalized rich club coefficient vs. degree

12.3.3 Rich-club attributes

The function `rich_clubAttrs` will assign vertex- and edge-level attributes based on membership in the rich-club. The function requires a range of degrees in which $\phi_{norm} > 1$ was determined to be significant. The attributes assigned by the function are:

rich (vertex-level) binary value indicating whether or not the vertex is in the rich club

type.rich (edge-level) Either `rich-club` (edges connecting 2 rich-club vertices), `feeder` (edges connecting 1 rich-club and 1 non-rich-club vertex), or `local` (edges connecting 2 non-rich-club vertices)

¹These probably don't look like the "familiar" plots from the literature; this is likely because I chose to generate a small number of random graphs.

color.rich (vertex-level) Either `red` (for rich-club vertices) or `gray` (for non-rich-club vertices)

color.rich (edge-level) Either `red` (for rich-club connections), `orange` (for feeder connections), or `green` (for local connections)

size.rich (vertex-level) Either 3 for non-rich-club vertices, or 15 for rich-club vertices

size.rich (edge-level) Either 3.5 for rich-club connections, 1.5 for feeder connections, or 0.5 for local connections

An example plot is shown in [Figure 12.4](#). This isn't the best solution, but clearly highlights the rich-club vertices. The code can easily be adjusted to increase the size of other vertices/edges.

```
g[[1]][[N]] <- rich_club_attrs(g[[1]][[N]],  
  c(rich_core(g[[1]][[N]])$k.r, 12))  
  
# Alternatively, the degree range could use the following command, but in the  
# current example, the number of random graphs was very low  
#rich.dt[density == densities[N] & Group == groups[1] & p.fdr < 0.05, range(k)]  
  
plot(g[[1]][[N]], vertex.label=NA, vertex.color='color.rich',  
  edge.color='color.rich', edge.width='size.rich', vertex.size='size.rich',  
  show.legend=TRUE)
```

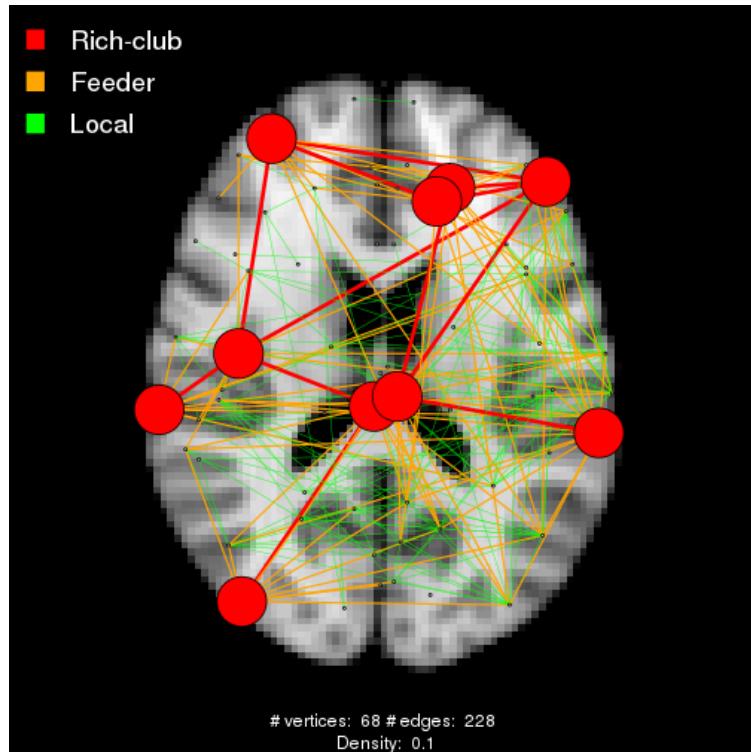


Figure 12.4: Rich-club attributes.

12.4 Single-subject networks

To generate random graphs in the case of single-subject data, the code is largely the same as in [Random graph generation](#). Just substitute `g.norm` for `g` (or whatever your graph list object happens to be named). Once you've done that, to get normalized rich club coefficients into a single `data.table`, you will have to use the following code:

```
# Get everything into a single data.table
deg.max <- unlist(sapply(g.norm, sapply, sapply, function(x) nrow(x$rich)))
thr_all <- rep(unlist(sapply(ind, function(x)
                           rep(thresholds, each=length(x))), times=deg.max))
dens_all <- rep(unlist(sapply(g.norm, sapply, sapply, graph_attr, 'density')),
                 times=deg.max)
k_all <- unlist(lapply(g.norm, lapply, lapply, function(x) seq_along(x$rich$Nk)))
group_vec <- rep(unlist(sapply(g.norm, sapply, sapply, graph_attr, 'Group')),
                  times=deg.max)
ids_all <- rep(unlist(sapply(g.norm, sapply, sapply, graph_attr, 'name')),
               times=deg.max)
rich.dt <- data.table(threshold=thr_all,
                      density=dens_all,
                      k=k_all,
                      phi=unlist(lapply(phi.norm, lapply, lapply, with, phi.norm)),
                      p=unlist(lapply(phi.norm, lapply, lapply, with, p)),
                      Group=group_vec,
                      Study.ID=ids_all)

rich.dt[, Group := as.factor(Group)]
rich.dt[, p.fdr := p.adjust(p, 'fdr'), by=.threshold, Study.ID]
rich.dt <- rich.dt[complete.cases(rich.dt)]
```

To plot rich-club graphs for multi-subject DTI data, you will have to change the function call of `plot_rich_norm` to `facet.by='threshold'` (assuming this is how you generated the connectivity matrices to begin with):

```
plot_rich_norm(rich.dt, facet.by='threshold', thresholds[1:5])
```

13

Bootstrapping and permutation testing

13.1 Bootstrapping

In structural covariance analyses, since there is only one graph per group (at a given density)—as atlas-based brain regions typically are different sizes—it is not possible to directly compute the within-group variability of graph measures (e.g., *modularity*). In this case, *bootstrapping* is necessary. The function `brainGraph_boot` will perform bootstrap resampling in this case; the `boot` package does all of the resampling.(19)

13.1.1 Function arguments

```
args(brainGraph_boot)

## function (densities, resids, R = 1000, measure = c("mod", "E.global",
##     "Cp", "Lp", "assortativity", "strength", "mod.wt", "E.global.wt"),
##     conf = 0.95, .progress = TRUE)
## NULL
```

densities The (numeric) vector of network densities (since the function creates networks of the same density for bootstrap samples).

resids The `data.table` of residuals that is output by `get.resid`.

R Integer; the number of bootstrap samples to generate (default: `1000`).

measure Character string indicating which *global* graph metric to test (default: `'mod'`; i.e., modularity)

conf The confidence level; the default, `0.95`, returns 95% confidence intervals.

.progress Logical indicating whether or not to print a progress bar (default: `TRUE`).

There are several graph-level metrics you can choose from; currently, the options are: *modularity (weighted and unweighted)*, *global efficiency (weighted and unweighted)*, *clustering coefficient*, *characteristic path length*, *(degree) assortativity*, and *mean graph strength*. Your data may also have an arbitrary number of groups (i.e., not just 2).

13.1.2 Return value

The returned object is of class `brainGraph_boot`, containing:

measure The global graph measure

densities The vector of densities

groups A character vector of the subject groups

conf The confidence level

boot A *list* (with length equal to the number of groups). Each element of the list is an object of class **boot**. See the help file for more information (by typing `help(boot)`).

13.1.3 Code example

In the following code block, I show how to estimate the standard error and confidence intervals for *modularity*.

```
# For modularity, the Louvain algorithm is used
kNumBoot <- 1e3
bootmod <- brainGraph_boot(densities, resids.all, R=kNumBoot, measure='mod',
                            .progress=FALSE)
```

The `summary` method prints some analysis-specific information, and then a `data.table` with the observed values, standard errors, and confidence intervals for each group and density tested.

```
summary(bootmod)

## Bootstrap analysis
## -----
## Graph metric: Modularity
## Number of bootstrap samples generated: 1000
## 95 % confidence intervals
##
##      Group density Observed     se ci.low ci.high
## 1: Control    0.05    0.57 0.049    0.54    0.73
## 2: Control    0.06    0.54 0.050    0.49    0.69
## 3: Control    0.07    0.51 0.051    0.45    0.65
## 4: Control    0.08    0.50 0.051    0.45    0.65
## 5: Control    0.09    0.49 0.050    0.45    0.64
## 6: Control    0.10    0.45 0.050    0.39    0.59
## 7: Control    0.11    0.44 0.049    0.38    0.57
## 8: Control    0.12    0.42 0.048    0.36    0.54
## 9: Control    0.13    0.40 0.047    0.34    0.53
## 10: Control   0.14    0.39 0.046    0.34    0.52
## 11: Control   0.15    0.38 0.045    0.32    0.50
## 12: Control   0.16    0.37 0.043    0.32    0.48
## 13: Control   0.17    0.34 0.042    0.29    0.45
## 14: Control   0.18    0.34 0.042    0.29    0.45
## 15: Control   0.19    0.32 0.041    0.26    0.42
## 16: Control   0.20    0.30 0.040    0.23    0.38
## 17: Patient   0.05    0.57 0.052    0.48    0.68
## 18: Patient   0.06    0.51 0.048    0.40    0.59
## 19: Patient   0.07    0.51 0.046    0.42    0.60
## 20: Patient   0.08    0.51 0.044    0.45    0.62
## 21: Patient   0.09    0.50 0.042    0.45    0.61
## 22: Patient   0.10    0.49 0.040    0.46    0.62
## 23: Patient   0.11    0.48 0.039    0.45    0.60
## 24: Patient   0.12    0.48 0.037    0.47    0.62
```

```
## 25: Patient    0.13    0.46 0.036    0.45    0.60
## 26: Patient    0.14    0.44 0.035    0.42    0.56
## 27: Patient    0.15    0.42 0.034    0.40    0.54
## 28: Patient    0.16    0.41 0.033    0.38    0.51
## 29: Patient    0.17    0.39 0.032    0.37    0.49
## 30: Patient    0.18    0.38 0.032    0.35    0.48
## 31: Patient    0.19    0.37 0.031    0.35    0.47
## 32: Patient    0.20    0.34 0.030    0.29    0.41
##          Group density Observed      se ci.low ci.high
```

13.1.4 Plotting the results

The shaded regions in the top of [Figure 13.1](#) are ± 1 standard error, and in the bottom represent the 95% confidence region (calculated using the normal approximation). I use the function `grid.arrange` to plot both in the same plot device.

```
bootmod.p <- plot(bootmod)
p1 <- bootmod.p$se + theme(legend.position=c(1, 1), legend.justification=c(1, 1))
p2 <- bootmod.p$ci + theme(legend.position=c(1, 1), legend.justification=c(1, 1))
gridExtra::grid.arrange(p1, p2)
```

13.2 Permutation testing

Bootstrapping can give you an estimate of the *variability* of a group measure (e.g., modularity). In order to determine the *significance* of a between-group difference, you need to do permutation testing.

13.2.1 Function arguments

```
args(brainGraph_permute)

## function (densities, resids, N = 5000, perms = NULL, auc = FALSE,
##           level = c("graph", "vertex", "other"), measure = c("btwn.cent",
##                     "degree", "E.nodal", "ev.cent", "knn", "transitivity",
##                     "vulnerability"), atlas = NULL, .function = NULL)
## NULL
```

densities

resids

N The number of permutations (default: `5000`)

perms A permutation matrix, if you would like to supply your own

auc Logical indicating whether or not to calculate differences in the *area-under-the-curve (AUC)* of the graph metrics (default: `FALSE`)

level Character string indicating which level the network measure is (either graph, vertex, or “other”). If `level='other'`, then you must supply a custom function via `.function` (see below)

measure Character string indicating the name of the network measure to calculate

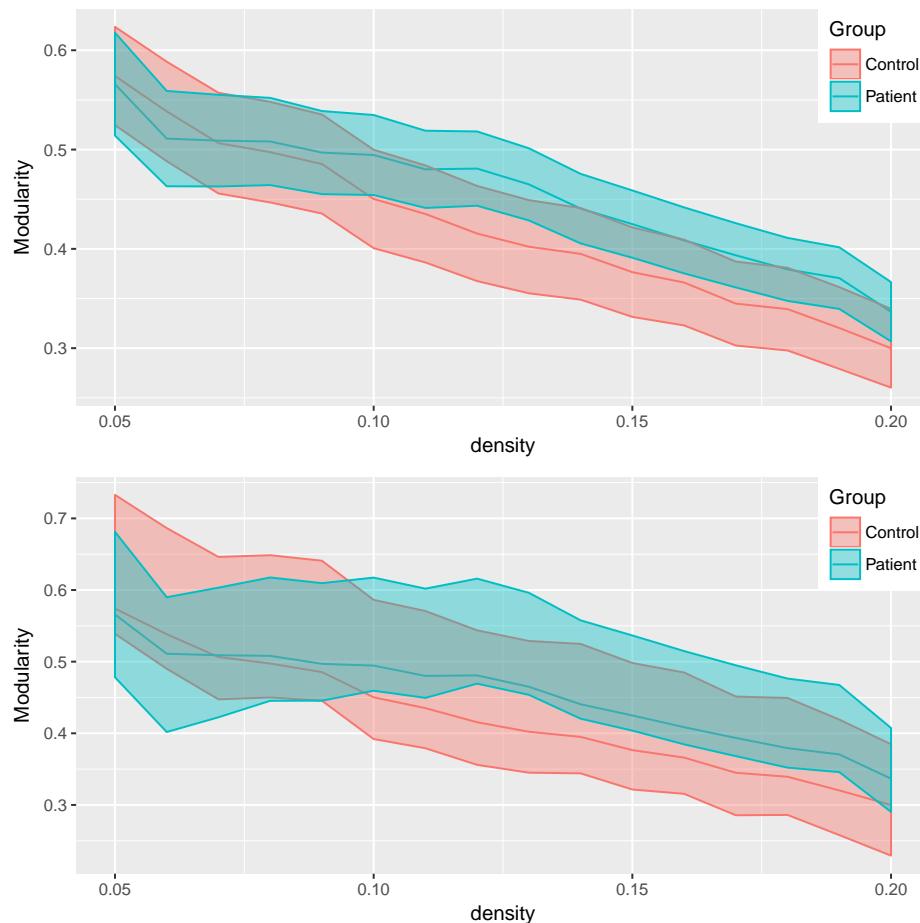


Figure 13.1: **Bootstrap analysis.** Modularity plotted across densities

atlas Character string indicating which brain atlas the network data was generated from. Required if `level='graph'`

.function A custom function if you would like to calculate permutation differences for a network measure that is not hard-coded.

13.2.2 Return value

The function returns an object of class `brainGraph_permute`, with elements:

atlas

auc

N

level

measure

densities

resids

DT A `data.table` with the permutation differences for each density (if `auc=FALSE`), and each region (there are multiple if `level='vertex'`).

obs.diff A `data.table` of the observed group difference. The number of rows equals the number of densities. If `level='vertex'`, the number of columns equals the number of regions.

groups Character string containing the group names

13.2.3 Graph-level

Several graph-level measures are calculated: *modularity*, *clustering coefficient*, *average path length*, *assortativity (degree and lobe)*, *asymmetry*, and *global efficiency*.

```
kNumPerms <- 1e3
myPerms <- permute::shuffleSet(n=nrow(resids.all), nset=kNumPerms)
perms.all <- brainGraph_permute(densities, resids.all, perms=myPerms,
                                 level='graph', atlas=atlas)
```

For the `summary` method, if `level='graph'`, then you must choose which network measure to summarize. You additionally specify an `alternative` hypothesis, `alpha` level, and which P-value to use for determining significance (either the standard P-value, or FDR-adjusted). Here, I show the summary for `Lp`. In this case, the group difference was significant for only one density.

```
summary(perms.all, measure='Lp', alt='less')

##
## Permutation analysis
## -----
## # of permutations: 1,000
## Level: graph
## Graph metric: Characteristic path length
## Alternative hypothesis: Control - Patient < 0
## Alpha: 0.05
##
##   densities region Lp.Control Lp.Patient obs.diff ci.low ci.high
## 1:      0.08    graph       2.6        3.2     -0.62   -0.61     1.1
##   perm.diff      p p.fdr
## 1:     -0.12  0.047  0.18
```

Plotting: graph-level

The `plot` method has the same arguments as the `summary` method, and returns a list with two `ggplot` objects:

1. A line plot of the *observed* graph-level measure across densities, with an asterisk added if $p < \alpha$; a blue asterisk is added if $\alpha < p < 0.10$ (i.e., a “trend” towards significance). This is shown in [Figure 13.2](#).
2. A line plot of the observed group *difference* across densities. Also shown are dashed lines of the $(1 - \alpha)\%$ confidence interval based on the permutation distribution (see [Figure 13.3](#) and the following paragraph).

```
permPlot <- plot(perms.all, measure='Lp', alt='less')
print(permPlot[[1]])
```

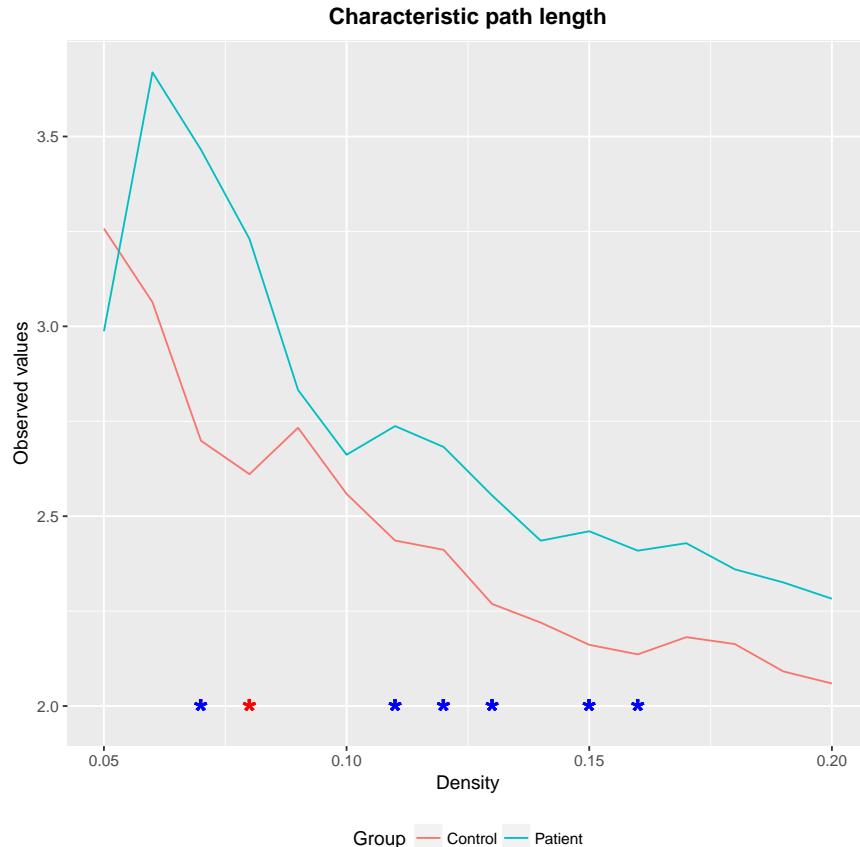


Figure 13.2: **Permutation testing, graph-level.** Observed avg. path length across densities

Instead of plotting the observed value for both groups, you can also plot the group *differences* along with a $(1 - \alpha)\%$ confidence interval. In Figure 13.3, the red line indicates observed between-group differences, the central dashed line is the mean permutation difference, and the outer dashed lines are upper and lower bounds. In this example, I used a one-sided test, assuming group 1 would be lower than group 2.

```
print(permPlot[[2]])
```

13.2.4 Vertex measures

You can also do permutation testing for *vertex*-level measures (e.g., *betweenness centrality*) to look for group differences. See Wang et al. (82) for an example application.

Since a calculation is required at each vertex for each permutation and density, this may take considerably longer than in the previous section. Other vertex-level measures that are hard-coded are: *degree*, *k-nearest neighbor degree*, *nodal efficiency*, *transitivity*, and *vulnerability*.

```
perms.btwn <- brainGraph_permute(densities[N:(N+5)], resids.all, perms=myPerms,
                                    level='vertex')
```

The `summary` method has the same type of output as with graph-level measures:

```
summary(perms.btwn)
```

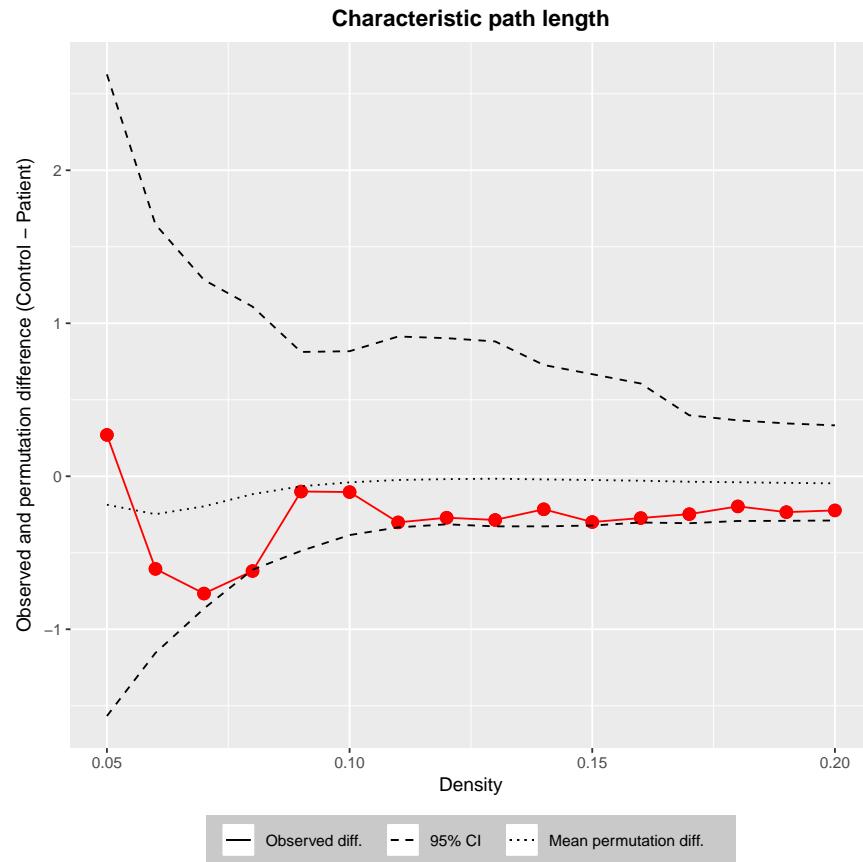


Figure 13.3: **Permutation testing, graph-level.** Observed and permuted differences in avg. path length across densities

```
## 
## Permutation analysis
## -----
## # of permutations: 1,000
## Level: vertex
## Graph metric: Betweenness centrality
## Alternative hypothesis: Control - Patient != 0
## Alpha: 0.05
## 
##      densities region btwn.cent.Control btwn.cent.Patient obs.diff ci.low
## 1:      0.10    1TP                  0.0          101     -101     -67
## 2:      0.11    1TP                  0.0          76      -76     -55
## 3:      0.11   rLING                 8.1         346     -337     -286
## 4:      0.12    1TP                  0.0          72      -72     -44
## 5:      0.12   rLING                10.3         327     -316     -269
## 6:      0.15   LLOF                 49.4         235     -186     -146
## 7:      0.15   1PARH                 0.0          62      -62      0
## 8:      0.15   rLING                36.2         247     -211     -212
##      ci.high perm.diff      p p.fdr
## 1:     102      1.53 0.037  1.00
## 2:      87      3.78 0.044  0.72
```

```
## 3:    256   -28.84  0.012  0.72
## 4:     94    4.85  0.042  0.60
## 5:    217   -30.38  0.008  0.54
## 6:    162     0.34  0.021  0.84
## 7:     63    5.94  0.044  0.84
## 8:    177   -26.06  0.039  0.84
```

Plotting: vertex-level

The `plot` method for vertex-level measures is slightly different. There is only one type of plot, a *barplot* of the permutation differences at those vertices for which $P_{sig} < \alpha$ (depending on the function arguments). The output is shown in Figure 13.4; the horizontal red line segments represent the *observed* between-group differences.

```
plot(perms.btwn)
```

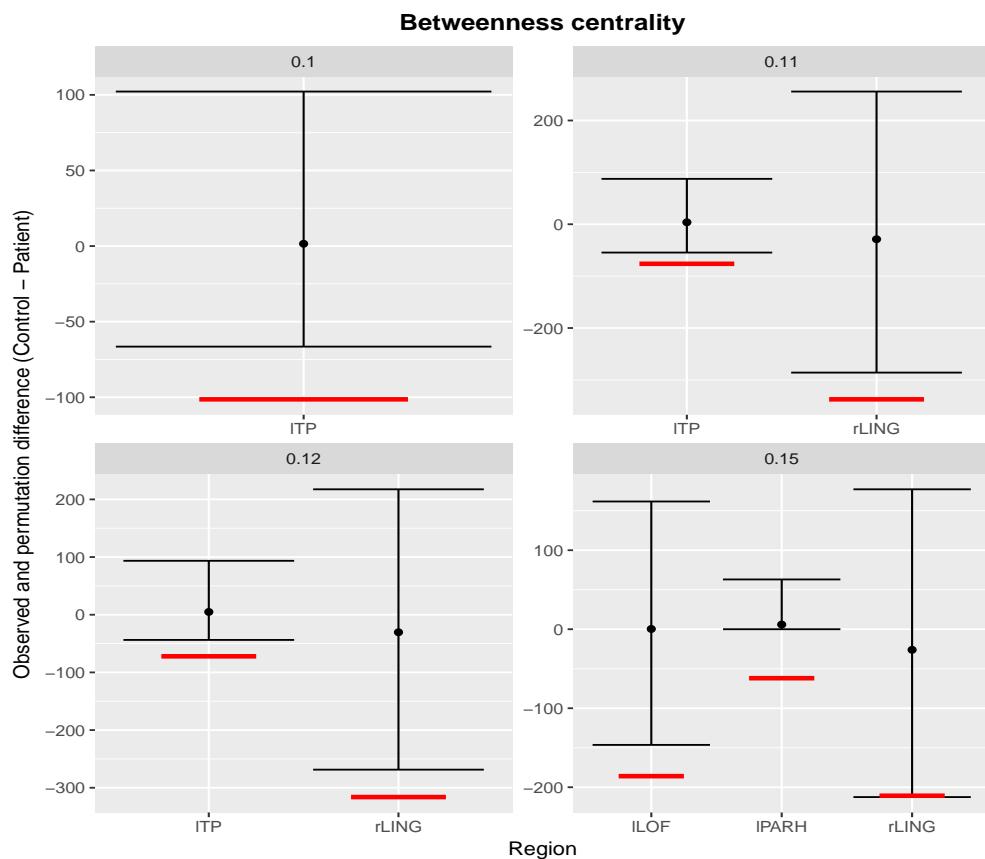


Figure 13.4: **Permutation testing, vertex-level.** Group differences in vertex betweenness centrality (observed difference in red)

13.2.5 Area-under-the-curve (AUC)

You can, alternatively, calculate the between-group difference in the *area-under-the-curve (AUC)* of a given graph- or vertex-level measure across all densities (see e.g., He et al. (34), Hosseini et al. (38)). The usage is identical to that of the previous sections, except you add `auc=TRUE` to the function call.

```
kNumPerms.auc <- 1e2
myPerms.auc <- permute::shuffleSet(n=nrow(resids.all), nset=kNumPerms.auc)
perms.all.auc <- brainGraph_permute(densities, resids.all, perms=myPerms.auc,
                                      level='graph', atlas=atlas, auc=TRUE)
```

Similarly, this can be done for vertex-level measures. The `plot` method will only work if `level='vertex'`

```
perms.btwn.auc <- brainGraph_permute(densities, resids.all, perms=myPerms.auc,
                                         level='vertex', auc=TRUE)
plot(perms.btwn.auc, alt='less')
```

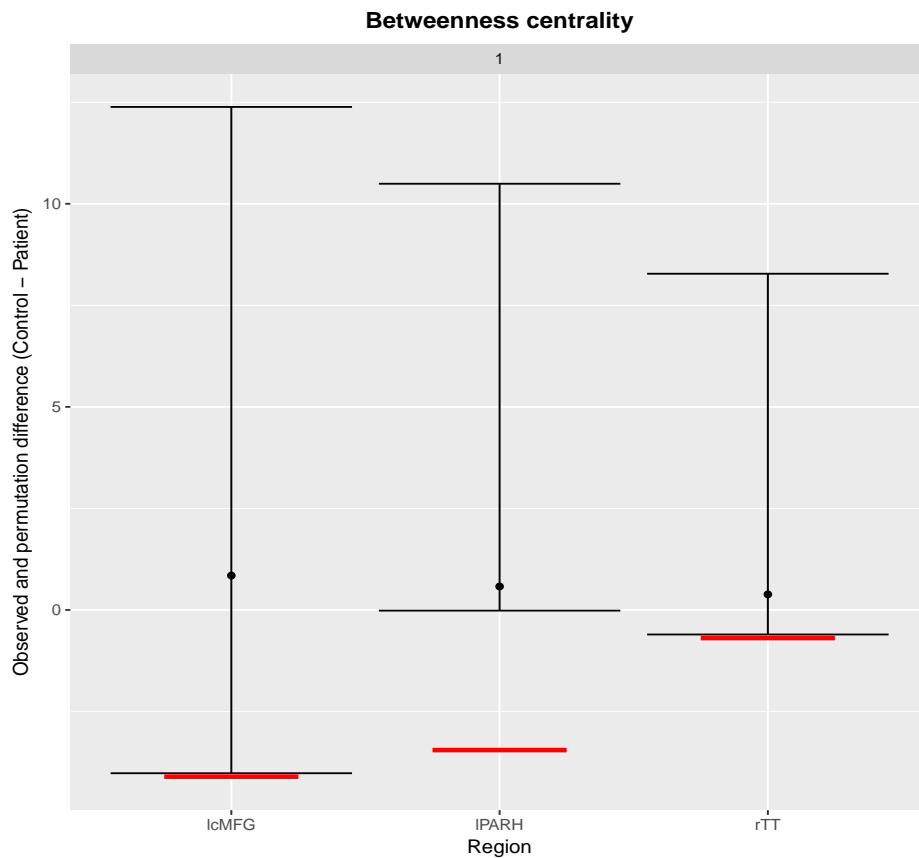


Figure 13.5: **Permutation testing, vertex-level.** Group differences in AUC of vertex betweenness centrality (observed difference in red)

13.2.6 Custom function

Perhaps the nicest feature of `brainGraph_permute` is one that mimics the `boot` function: you can choose to pass a custom function if you want to calculate permutations for a graph measure that I didn't hard-code. Your custom function must take 2 arguments:

- g A list (of lists) of graph objects
- densities** The (numeric) vector of densities

The following example shows the code necessary to calculate the difference in AUC for *closeness centrality*. This example only does 100 permutations per density, which only takes 40 seconds (total, for all 36 densities).

```
# Custom function: determine difference in closeness centrality
clocent.diffs.perm <- function(g, densities) {
  meas <- lapply(g, function(x) t(sapply(x, function(y) centr_clo(y)$res)))
  meas.diff <- sapply(seq_along(V(g[[1]][[1]])), function(x)
    brainGraph:::auc_diff(densities, cbind(meas[[1]][, x], meas[[2]][, x])))
  tmp <- as.data.table(t(meas.diff))
  setnames(tmp, 1:ncol(tmp), V(g[[1]][[1]])$name)
  return(tmp)
}

perms.clocent <- brainGraph_permute(densities, resids.all, perms=myPerms[1:1e2, ],
                                      level='other', .function=clocent.diffs.perm,
                                      auc=TRUE)
```

Since `auc=TRUE`, the `summary` method only shows results from one “density”:

```
summary(perms.clocent, alt='less')

##
## Permutation analysis
## -----
## # of permutations: 100
## Level: vertex
## Graph metric:
## Area-under-the-curve (AUC) calculated across 16 densities:
## 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16 0.17 0.18 0.19 0.2
## Alternative hypothesis: Control - Patient < 0
## Alpha: 0.05
##
##   densities   region other.Control other.Patient obs.diff ci.low ci.high
## 1:       1     lcACC        0.00      0.000 -0.014 -0.0118  0.027
## 2:       1 rperiCAL        0.12      0.095 -0.012 -0.0084  0.031
##   perm.diff      p
## 1: 0.0032 0.0198
## 2: 0.0022 0.0099
```

14

Further analysis

There is of course much more you can do with network data. In this Chapter I will briefly describe some of what is available in my package, and how to perform these analyses.

14.1 Robustness

14.1.1 Targeted attack

A targeted attack analysis can give further insight into a network's connectivity. In this analysis, you first sort vertices in order (from high to low) of a measure of "strength" of some kind. In my function, **robustness**, the choices for strength are either *degree* or *betweenness centrality*. Vertices are successively removed, and the maximal component size is calculated. (Edges may also be removed in order of *edge betweenness*). See Albert et al. (1), Bernhardt et al. (7) for more information.

Here, I will successively remove vertices ordered both by their degree and their betweenness centrality, and plot, for each group (at a single density), the ratio of the remaining maximal component size to the initial maximal component size. The result is shown in Figure 14.1.

```
v.removed <- seq(0, 1, length=(kNumVertices + 1))
e.removed <- seq(0, 1, length=(ecount(g[[1]][[N]]) + 1))
attack.vertex.degree <- c(sapply(g, function(x)
  robustness(x[[N]], type='vertex', measure='degree')))
attack.vertex.degree <- data.table(comp=attack.vertex.degree,
  removed=rep(v.removed, 2),
  Group=rep(groups, each=(kNumVertices + 1)))
attack.vertex.btwn <- c(sapply(g, function(x)
  robustness(x[[N]], type='vertex', measure='btwn.cent')))
attack.vertex.btwn <- data.table(comp=attack.vertex.btwn,
  removed=rep(v.removed, 2),
  Group=rep(groups, each=(kNumVertices + 1)))
attack.edge <- c(sapply(g, function(x) robustness(x[[N]], type='edge')))
attack.edge <- data.table(comp=attack.edge,
  removed=rep(e.removed, 2),
  Group=rep(groups, each=(ecount(g[[1]][[N]]) + 1)))

attack.vertex <- rbind(attack.vertex.degree, attack.vertex.btwn)
attack.vertex$type <- rep(c('deg', 'btwn'), each=2*(kNumVertices+1))

mylabels <- gsub('\\.', ', ', attack.vertex[, levels(interaction(Group, type))])
attack <- ggplot(data=attack.vertex,
```

```

aes(x=removed, y=comp, col=interaction(Group, type),
    linetype=interaction(Group, type))) +
geom_line() +
geom_abline(slope=-1, intercept=1, col='gray', lty=2) +
scale_color_manual(name='Group & type',
    labels=mylabels,
    values=rep(c('red', 'cyan3'), times=2)) +
scale_linetype_manual(name='Group & type',
    labels=mylabels,
    values=c(1, 1, 2, 2)) +
theme(legend.position=c(1, 1), legend.justification=c(1, 1))
print(attack)

```

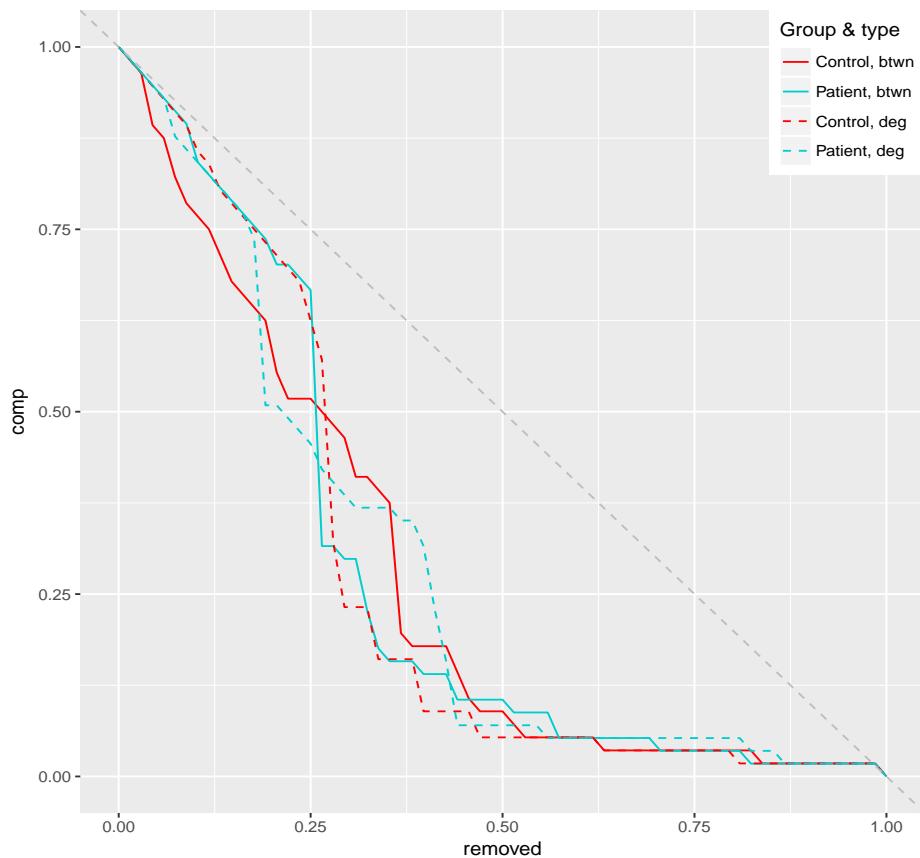


Figure 14.1: Maximal component size as a function of vertices removed.

If you are interested in *vulnerability*, see the function `vulnerability`; also, each graph is given both global- and vertex-level attributes called `vulnerability` after calling `set_brainGraph_attr`.

14.1.2 Random failure

In a *random failure* analysis, you choose a vertex (edge) at random, remove it, and calculate the maximum component size. This is repeated for many iterations (here, I only use 100 to save time).

Here, I will perform this analysis for both vertices and edges. The graphs should be relatively robust to this kind of removal for both vertices and edges. The plot is shown in Figure 14.2, and includes the targeted attack plots.

```

failure.vertex <- c(sapply(g, function(x)
                           robustness(x[[N]], measure='random', N=1e2)))
failure.edge <- c(sapply(g, function(x)
                           robustness(x[[N]], type='edge', measure='random', N=1e2)))

failure.vertex <- data.table(comp=failure.vertex,
                             removed=rep(seq(0, 1, length=(kNumVertices + 1)), 2),
                             Group=rep(groups, each=(kNumVertices + 1)))
failure.edge <- data.table(comp=failure.edge,
                            removed=rep(seq(0, 1, length=ecount(g[[1]][[N]]) + 1), 2),
                            Group=rep(groups, each=(ecount(g[[1]][[N]]) + 1)))

failure.edge[, type := 'Random edge removal']
failure.vertex[, type := 'Random vertex removal']
failure.dt <- rbind(failure.edge, failure.vertex)
attack.vertex.btwn[, type := 'Targeted vertex attack']
attack.edge[, type := 'Targeted edge attack']
robustness.dt <- rbind(failure.dt, attack.vertex.btwn, attack.edge)

```

```

ggplot(robustness.dt, aes(x=removed, y=comp, col=Group)) +
  geom_line() +
  facet_wrap(~ type) +
  geom_abline(slope=-1, intercept=1, col='gray', lty=2) +
  theme(legend.position=c(0, 0), legend.justification=c(0, 0)) +
  xlab('% edges/vertices removed') +
  ylab('% of max. component remaining')

```

14.2 Euclidean distance

It's very easy to get the spatial distance of edges. However, note that this distance is Euclidean (i.e., it doesn't follow a geodesic along the cortical surface), and it is based on coordinates that represent (roughly) the median coordinates of the atlas in MNI space.

You will notice that in my code, I use a *Kruskal-Wallis* test. This is an extension of the *Wilcoxon* test for more than 2 groups. Using the Kruskal-Wallis test in the code allows for an arbitrary number of subject groups, and if you only have 2, then it is equivalent to a Wilcoxon test anyway.

```

dists.dt <- data.table(density=rep(rep(densities, length(groups)),
                                    times=rep(sapply(g[[1]], ecoun, length(groups))),
                                    dists=do.call('c', sapply(g, sapply, function(x)
                                    E(x)$dist)),
                                    Group=rep(groups, times=rep(sum(sapply(g[[1]], ecoun)), length(groups))))
dists.dt[, Group := as.factor(Group)]
setkey(dists.dt, density, Group)
dists.dt[, med.dist := median(dists), by=.density, Group]

# Do a Kruskal-Wallis test at each density
dists.dt[, p := kruskal.test(dists ~ as.numeric(Group))$p.val, by=density]
p.fdr <- p.adjust(unique(dists.dt$p), 'fdr')

```

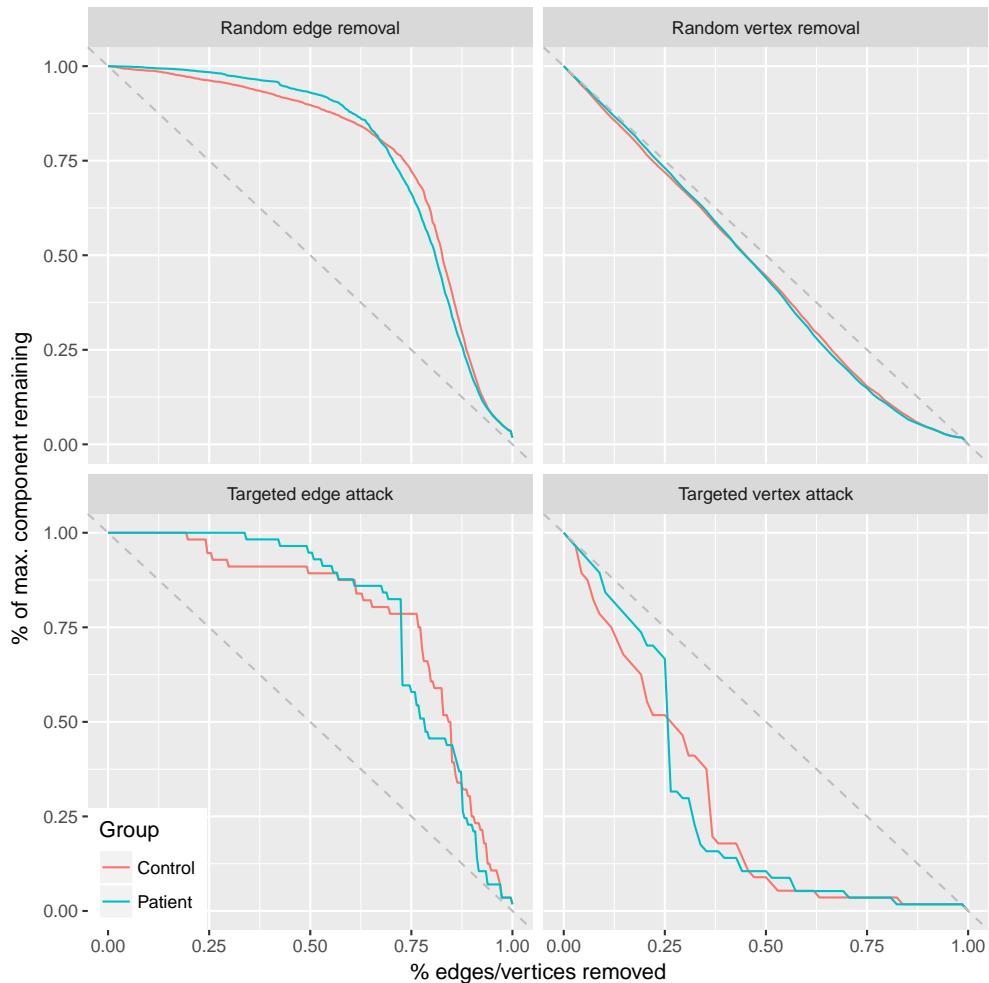


Figure 14.2: Maximal component size as a function of vertices (edges) removed.

```
dists.dt$p.fdr <- rep(rep(p.fdr, length(groups)),
                      times=rep(sapply(g[[1]], ecount), each=length(groups)))
dists.dt$sig <- ifelse(dists.dt$p.fdr < .05, '*', '')
dists.dt$trend <- with(dists.dt,
                        ifelse(p.fdr > .05 & p.fdr < .1, '*', ''))
```

The following code example and Figure 14.3 show group-wise histograms of edge distances for 2 densities. In this case, the control group tends to have more long-range connections.

```
# Plot at a couple densities
plot_dists_density <- function(dists.dt, densities) {
  dat <- dists.dt[density %in% densities]
  meandt <- dat[, .(avg=median(dists)), by=c('density', 'Group')]
  distplot <- ggplot(dists.dt[density %in% densities], aes(x=dists)) +
    geom_histogram(aes(y=..density.., fill=Group),
                  binwidth=10, alpha=0.4, position='dodge') +
    geom_vline(data=meandt, aes(xintercept=avg, col=Group), lty=2, size=0.5) +
    facet_grid(. ~ density) +
    geom_density(aes(col=Group), size=0.8) +
```

```

xlab('Edge distance (mm)') +
theme(legend.position=c(1, 1), legend.justification=c(1, 1),
      legend.background=element_rect(size=0.5))
return(distplot)
}
print(plot_dists_density(dists.dt, densities[N:(N+1)]))

```

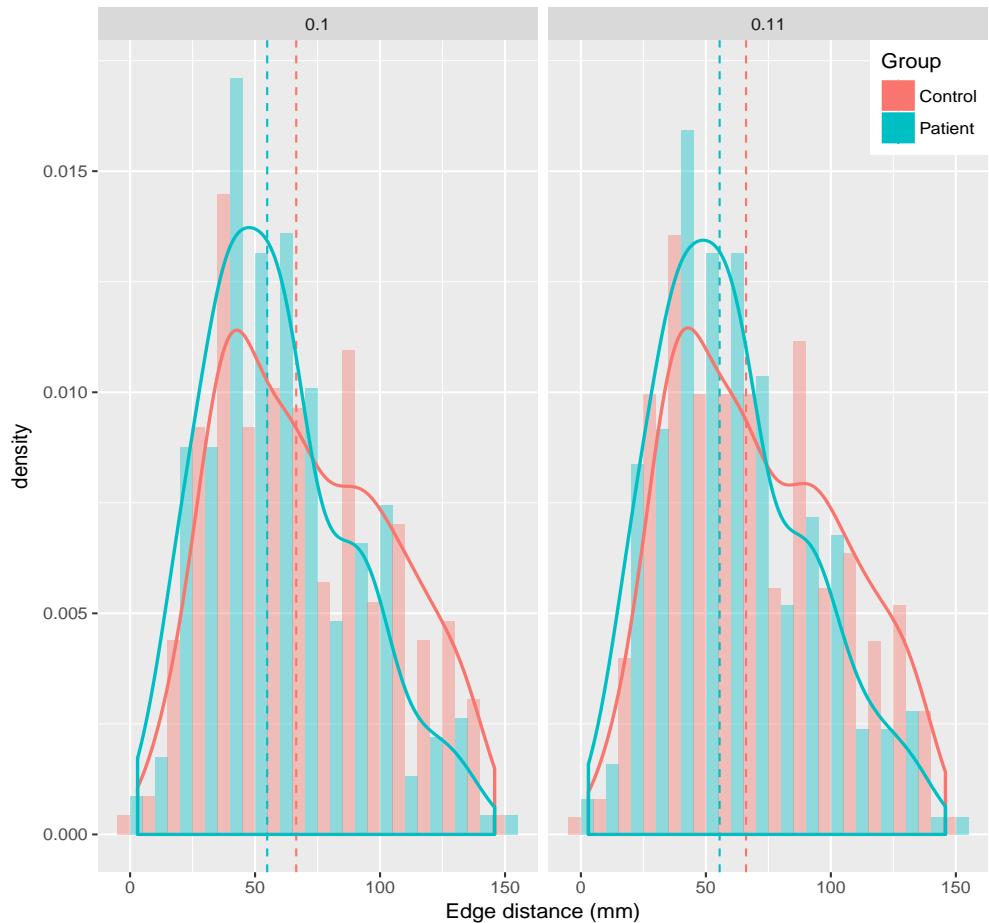


Figure 14.3: Edge distances (in mm)

You can also plot the average edge distance across all densities, with a shaded region signifying the confidence interval (here I plot the 99th %ile). This is shown in [Figure 14.4](#).

```

plot_dists_mean <- function(dists.dt) {
  ggplot(dists.dt, aes(x=density, y=dists, col=Group)) +
    stat_smooth(level=.99) +
    geom_text(aes(y=51, label=sig), col='red', size=7) +
    geom_text(aes(y=51, label=trend), col='blue', size=7) +
    ylab('Edge distance (mm)') +
    theme(legend.position=c(1, 0.25), legend.justification=c(1, 0),
          legend.background=element_rect(size=0.5))
}
print(plot_dists_mean(dists.dt))

```

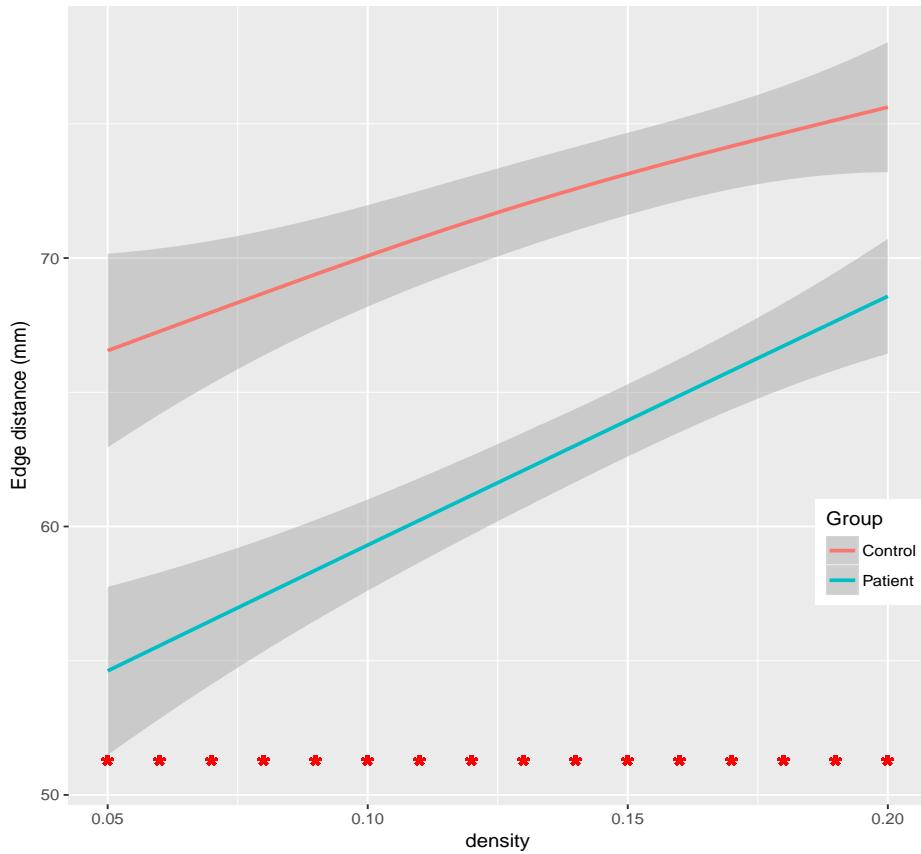


Figure 14.4: Average edge distances (in mm) with 99% confidence intervals

14.3 Individual contributions

Saggar et al. (2015) recently introduced two methods for estimating the individual contributions of subjects to a group graph (68). I wrote two functions to calculate these measures: `aop` (“add-one-patient”) and `loo` (“leave-one-out”). This is useful for structural covariance networks in which there is just a single graph for each group. For both functions, you can calculate either a “global” or a “regional” metric. For the global metrics, these can easily be merged with other data so you can correlate the individual contribution (`IC`) with some variable of interest (e.g., *full-scale IQ (FSIQ)*).

14.3.1 Add one patient

With this method, a comparison is made between the correlation matrix of the entire control group and a correlation matrix of the control group *with a single patient added*. In the code sample below, it is assumed that the control group is *group 1* (this can be changed by the argument `control.value`). The code will work with any number of groups (i.e., if you have one control group and multiple patient groups).

```
IC.aop <- aop(resids.all, corrs[[1]]$R)
RC.aop <- aop(resids.all, corrs[[1]]$R, level='regional')
```

We can also plot the regional contribution for the group (see Figure 14.5):

```
ggplot(RC.aop, aes(x=region, y=RC, col=Group, group=Group)) +
  geom_line(stat='summary', fun.y=mean) +
  theme(legend.position='none',
        axis.text.x=element_text(size=6, angle=45, vjust=0.5))
```

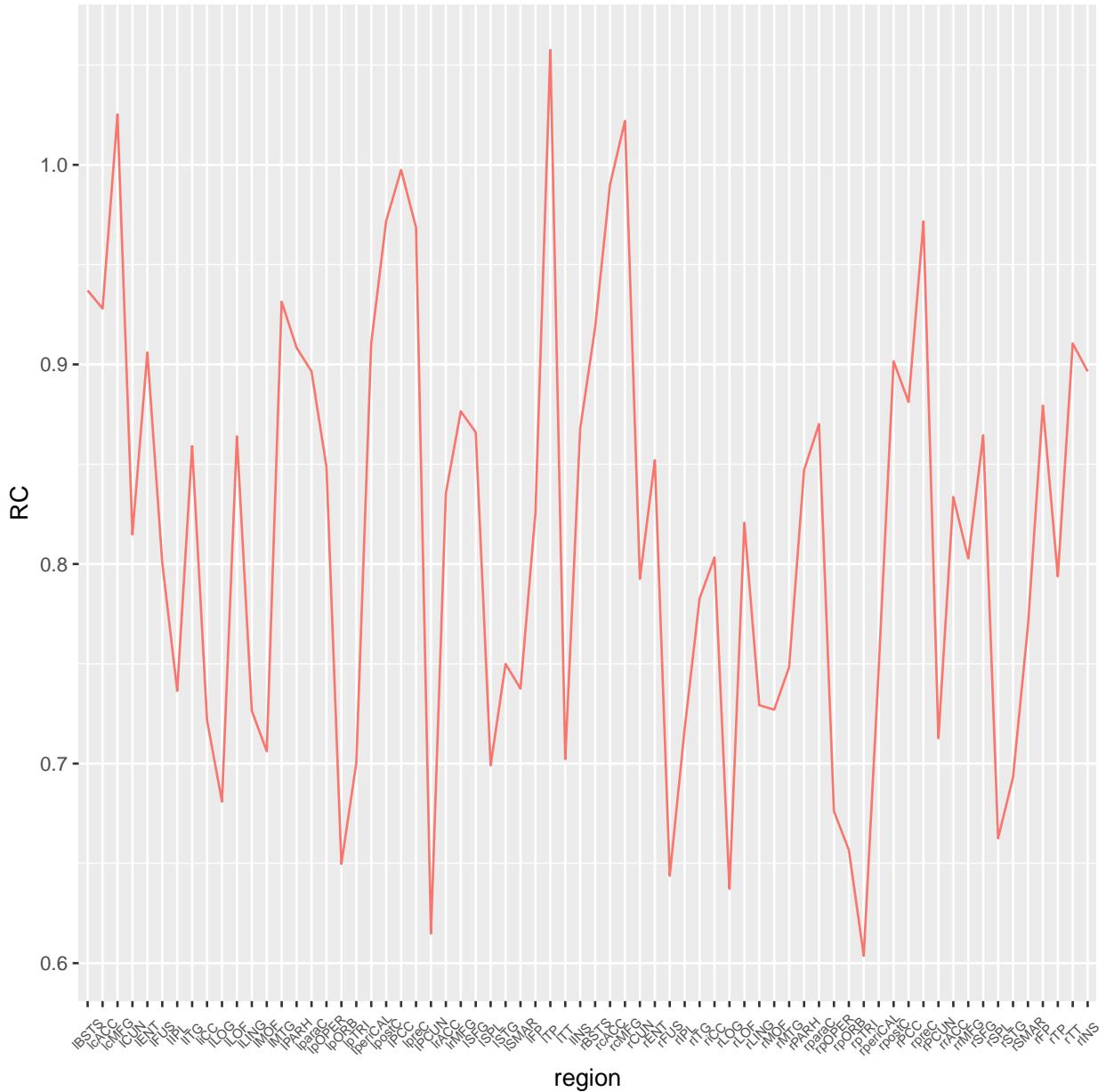


Figure 14.5: Regional contribution; add-one-patient

14.3.2 Leave one out

With this method, a comparison is made between the correlation matrix of the entire group, and a correlation matrix of the group *excluding a single subject*. Function use is simple:

```
IC.loo <- loo(resids.all, corrs)
RC.loo <- loo(resids.all, corrs, 'regional')
```

We can also plot the regional contribution for the group (see Figure 14.6):

```
ggplot(RC.loo, aes(x=region, y=RC, col=Group, group=Group)) +
  geom_line(stat='summary', fun.y=mean) +
  theme(legend.position='bottom',
        axis.text.x=element_text(size=6, angle=45, vjust=0.5))
```

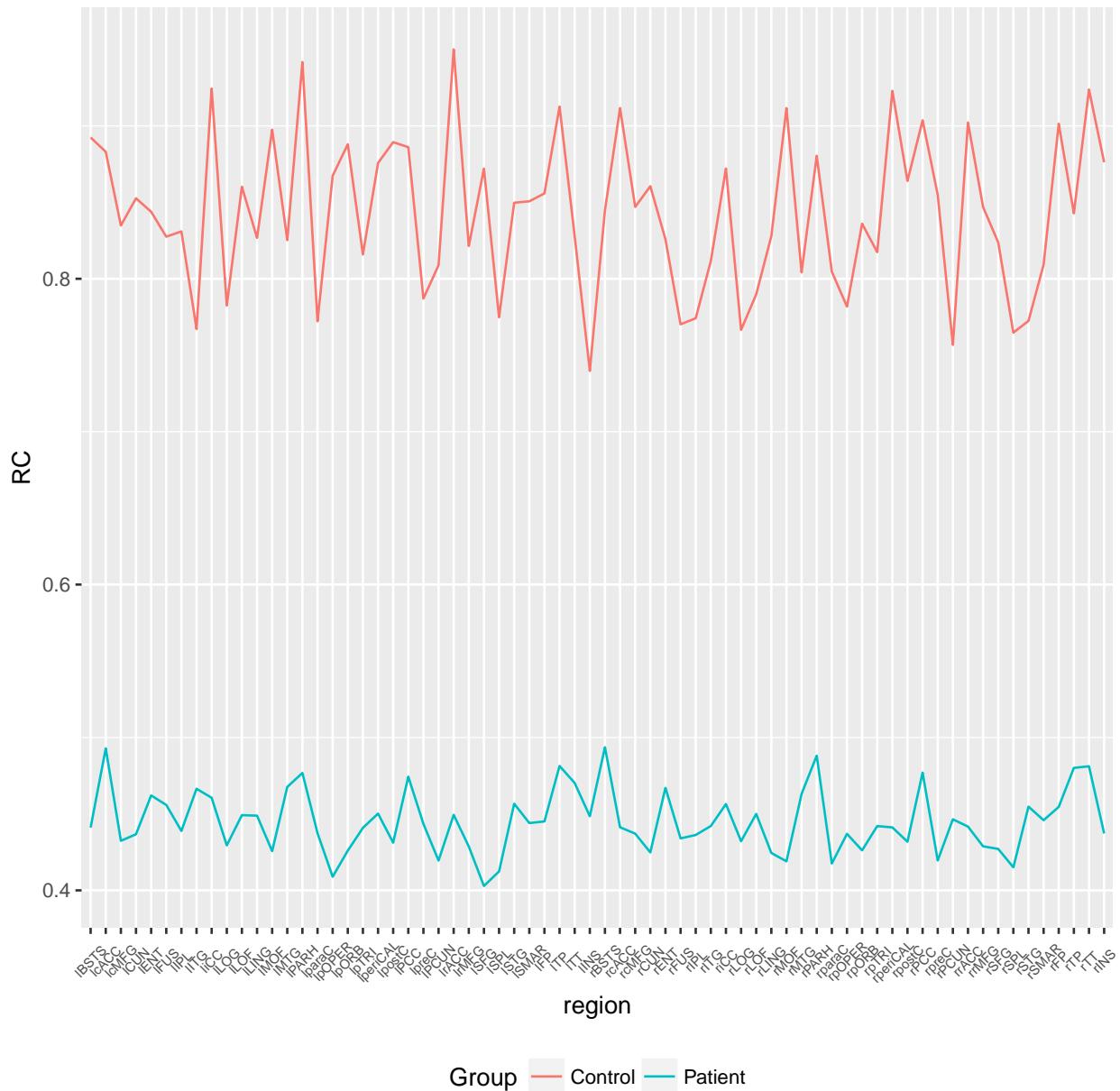


Figure 14.6: Regional contribution; leave-one-out

Part VI

Visualization

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15

GUI and other plotting functionality

15.1 The GUI

I created a GUI to quickly and flexibly compare graphs (two at a time); the function to open it is `plot_brainGraph_gui`. See [Figure 15.1](#) for a screenshot.

The most obvious feature of the GUI is that there are two plotting sections for showing 2 groups (or subjects) side-by-side. Alternatively, if you have a single group, you can look at different densities or different orientations.

The # of vertices, # of edges, and the graph's density are printed at the bottom of each figure window. At the top of each figure window, the graph's `name` attribute is printed (in this case, group).

15.1.1 Orientation

You can choose one of: *axial*, *sagittal (L)*, *sagittal (R)*, or *circular*. The sagittal plots show only *intra*-hemispheric edges. If you choose *circular*, there is a slider widget beneath each plot that controls the edge curvature.

15.1.2 Hemi/Edges

This option lets you show a subset of edges based on vertex classification/grouping. The default is to show all edges; you may also choose to show one hemisphere individually or only *inter*-hemispheric edges. There are options to show only edges between homologous regions, as well. Finally, you can select only inter-/intra-community edges, and inter-/intra-lobar edges.

15.1.3 Legend

If vertices are colored by *lobe*, *class*, or *network*, then you may choose to show a legend. The numbers represent the # of vertices present out of the total # of vertices for that lobe/class/network in that specific atlas.

15.1.4 Vertex “decorations”

- *Vertex labels*: you can show or hide the labels. The label placement and text color isn't very “smart”, but I have attempted to code it such that labels won't be placed on top of one another. Showing labels would not be feasible for atlases with long vertex names (e.g., the *Destrieux* atlas).
- *Vertex color*: vertices will be colored according to either community membership (weighted or unweighted), lobe membership (as in [Figure 15.1](#)), component membership (useful if your graph is disconnected), and for the *Destrieux* atlas, I included a `Class` attribute, where `Class` is either G

(*gyral*), *S* (*sulcal*), or *G & S* (*gyral and sulcal*). For the *Dosenbach160* atlas, there is also an option to color vertices by `network` (e.g., *Default-mode*).

- *Vertex size*: vertices will be scaled to reflect a number of vertex attributes (e.g., degree, betweenness centrality, etc.). The dropdown menu lists them all. Unfortunately, the same scaling is used for most of the vertex measures; the default I chose is to be between 0 and 15. Vertices with size larger than 15 (which is unitless) can end up “blocking” other vertices. For large graphs, it would be too cluttered to be useful.
- There is also an entry for `Other`, which is useful if your graph has vertex attributes I haven’t hard-coded. For example, if you have a *P-value* attribute for each vertex, you can type that in the `Other` entry.
- You can remove vertices with values below a certain minimum (see `Min. 1` and `Min. 2`).
- Finally, there are text boxes for writing a simple logical equation. For example, to keep vertices with *degree* above 10 *AND* *Frontal lobe regions*, you would write `degree > 10 & lobe == 'Frontal'`.

15.1.5 Edge “decorations”

- *Edge width*: edge widths will be scaled to reflect edge betweenness, edge distance (Euclidean), or edge weight (if the graph is weighted); there is also an entry for `Other` (as with vertices) for a custom edge attribute.
- You can specify both minimum and maximum values, below/above which all edges will be removed. These values can be different for the two displayed graphs.
- *Edge color* is tied to vertex color; edges are colored gray if they are connecting vertices with different memberships (community, lobe, etc.).

15.1.6 Lobe

At the bottom-left of the GUI, you can choose to see vertices of all lobes, or *any* combination of other lobes (e.g., if you want to see Frontal & Temporal & Occipital only). To select multiple lobes, you can press `ctrl` and click, or hold `shift` and use the arrow keys.

15.1.7 Neighborhoods

In the dropdown `Plot` menu at the top of the window, there is an option to plot vertex neighborhoods. An example screenshot is in [Figure 15.2](#); in this case, I am looking at the union of neighborhoods of 3 vertices. The main title of the plot lists the vertex names, which are colored in yellow (default) for convenience. To select multiple vertices, you can press `ctrl` and click, or hold `shift` and use the arrow keys.

15.1.8 Communities

From the same dropdown menu, you can plot individual (or any combination of multiple) communities. [Figure 15.3](#) shows an example. The numbering here is in order from largest to smallest. Communities with 2 or fewer members are not included. Here I show the 2 largest (*red* is for the largest, *green* for the second-largest). To select multiple communities, you can press `ctrl` and click, or hold `shift` and use the arrow keys.

15.1.9 Keyboard shortcuts

There are a number of keyboard shortcuts available.

alt+f Opens the *File* dropdown menu

alt+p Opens the *Plot* dropdown menu

ctrl+e Plot Entire graphs
ctrl+n Plot Neighborhoods
ctrl+c Plot Communities
alt+o Same as clicking *Ok*
alt+n Same as clicking *Picking new graphs*
alt+l Toggle the vertex label checkbox
alt+d Toggle the *Show diameter* checkbox
ctrl+1 Save figure 1 (left)
ctrl+2 Save figure 2 (right)
ctrl+q Quit

15.2 Other plotting

15.2.1 Adjacency matrix plots

It is possible to plot the adjacency matrices. I haven't found these to be particularly useful, except when viewing the vertices in a specific order (e.g., by community membership). This is the default in the function `plot_corr_mat`. Figures 15.4 and 15.5 show them clustered into communities, and Figures 15.6 and 15.7 show them clustered into lobes (zoom in to read the axis labels).

```
matplot.comm1 <- plot_corr_mat(corr[[1]]$r.thresh[, , 10], type='comm',
                                g=g[[1]][[10]], group=groups[1])
matplot.comm2 <- plot_corr_mat(corr[[2]]$r.thresh[, , 10], type='comm',
                                g=g[[2]][[10]], group=groups[2])
matplot.lobe1 <- plot_corr_mat(corr[[1]]$r.thresh[, , 10], type='lobe',
                                g=g[[1]][[10]], group=groups[1])
matplot.lobe2 <- plot_corr_mat(corr[[2]]$r.thresh[, , 10], type='lobe',
                                g=g[[2]][[10]], group=groups[2])

# To plot both in the same device:
#grid.arrange(matplot.comm1, matplot.comm2, nrow=1, ncol=2)
print(matplot.comm1)
```

```
print(matplot.comm2)
```

```
print(matplot.lobe1)
```

```
print(matplot.lobe2)
```

15.2.2 Plot global graph measures

Assuming you have already “tidied” your data (see [Tidying Data](#)), this can be done very easily with one function, `plot_global`, and is shown in [Figure 15.8](#). There is an option to include a dashed vertical line at a density of interest (e.g., if your main analysis focuses on one density, but you want to report results for multiple in a compact way). You can also include data from a permutation analysis `data.table` to add asterisks for significance (currently, it will only plot red asterisks for $P < 0.05$ and blue for $0.05 \leq P < 0.10$). You also need to provide a character vector of the *alternative hypotheses* in the order of the columns of the permutation data table (excluding `density`). Finally, there is an option to change the facet label names (e.g., from `Cp` to `Clustering coeff.`).

This isn’t the cleanest solution, but all of the ugly code is hidden in the function. I wrote this function to prepare a figure easily for a manuscript (because I have a separate script to produce all figures for a given manuscript; this reduces the code I have to write for those). This function *should* be straightforward and flexible.

```
# Re-name the facet labels to whatever you want
# Match to the order of `dt.G.tidy[, levels(variable)]`-
level.names <- c('Clustering coefficient', 'Char. path length',
                 'Global efficiency', 'Modularity', 'Max. conn. comp.',
                 '# of triangles', 'Diameter', 'Transitivity',
                 'Degree assortativity', 'Lobe assortativity',
                 'Lobe & hemi. assort.', 'Asymmetry Index', 'Spatial distance',
                 '# of hubs', 'Local efficiency', 'Vulnerability')

# mod, Cp, Lp, assortativity, E.global, assortativity.lobe, asymm
alt <- c('less', 'two.sided', 'less', 'less', 'two.sided', 'less', 'less')
print(plot_global(dt.G.tidy, vline=densities[N], level.names=level.names,
                  exclude='assortativity.lobe.hemi', perms=perms.all,
                  g=g, alt=alt))
```

15.2.3 Save a three-panel plot of the brain graphs

The function `plot_brainGraph_multi` will save a *PNG* file of the left sagittal, axial, and right sagittal views for one or more groups. It currently only works for group-level graphs (i.e., list objects with 2 levels). You have the option of specifying conditions for subsetting the graphs (via the `subgraph` argument); you can specify a single condition to be applied to all groups, or multiple conditions (equaling in length to the number of groups). If you would like to have a single group and multiple subsets in the same plot, then repeat the group number in the `groups` argument. The following code block shows an example command, and its output is in [Figure 15.9](#). To increase the size of the panel titles, supply the argument `cex.main` (with a value greater than 2.5).

```
plot_brainGraph_multi(g, groups=1:2, N=5,
                      subgraph='coreness > 5', filename='kcore5.png', main='k-core 5',
                      vertex.color='color.lobe', edge.color='color.lobe', vertex.label.cex=2)
```

15.2.4 Plot vertex-level measures

You can use the function `plot_vertex_measures` to plot a series of boxplots for a single vertex-level measure (e.g., *betweenness centrality*), grouped by *lobe* (the default), *network* (in the `dosenbach160` atlas), *hemi*, etc. This requires having a “tidied” dataset (see [Tidying Data](#)). An example is shown in [Figure 15.10](#).

```
plot_vertex_measures(dt.V.tidy[density == densities[N]], facet.by='lobe',
                      'btwn.cent', show.points=TRUE,
                      ylabel='Betweenness centrality')
```

15.2.5 Plot group-wise volumetric data for ROI's

It is very easy to plot group-wise volumetric data either in the form of histograms or violin plots. The function `plot_volumetric` will do this. An example is shown in [Figure 15.11](#). You may also choose an integer vector as the second argument; in that case, the regions with those indices will be determined by the ordering in the input. You can choose as many regions at a time as you like, but more than 9 at a time might get cluttered.

```
plot_volumetric(all.dat.tidy, c('1SMAR', 'rSMAR'), 'histogram')
```

An example of looking at 9 regions at once is shown in [Figure 15.12](#).

```
plot_volumetric(all.dat.tidy, 1:9, 'violin')
```

15.2.6 Save a list of graph plots

The function `plot_brainGraph_list` will save a series of *PNG* files of axial graph plots. The list may contain graphs for a single subject group at each density/threshold, or the list may represent single subject graphs; in the latter case, this is a quick way to “scroll” through all of the graphs to check for potential outliers/issues.¹ There is an option to highlight edge differences between subsequent graphs, and to color the vertices (either all the same color (default), or by lobe/community membership). You may also pass arguments that will go to `plot_brainGraph`, such as `vertex.label=NA` to omit vertex labels. The basic command is:

```
plot_brainGraph_list(g[[1]], 'group1_dk', diffs=TRUE)
```

There is also an option to view only a subgraph of vertices. The `subgraph` argument accepts logical expressions joined by `&` and/or by `|` for multiple conditions. For example, if you only want to plot vertices with degree greater than 10 and nodal efficiency greater than 0.5, you type:

```
plot_brainGraph_list(g[[1]], 'group1', subgraph='degree > 10 & E.nodal > 0.5')
```

After this, you can convert this series of *PNG*'s to either a *GIF* or to a video file. Converting to a *GIF* is done using `ImageMagick`, a powerful command-line utility for general image processing. You may then view the *GIF* in any image viewer, or, on Linux, `gifview` lets you step through each frame. Converting to a video will require a tool called `ffmpeg` (available on Linux).

Convert to gif

```
# The delay argument means show each frame for 0.5 seconds (i.e. 50/100)
convert -delay 50 -loop 0 *.png animation.gif

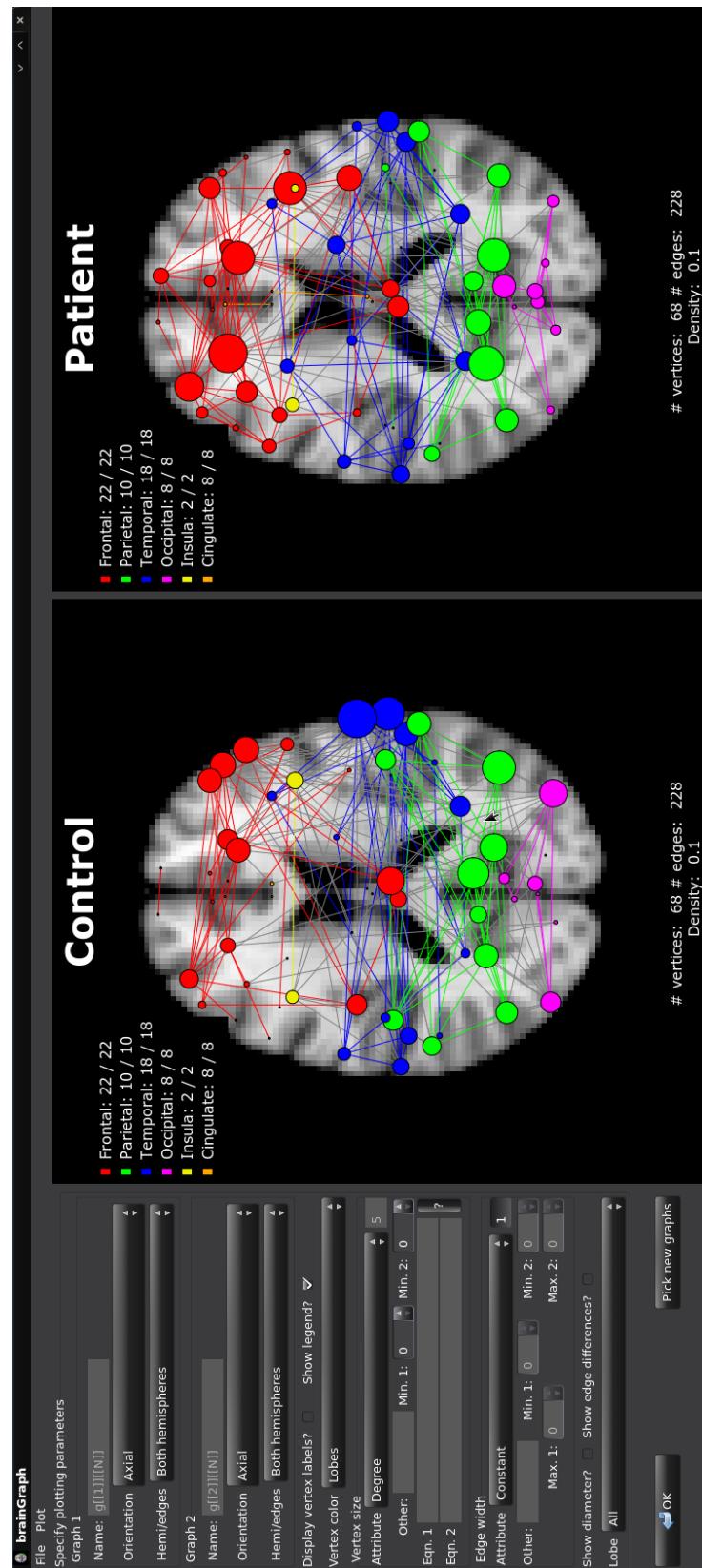
# Each frame will be displayed for 0.5 seconds
ffmpeg -framerate 2 -i group1_dk_%03d.png -c:v libx264 -r 30 \
-pix_fmt yuv420p out.mp4
```

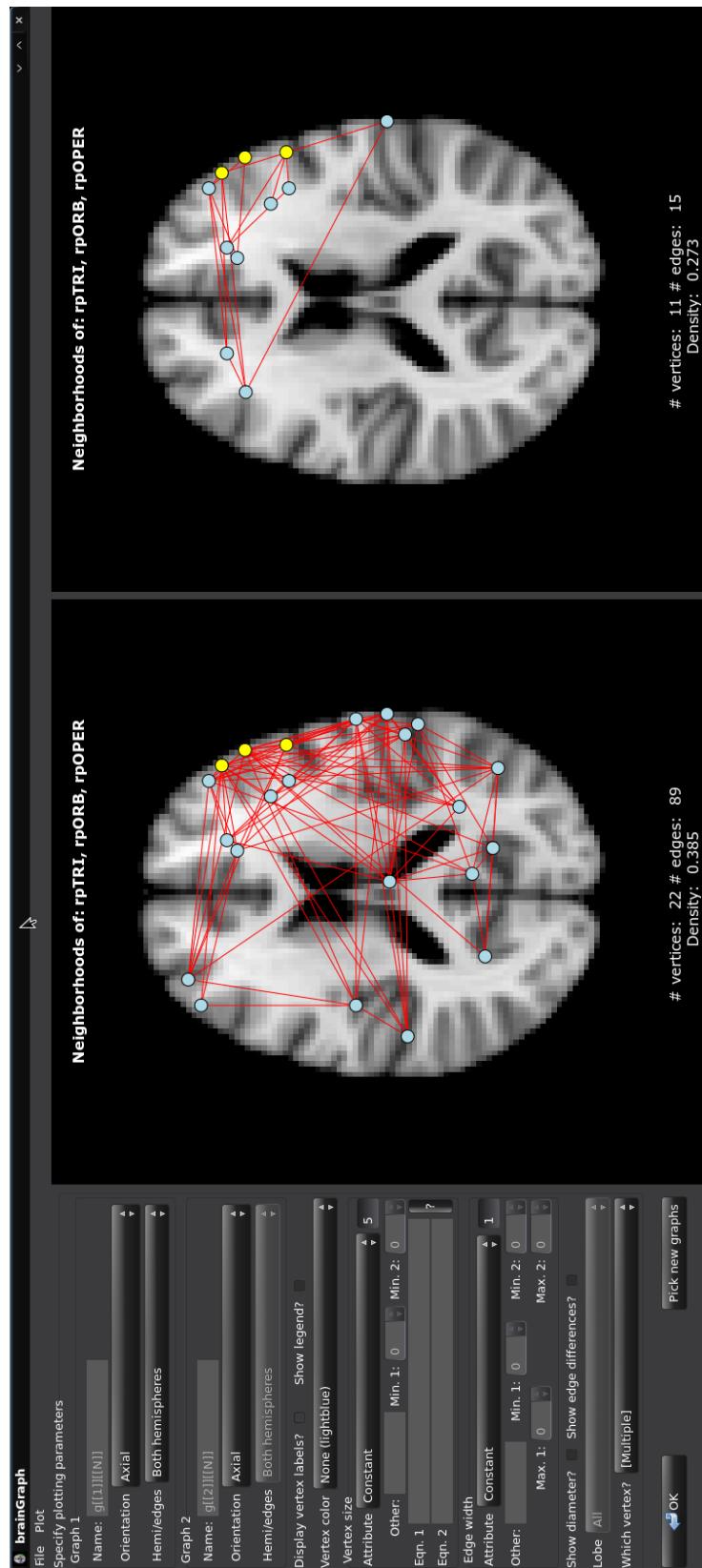
¹I plan on including some sort of outlier detection in the future.

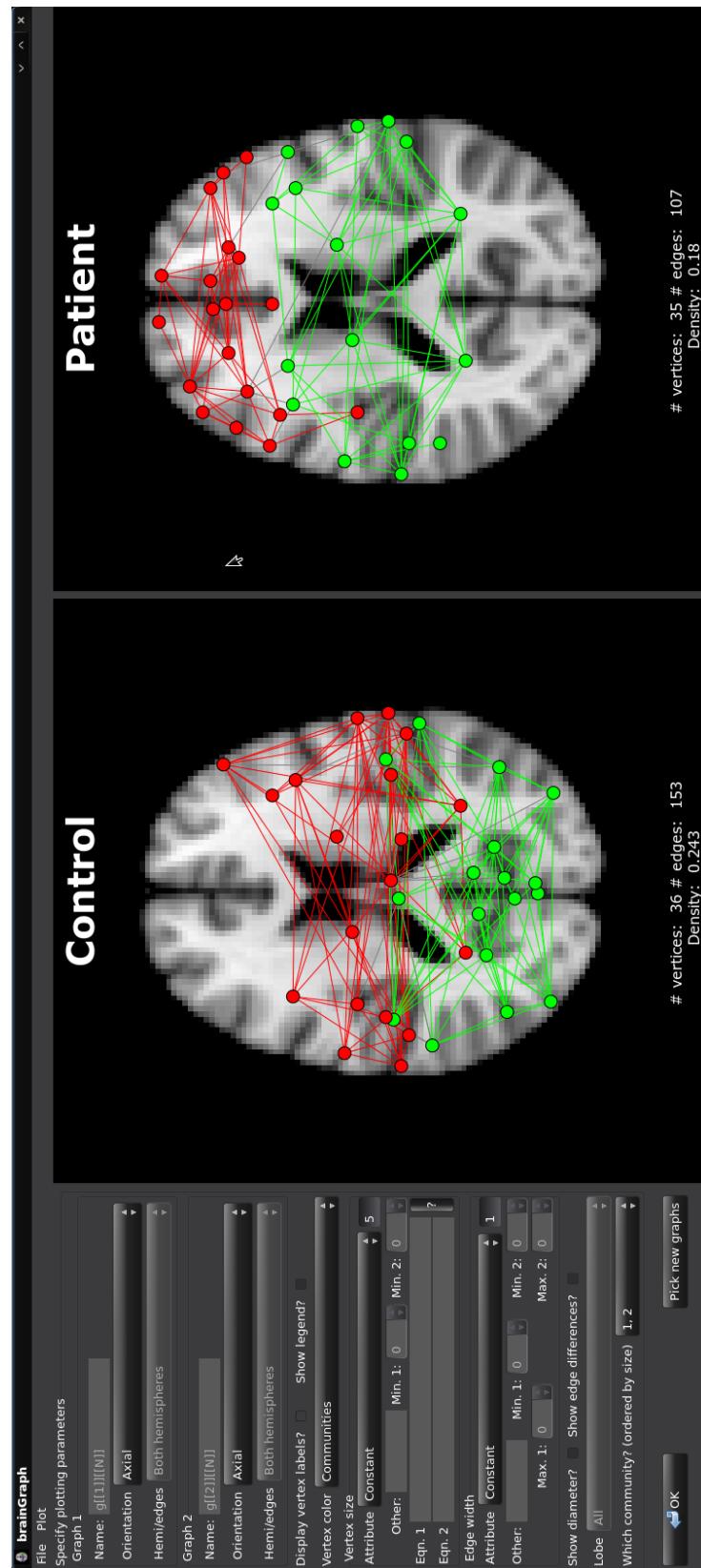
15.2.7 Other visualization tools

There are, of course, other visualization tools that are certainly more polished than this one. `igraph` can write graph objects that will work for several, e.g., `Pajek`. For a brain-specific tool, `write_brainnet` will save the `.node` and `.edge` files necessary for visualization with *BrainNet Viewer* (89). You can choose to color vertices by *community*, *lobe*, or *connected component* membership (or any other grouping/classification, provided it is a vertex attribute). You can scale vertex size by any vertex attribute the graph contains (e.g., *degree*, *betweenness centrality*, etc.). Finally, you can choose an edge attribute to write out a weighted adjacency matrix (e.g., `t.stat` from the `NBS` function). This tool requires `Matlab`, and while it is relatively slow, produces great figures.

```
write_brainnet(g[[1]][[N]], node.color='community', node.size='degree',
                edge.wt='t.stat', file.prefix='group1')
```

Figure 15.1: The `brainGraph` plotting GUI.

Figure 15.2: The **brainGraph** plotting GUI; neighborhoods.

Figure 15.3: The **brainGraph** plotting GUI; communities.

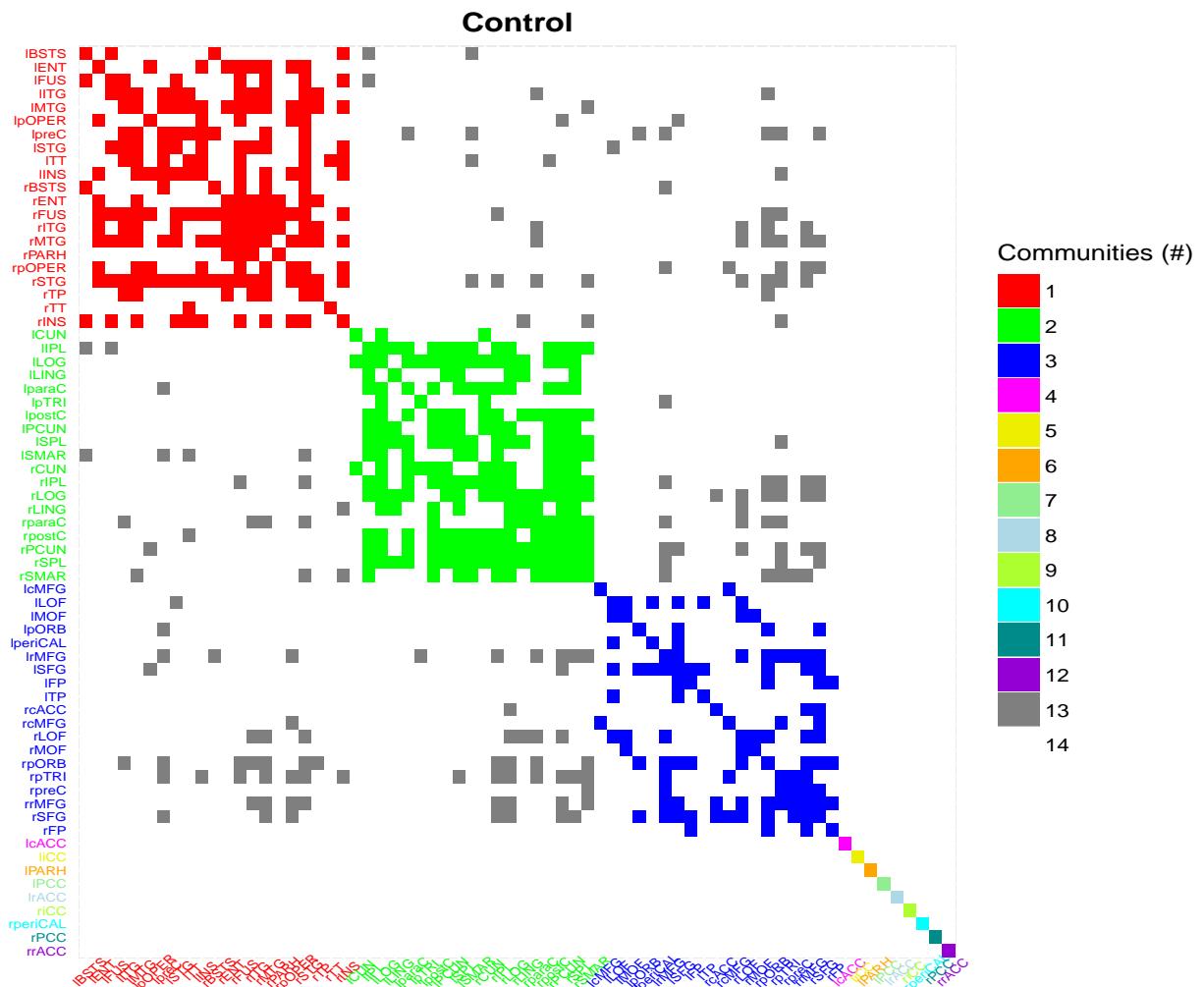


Figure 15.4: Adjacency matrix, group 1.

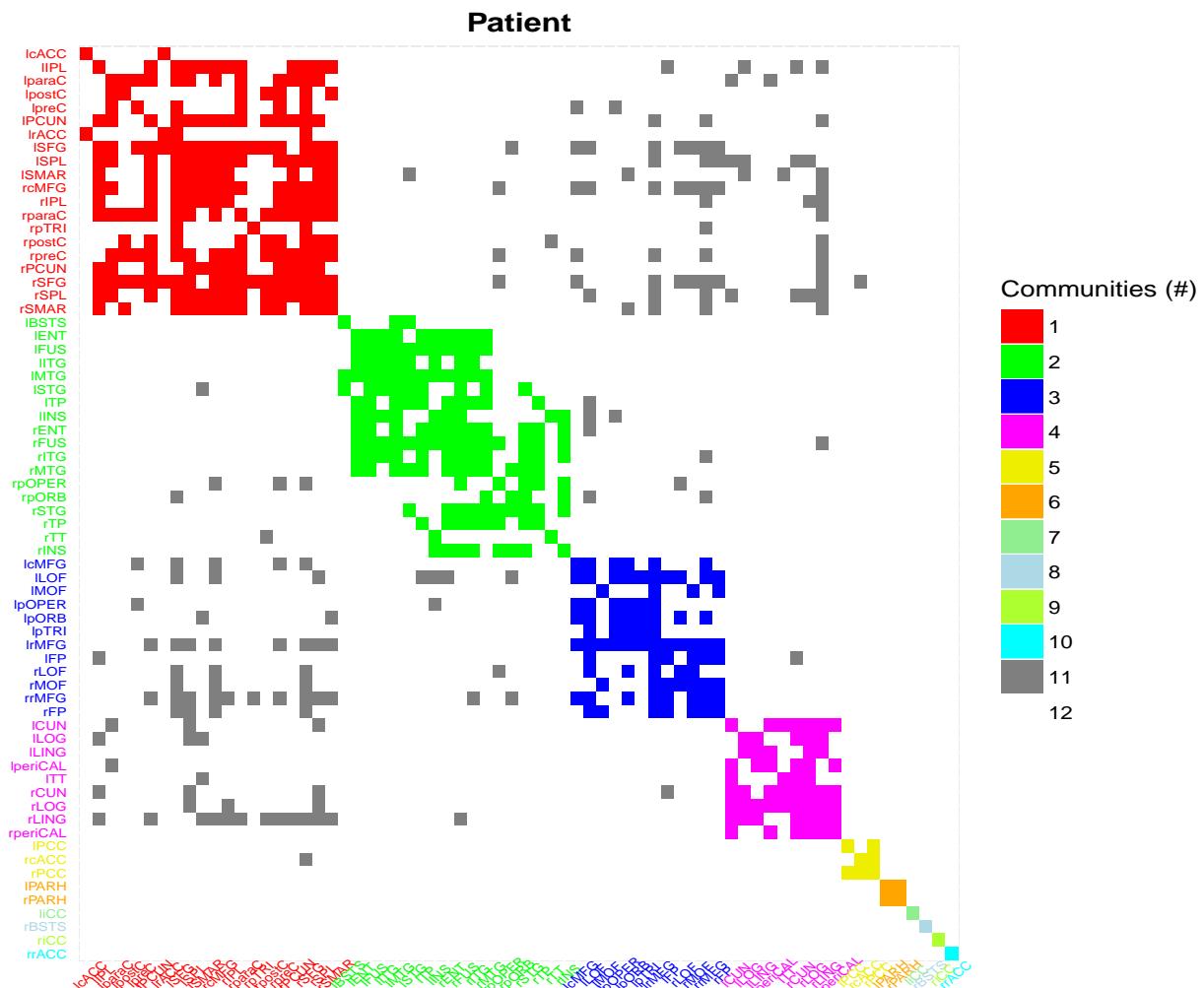


Figure 15.5: Adjacency matrix, group 2.

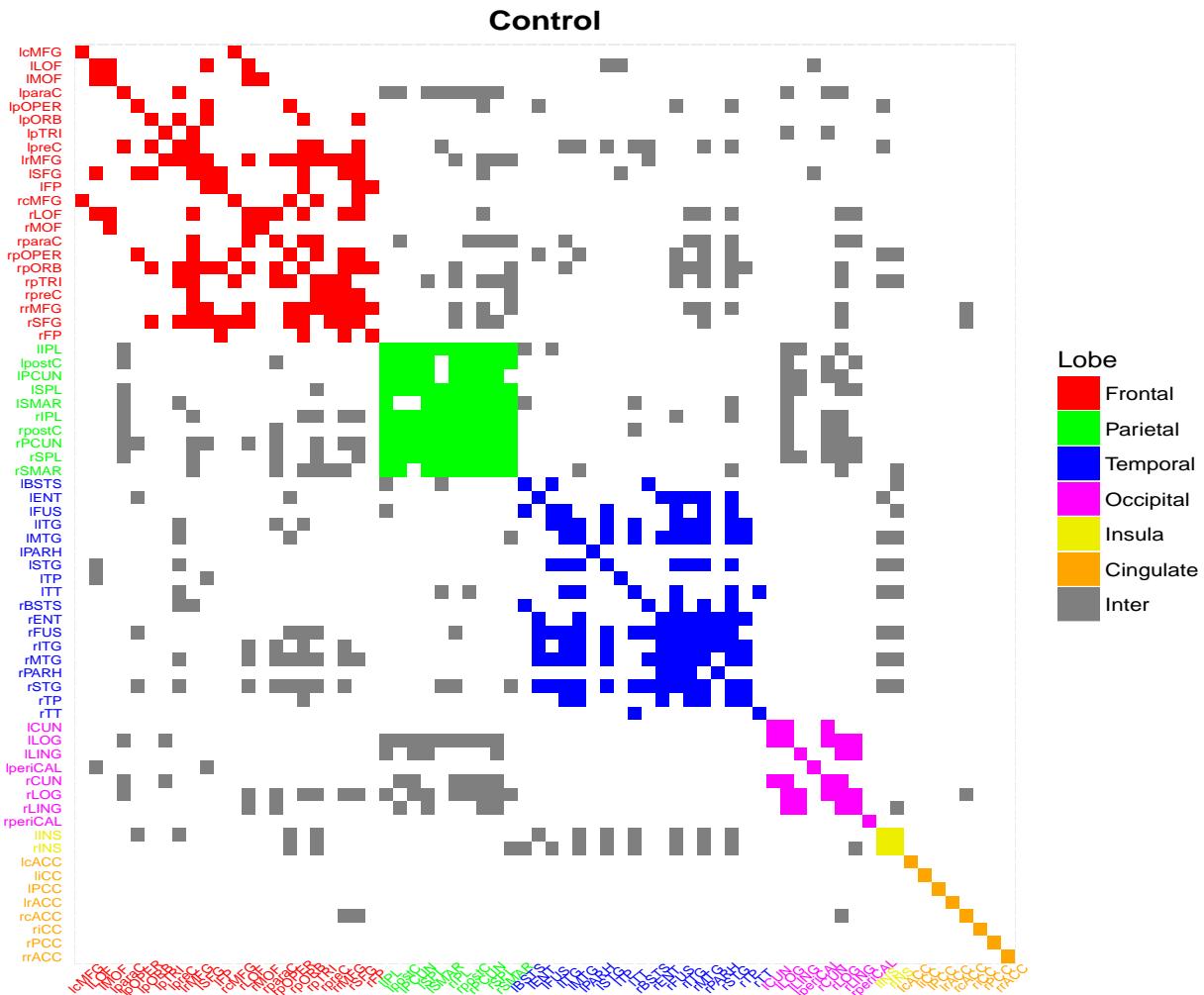


Figure 15.6: Adjacency matrix, group 1.

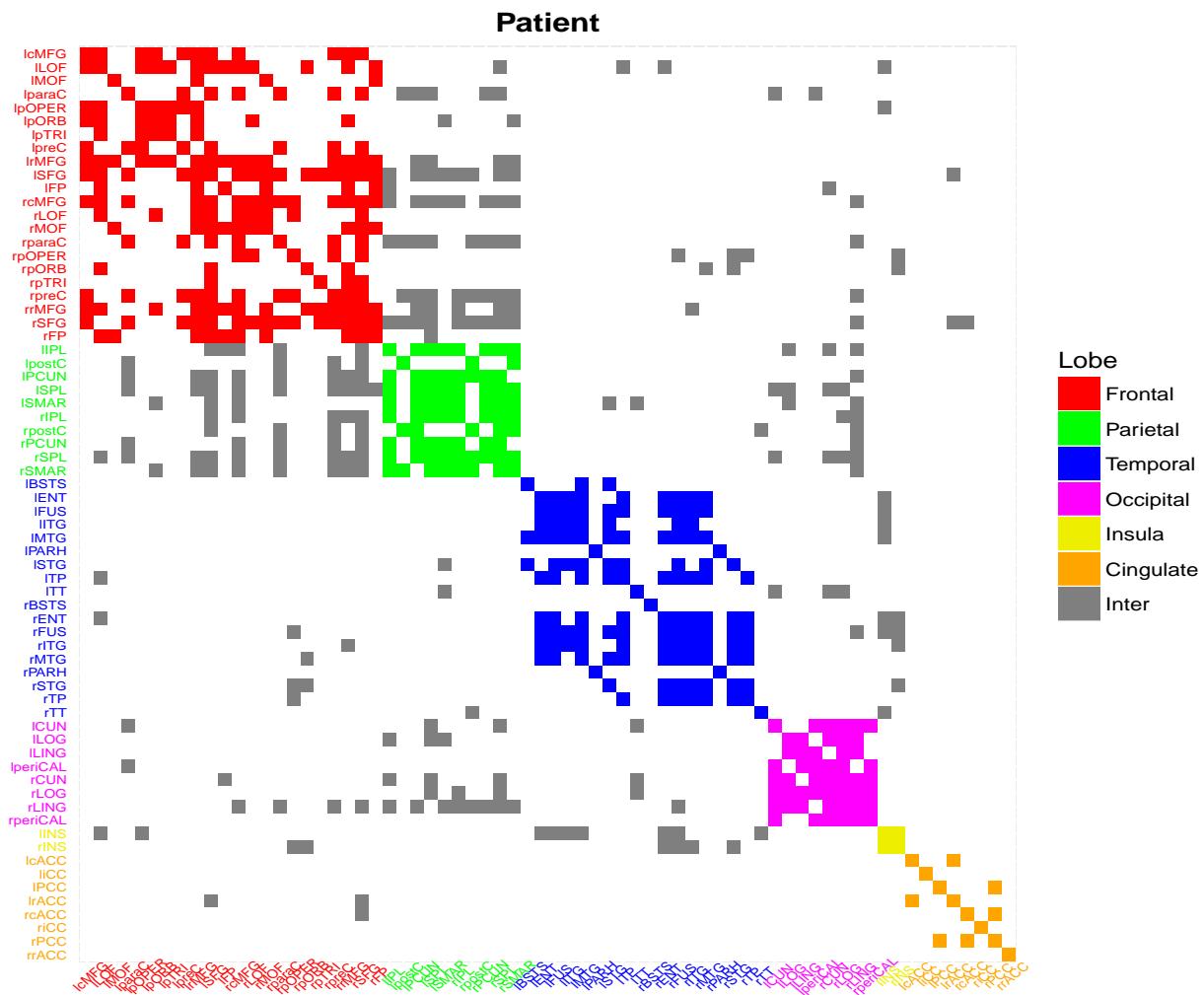


Figure 15.7: Adjacency matrix, group 2.

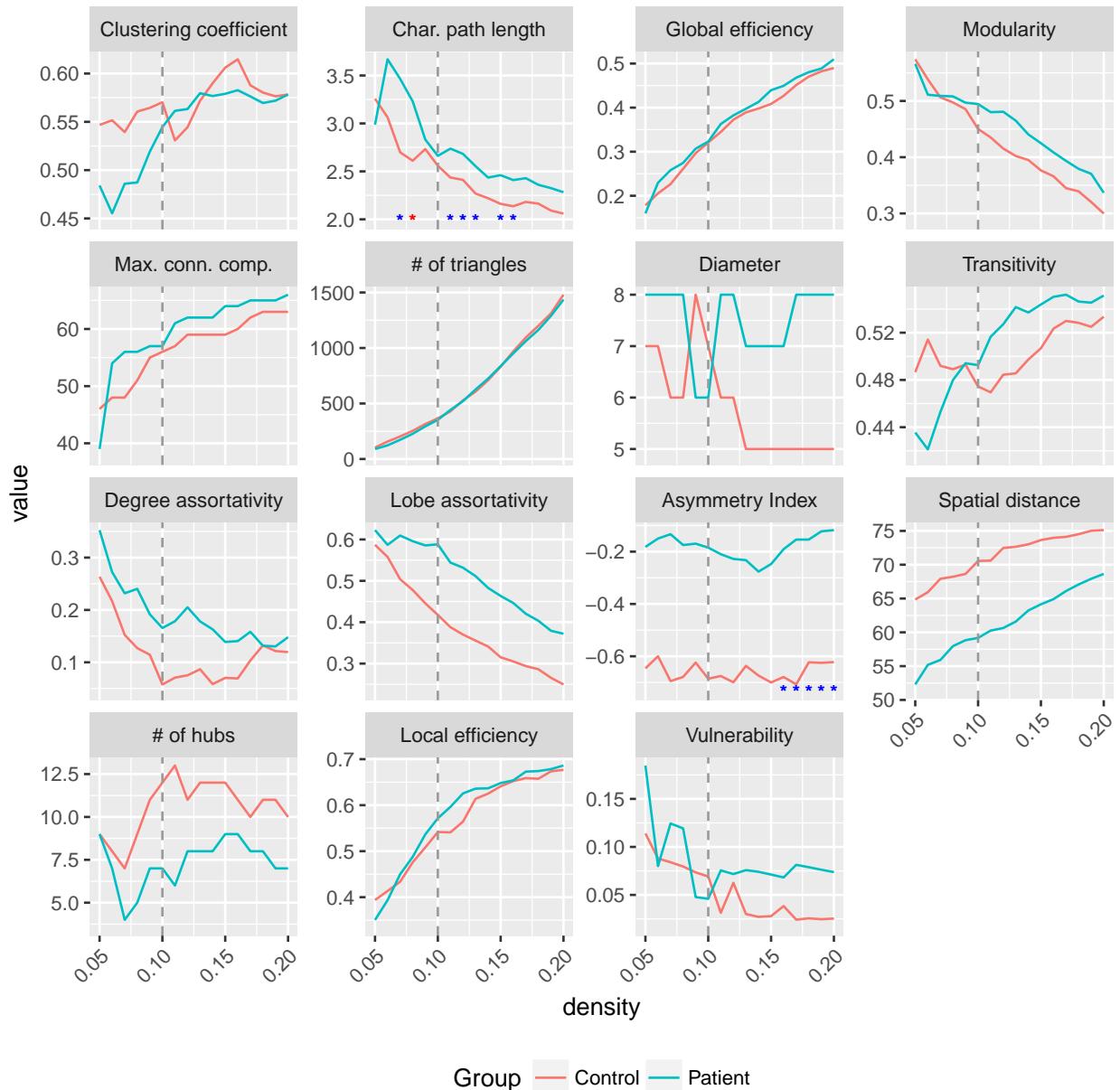


Figure 15.8: Global graph measures vs. density

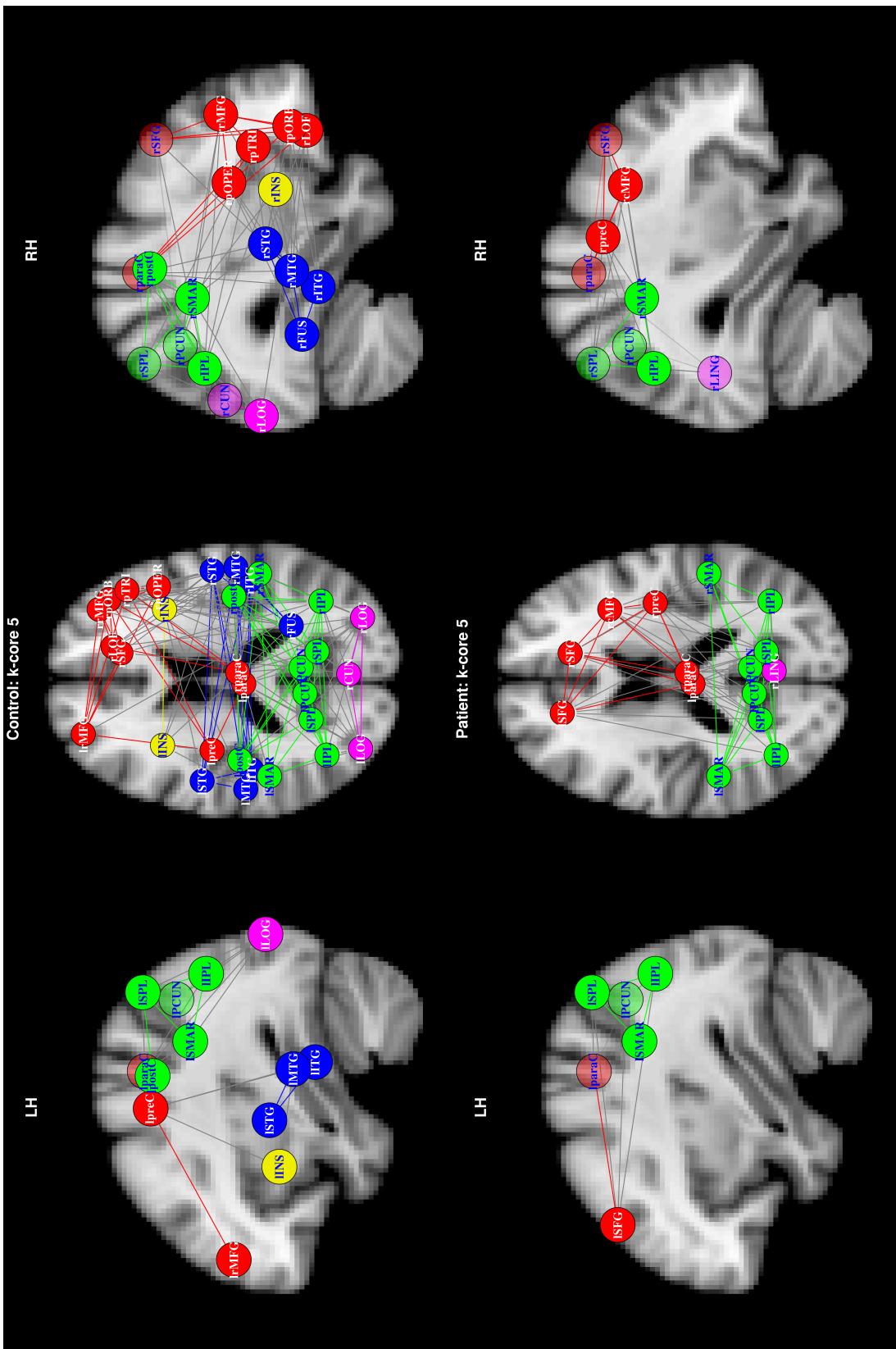


Figure 15.9: Vertices for which “coreness” is greater than 5.

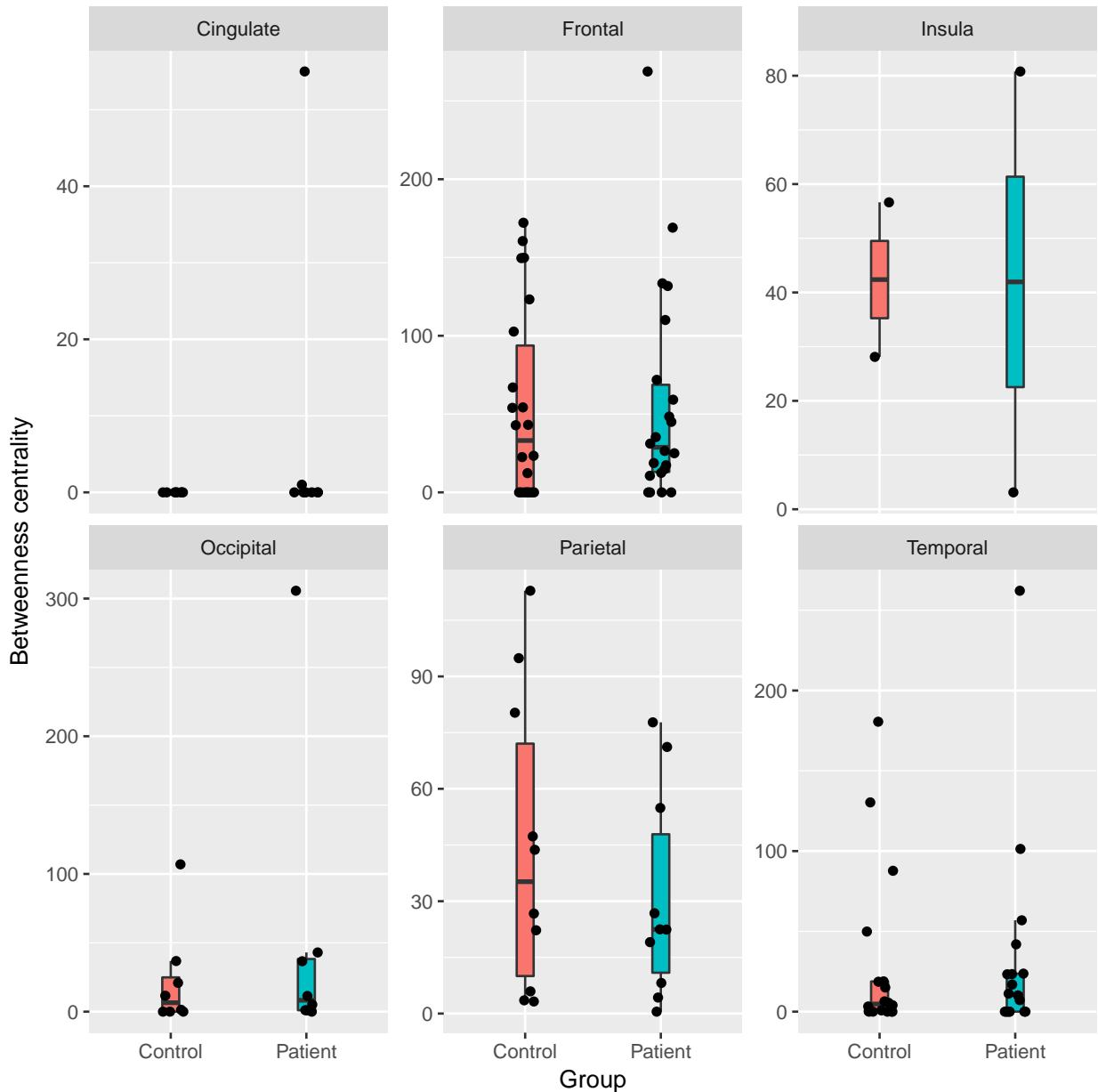


Figure 15.10: Vertex-level graph measures by lobe.

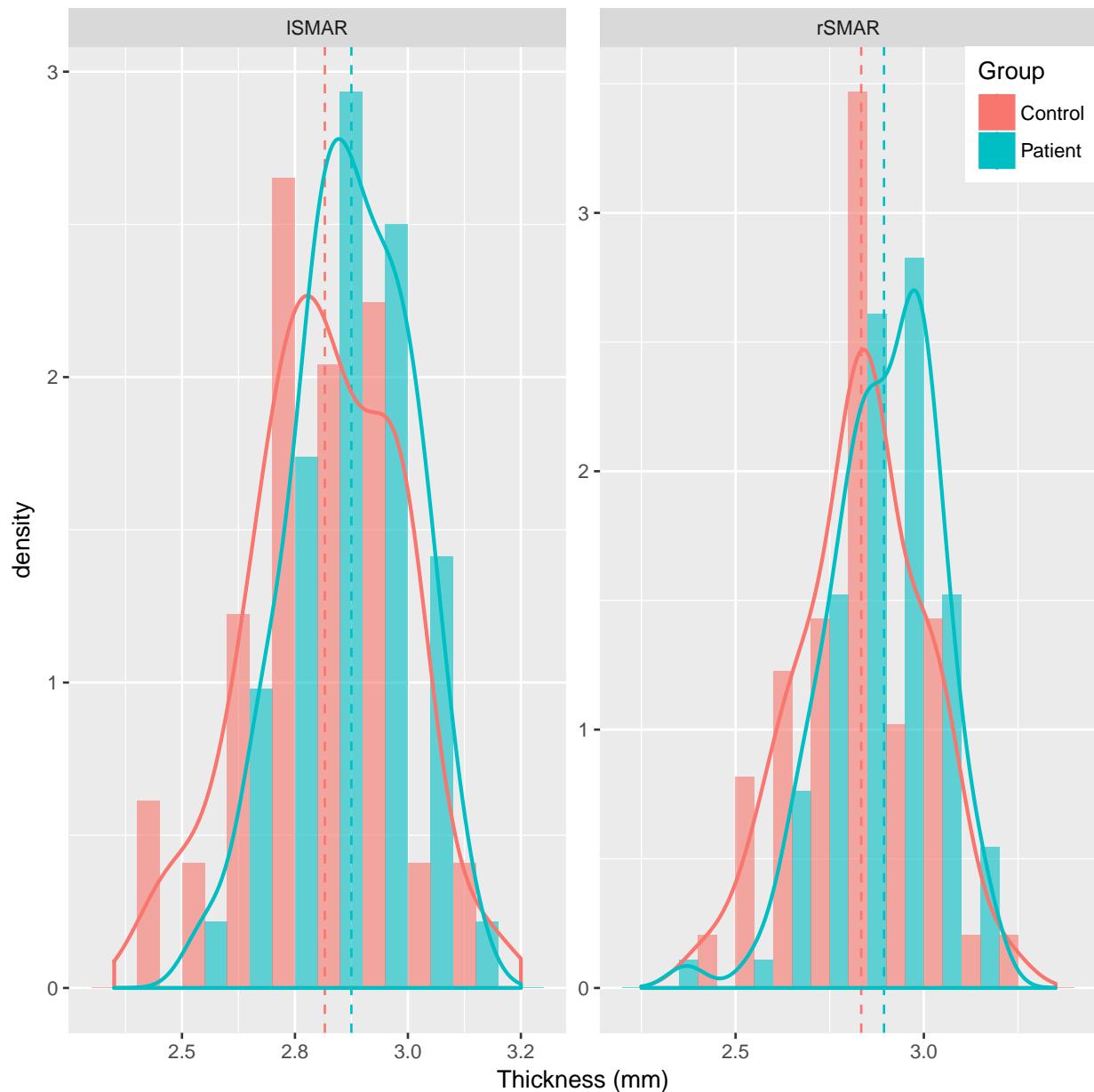


Figure 15.11: Cortical thickness.

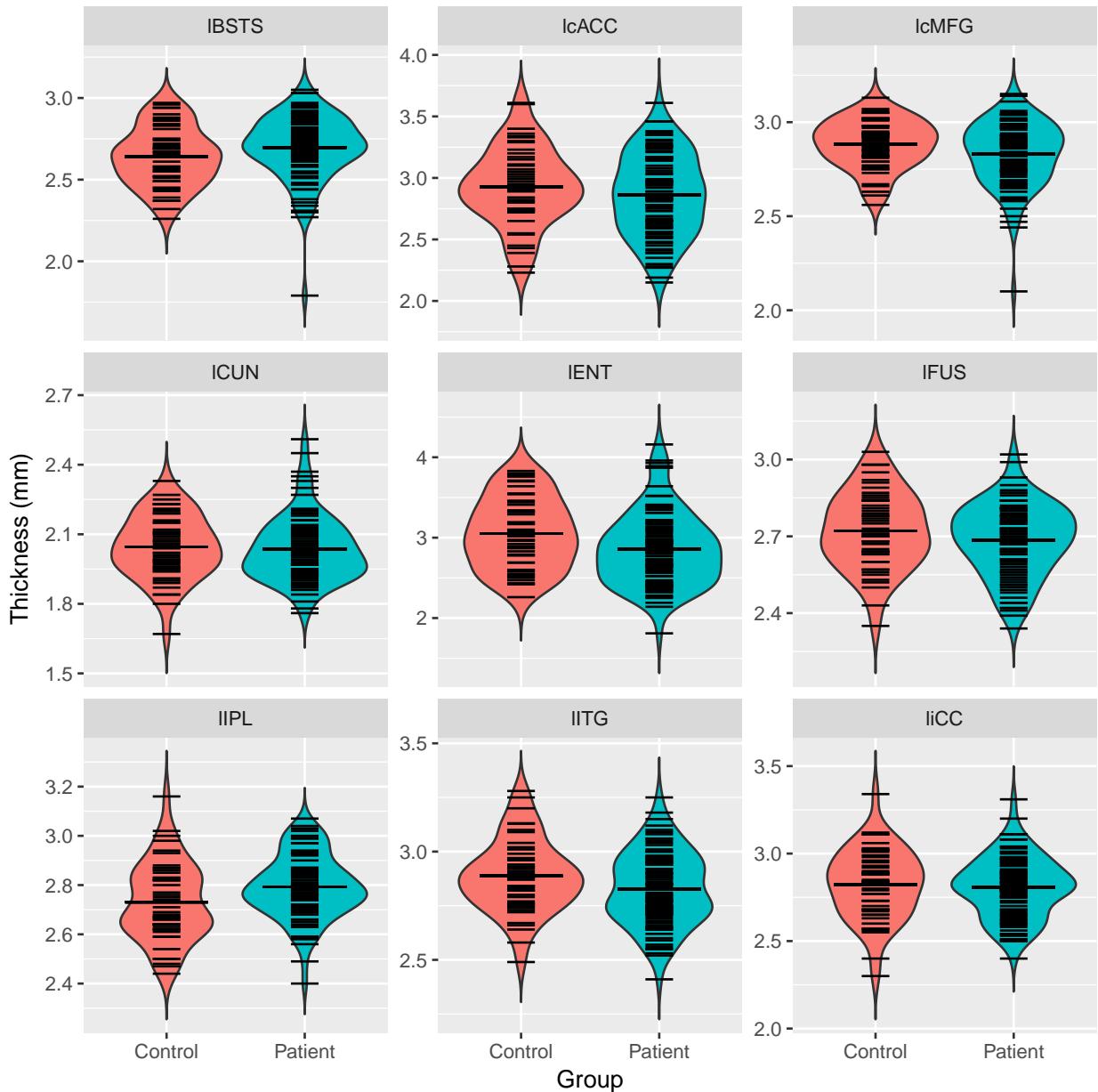


Figure 15.12: Cortical thickness.

A

Attributes created by `set_brainGraph_attr`

In this section I list the attributes that are created by the function `set_brainGraph_attr`. They are separated by the “level” to which they are assigned.

A.1 Graph-level

A.1.1 Bookkeeping

Some attributes are included only for “bookkeeping” purposes. Most are optional, but I suggest supplying them.

version The version of `brainGraph` that was used to create the graph

Group The subject/patient group name

name The subject/study ID of the subject

modality The imaging modality

weighting The edge weighting. For example, `fa` (for FA-weighted matrices from tractography), or `partial` (for partial correlation coefficients).

threshold The threshold applied to the raw connectivity matrices.

A.1.2 Unweighted

atlas The atlas (e.g., `dk` for *Desikan-Killiany*)

Cp The graph’s *clustering coefficient* (using the `localaverage` option)

Lp Characteristic path length

rich A `data.frame` of the rich-club coefficients and subgraph sizes

E.global The *global efficiency*

E.local The mean *local efficiency* across vertices

mod The *modularity* (calculated using the Louvain algorithm Blondel et al. (9))

density

conn.comp A `data.frame` of the sizes of *connected components* present in the graph

max.comp The size of the largest connected component

num.tri The number of *triangles* in the graph

diameter

transitivity

assortativity The graph's *degree assortativity*

assortativity.lobe The graph's assortativity, calculated using `lobe` membership

assortativity.lobe.hemi The graph's assortativity, calculated using `lobe` and `hemi` membership

assortativity.class The graph's assortativity, calculated using `class` membership (if the atlas is `destrieux`)

assortativity.network The graph's assortativity, calculated using `network` membership (if the atlas is `dosenbach160`)

asymm Edge asymmetry

spatial.dist Mean of all edge distances

vulnerability The maximum *vulnerability* across vertices

num.hubs The number of `hubs`

A.1.3 Weighted

strength Average vertex *strength*

rich.wt A `data.frame` of the weighted rich-club coefficients and subgraph sizes

mod.wt The *weighted modularity*; i.e., the modularity calculated while taking into account edge weights

E.local.wt The average of the vertices' weighted `local efficiency`

E.global.wt The weighted `global efficiency`

diameter.wt The graph's `diameter`, taking into account edge weights

A.2 Vertex-level

degree

name The name of the brain region for each vertex

lobe The lobe membership (e.g., `Frontal`)

hemi The hemisphere; either L, R, or B (for "both")

lobe.hemi An integer corresponding to a combination of the `lobe` and `hemi` attributes

class The "class", if the atlas is `destrieux`. Either G (gyral), S (sulcal), or G_and_S (both)

network The "network", if the atlas is `dosenbach160`

x,y,z The spatial coordinates

x.mni,y.mni,z.mni The spatial coordinates (same as above)

color.lobe The colors corresponding to `lobe` membership

color.class The colors corresponding to `class` membership (if the atlas is `destrieux`)

color.network The colors corresponding to `network` membership (if the atlas is `dosenbach160`)

asymm Edge asymmetry for each vertex

dist For each vertex, the mean edge distance of its connections

dist.strength For each vertex, `dist` multiplied by the `degree`

knn Average nearest neighbor degree

Lp The vertices' average shortest path lengths

btwn.cent Betweenness centrality

ev.cent Eigenvector centrality

lev.cent Leverage centrality

hubs Binary vector; assigned “1” if the vertex’s `btwn.cent` is at least one standard deviation above the mean across vertices

k.core The vertex’s *core* membership

transitivity Transitivity

E.local The *local efficiency*

E.nodal The *nodal efficiency*

vulnerability

eccentricity The shortest path length from one vertex to the farthest other vertex in the graph

comm Integer vector of the vertices’ community membership

comp Integer vector of the vertices’ *connected component* membership

color.comm Colors corresponding to community membership

color.comp Colors corresponding to component membership

GC The *gateway coefficient*

PC The *participation coefficient*

z.score The *within-module degree z-score*

A.2.1 Weighted

strength

knn.wt Average *nearest neighbor* strength

s.core The vertices’ *s-core* membership

comm.wt The vertices’ (weighted) community membership

color.comm.wt The colors corresponding to weighted community membership

GC.wt The weighted version of the *gateway coefficient*

PC.wt The weighted version of the *participation coefficient*

z.score.wt The weighted version of the `within-module degree z-score`

transitivity.wt Weighted transitivity

E.local.wt The weighted local efficiency

E.nodal.wt The weighted nodal efficiency

Lp.wt The vertices' average shortest path lengths, taking into account edge weights

A.3 Edge-level

weight Edge weight

color.lobe The colors corresponding to `lobe` membership

color.class The colors corresponding to `class` membership (if the atlas is `destrieux`)

color.network The colors corresponding to `network` membership (if the atlas is `dosenbach160`)

color.comm The colors corresponding to *community* membership

color.comp The colors corresponding to *component* membership

color.comm.wt The colors corresponding to *weighted community* membership

dist The Euclidean distance of the edge

btwn Edge betweenness

B

Benchmarks

Most functions will run quickly on just about any machine, since `igraph` is based on C routines. Nevertheless, here is some benchmarking information. The more CPU cores you have, the better.

The timing of the graph algorithms is extremely fast for “small” graphs (e.g., with any atlas-based brain parcellation), and are generally going to take either $O(n)$ or $O(m)$ time, where n is the # of vertices, and m is the # of edges. The longest processing times will be [Random graph generation](#), [Bootstrapping](#), [Permutation Testing](#), and [Random Failure Analysis](#).

B.1 Since v1.0.0

I updated several functions for v1.0.0 which now run significantly faster. I list the speed increases for several functions and a few different graph sizes and densities in [Table B.1](#) (cortical thickness covariance; 68 vertices), [Table B.2](#) (DTI tractography; 76 vertices), and [Table B.3](#) (resting-state fMRI; 160 vertices). For a given graph and vertex measure, the improvements tend to be less than 1 second, but when repeated for a large number of subjects and densities/thresholds, can amount to a lot of saved time. Furthermore, speed improvements are larger for larger graphs. Finally, these improvements can add up considerably when doing, for example, permutation testing with thousands of repetitions.

All testing was done on the same system; i.e., CentOS 7.3.1611, 64-bit: Intel Core i7-6500U (4 cores @ 2.50 GHz). The tests were run on R version 3.3.3 (2017-03-06). For each function, I started a new instance of R and calculated the times using `microbenchmark`.

The speed improvements are most significant for `within_module_deg_z_score`, `edge_asymmetry`, `part_coeff`, and `centr_lev`, and increase with increasing vertex and edge counts. Random graph selection (controlling for clustering), with `sim.rand.graph.par`, shows the largest improvements in *absolute* time: generating 100 random graphs at a single density is **15 to 52** minutes faster. Since this is often repeated across several densities, the savings can reach several hours.

In the last section of [Table B.2](#) and [Table B.3](#), I show the timings for creating graphs and assigning attributes (via `set_brainGraph_attr`) for a group of 44 and 22 subjects, respectively, at 5 different densities. I used the new function argument `A`, supplying the weighted adjacency matrix (which we already create; see [Graph creation](#)). The speed increases range from about 40 to 60 seconds per threshold/density; this should scale linearly with an increase in subject numbers, and possibly supra-linearly with increase in graph size (vertex and edge counts).

B.1.1 Other benchmarks

[Table B.4](#), [Table B.5](#), and [Table B.6](#) list some runtimes for `brainGraph_GLM` and `mtpc`, respectively. The system is the same as above. For the GLM table, there are 2 groups and 156 subjects total. The graphs have 76 vertices (the `dkt.scgm` atlas). Where only 80 (or 103) subjects are mentioned, the atlas used was `dk.scgm`

Function	m (ρ)	# reps	Old	New	Speedup
edge_asymmetry (vertex)	114 (5.0%)	1000	0.1049	0.0021	50.5x
	616 (27.0%)	1000	0.1724	0.0026	67.0x
	1139 (50.0%)	1000	0.2316	0.0032	71.6x
edge_asymmetry (hemi)	114 (5.0%)	1000	0.0075	0.0032	2.34x
	616 (27.0%)	1000	0.0114	0.0046	2.49x
	1139 (50.0%)	1000	0.0176	0.0068	2.58x
vertex_spatial_dist	114 (5.0%)	1000	0.0619	0.0193	3.21x
	616 (27.0%)	1000	0.1041	0.0235	4.43x
	1139 (50.0%)	1000	0.1451	0.0272	5.33x
part_coeff	114 (5.0%)	1000	0.2050	0.0014	142x
	616 (27.0%)	1000	0.1255	0.0009	137x
	1139 (50.0%)	1000	0.1195	0.0008	141x
within-module degree z-score	114 (5.0%)	1000	0.0452	0.0013	34x
	616 (27.0%)	1000	0.0550	0.0007	76x
	1139 (50.0%)	1000	0.0576	0.0007	87x
centr_lev	114 (5.0%)	1000	0.0656	0.0009	71x
	616 (27.0%)	1000	0.0765	0.0012	64x
	1139 (50.0%)	1000	0.0788	0.0012	63x
local_efficiency	114 (5.0%)	1000	0.0851	0.0531	1.60x
	616 (27.0%)	1000	0.1255	0.0766	1.64x
	1139 (50.0%)	1000	0.1379	0.0873	1.58x
Random graphs (w/ clustering) 100 iter's	114 (5.0%)	100	953.609	56.977	16.74x
	616 (27.0%)	100	531.973	60.204	8.84x
	1139 (50.0%)	100	974.534	93.995	10.37x
Random graphs (w/ clustering) 250 iter's	114 (5.0%)	100	924.368	58.391	15.83x
	616 (27.0%)	100	1290.226	126.051	10.24x
	1139 (50.0%)	100	3359.081	253.283	13.26x

Table B.1: **Speed increases for a graph with 68 vertices.** All times are the median (in seconds) based on the number of repetitions.
 m : # of edges; ρ : graph density

which has 82 vertices. In some cases, v2.0.0 is actually faster (despite the more complex randomization algorithm); this improvement adds up when multiple contrasts are used in a single function call.

For some other functions:

- The `dk` atlas (**68 vertices**) for cortical thickness covariance:
 - *Random graph generation (control for clustering)*: for 1 group and 1 density (22%), generating 1,000 random graphs, total processing time was **9 min. 58 sec.**. Compared to a runtime of 5 hr. 17 min. in the older version (which was on a machine with more and faster CPU cores), this is a more than **32x** speed increase.
- The `dkt` atlas (**62 vertices**) for cortical thickness covariance:
 - *Random graph generation (control for clustering)*: for 2 groups and 44 densities (from 7-50%, steps of 1%), and with 100 random graphs generated (per density per group) (i.e., 8,800 graphs), total processing time was (estimated to be) **2 hr. 29 min.**. The # of iterations per graph was limited to 100 (the default value for the `max.iters` argument to `sim.rand.graph.clust`; see **Random**

graph generation). Compared to a runtime of 18 hr. 33 min. in the older version (and on a machine with more and faster CPU cores), this is a **7.5x** speed increase.

- The `dk.scgm` atlas ([82 vertices](#)) for DTI tractography:
 - *Random graph generation*: for 3 groups, 30 thresholds, and 104 subjects total, generating 100 random graphs for all combinations (i.e., 312,000 graphs) took **6 hr. 6 min.**. Total disk space used was **4.0 GB**. The bulk of the increase in processing time was due to several of the thresholds containing *unconnected graphs*; for the connected graphs, generating 100 random graphs for 36 subjects took between **0 min. 42 sec. – 1 min. 32 sec.** per threshold.
 - *Random graph generation*: for 3 groups and 30 thresholds, generating 1,000 random graphs for all combinations (i.e., 90,000 graphs) took **2 hr. 29 min.**. Total disk space used was **1.2 GB**.
 - *NBS*: for 2 groups, with 80 subjects total; 5,000 permutations took from **2 min. 56 sec. – 9 min. 37 sec.** (depending on the overall connectivity density, which in this study ranged from 5.6% – 31.1%).

Function	m (ρ)	# reps	Old	New	Speedup
edge_asymmetry (vertex)	146 (5.1%)	1000	0.2103	0.0028	74x
	342 (12.0%)	1000	0.2672	0.0035	77x
	703 (24.7%)	1000	0.3374	0.0042	81x
edge_asymmetry (hemi)	146 (5.1%)	1000	0.0096	0.0041	2.34x
	342 (12.0%)	1000	0.0151	0.0062	2.43x
	703 (24.7%)	1000	0.0246	0.0099	2.48x
vertex_spatial_dist	146 (5.1%)	1000	0.0634	0.0276	2.3x
	342 (12.0%)	1000	0.0731	0.0303	2.4x
	703 (24.7%)	1000	0.0847	0.0339	2.5x
part_coeff	146 (5.1%)	1000	0.1671	0.0011	151x
	342 (12.0%)	1000	0.1350	0.0010	134x
	703 (24.7%)	1000	0.1327	0.0010	134x
within-module degree z-score	146 (5.1%)	1000	0.0893	0.0009	96x
	342 (12.0%)	1000	0.0935	0.0008	117x
	703 (24.7%)	1000	0.0974	0.0007	131x
centr_lev	146 (5.1%)	1000	0.1201	0.0014	87x
	342 (12.0%)	1000	0.1220	0.0014	86x
	703 (24.7%)	1000	0.1228	0.0015	82x
local efficiency (weighted)	146 (5.1%)	1000	0.1717	0.1330	1.29x
	342 (12.0%)	1000	0.1813	0.1374	1.32x
	703 (24.7%)	1000	0.1912	0.1466	1.30x
local efficiency (unweighted)	146 (5.1%)	1000	0.1612	0.1275	1.26x
	342 (12.0%)	1000	0.1688	0.1311	1.29x
	703 (24.7%)	1000	0.1716	0.1365	1.26x
set_brainGraph_attr (44 subjects)	146 (5.1%)	1	61.617	25.148	2.45x
	240 (8.4%)	1	61.317	26.197	2.34x
	342 (12.0%)	1	62.001	26.825	2.31x
	516 (18.1%)	1	65.889	30.571	2.16x
	703 (24.7%)	1	67.703	32.979	2.05x

Table B.2: **Speed increases for a graph with 76 vertices.** All times are the median (in seconds) based on the number of repetitions.

m: # of edges; ρ : graph density

Function	m (ρ)	# reps	Old	New	Speedup
edge_asymmetry (vertex)	549 (4.3%)	1000	0.3362	0.0025	132x
	1623 (12.8%)	1000	0.4526	0.0025	178x
	3955 (31.1%)	1000	0.7378	0.0031	236x
edge_asymmetry (hemi)	549 (4.3%)	1000	0.0085	0.0034	2.47x
	1623 (12.8%)	1000	0.0125	0.0051	2.44x
	3955 (31.1%)	1000	0.0207	0.0085	2.43x
vertex_spatial_dist	549 (4.3%)	1000	0.2073	0.0408	5.1x
	1623 (12.8%)	1000	0.3445	0.0468	7.4x
	3955 (31.1%)	1000	0.6145	0.0553	11.0x
part_coeff	549 (4.3%)	1000	0.4561	0.0022	211x
	1623 (12.8%)	1000	0.3961	0.0015	264x
	3955 (31.1%)	1000	0.4653	0.0014	343x
within-module degree z-score	549 (4.3%)	1000	0.1229	0.0013	96x
	1623 (12.8%)	1000	0.1461	0.0010	135x
	3955 (31.1%)	1000	0.1884	0.0010	178x
centr_lev	549 (4.3%)	1000	0.1801	0.0029	62x
	1623 (12.8%)	1000	0.1892	0.0032	60x
	3955 (31.1%)	1000	0.1857	0.0033	56x
local efficiency (weighted)	549 (4.3%)	1000	0.3132	0.1824	1.37x
	1623 (12.8%)	1000	0.3592	0.2114	1.70x
	3955 (31.1%)	1000	0.4999	0.3151	1.59x
local efficiency (unweighted)	549 (4.3%)	1000	0.2773	0.1571	1.77x
	1623 (12.8%)	1000	0.3357	0.1949	1.72x
	3955 (31.1%)	1000	0.3353	0.2142	1.57x
set_brainGraph_attr (22 subjects)	549 (4.3%)	1	62.012	23.034	2.69x
	963 (7.6%)	1	75.234	25.453	2.96x
	1623 (12.8%)	1	72.126	28.202	2.56x
	2583 (20.3%)	1	82.864	31.963	2.59x
	3955 (31.1%)	1	97.681	39.048	2.50x

Table B.3: **Speed increases for a graph with 160 vertices.** All times are the median (in seconds) based on the number of repetitions.

m: # of edges; ρ : graph density

Level	# reps	Runtime (s)
graph	10,000	8.703
	10,000	11.219
	10,000	11.479
vertex	5,000	35.235
	5,000	35.098
	5,000	34.759

Table B.4: **Runtimes for brainGraph_GLM for graphs with 76 vertices.** These analyses were for 156 subjects in 2 groups.

Level	N	Runtime (s)	
		80 sub.	156 sub.
Graph	5,000	73.618	70.631
		73.373	88.962
		74.366	93.684
Vertex	1,000	86.427	89.560
		87.291	90.917
Vertex	2,000	178.248	202.044
		179.312	205.846
		448.524	502.414
	5,000	440.946	507.429

Table B.5: **Runtimes for mtpc for graphs with 76 or 82 vertices and 15 thresholds.**

N: # of permutations

Level	Runtime (s)		
	1 con.	2 con.	3 con.
Graph	153.623	281.572	457.312
	152.193	281.152	435.029
	154.747	285.569	437.076
	159.749	280.483	456.382
	157.722	283.426	428.564
Vertex	711.027	757.598	1947.120
	688.052	760.485	1971.640
	704.171	784.705	1978.283
	683.840	785.550	
	714.713	792.197	

Table B.6: **Runtimes for mtpc for graphs with 82 vertices and 30 thresholds.** There were 10,000 and 5,000 permutations for graph- and vertex-level analyses, respectively. The analyses for 1 and 3 contrasts contained data for 103 subjects; for 2 contrasts there were only 44, indicating an effect of # of subjects in addition to # of contrasts, # of thresholds, and # of permutations..
con: contrasts

Level	# outcomes	# mediators	N	Runtime (s)
1	1	1		32.503
			1,000	33.458
				32.694
	5,000	6		123.318
				129.577
				127.223
Vertex				
3	100	6		222.840
				223.920
				224.796
	1,000	6		669.151
				649.174
				647.234

Table B.7: **Runtimes for mediation for graphs with 82 vertices.** These analyses were for 71 subjects in 2 groups. In the case that the # of outcomes and # of mediators is more than 1, the runtime is for the entire loop across the combination.

N: # of bootstrap samples

C

Computing environment

This document was typeset with L^AT_EX (through the `knitr` package in R), using the `book` document class. The main typeface is Computer Modern, designed by Donald Knuth for T_EX. The bibliography was typeset with BibT_EX using the `natbib` package.

The following versions of R, the operating system, and R packages used include:

- R version 3.4.3 (2017-11-30), x86_64-redhat-linux-gnu
- Running under: CentOS Linux 7 (Core)
- Matrix products: default
- BLAS/LAPACK: /usr/lib64/R/lib/libRblas.so
- Base packages: base, datasets, graphics, grDevices, methods, parallel, stats, utils
- Other packages: brainGraph 2.0.2, cairoDevice 2.24, colorout 1.1-2, data.table 1.10.4-3, doMC 1.3.5, foreach 1.4.4, ggplot2 2.2.1.9000, gridExtra 2.3, igraph 1.1.2, iterators 1.0.9, knitr 1.20, nvimcom 0.9-62, pacman 0.4.6, permute 0.9-4, plyr 1.8.4, RGtk2 2.20.34, setwidth 1.0-4
- Loaded via a namespace (and not attached): abind 1.4-5, acepack 1.4.1, ade4 1.7-10, backports 1.1.0, base64enc 0.1-3, bitops 1.0-6, boot 1.3-20, checkmate 1.8.2, cluster 2.0.6, codetools 0.2-15, colorspace 1.3-1, compiler 3.4.3, digest 0.6.15, evaluate 0.10, expm 0.999-2, foreign 0.8-69, Formula 1.2-1, ggrepel 0.7.0, grid 3.4.3, gtable 0.2.0, highr 0.6, Hmisc 4.1-1, htmlTable 1.11.2, htmltools 0.3.6, htmlwidgets 0.9, labeling 0.3, lattice 0.20-35, latticeExtra 0.6-28, lazyeval 0.2.1, lme4 1.1-15, lpSolve 5.6.13, magrittr 1.5, MASS 7.3-48, Matrix 1.2-12, mediation 4.4.6, minqa 1.2.4, munsell 0.4.3, mvtnorm 1.0-6, nlme 3.1-131, nloptr 1.0.4, nnet 7.3-12, oro.nifti 0.9.1, pillar 1.1.0, pkgconfig 2.0.1, RColorBrewer 1.1-2, Rcpp 0.12.15, RcppEigen 0.3.3.4.0, rlang 0.2.0, RNifti 0.7.1, rpart 4.1-11, rstudioapi 0.7, sandwich 2.4-0, scales 0.5.0.9000, splines 3.4.3, stringi 1.1.6, stringr 1.3.0, survival 2.41-3, tibble 1.4.2, tools 3.4.3, withr 2.1.1.9000, zoo 1.8-0

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