BrainSuite Statistics toolbox in R (bssr)

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outline

- Introduction to **bssr**
- Checking the **bssr** installation
- Tutorial for running Statistical Analysis
    - volumetric analysis — sMRI
    - surface based analysis — cortical thickness
    - volumetric analysis — dMRI
    - ROI analysis — cortical, subcortical and diffusion measures

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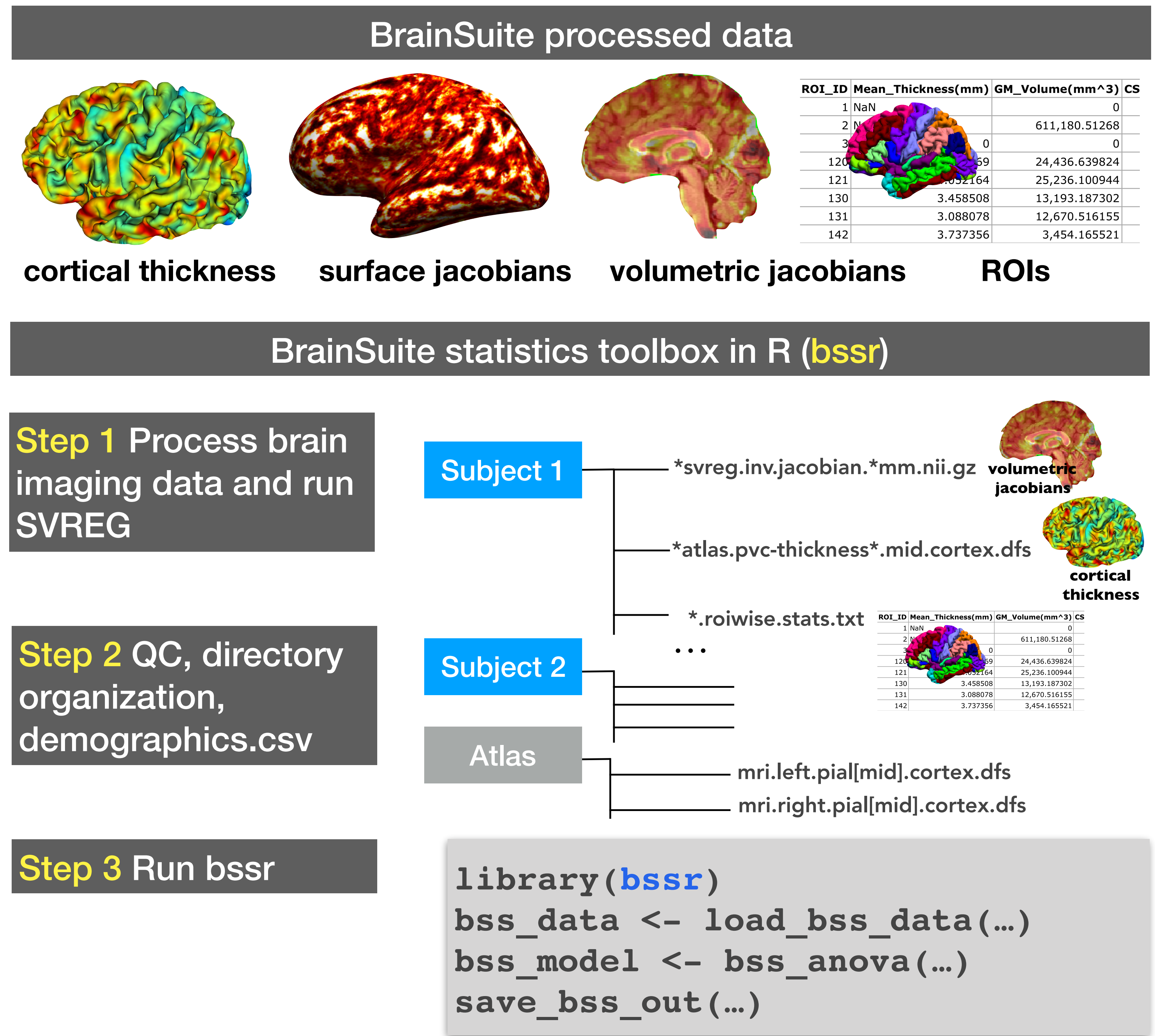
brainsuite statistical toolbox in R*

- Performs structural group analysis for cortical surfaces
- Implemented in R
- Cross-platform - Windows, Mac, Linux
- Offers following statistical methods
  - ANCOVA, GLM, correlations
  - Provision for Multiple testing - FDR, permutations
- Uses R data.table to efficiently vectorize operations



* Open Source - Distributed under GPL v2

i processed some data in BrainSuite...
now what ?

- Should I use cortical based morphometry or tensor based morphometry?

- What is the main effect of diagnosis on brain structure?

- How does cortical thickness relate to age?
    - Does the relationship change if gender is considered?
    - What if I add extra factors (covariates)?

i processed some data in BrainSuite…
now what ?

- How does a particular diagnosis influence volumetric changes in the brain?

- What if I have a hypothesized brain region of interest (ROI)?

- How to conduct a statistical analysis comparing brains of patients with healthy controls in a population?

frequently used statistical methods

- General Linear Modeling
- ANOVA — compare population means, 1-way, 2-way
- General Linear Mixed Modeling

Fundamental tool: Linear regression

linear regression

- Simple linear regression

$$Y = \beta_0 + \beta_1 X + \epsilon$$

- Multiple linear regression

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots + \epsilon$$

Assumptions

- Linearity
- Homoscedasticity
- Normality
- Independence

Goal: Choose the parameters β_i to minimize ϵ

model inference

- Which model is better?

- For example

    - Is cortical thickness affected by Age and/or Sex?

model 1: $\text{Thickness} = \beta_0 + \beta_1 \text{Age} + \epsilon$

model 2: $\text{Thickness} = \beta_0 + \beta_1 \text{Sex} + \epsilon$

model 3: $\text{Thickness} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{Sex} + \epsilon$

model inference

- Modified question
  - Is cortical thickness affected by Age when controlling for Sex?

full model: $\text{Thickness} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{Sex} + \epsilon$

  - Could have stopped here, but …

null model: $\text{Thickness} = \beta_0 + \beta_1 \text{Sex} + \epsilon$

… we will do a model comparison

```
compare(fullmode, nullmodel)
```

brainsuite statistical toolbox in R*

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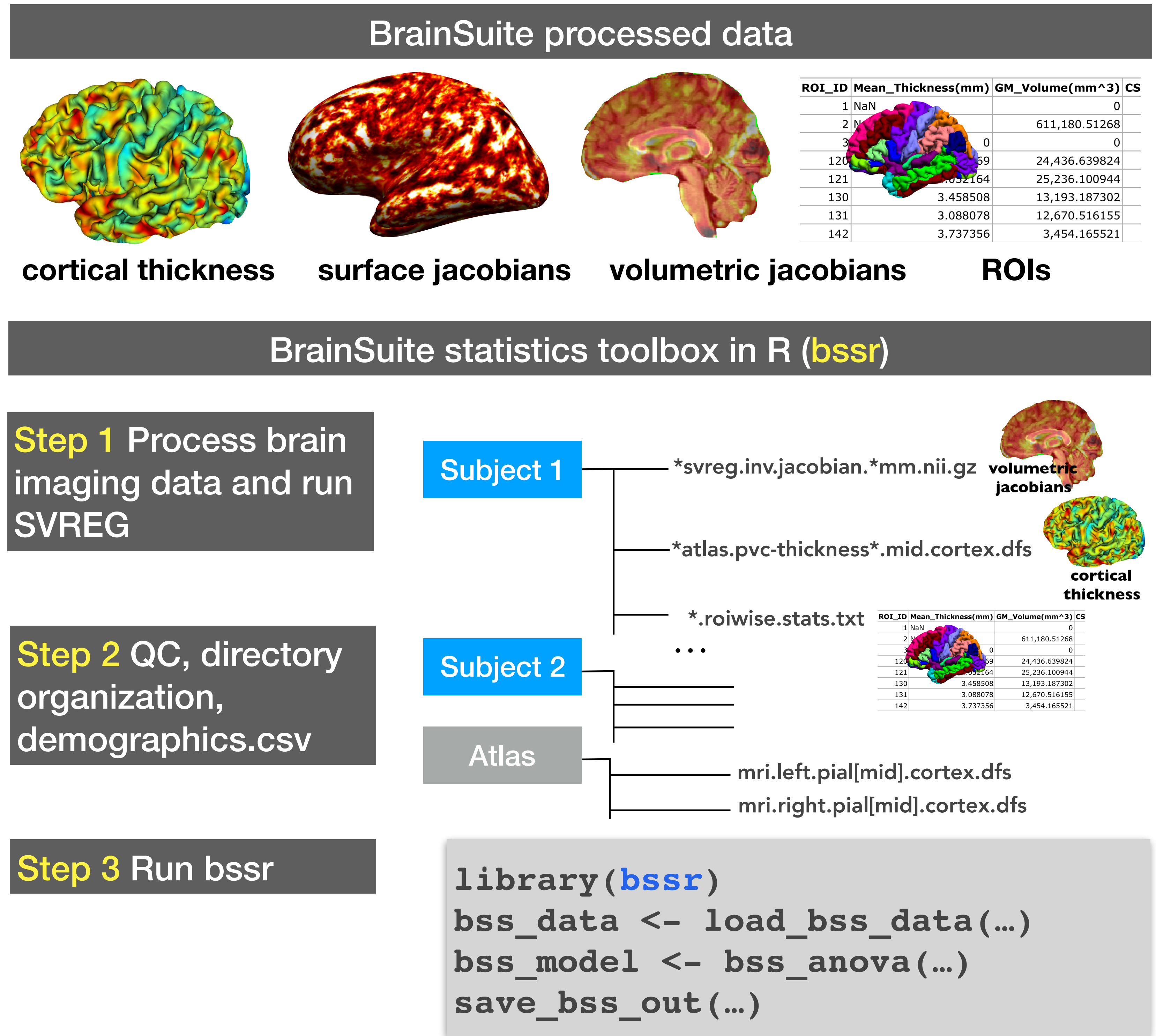

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notes on bssr installation

Ensure R/RStudio is installed

Download bssr.zip from http://brainsuite.org/bssr and extract

Open RStudio and install **`devtools`**

```
install.packages("devtools")
```

Install bssr

```
devtools::install("\path\to\bssr")
```

check your bssr installation

Open RStudio

```
library(bssr)

get_brainsuite_install_path()
```

to get help

```
?bssr
```

bssr {bssr} R Documentation

bssr: BrainSuite Statistics toolbox

Description

The BrainSuite Statistics toolbox allows the application of advanced statistical models to volumetric image, cortical surface and sulcal curve based outputs generated from BrainSuite. This enables population or group analysis of cortical or sulcal morphology. Available statistical models/tests are: Pearson correlation General linear model ANOVA Paired and Independent samples t-test

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[Package *bssr* version 0.1.1 Index]

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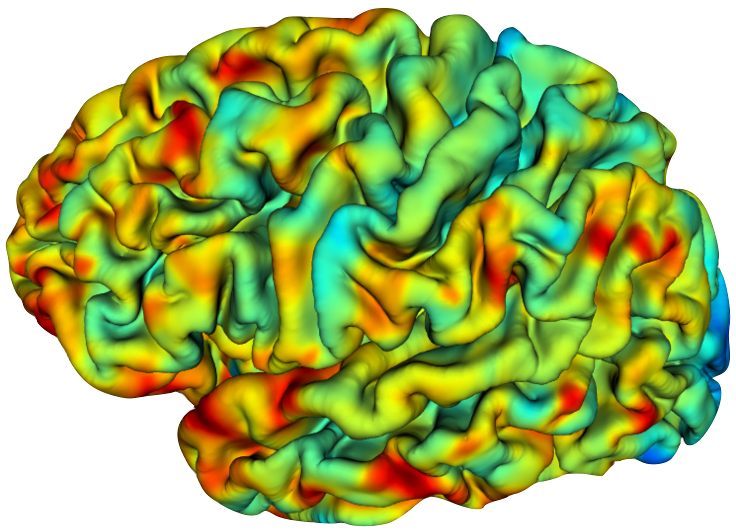
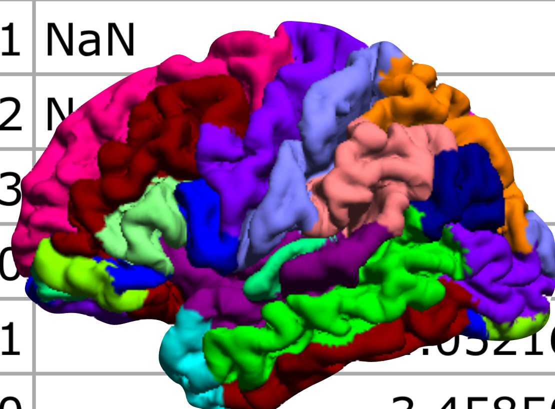
neuroimaging phenotypes (svreg)



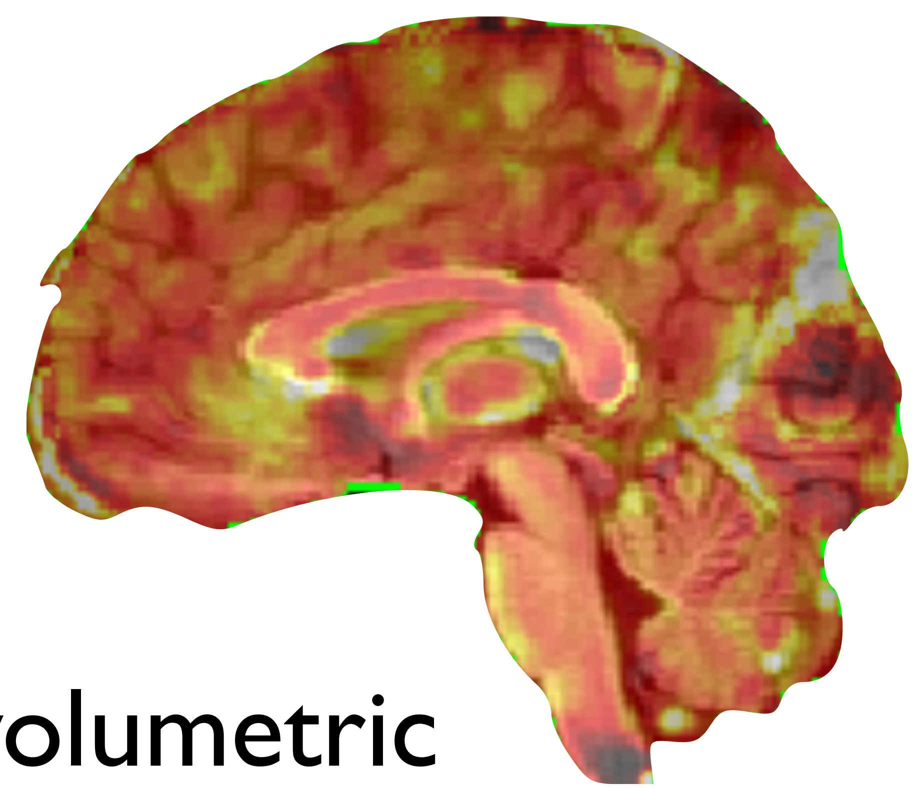
cortical thickness

surface jacobians

ROI_ID	Mean_Thickness(mm)	GM_Volume(mm^3)	CS
1	NaN	0	
2	[illegible]	611,180.51268	
3	0	0	
120	[illegible]	24,436.639824	
121	[illegible]	25,236.100944	
130	3.458508	13,193.187302	
131	3.088078	12,670.516155	
142	3.737356	3,454.165521	



ROIs



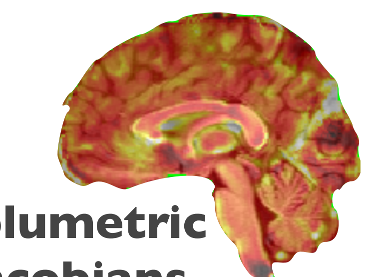
volumetric jacobians

before running bss

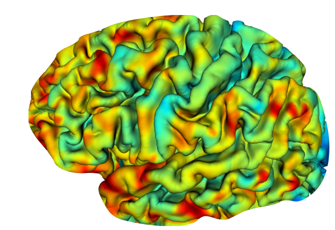
Data Requirements:

- Process Cortical Surface extraction and execute svreg using BrainSuite
- The processed directory will have the following structure

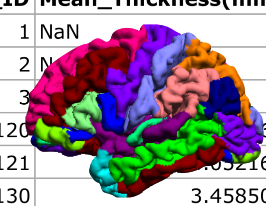
Subject 1
- *svreg.inv.jacobian.*mm.nii.gz



- *atlas.pvc-thickness*.mid.cortex.dfs



- *.roiwise.stats.txt



ROI_ID	Mean_Thickness(mm)	GM_Volume(mm^3)	CS
1	NaN	0	
2	[illegible]	611,180.51268	
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120	[illegible]	24,436.639824	
121	[illegible]	25,236.100944	
130	3.458508	13,193.187302	
131	3.088078	12,670.516155	
142	3.737356	3,454.165521	

ROIs

. . .

Subject 2

Atlas
- mri.left.pial[mid].cortex.dfs
- mri.right.pial[mid].cortex.dfs

smoothing data before analysis

- Why should smoothing be performed?
    - Improve signal/noise ratio (SNR)
    - Regularize anatomical misalignments
    - Improve sensitivity of detection (fMRI activations)
    - Boost statistical power
    - RFT type approaches — required

but don't go overboard — may lose signal if you oversmooth

3 step process for running bss

Load bssr package

```
library(bssr)
```

Load data

```
bss_data <- load_data(type=,…)
```

Specify the model/test

```
bss_model <- bss_anova(main_effect=,
                           covariates=, bss_data)
bss_model <- bss_corr(corr_var=, bss_data)
bss_model <- bss_ttest(group_var=, bss_data, paired=)
```

Save statistical outputs

```
save_bss_out(bss_data, bss_model, outdir=)
```

outputs from bss

- For ANOVA

1. p-values for main effect
2. adjusted (FDR) p-values for main effect

- For correlation analysis

1. Pearson correlation coefficient mapped on atlas
2. masked correlation coefficient after FDR
3. p-values denoting significance of correlation
4. adjusted (after FDR) p-values

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data: Rockland 25 dataset – processing parameters

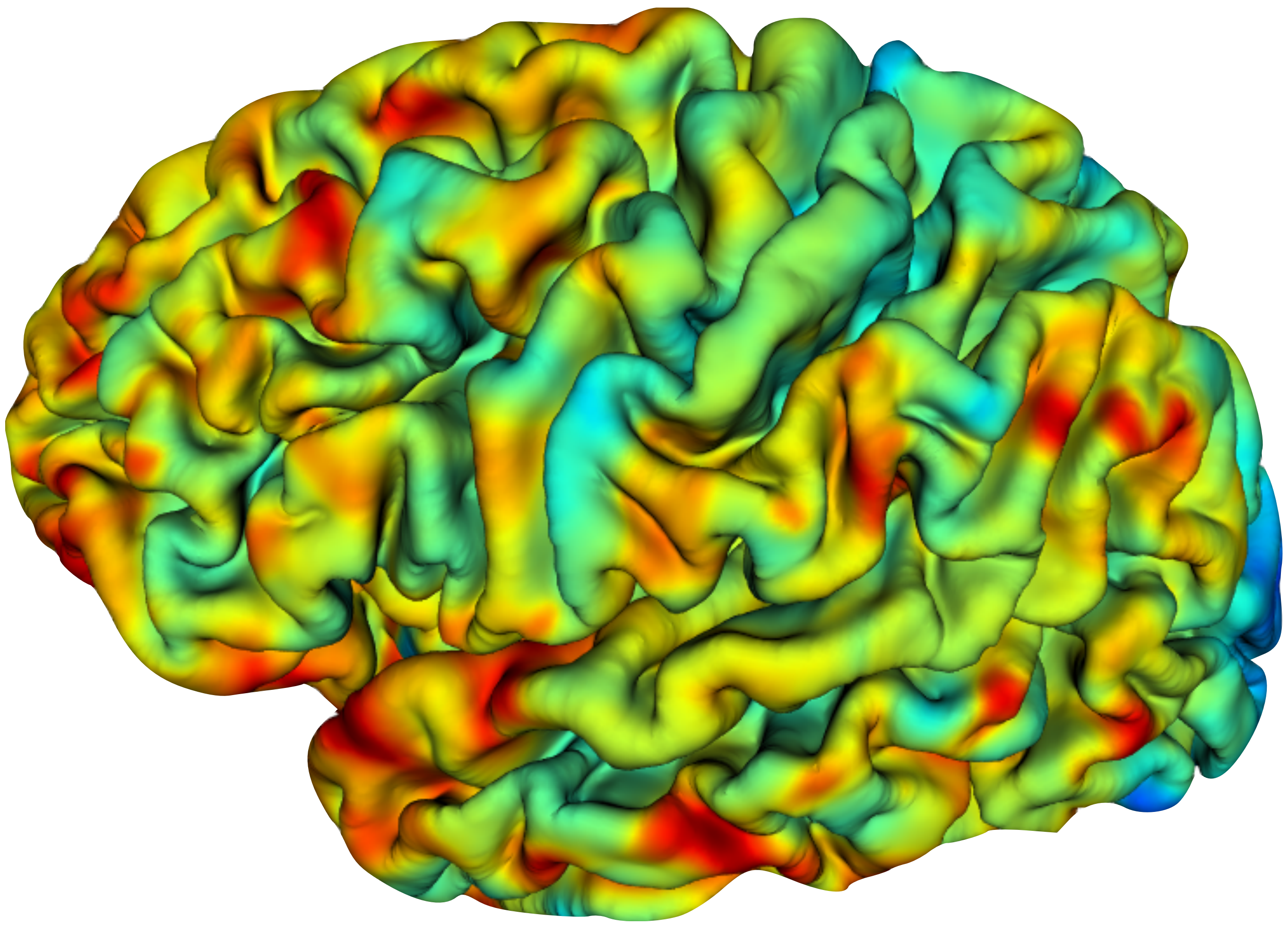
http://fcon_1000.projects.nitrc.org/indi/enhanced/studies.html

- Raw MRI data underwent skull stripping, bias field correction, WM/GM segmentation, and cortical surface extraction
- All subjects were registered to BrainSuiteAtlas1 using SVREG
- Diffusion Processing was done using BDP
- Cortical thickness was smoothed at 5mm kernel size
- Volumetric Jaocbian determinants were smoothed at 2mm kernel size
- Fractional Anisotropy was smoothed at 2mm kernel size

check the data

- Make sure SVREG outputs exist
- Make sure a valid demographics file (tsv or csv) exists

cortical thickness analysis



cortical thickness

cortical thickness analysis

- ANOVA for left hemisphere
  - Effect of age on cortical thickness when controlled for sex
- Correlation for right hemisphere
  - Correlation of age with cortical thickness

cortical thickness analysis

- ANOVA for left hemisphere
  - Effect of age on cortical thickness when controlled for sex

Step 1

```
bss_data <- load_bss_data(type="cbm",
       subjdir = "~/Desktop/Rockland25data",
       csv = "~/Desktop/Rockland25data/Rockland25.tsv",
       hemi="left", smooth=5)
```

Step 2

```
bss_model <- bss_anova(main_effect = "age",
                             covariates = "sex",
                                 bss_data = bss_data)
```

Step 3

```
save_bss_out(bss_data, bss_model,
                    outdir="~/Desktop/cbm_anova")
```

cortical thickness – visualization of results

Visualize in BrainSuite

For p-values

- Load `*_log_pvalues.dfs (log_pvalues_adjusted).dfs`
- It should automatically show color-coded log p-values

For t-statistics

- Load `*tvalues.dfs`
- It should automatically show color-coded t statistics

cortical thickness analysis

- Correlation for right hemisphere
  - Correlation of age with cortical thickness

Step 1

```
bss_data <- load_bss_data(type="cbm",
       subjdir = "~/Desktop/Rockland25data",
       csv = "~/Desktop/Rockland25data/Rockland25.tsv",
       hemi = "right", smooth=5)
```

Step 2

```
bss_model <- bss_corr(corr_var = "age", bss_data = bss_data)
```

Step 3

```
save_bss_out(bss_data, bss_model,
                    outdir="~/Desktop/cbm_corr")
```

cortical thickness – visualization of results

Visualize in BrainSuite

For correlations

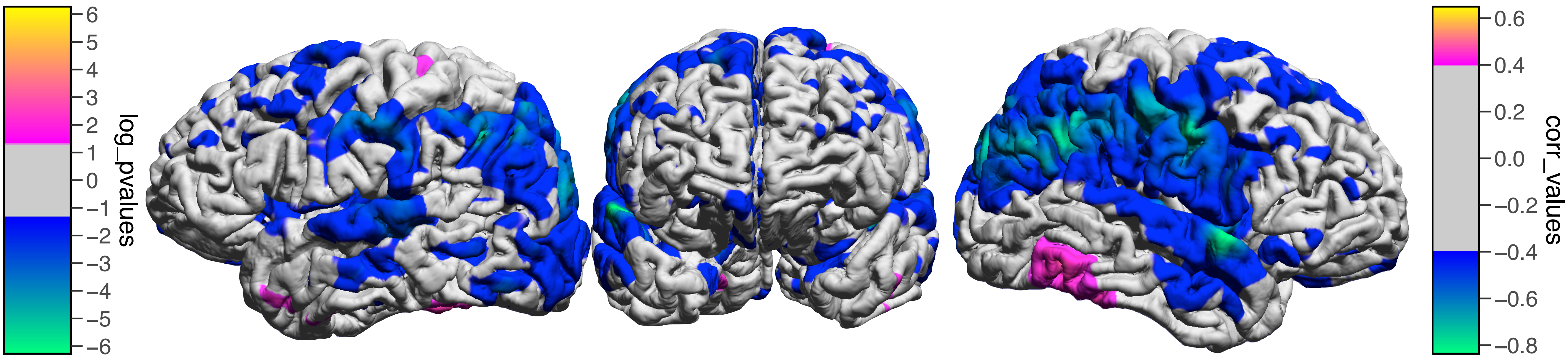
- Load `*corr_values.dfs`
- It should automatically show color-coded correlations

For p-values

- Load `*_log_pvalues.dfs (log_pvalues_adjusted).dfs`
- It should automatically show color-coded log p-values

cortical thickness – visualization of results

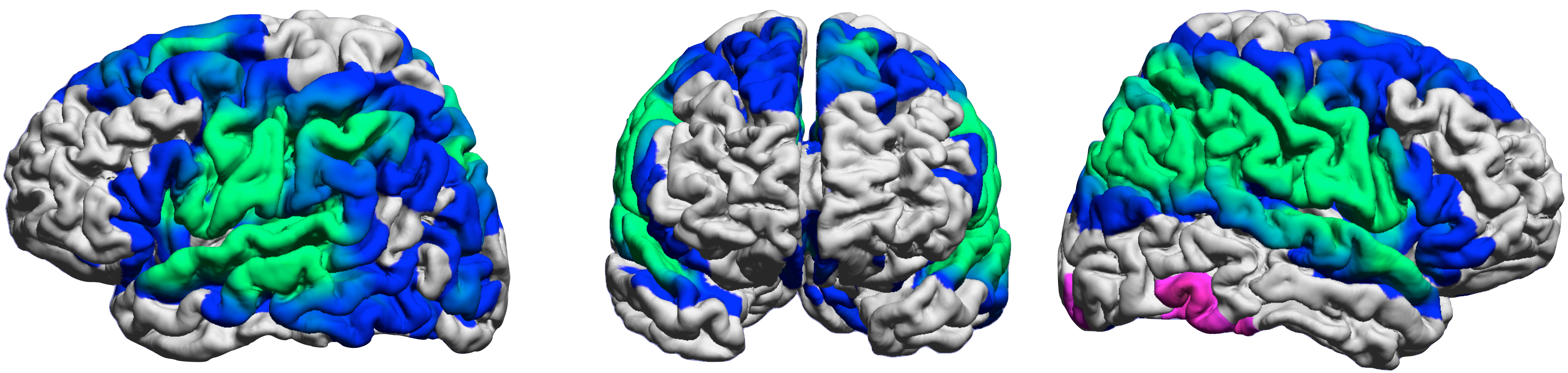
- Left hemisphere: ANOVA (Effect of age controlling for sex)
- Right hemisphere: Correlation (with age)



Rockland dataset: N=25, Age - 16~84 years, 18 f / 7 m

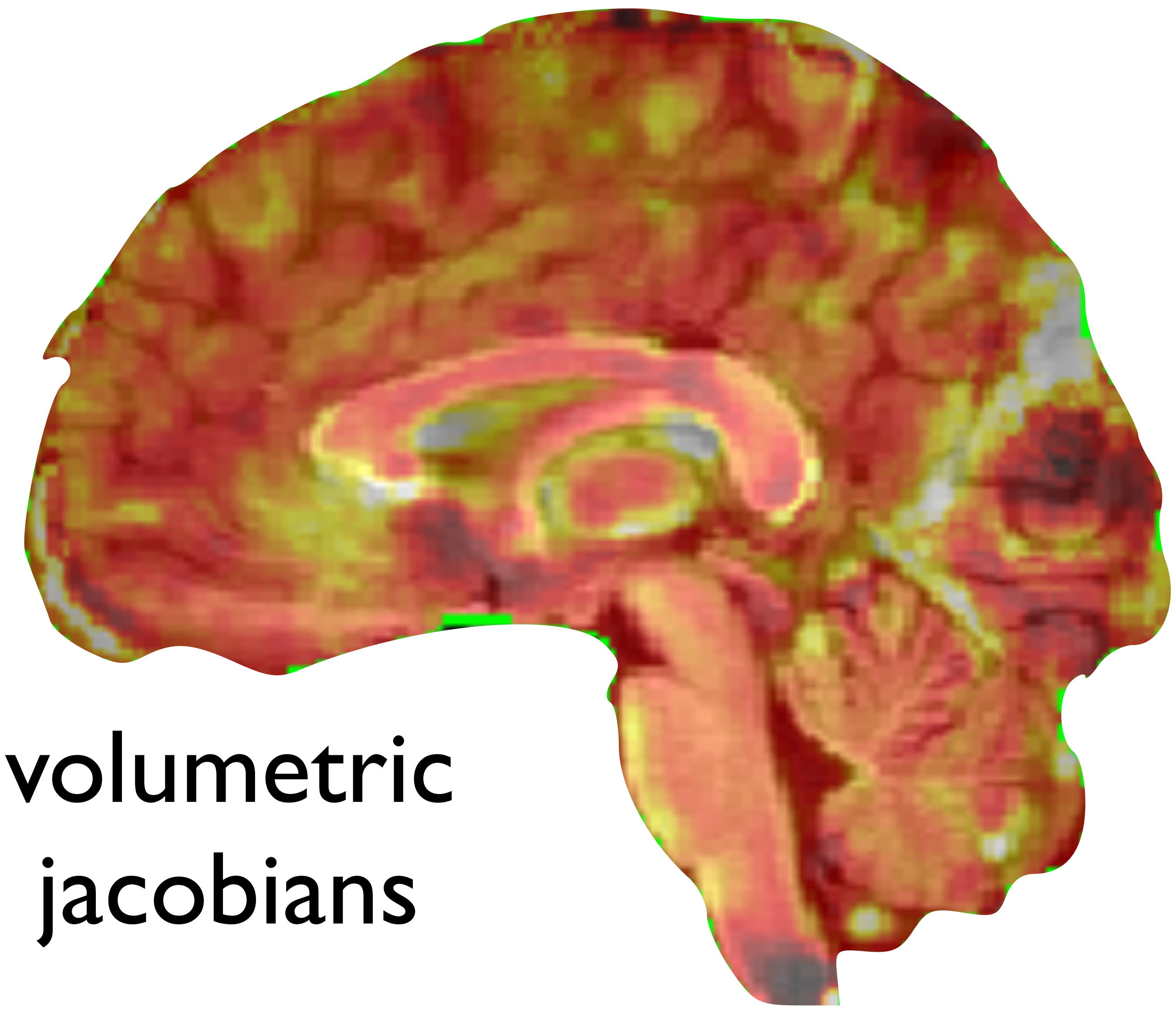
cortical thickness
– results on a larger dataset (N=160)

- Left hemisphere: ANOVA (Effect of age controlling for sex)
- Right hemisphere: Correlation (with age)



Rockland dataset: N=160, Age - 16~85 years, 98 f / 62 m

tensor-based morphometry



tensor-based morphometry

- ANOVA for volumetric Jacobians
  - Effect of age on cortical thickness when controlled for sex

Step 1

```
bss_data <- load_bss_data(type="tbm",
       subjdir = "~/Desktop/Rockland25data",
       csv = "~/Desktop/Rockland25data/Rockland25.tsv",smooth=2)
```

Step 2

```
bss_model <- bss_anova(main_effect = "age",
                             covariates = "sex",
                                 bss_data = bss_data)
```

Step 3

```
save_bss_out(bss_data, bss_model,
                  outdir="~/Desktop/tbm_anova")
```

tbm – visualization of results

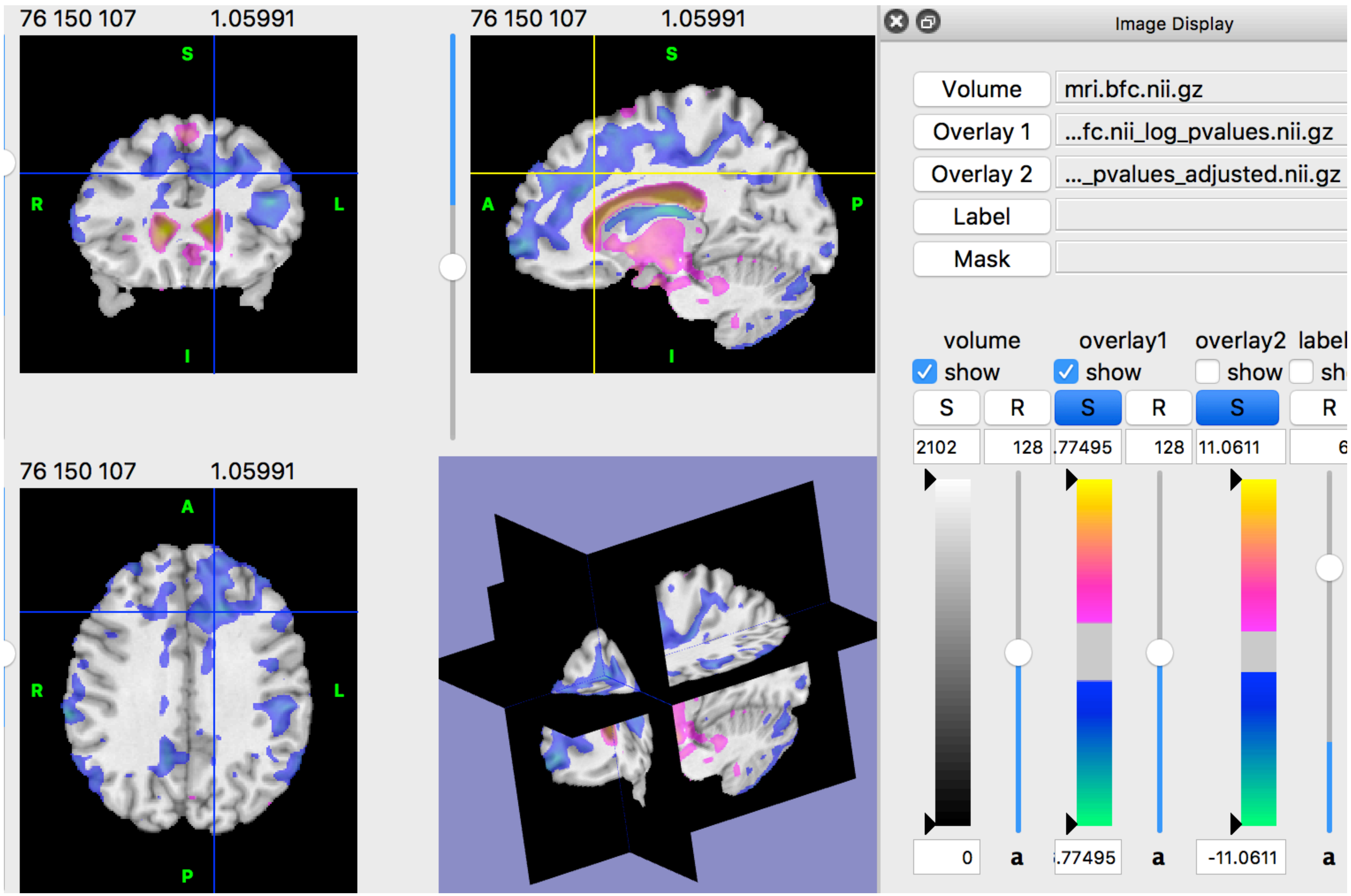
Visualize in BrainSuite

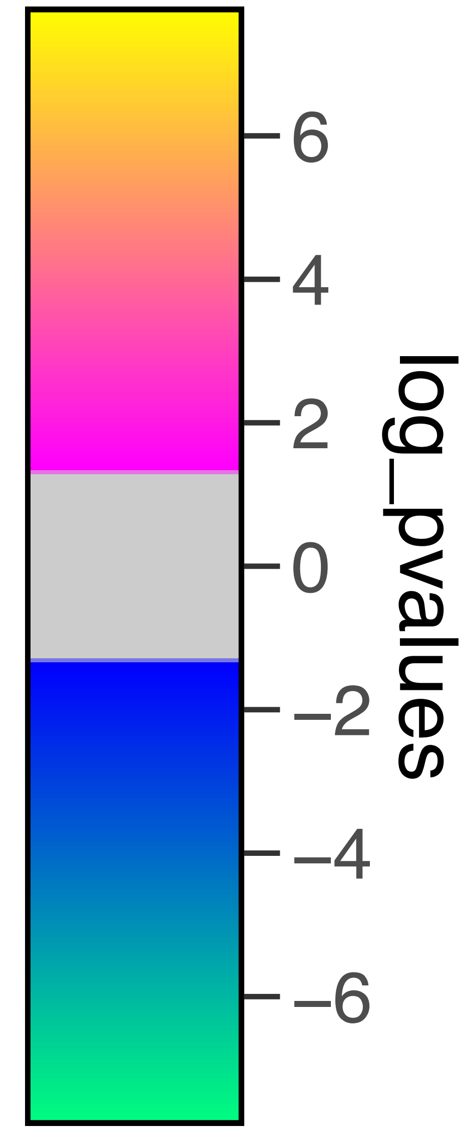
For p-values

- Load atlas `mri.bfc.nii.gz`
- Overlay `*_log_pvalues.nii.gz`
- Drag and drop the LUT `*log_pvalues.lut`
- Right click on the overlay colormap and select the LUT
- Click the "S" button to make the colormap symmetric

tbm – visualization of results

- ANOVA for volumetric Jacobians
  - Effect of age on cortical thickness when controlled for sex

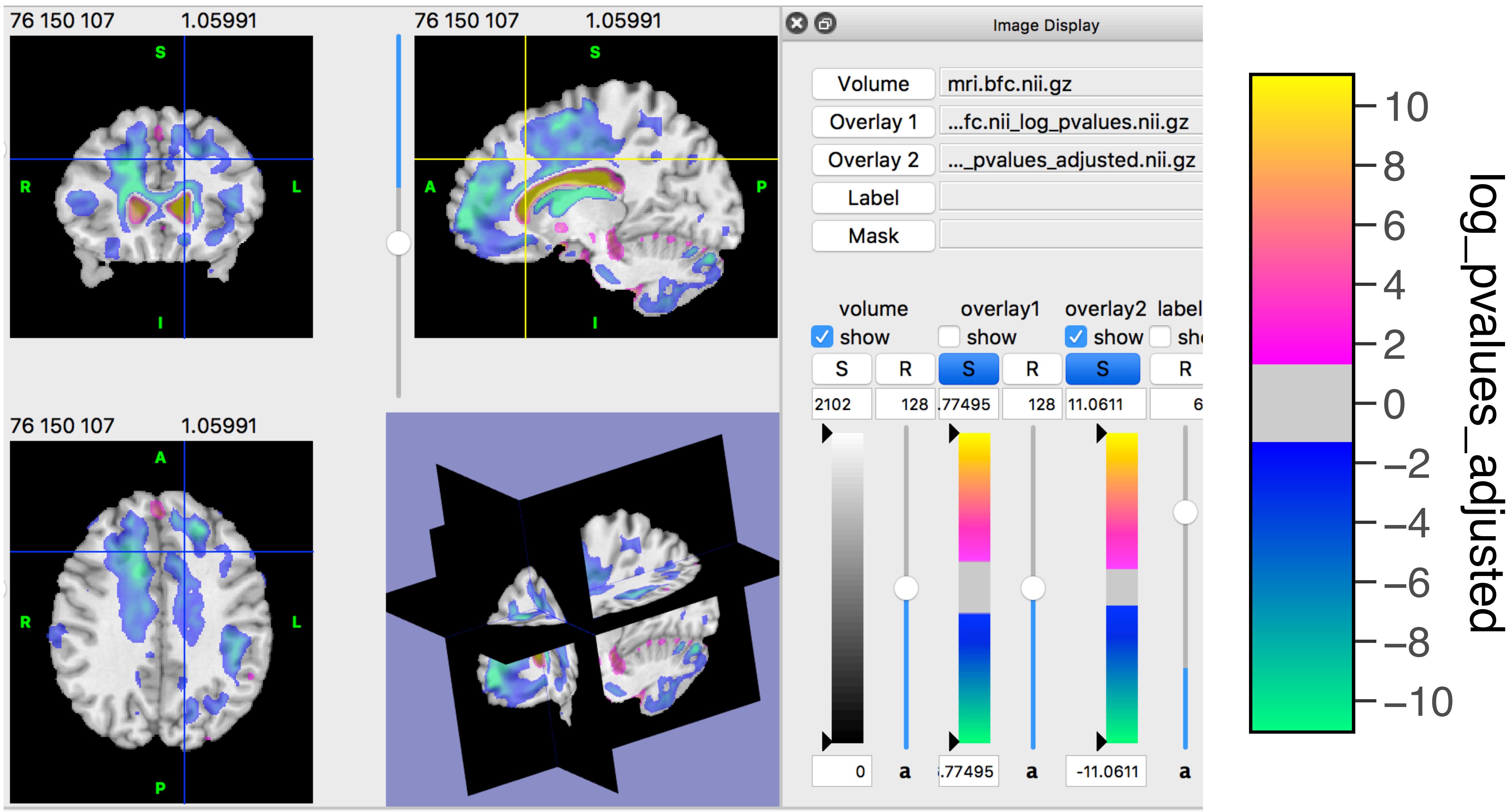




Rockland dataset: N=25, Age - 16~84 years, 18 f / 7 m

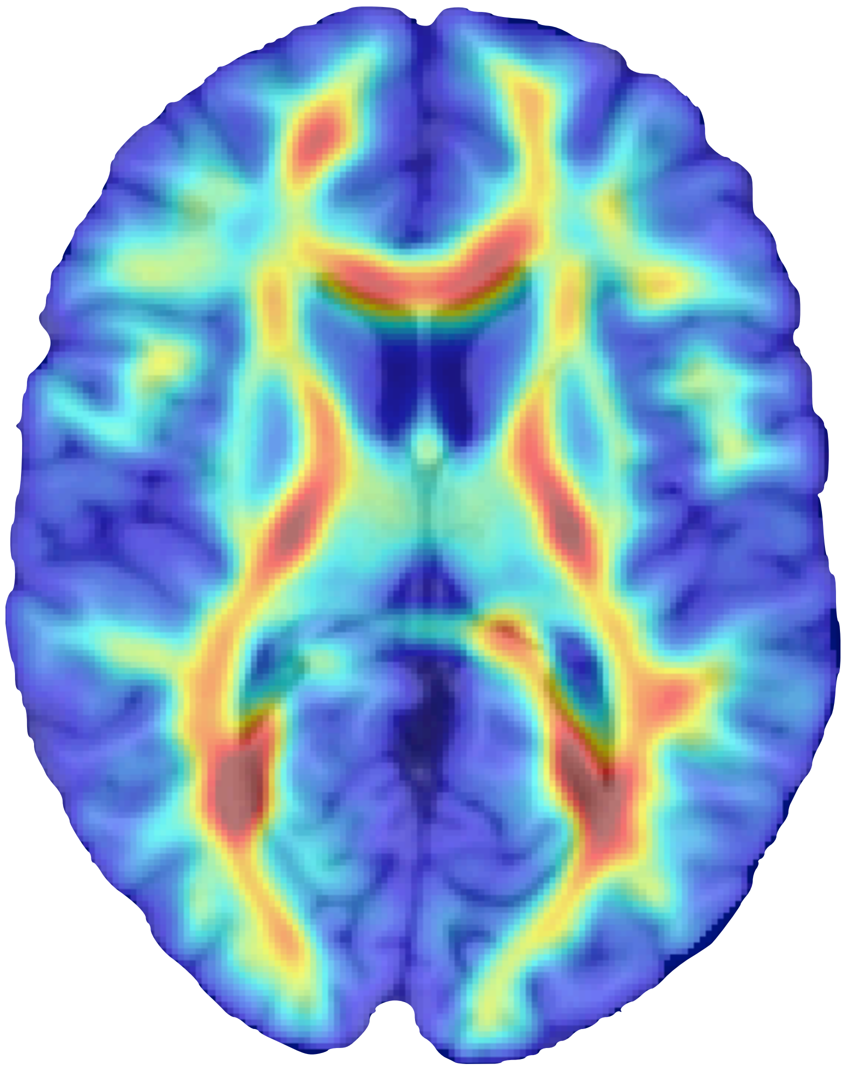
tbm – results on a larger dataset (N=160)

- ANOVA for volumetric Jacobians
  - Effect of age on cortical thickness when controlled for sex



Rockland dataset: N=160, Age - 16~85 years, 98 f / 62 m

analysis of diffusion parameter maps – FA



fractional anisotropy

diffusion parameter maps

- ANOVA for FA
  - Effect of age on FA when controlled for sex

Step 1

```
bss_data <- load_bss_data(type="dbm",
        subjdir = "~/Desktop/Rockland25data",
        csv = "~/Desktop/Rockland25data/Rockland25.tsv",
        measure="FA", smooth=2)
```

Step 2

```
bss_model <- bss_anova(main_effect = "age",
                             covariates = "sex",
                                 bss_data = bss_data)
```

Step 3

```
save_bss_out(bss_data, bss_model,
                  outdir="~/Desktop/FA_anova")
```

FA analysis – visualization of results

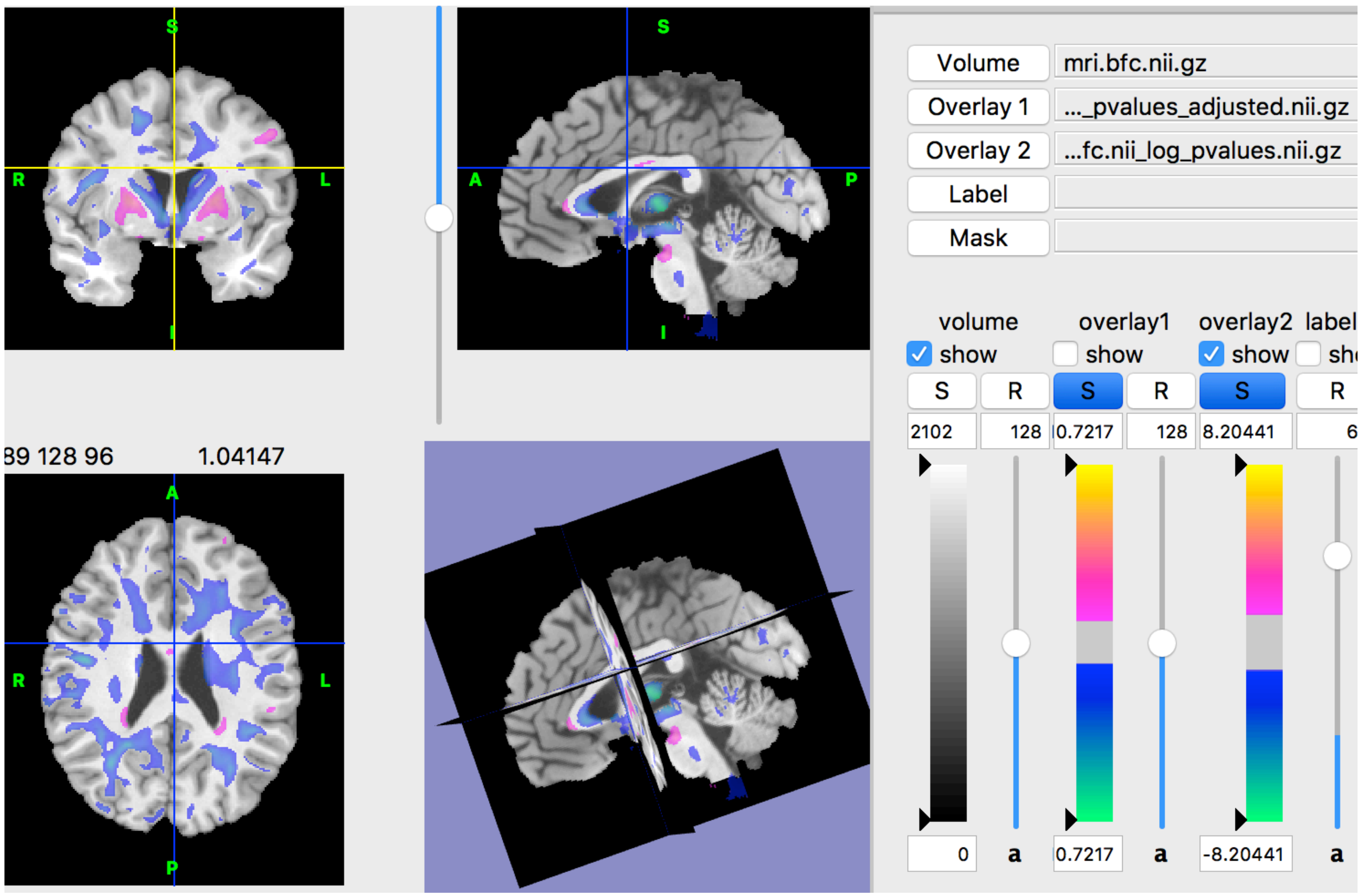
Visualize in BrainSuite

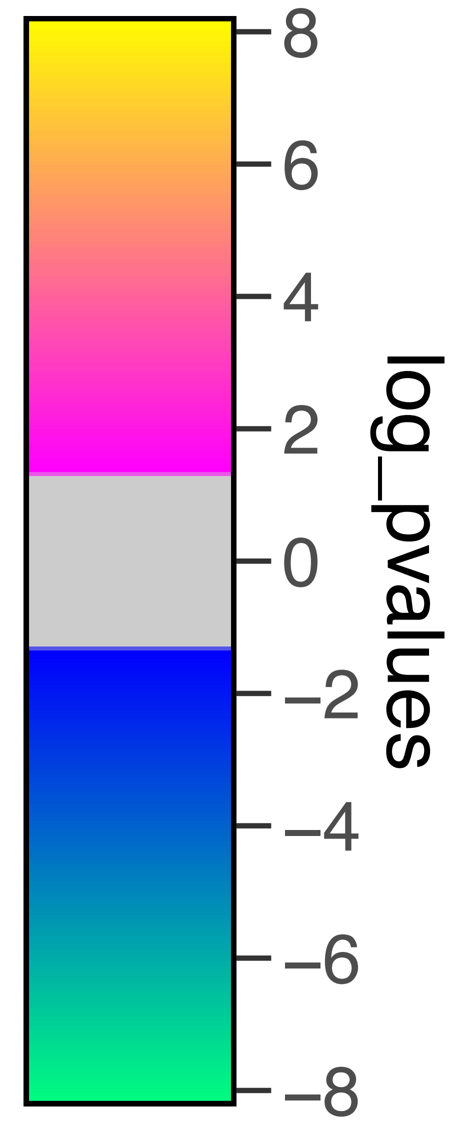
For p-values

- Load atlas `mri.bfc.nii.gz`
- Overlay `*_log_pvalues.nii.gz`
- Drag and drop the LUT `*log_pvalues.lut`
- Right click on the overlay colormap and select the LUT
- Click the "S" button to make the colormap symmetric

FA – visualization of results

- ANOVA for FA
  - Effect of **age** on FA when controlled for **sex**

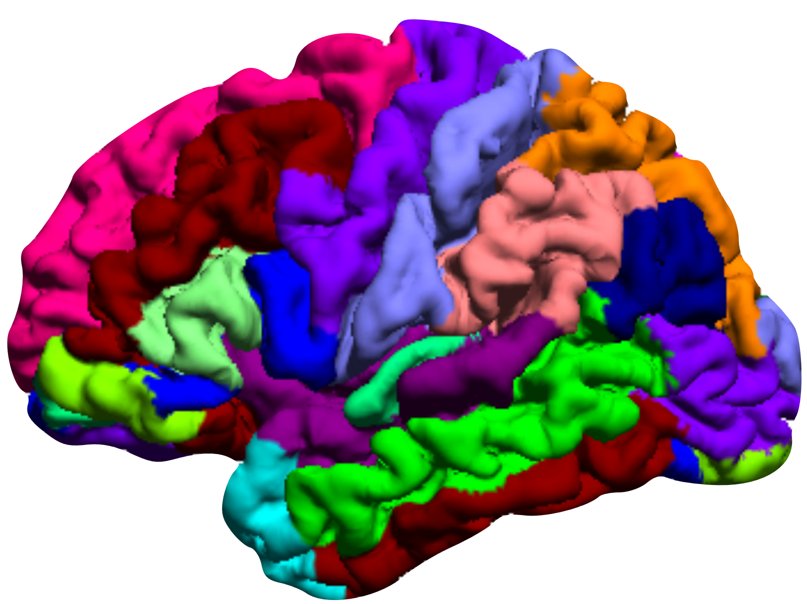




Rockland dataset: N=25, Age - 16~84 years, 18 f / 7 m

ROI analysis

```
<label id="346" tag="Amg" color="0xff8000" fullname="R. amygdala"/>
<label id="347" tag="Amg" color="0x7fff" fullname="L. amygdala"/>
<label id="400" tag="OL" color="0xafec0d" fullname="R. Occipital Lobe"/>
<label id="401" tag="OL" color="0x5013f2" fullname="L. Occipital Lobe"/>
<label id="420" tag="SOG" color="0xafec0d" fullname="R. lateral occipital lobe"/>
<label id="421" tag="SOG" color="0x5013f2" fullname="L. lateral occipital lobe"/>
<label id="422" tag="SOG" color="0x807f00" fullname="R. superior occipital gyrus"/>
<label id="423" tag="SOG" color="0x7f80ff" fullname="L. superior occipital gyrus"/>
<label id="424" tag="MOcG" color="0x80ff00" fullname="R. middle occipital gyrus"/>
<label id="425" tag="MOcG" color="0x7f00ff" fullname="L. middle occipital gyrus"/>
<label id="440" tag="IOG" color="0xafec0d" fullname="R. infero/mesial occipital lobe"/>
<label id="441" tag="IOG" color="0x5013f2" fullname="L. infero/mesial occipital lobe"/>
<label id="442" tag="IOG" color="0x7f00ff" fullname="R. inferior occipital gyrus"/>
<label id="443" tag="IOG" color="0x80ff00" fullname="L. inferior occipital gyrus"/>
<label id="444" tag="LiG" color="0x7f007f" fullname="R. lingual gyrus"/>
<label id="445" tag="LiG" color="0x80ff80" fullname="L. lingual gyrus"/>
<label id="446" tag="Cun" color="0xff80ff" fullname="R. cuneus"/>
<label id="447" tag="Cun" color="0x7f00" fullname="L. cuneus"/>
<label id="500" tag="Ins" color="0x7fff80" fullname="R. Insula"/>
<label id="501" tag="Ins" color="0x80007f" fullname="L. Insula"/>
<label id="600" tag="CGS" color="0xafec0d" fullname="R. Central gray structures"/>
<label id="601" tag="CGS" color="0x5013f2" fullname="L. Central gray structures"/>
<label id="610" tag="BG" color="0xafec0d" fullname="R. basal ganglia"/>
```



ROI_ID	Mean_Thickness(mm)	GM_Volume(mm^3)	CS
1	NaN	0	
2	NaN	611,180.51268	
3	0	0	
120	3.792369	24,436.639824	
121	4.052164	25,236.100944	
130	3.458508	13,193.187302	
131	3.088078	12,670.516155	
142	3.737356	3,454.165521	

ROI analysis

- ANOVA for Left Superior Frontal gyrus
  - Effect of age on thickness of ROI 121 when controlled for sex

Step 1

```
bss_data <- load_bss_data(type="roi",
      subjdir = "~/Desktop/Rockland25data/",
          csv="~/Desktop/Rockland25data/Rockland25.tsv",
               roiid=121, roimeas="gmthickness")
```

Step 2

```
bss_model <- bss_anova(main_effect = "age",
                             covariates = "sex",
                                 bss_data = bss_data)
```

Step 3

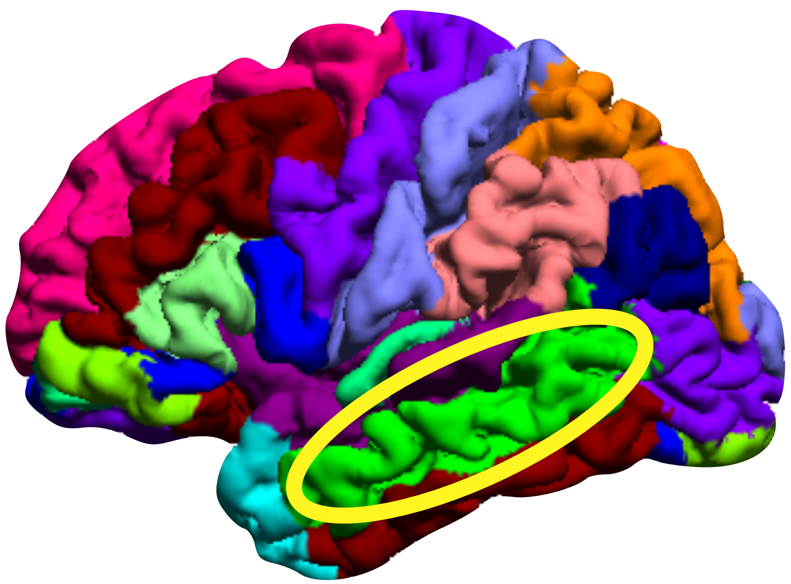
```
save_bss_out(bss_data, bss_model,
                    outdir="~/Desktop/roi_121")
```

ROI analysis – visualization of results

- Go to the output directory `roi_121`
- Open `report.html`

ROI analysis – dynamic html reports

- Effect of age on thickness of ROI 121 when controlled for sex



```
### BrainSuite ROI statistical analysis report
```{r echo=FALSE, message=FALSE, warning=FALSE, load_data}

DT::datatable(bss_data@demographics)

```

```{r warning=FALSE, run_command}
lm_full <- lm(ROI_121 ~ age + sex, data = bss_data@demographics)
lm_null <- lm(ROI_121 ~ sex, data = bss_data@demographics)
pander::pander(anova(lm_full, lm_null))
```

Main effect of 121 gmthickness on age controlling for sex
```

BrainSuite ROI statistical analysis report

Show 10 entries

Search:

	subjID	age	sex	handedness	File_roi	ROI_121
1	sub-A00044171_ses-DS2	18	FEMALE	RIGHT	~/Desktop/Rockland25data//sub-A00044171_ses-DS2/sub-A00044171_ses-DS2.roiwise.stats.txt	5.142743
2	sub-A00052197_ses-DS2	18	MALE	RIGHT	~/Desktop/Rockland25data//sub-A00052197_ses-DS2/sub-A00052197_ses-DS2.roiwise.stats.txt	5.252598
3	sub-A00053546_ses-DS2	18	MALE	RIGHT	~/Desktop/Rockland25data//sub-A00053546_ses-DS2/sub-A00053546_ses-DS2.roiwise.stats.txt	4.874314
4	sub-A00029303_ses-DS2	19	FEMALE	RIGHT	~/Desktop/Rockland25data//sub-A00029303_ses-DS2/sub-A00029303_ses-DS2.roiwise.stats.txt	4.916852

```
lm_full <- lm(ROI_121 ~ age + sex, data = bss_data@demographics)
lm_null <- lm(ROI_121 ~ sex, data = bss_data@demographics)
pander::pander(anova(lm_full, lm_null))
```

Analysis of Variance Table

Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
22	7.807	NA	NA	NA	NA
23	10.09	-1	-2.279	6.421	0.01891

Main effect of 121 gmthickness on age controlling for sex

Rockland dataset: N=25, Age - 16~84 years, 18 f / 7 m

plans for the future

- Mixed Models
- New imaging phenotypes
  - Diffusion Tensors
  - Fiber Tracts (Curves)
- GUI Interface for Model specification
- Explore alternatives implementations using stats models
- Generate graphics for ROI analyses — regression, correlation, scatter plots, box plots