Normative modeling in Schizophrenia - Analysis of the 34 regions parcellation

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Packages and libraries

```
library("easypackages") # install.packages("easypackages")

# get a list of all the needed packages
list.of.packages <- c("viridis", "tidyverse", "MatchIt", "grid", "png",
                      "gridExtra", "parallel", "nlme", "JMbayes",
                      "BiocManager", "Biostrings", "lme4", "ggplot2",
                      "Hmisc", "devtools", "longCombat", "neuroCombat",
                      "tinytex", "knitr", "dplyr", "variancePartition",
                      "Rmisc", "doParallel")

new.packages <- list.of.packages[!(list.of.packages %in% installed.packages()[,"Package"])]
  if(length(new.packages)>0) { install.packages(new.packages)}

# load them all
libraries(list.of.packages)
ncores <- detectCores() # Number of cores available in pc
rm(list.of.packages, new.packages)
```

Set working directory and load functions

```
setwd("/data_J/Scripts")
source("1_DataPreparation.R")
source("2_RegressionModel.R")
source("3_Statistics.R")
source("4_EDA.R")
```

Data preparation

Options of DataPreparation function:

- parc = "parc35" or "parc308" (whether to use the 34 regions parcellation or the 308 regions one)
- harmonization= "lC" or "nC" (whether to use lonCombat or NeuroCombat harmonization)
- match = T or F (whether to use match-it or not)

```
df_lC_NO_matched <- DataPreparation(parc = "parc35",
                                    harmonization = "lC",
                                    match = F)
```

```
## File parc35 already exists, reading file...
## File with longCombat harmonization already exists, reading file...
## Done!
```

```
df_lC_matched <- DataPreparation(parc = "parc35",
                                 harmonization = "lC",
                                 match = T)
```

```
## File parc35 already exists, reading file...
## File with longCombat harmonization already exists, reading file...
## File with MATCH-IT already exists, reading file...
## Done!
```

Warning: Fewer control units than treated units; not all treated units will get a match.

Stack Overflow: This warning is because our treated group is larger than our control group (this happens in timepoint = 2). If you're doing 1:1 matching without replacement, all the control units will be used up before all the treated units get a match. **To remedy this, you need to match with replacement or think about whether you actually want to generalize to the control population and switch the labels on the treatment groups**. You can do this by creating a new variable, say notY, which is 1 - Y and then performing the same operations.

The match in *sex variable* is not exact. Anyway, the match in # patients, # controls is done well (¿is it enough?)

NO MATCHED DATASET

NO MATCHED	timepoint 1	timepoint 2	timepoint 3
# controls	298	293	109
# patients	169	168	50

Timepoint 1	sex 0	sex 1
# controls	131	167
# patients	38	131

Timepoint 2	sex 0	sex 1
# controls	130	163
# patients	38	130

Timepoint 3	sex 0	sex 1
# controls	50	59

Timepoint 3	sex 0	sex 1
# patients	7	43

MATCHED DATASET

Number of patients vs number of controls per timepoint is not exactly the same:

MATCHED	timepoint 1	timepoint 2	timepoint 3
# controls	169	164	49
# patients	169	164	49

Timepoint 1	sex 0	sex 1
# controls	38	131
# patients	38	131

Timepoint 2	sex 0	sex 1
# controls	37	127
# patients	38	126

Timepoint 3	sex 0	sex 1
# controls	8	41
# patients	7	42

Exploratory Data Analysis

Show relevant figures and analytics before and after data preparation. For example, age of controls vs age of patients in the raw df vs the match-it df:

Matching ages:

```r
EDA_match_ages(df_1C_NO_matched,"NO match-it")
```

```
##
## Ages that doesn't match in patients vs controls in  NO match-it  dataset are:
##   69 68 67 65 64 63 62 60 59
```

```r
EDA_match_ages(df_1C_matched,"match-it")
```

```
##
## Ages that doesn't match in patients vs controls in  match-it  dataset are:
##   60 58 57 56 46
```

Linear Mixed Effects Model Regresion

Calling the *run_NormativeModel* function with different datasets. This will return the z scores (one for each region for each timepoint of each subject)

NO Match-it dataframe (longCombat):

```
Zs_NOmatch <- run_NormativeModel(df_lC_NO_matched,
                                 measure = "CT_freesurfer",
                                 parc = "parc35",
                                 match = "NOmatch",
                                 harmonization = "lC")
```

Match-it dataframe (longCombat):

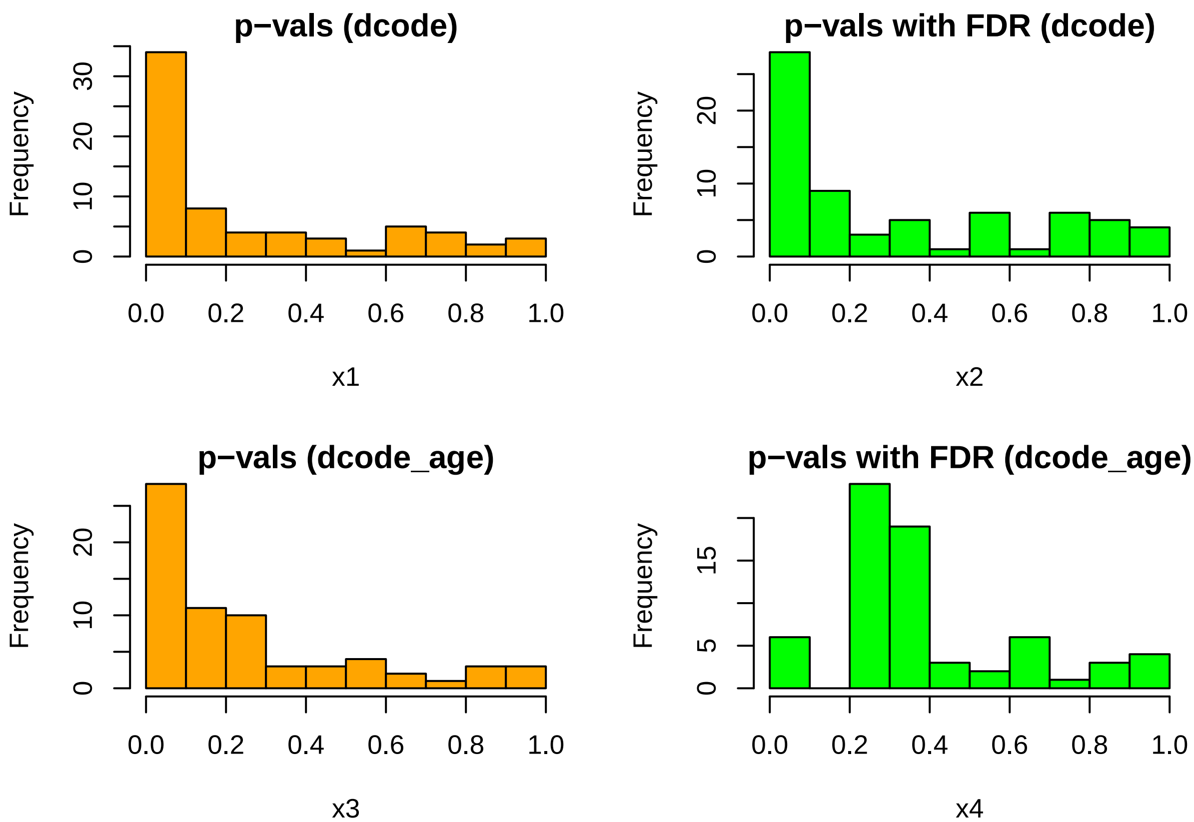
```
Zs_match <- run_NormativeModel(df_lC_matched,
                               measure = "CT_freesurfer",
                               parc = "parc35",
                               match = "match",
                               harmonization = "lC")
```

Match-it dataframe (Age*Diagnosis) BEFORE EXCLUDING DEVIANTS

```
p_val <- run_AgeDiagnosisModel(df_lC_matched,
                               measure = "CT_freesurfer",
                               Z = NULL,
                               exclude_deviants = F)

p_val_FDR <- Apply_FDR_Correction(p_val)
```

```
## Without FDR correction:
## Variable dcode has statistical significance for  28 / 68 regions
## Variable dcode_age has statistical significance for  14 / 68 regions

##      reg       scode          age        euler      dcode   dcode_age
## [1,]   0 0.902627774 1.376441e-10 1.585103e-03 0.05520999 0.311477261
## [2,]   0 0.002974282 4.919699e-02 6.363141e-02 0.69065034 0.000958305
## [3,]   0 0.011063046 0.000000e+00 1.653418e-02 0.14065095 0.242002275
## [4,]   0 0.656891364 1.284373e-06 3.036019e-05 0.47491087 0.813085773

## With FDR correction:
## Variable dcode has statistical significance for  20 / 68 regions
## Variable dcode_age has statistical significance for  3 / 68 regions

##      reg      scode          age        euler     dcode  dcode_age
## [1,]   0 0.96138159 2.752882e-10 0.0063404134 0.1294579 0.42360908
```

```
## [2,]    0 0.02596661 5.395799e-02 0.1395785747 0.7960038 0.03738268
## [3,]    0 0.05645537 0.000000e+00 0.0505620137 0.2452375 0.34434681
## [4,]    0 0.82496212 1.940831e-06 0.0002195698 0.6093196 0.87761639
```



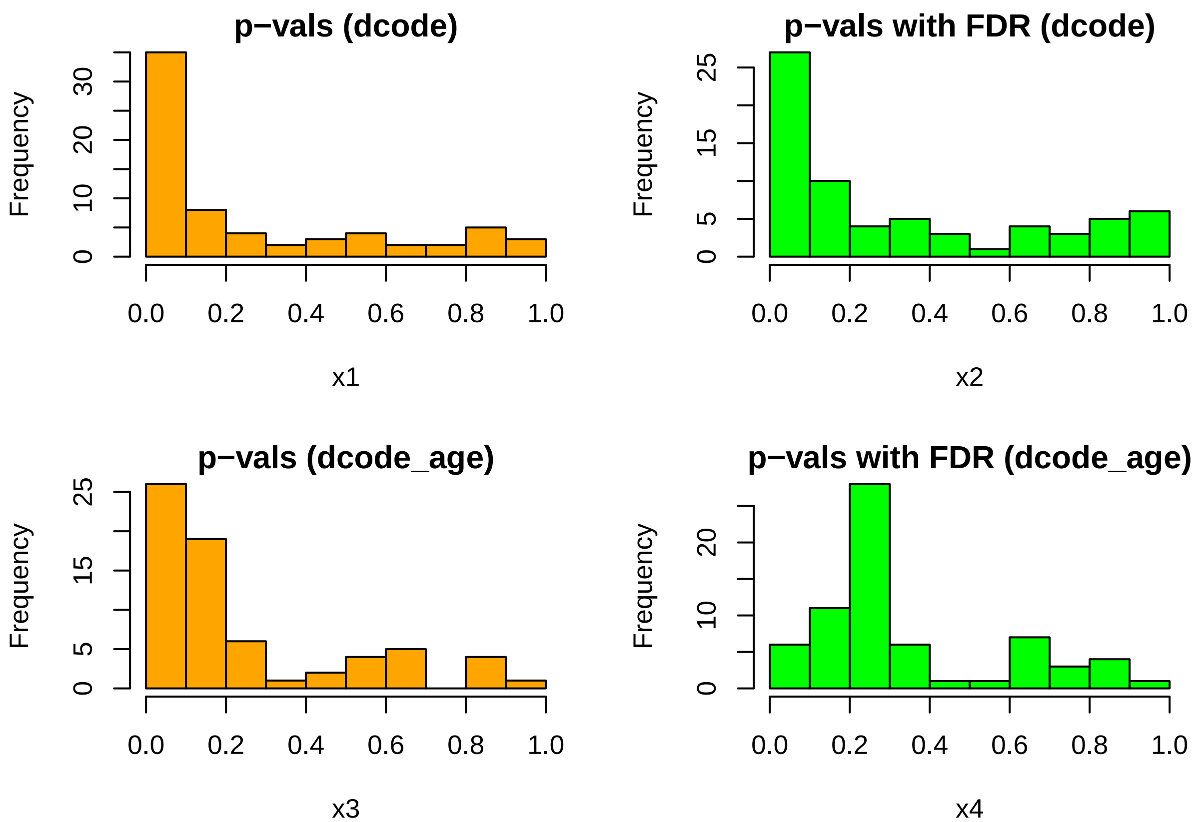
Match-it dataframe (Age*Diagnosis) AFTER EXCLUDING DEVIANTS

```r
p_val <- run_AgeDiagnosisModel(df_lC_matched,
                               measure = "CT_freesurfer",
                               Z = Zs_match,
                               exclude_deviants = T)

p_val_FDR <- Apply_FDR_Correction(p_val)
```

```
## Without FDR correction:
## Variable dcode has statistical significance for  28 / 68 regions
## Variable dcode_age has statistical significance for  17 / 68 regions
```

```
##      reg       scode          age        euler      dcode    dcode_age
## [1,]   0 0.897895774 9.864110e-12 8.442243e-05 0.06502851 0.1316012362
## [2,]   0 0.003033047 6.971218e-02 1.151092e-01 0.87177220 0.0008659586
## [3,]   0 0.011344863 0.000000e+00 1.293067e-02 0.12199549 0.1847867203
## [4,]   0 0.796635433 5.294333e-06 4.887556e-05 0.52064019 0.9225434551
```

```
## With FDR correction:
## Variable dcode has statistical significance for  22 / 68 regions
## Variable dcode_age has statistical significance for  3 / 68 regions

##       reg      scode          age        euler     dcode  dcode_age
## [1,]    0 0.96915734 2.235865e-11 0.0004415942 0.1473980 0.26320247
## [2,]    0 0.03033302 7.524489e-02 0.2206451814 0.9335941 0.03076526
## [3,]    0 0.05558303 0.000000e+00 0.0399675197 0.2167181 0.29551921
## [4,]    0 0.90303250 7.826406e-06 0.0002838175 0.6679912 0.92254346
```



Analysis of z-scores and computation of global scores

The following tables represent, **in terms of samples**, the number of deviations ($|Z| > 1.96$). It is calculated for each timepoint ($timepoint = 1, 2, 3$) and differentiated between controls and subjects.

NO MATCHED	timepoint 1	timepoint 2	timepoint 3
# total samples	31.688	31.348	10.744
# samples dev (%)	795 (2.51%)	696 (2.22%)	275 (2.56%)
# controls samples	20.264	19.924	7.412
# controls dev (%)	450 (2.22%)	335 (1.68%)	143 (1.93%)
# patients samples	11.424	11.424	3.332
# patients dev (%)	345 (3.02%)	361 (3.16%)	132 (3.96%)

MATCHED	timepoint 1	timepoint 2	timepoint 3
# total samples	22.916	22.304	6.664
# samples dev (%)	617 (2.69%)	519 (2.33%)	187 (2.81%)
# controls samples	11.492	11.152	3.332
# controls dev (%)	269 (2.34%)	176 (1.58%)	71 (2.13%)
# patients samples	11.424	11.152	3.332
# patients dev (%)	348 (3.05%)	343 (3.08%)	116 (3.48%)

In the following, we chose to work with the matched dataset and the Zs derived from its lme model, providing a better statistical support for the analysis.

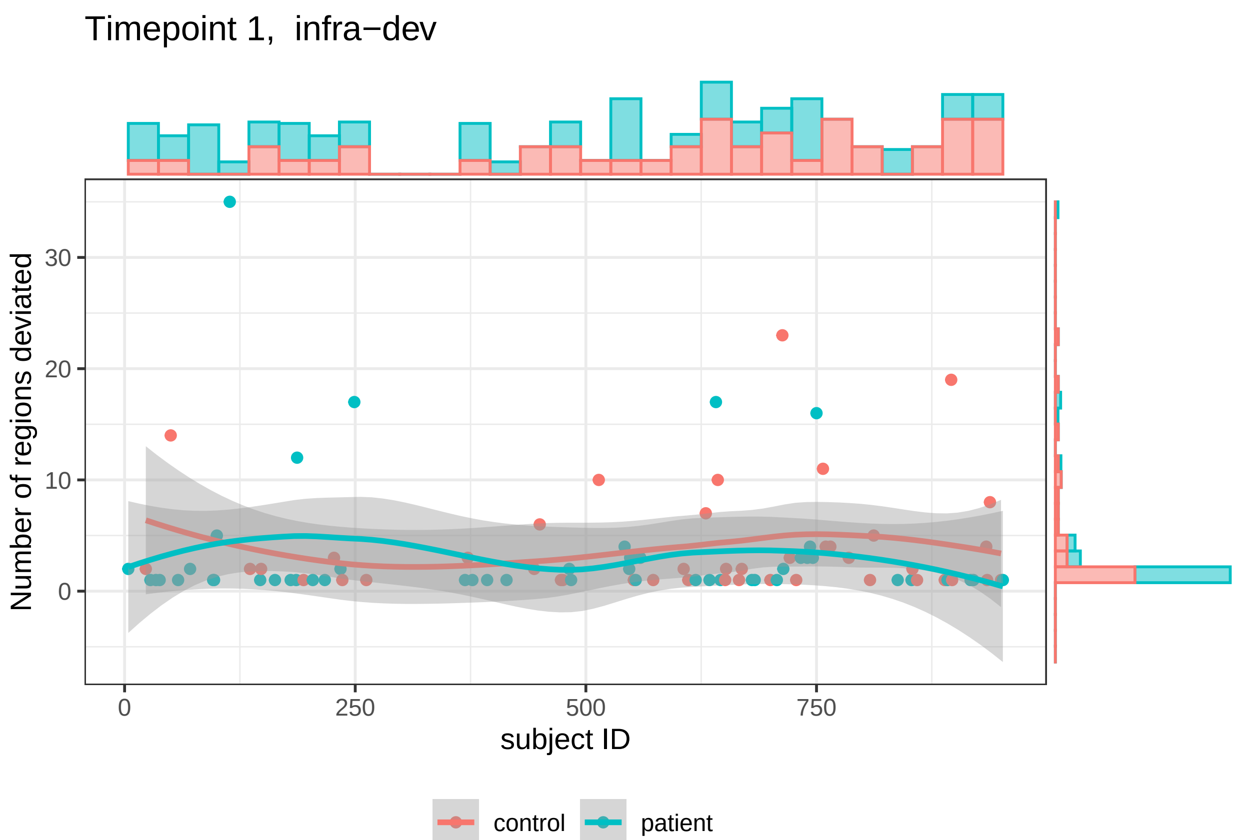
We computed the number of deviant samples ($Z < -1.96$ and $Z > 1.96$):

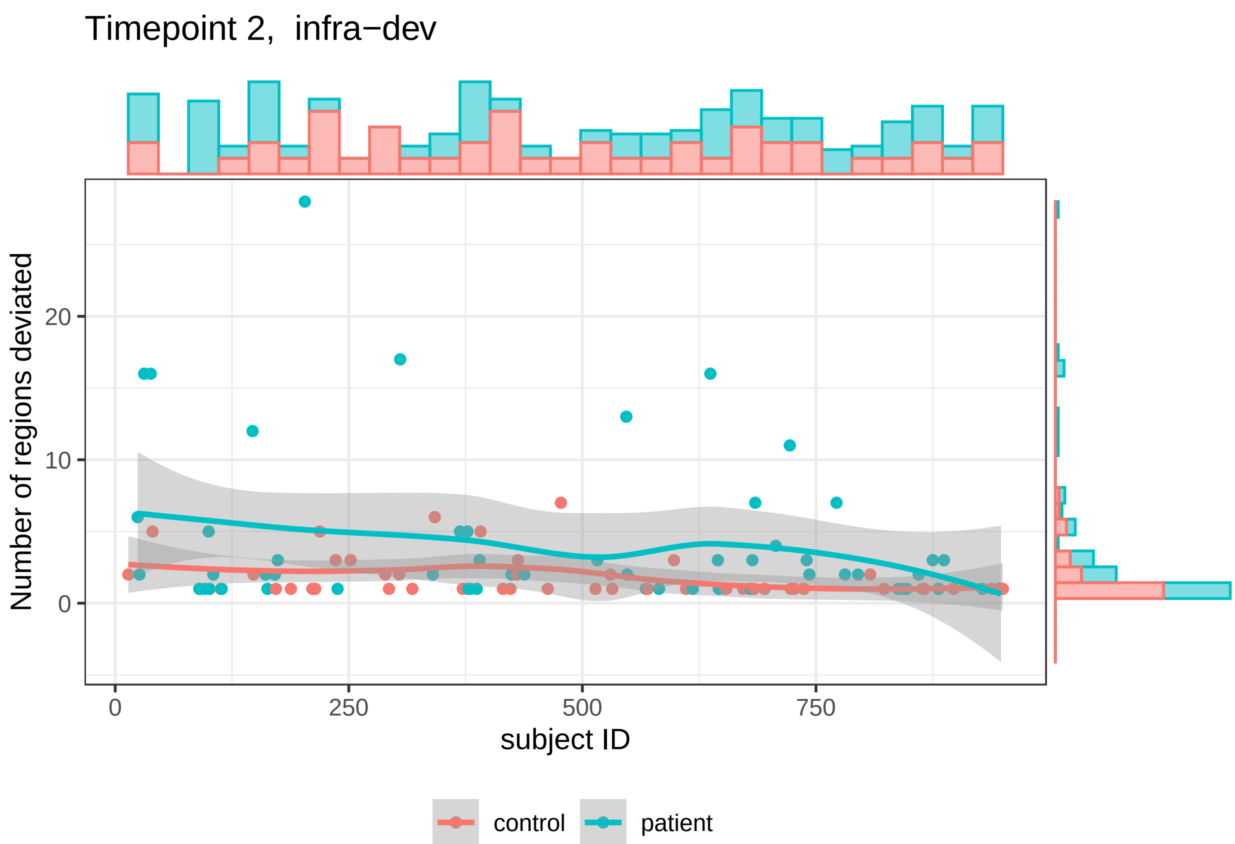
In terms of regions deviated:

	Infra-normal deviants	Non deviants	Supra-normal deviants	Deviants
tp 1	339 (1.48%)	22.299 (97.31%)	278 (1.21%)	617 (2.69%)
controls	172 ()	11.223 ()	97 ()	269 ()
patients	167 ()	11.076 ()	181 ()	348 ()
tp 2	322 (1.44%)	21.785 (97.67%)	197 (0.88%)	519 (2.33%)
controls	83 ()	10.976 ()	93 ()	176 ()
patients	239 ()	10.809 ()	104 ()	343 ()
tp 3	133 (2.00%)	6.477 (97.19%)	54 (0.81%)	187 (2.81%)
controls	39 ()	3.261 ()	32 ()	71 ()
patients	94 ()	3.216 ()	22 ()	116 ()
total	794 (1.53%)	50.561 (97.45%)	529 (1.02%)	1.323 (2.55%)

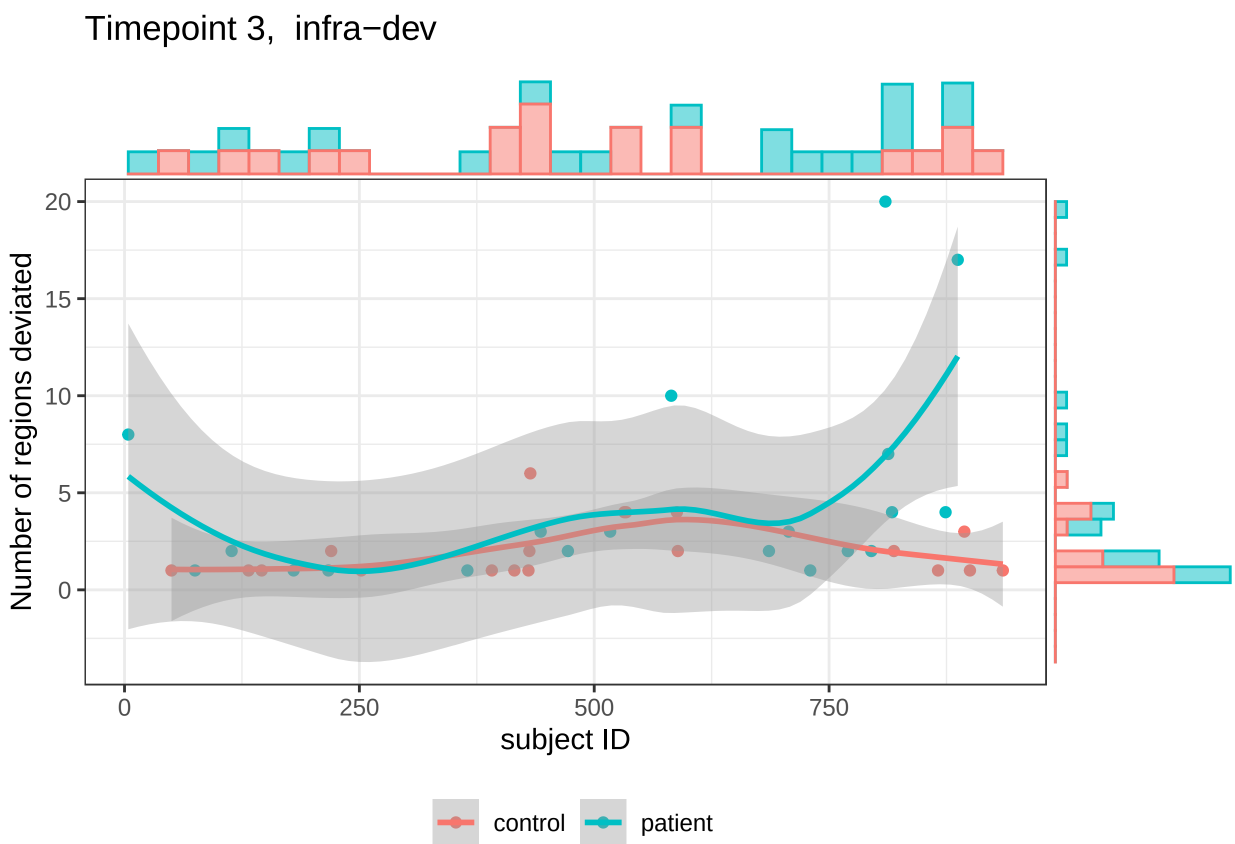
```
library("ggExtra") #install.packages("ggExtra")
for (d in c("infra-dev","supra-dev")){
 for (tp in 1:3) {
  data <- Zs_match %>%
    mutate(deviant = ifelse(z > -1.96 & z < 1.96, 0, z)) %>%
    mutate(deviant = ifelse(z < -1.96, -1, deviant)) %>%
    mutate(deviant = ifelse(z >  1.96,  1, deviant)) %>%
    mutate(deviant = factor(deviant,
                         labels = c("infra-dev","normal","supra-dev"))) %>%
    filter(deviant==d) %>%
    filter(timepoint==tp) %>%
    group_by(subID, group, deviant) %>%
    dplyr::summarise(n=n())

  p1 <- ggplot(data = data,
             mapping = aes(x = subID, y = n, colour = group)) +
    geom_point() +
    geom_smooth(method = "loess") +
    labs(title=paste0("Timepoint ", tp, ",  ",d),
```

```
        x = "subject ID",
        y = "Number of regions deviated") +
    theme_bw() +
    theme(legend.position = "bottom",
          legend.title = element_blank())

  # Replace "histogram" with "boxplot" or "density" for other types
  p2 <- ggMarginal(p1, type = "histogram", groupColour = TRUE, groupFill = TRUE)
  print(p2, newpage = TRUE)
 }
}
```

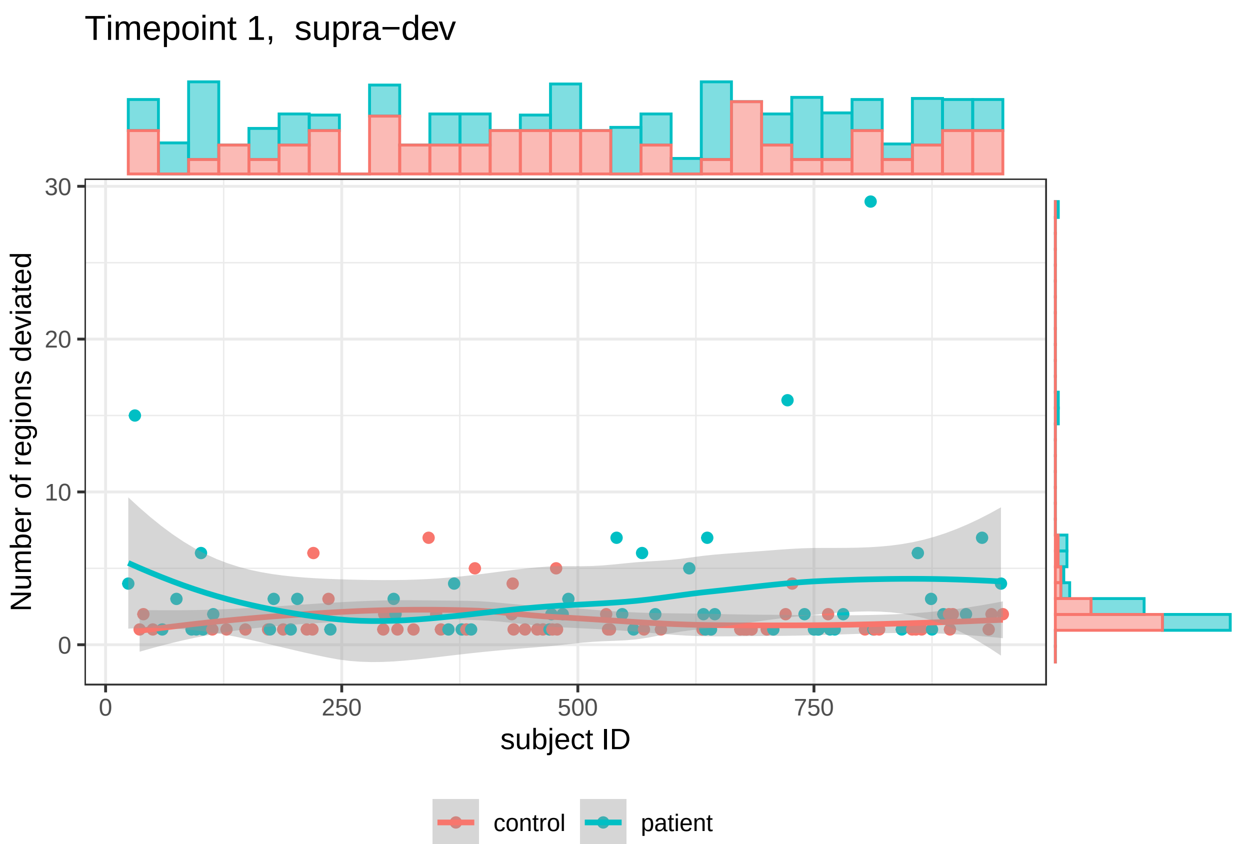


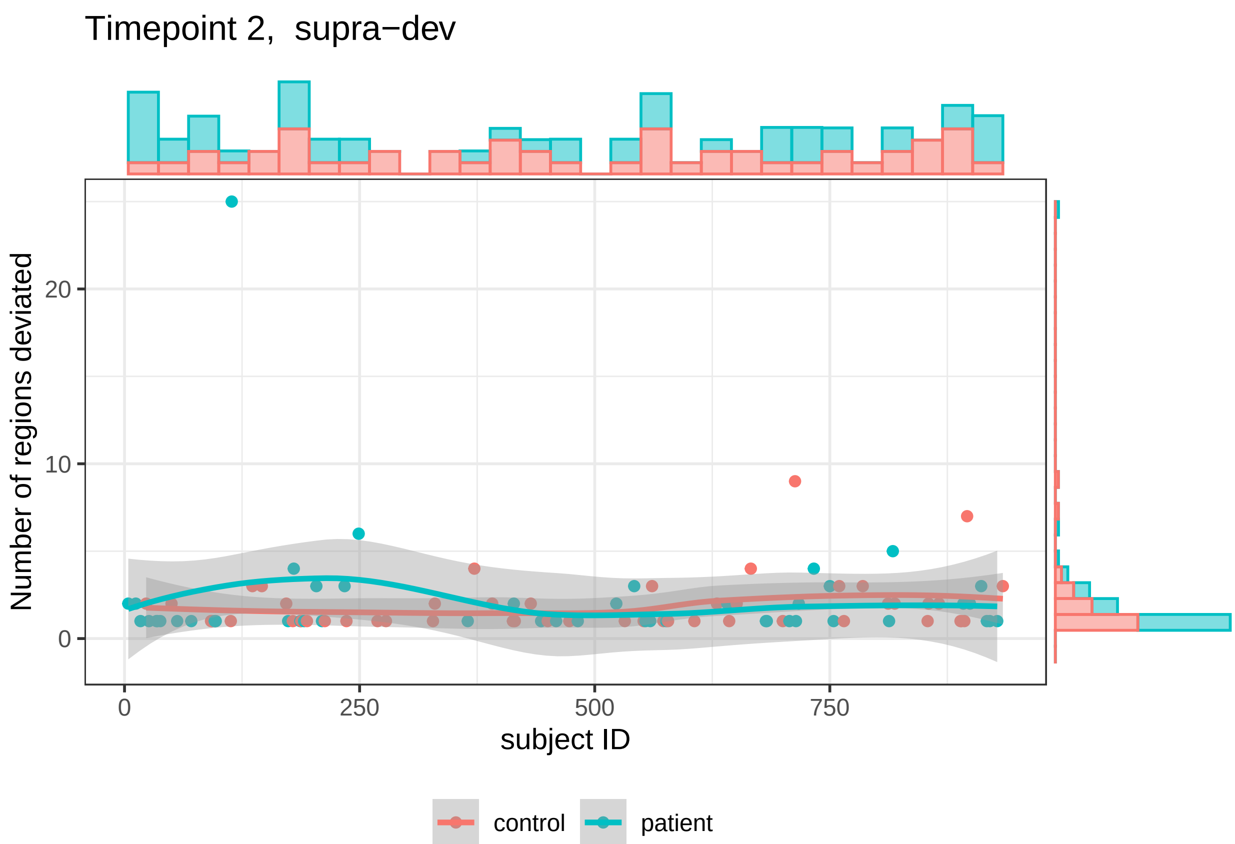


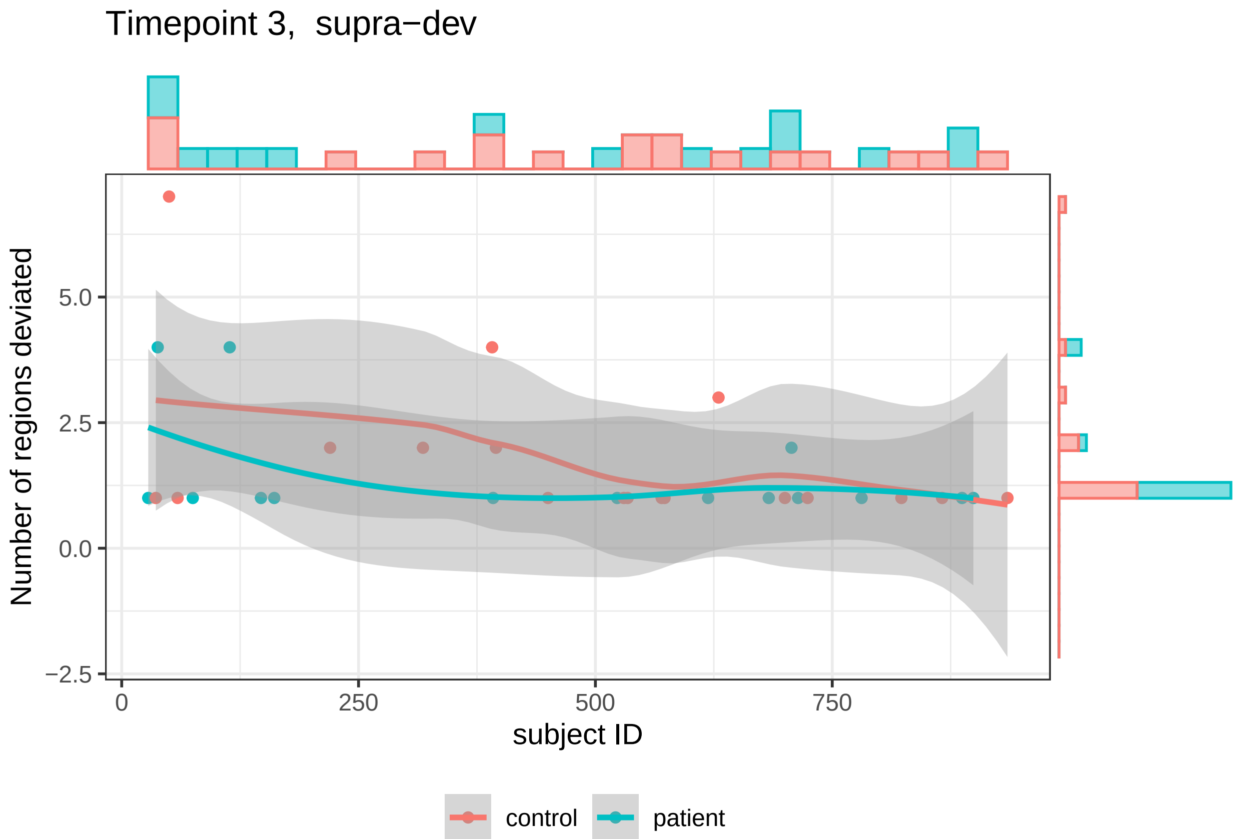
Timepoint 2, infra−dev
Number of regions deviated
20
10
0
0
250
500
750
subject ID
control
patient



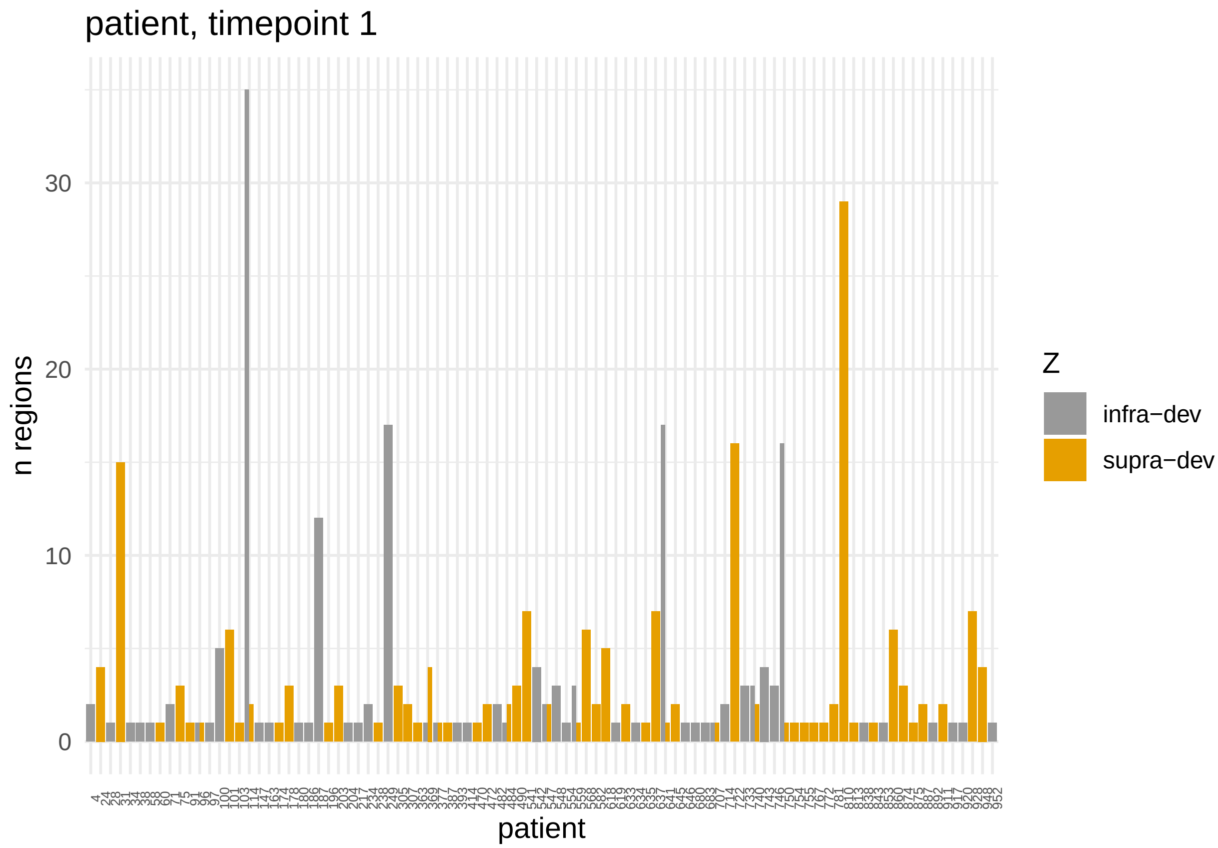
Timepoint 3, infra−dev
Number of regions deviated
20
15
10
5
0
0
250
500
750
subject ID
control
patient

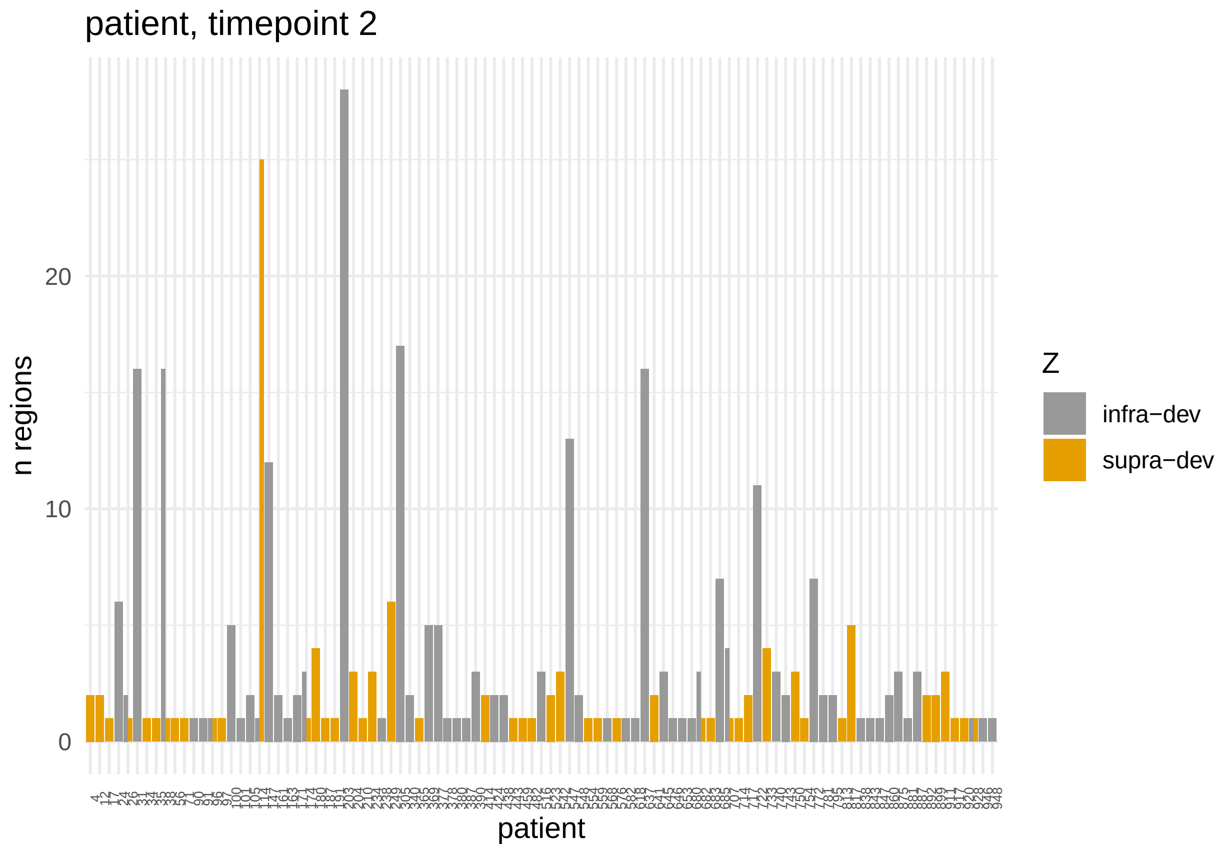

Timepoint 1, supra−dev
Number of regions deviated
30
20
10
0
0
250
500
750
subject ID
control
patient


Timepoint 2, supra−dev
Number of regions deviated
0
10
20
0
250
500
750
subject ID
control
patient

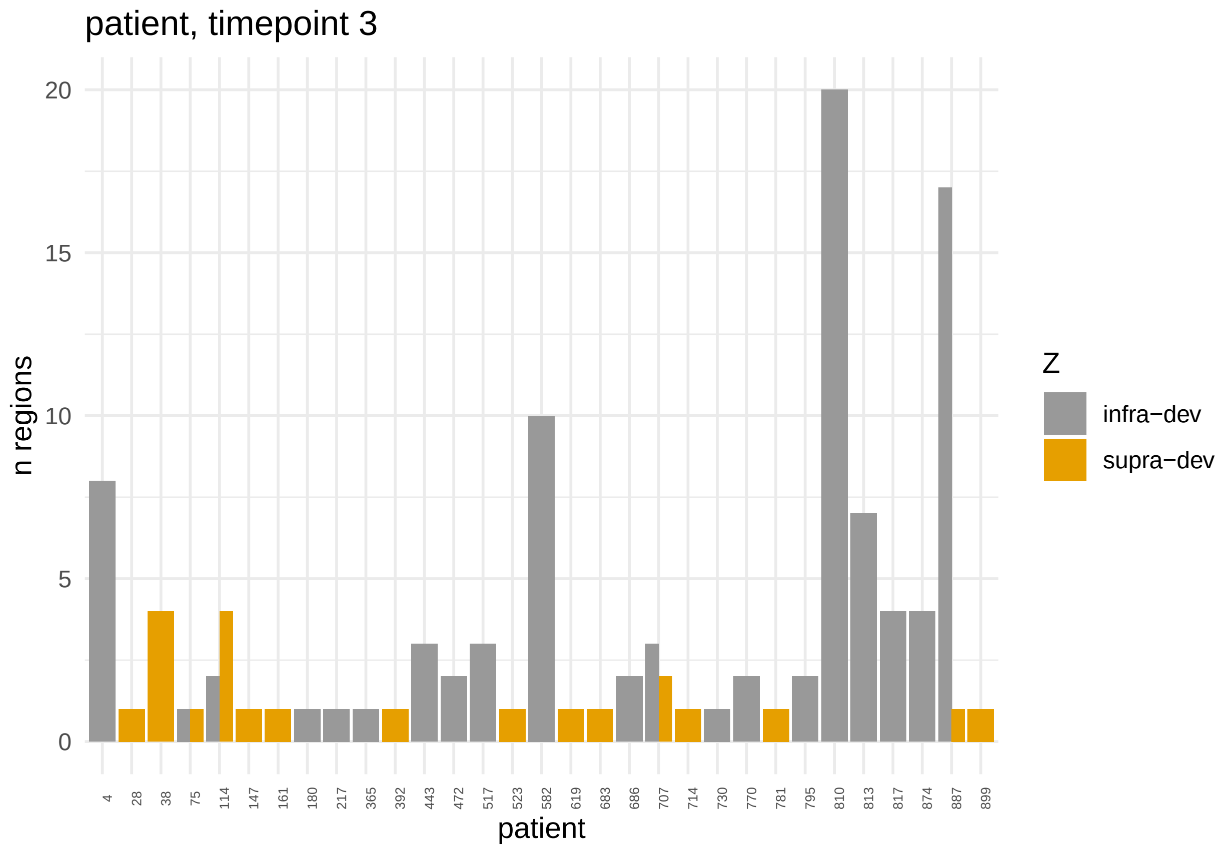



```
for (g in c("patient", "control")){
  for(tp in 1:3){
  data <- Zs_match %>%
    filter(timepoint==tp) %>%
    filter(group==g) %>%
    mutate(deviant = ifelse(z > -1.96 & z < 1.96, 0, z)) %>%
    mutate(deviant = ifelse(z < -1.96, -1, deviant)) %>%
    mutate(deviant = ifelse(z >  1.96,  1, deviant)) %>%
    filter(deviant!=0) %>%
    mutate(Z = factor(deviant, labels = c("infra-dev","supra-dev")),
           subID = factor(subID))

  # Bar chart side by side
  plot <- ggplot(data, aes(x = subID, fill = Z)) +
    geom_bar(position = position_dodge()) + # position_dodge() o "fill"
    labs(title=paste0(g,", timepoint ", tp), x= g , y = "n regions") +
    scale_fill_manual(values=c("#999999", "#E69F00")) +
    theme_minimal() +
    theme(axis.text.x = element_text(size = 5, angle = 90))
  print(plot)
 }
}
```

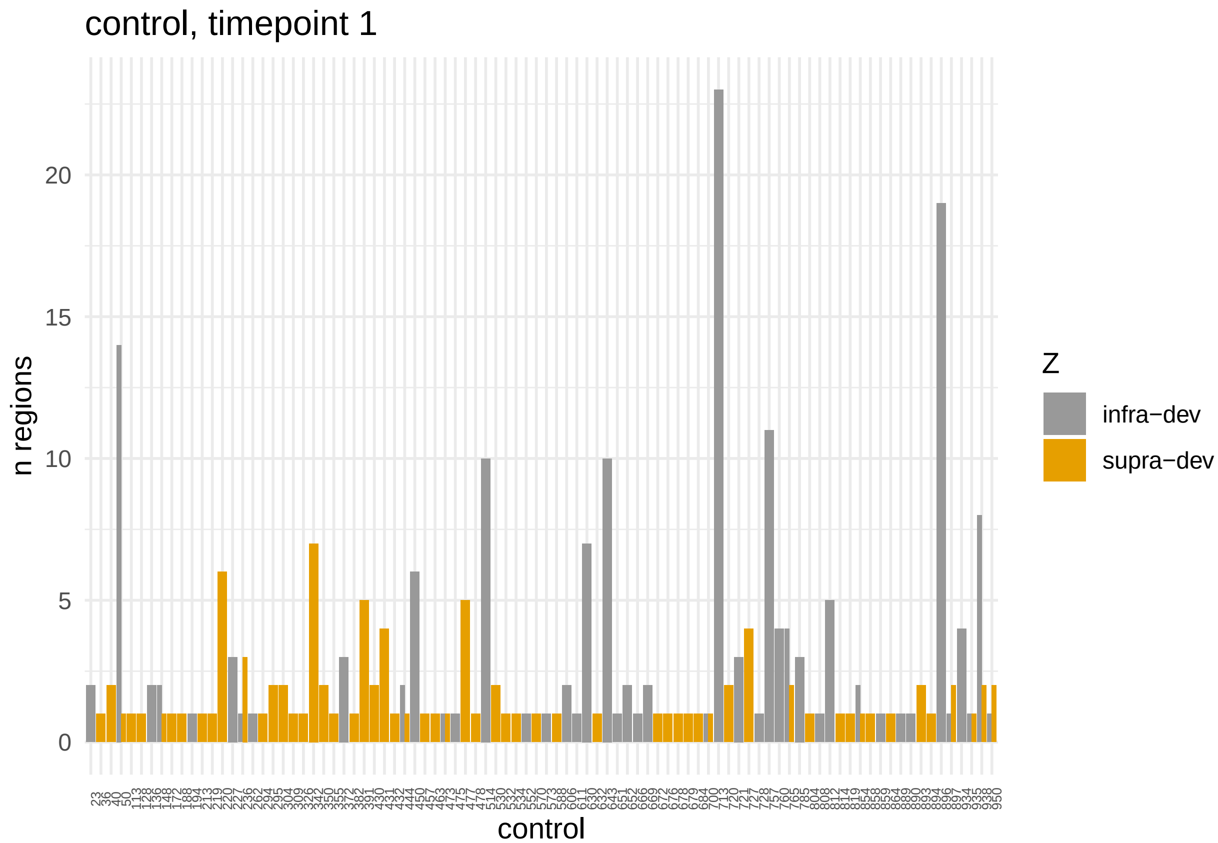

patient, timepoint 1
n regions
0
10
20
30
patient
Z
infra−dev
supra−dev

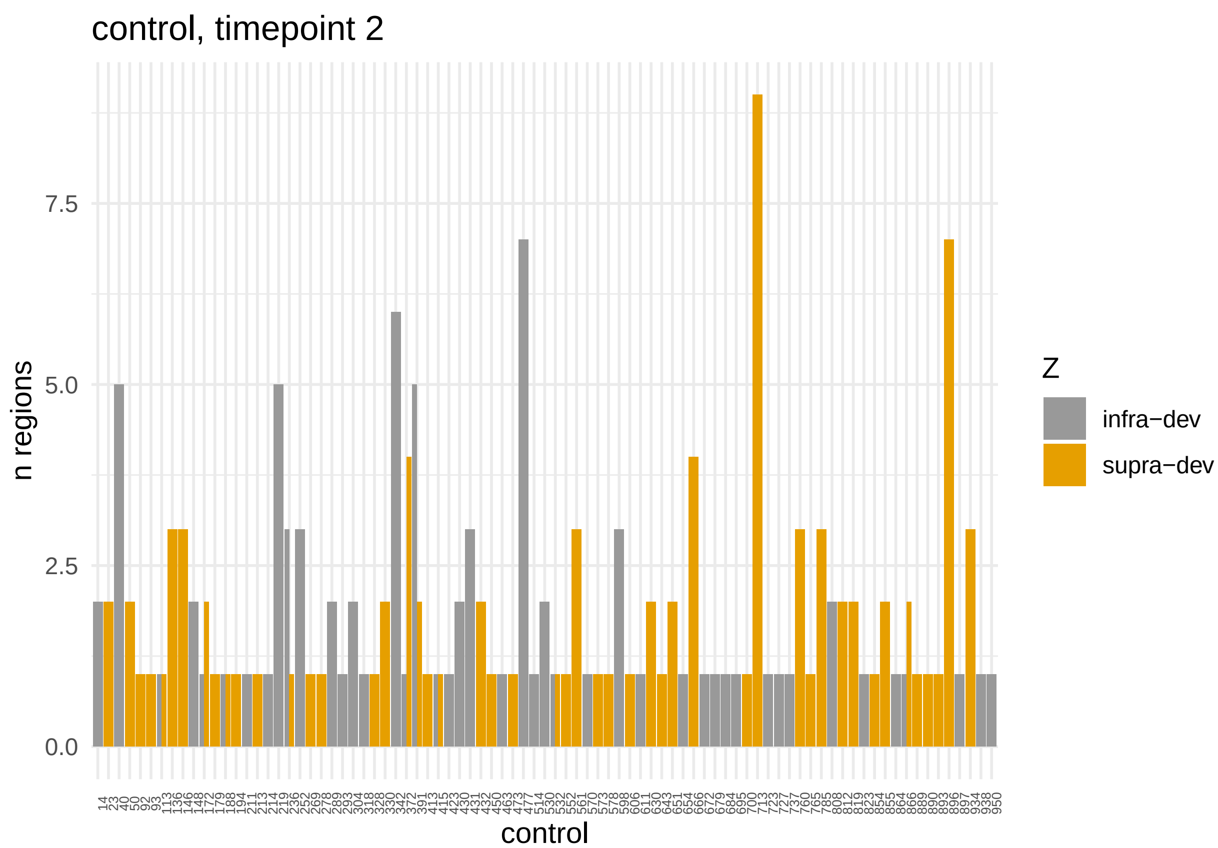


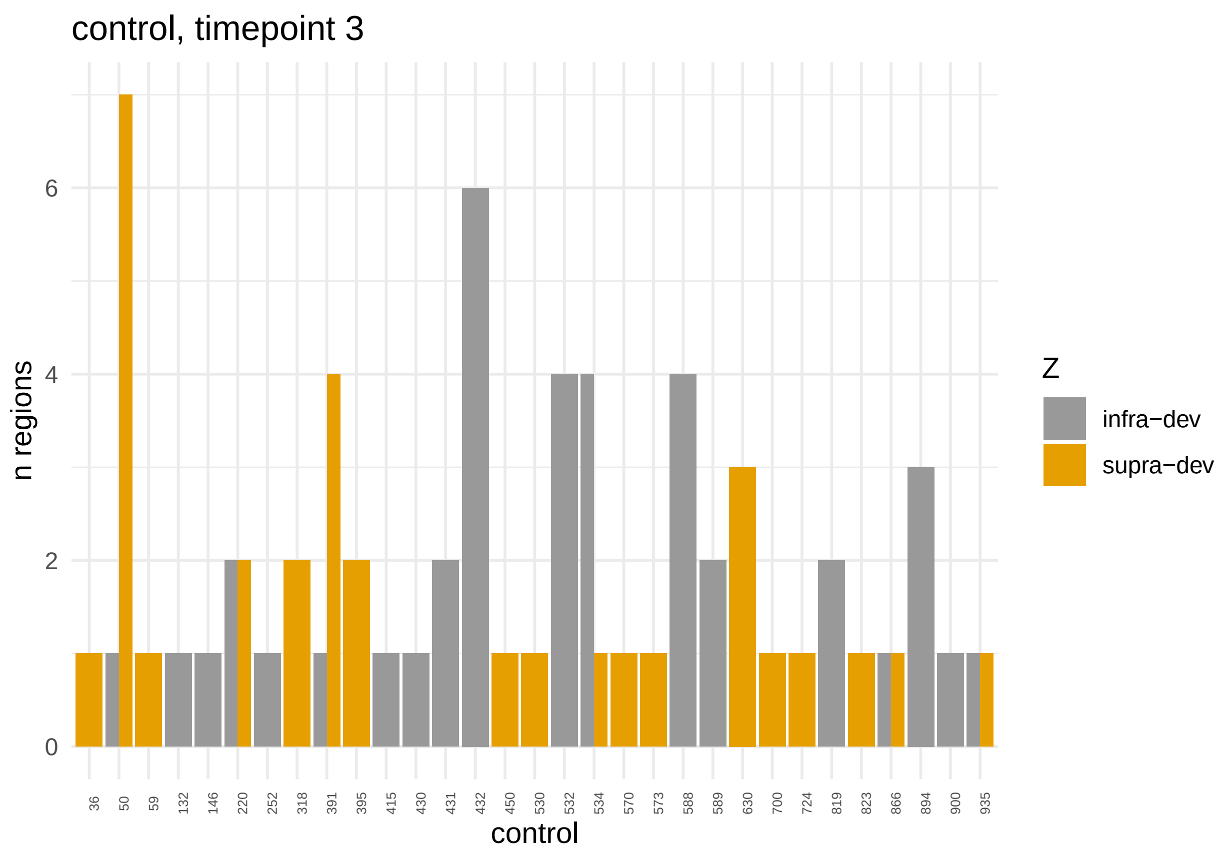
patient, timepoint 2
n regions
patient
Z
infra−dev
supra−dev



patient, timepoint 3
n regions
20
15
10
5
0
4
28
38
75
114
147
161
180
217
365
392
443
472
517
523
582
619
683
686
707
714
730
770
781
795
810
813
817
874
887
899
patient
Z
infra−dev
supra−dev


control, timepoint 1
n regions
0
5
10
15
20
control
Z
infra−dev
supra−dev


control, timepoint 2
n regions
7.5
5.0
2.5
0.0
control
Z
infra−dev
supra−dev



In terms of regions deviated:

	Infra-normal deviants	Non deviants	Supra-normal deviants	Deviants
tp 1	()	()	()	()
controls	()	()	()	()
patients	()	()	()	()
tp 2	()	()	()	()
controls	()	()	()	()
patients	()	()	()	()
tp 3	()	()	()	()
controls	()	()	()	()
patients	()	()	()	()
total	()	()	()	()

We computed the number of subjects that are **deviant at timepoint 1** and stay **deviant in subsequent timepoints**, for each region. A maximum of 5 subjects (1.48% of total subjects) fulfill that condition for any region.

	Condition
rh_cuneus_CT_freesurfer	5
lh_rostralmiddlefrontal_CT_freesurfer	4

	Condition
lh_temporalpole_CT_freesurfer	4

We computed the number of subjects that are **not deviant at timepoint 1** but become **deviant in subsequent timepoints**, for each region. A maximum of 20 subjects (5.93% of total subjects) fulfill that condition for any region.

	Condition
lh_lateraloccipital_CT_freesurfer	20
rh_temporalpole_CT_freesurfer	18
lh_posteriorcingulate_CT_freesurfer	18

---

1. Percentage of patients deviated from the normative range for any single cortical region

- Timepoint 1: No more than 6.548% of patients deviated from the normative range for any single cortical region.
- Timepoint 2: No more than 6.707% of patients deviated from the normative range for any single cortical region.
- Timepoint 3: No more than 10.204% of patients deviated from the normative range for any single cortical region.

---

2. Most common regions with infra-normal deviations. Percentage of patients.

- Timepoint 1: Infra-normal deviations in CT of subjects were most commonly located in **rh_fusiform_CT_freesurfer** cortices, although only 1.786% of patients showed significant deviations in these regions.
- Timepoint 2: Infra-normal deviations in CT of subjects were most commonly located in **rh_temporalpole_CT_freesurfer** cortices, although only 4.268% of patients showed significant deviations in these regions.
- Timepoint 3: Infra-normal deviations in CT of subjects were most commonly located in **lh_fusiform_CT_freesurfer** cortices, although only 8.163% of patients showed significant deviations in these regions.

DUDA: sacar la región y su porcentaje en los pacientes? Lo que hice fue sacar la región de los sujetos y el porcentaje para esa región concreta en los pacientes.

---

3. Most common regions with supra-normal deviations. Percentage of individuals.

- Timepoint 1: Supra-normal deviations in CT were most common in the **lh_lateraloccipital_CT_freesurfer** regions, 2.967% of individuals.

- Timepoint 2: Supra-normal deviations in CT were most common in the **lh__lateraloccipital__CT__freesurfer** regions, 2.134% of individuals.
- Timepoint 3: Supra-normal deviations in CT were most common in the **lh__parahippocampal__CT__freesurfer** regions, 3.061% of individuals.

---

4. Percentage of subjects with at least one region infra-normal deviated. Patients vs Healthy controls.

- Timepoint 1: Infra-normal deviations for at least one region were evident in 29.167% of patients, whereas this was the case for 26.036% of healthy individuals.
- Timepoint 2: Infra-normal deviations for at least one region were evident in 35.366% of patients, whereas this was the case for 27.439% of healthy individuals.
- Timepoint 3: Infra-normal deviations for at least one region were evident in 40.816% of patients, whereas this was the case for only 38.776% of healthy individuals.

---

5. Percentage of subjects with at least one region supra-normal deviated. Patients vs Healthy controls.

- Timepoint 1: Supra-normal deviations for at least one region were evident in 32.143% of patients and 34.32% of healthy individuals.
- Timepoint 2: Supra-normal deviations for at least one region were evident in 28.659% of patients and 29.878% of healthy individuals.
- Timepoint 3: Supra-normal deviations for at least one region were evident in 30.612% of patients and 36.735% of healthy individuals.

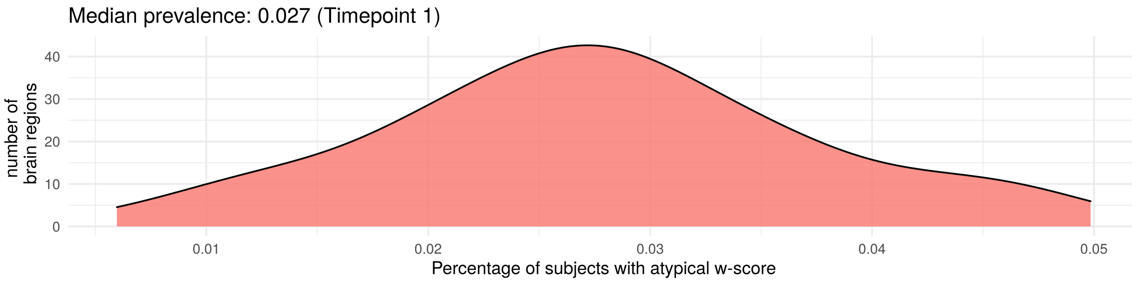
Percentage of deviant subjects for number of regions

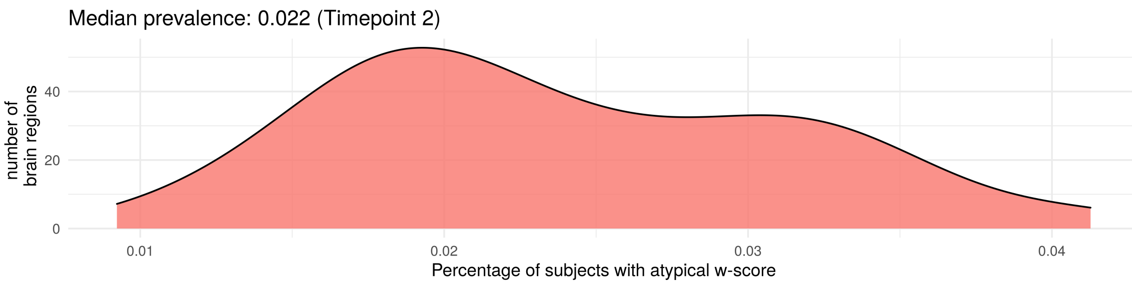
Figura B del paper de Bethlehem. En el eje de las x se representa el porcentaje de sujetos y en el eje y el número de regiones con el mismo ratio $\frac{|Z|>1.96}{|Z|<1.96}$. Se calcula para cada timepoint ($timepoint = 1, 2, 3$).

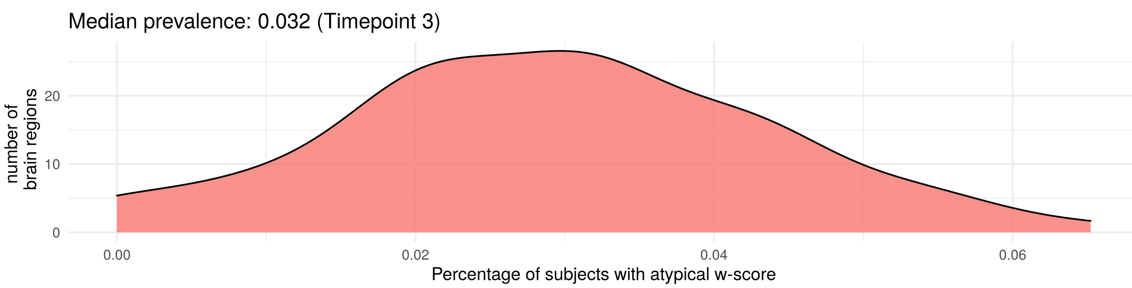
```
getStatistics(Zs= Zs_match,  lab= "lC_match_parc35", parc= "parc35")
getStatistics(Zs= Zs_NOmatch, lab= "lC_NOmatch_parc35", parc= "parc35")
```

Show the results from the global ratios obtained:

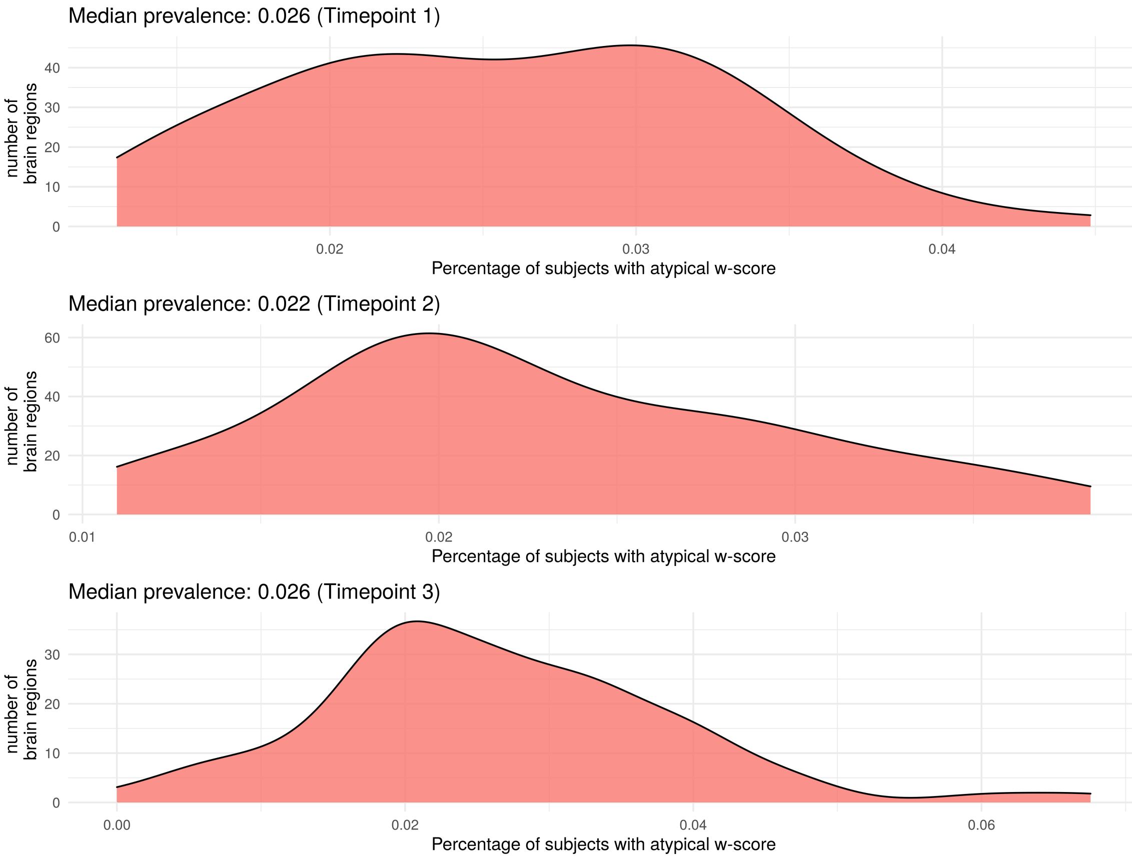
Match-it dataframe (longCombat):







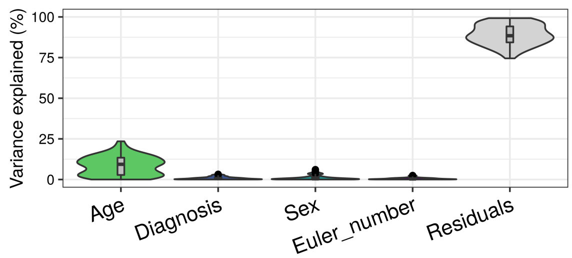
NO Match-it dataframe (longCombat):

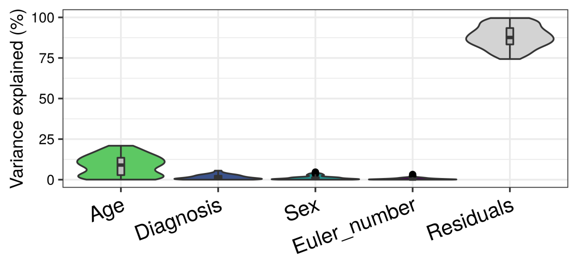


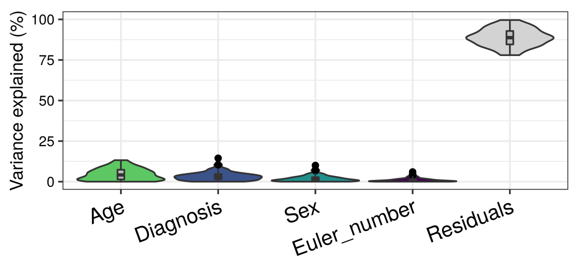
Variance contribution across measures

NO Match-it dataframe (longCombat):

```
variancePartition(df = df_lC_NO_matched,
                  measure = "CT_freesurfer",
                  lab = "lC_NO_matched_parc35",
                  par = "parc35")
```

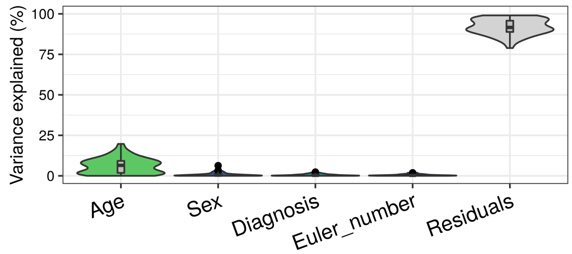


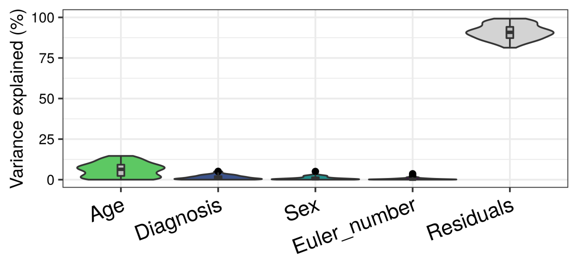


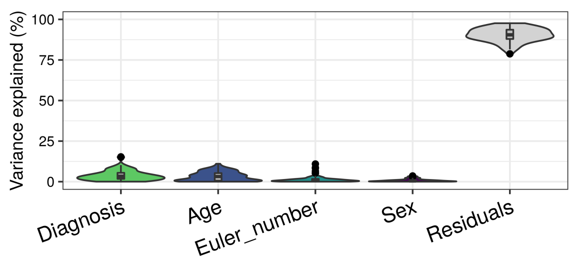


Match-it dataframe (longCombat):

```
variancePartition(df = df_lC_matched,
                  measure = "CT_freesurfer",
                  lab = "lC_matched_parc35",
                  par = "parc35")
```


Variance explained (%)
100
75
50
25
0
Age
Sex
Diagnosis
Euler_number
Residuals


Variance explained (%)
100
75
50
25
0
Age
Diagnosis
Sex
Euler_number
Residuals


Variance explained (%)
100
75
50
25
0
Diagnosis
Age
Euler_number
Sex
Residuals