Advantage of two scans in small populations demonstrated with a transgender dataset.

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Introduction

We have a dataset where FreeSurfer was used to determine cortical and subcortical brain anatomy in cis- and transgender population. For every participant two scans were administered (T1 and T2) and an average of both scans was computed. In this report we analyze the data from one scan and the average of both scans. Later on we show the advantage and increase in power obtained by admninistering 2 scans. One participant (P22) was removed from the analysis because no anatomical data was available for this participant.

Actual data

We first read in the data. In data.all all available measurements are stored (descriptive and anatomical) while in data.hyp the anatomical results for every region of interest stored. Both files contain data of T1, T2 and the average.

```
# Read in data
data.all <- read.csv("../1.Data/Behzad_all.csv", sep=";", dec=",")
data.hyp <- read.csv("../1.Data/Behzad_hyp.csv", sep=";", dec=",")

# Check data
dim(data.hyp)
```

```
## [1] 140  80
```

```
dim(data.all)
```

```
## [1] 140 820
```

The regions we are interested in are the cerebellum, caudate, putamen, nucleus accumenbens, thalamus, fusiform, pre-central gyrus, post-central gyrus, frontal poles and inferior parietal gyrus. Here we list the variables we selected from FreeSurfer that comply with these regions.

```
# Regions of interest
names(data.hyp[,55:80])
```

```
##  [1] "Tavg_LeftCerebellumWhiteMatter"
##  [2] "Tavg_LeftCerebellumCortex"
##  [3] "Tavg_RightCerebellumWhiteMatter"
##  [4] "Tavg_RightCerebellumCortex"
##  [5] "Tavg_L_caudalanteriorcingulate_volume"
##  [6] "Tavg_L_caudalmiddlefrontal_volume"
##  [7] "Tavg_L_fusiform_volume"
##  [8] "Tavg_L_inferiorparietal_volume"
##  [9] "Tavg_L_postcentral_volume"
## [10] "Tavg_L_precentral_volume"
## [11] "Tavg_L_frontalpole_volume"
## [12] "Tavg_R_caudalanteriorcingulate_volume"
## [13] "Tavg_R_caudalmiddlefrontal_volume"
```

```
## [14] "Tavg_R_fusiform_volume"
## [15] "Tavg_R_inferiorparietal_volume"
## [16] "Tavg_R_postcentral_volume"
## [17] "Tavg_R_precentral_volume"
## [18] "Tavg_R_frontalpole_volume"
## [19] "Tavg_LeftThalamusProper"
## [20] "Tavg_LeftCaudate"
## [21] "Tavg_LeftPutamen"
## [22] "Tavg_LeftAccumbensarea"
## [23] "Tavg_RightThalamusProper"
## [24] "Tavg_RightCaudate"
## [25] "Tavg_RightPutamen"
## [26] "Tavg_RightAccumbensarea"
```

Descriptives

In this section population parameters are presented.

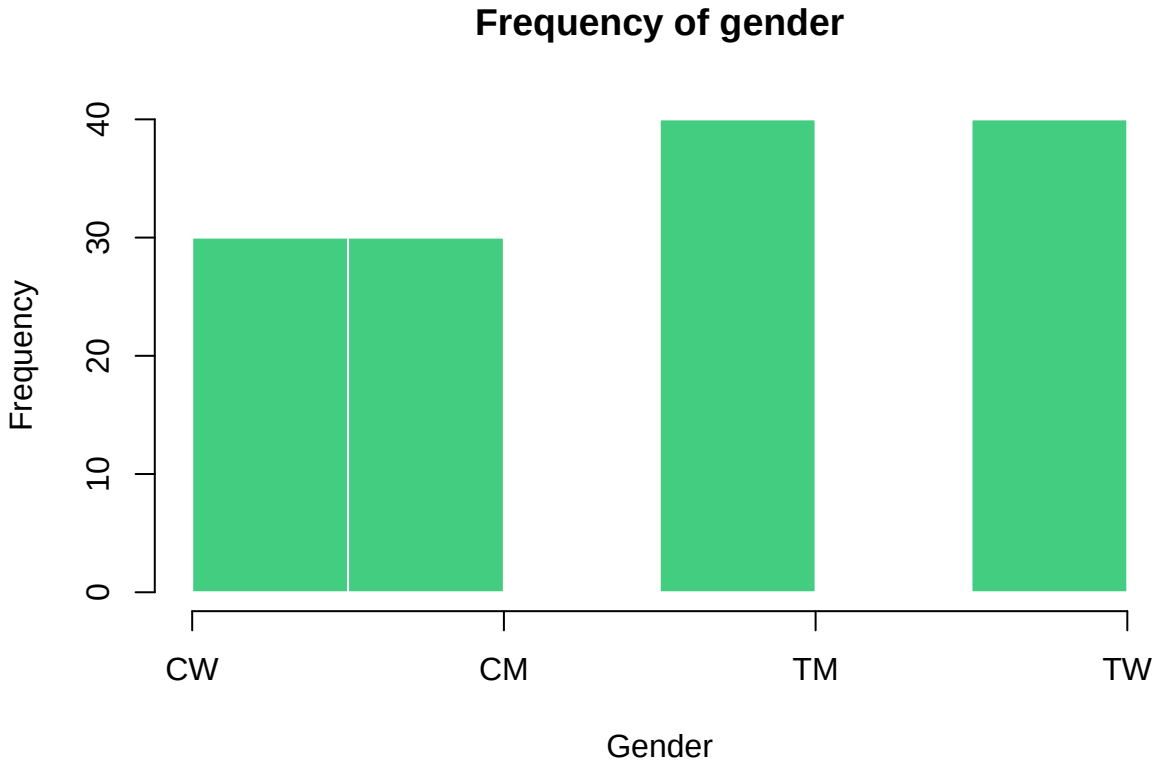
Gender

There were 60 cisgender and 80 transgender participants. One participant (P22) was removed from the analysis because no anatomical data was available for this participant.

```
ng1 <- sum(data.all[,2]==1)
ng2 <- sum(data.all[,2]==2)
ng3 <- sum(data.all[,2]==3)
ng4 <- sum(data.all[,2]==4)

paste("Cisgender women = ", ng1, ", cisgender men = ", ng2,
      ", transgender men = ", ng3, ", transgender women = ",ng4, sep="")
```

```
## [1] "Cisgender women = 30, cisgender men = 30, transgender men = 40, transgender women = 40"
```

```
hist(data.all[,2], xlab = "Gender", xaxt = "n", col = "seagreen3",
     border = "white", main = "Frequency of gender")
axis(1,at=c(1:4),labels=c("CW", "CM", "TM", "TW"))
```

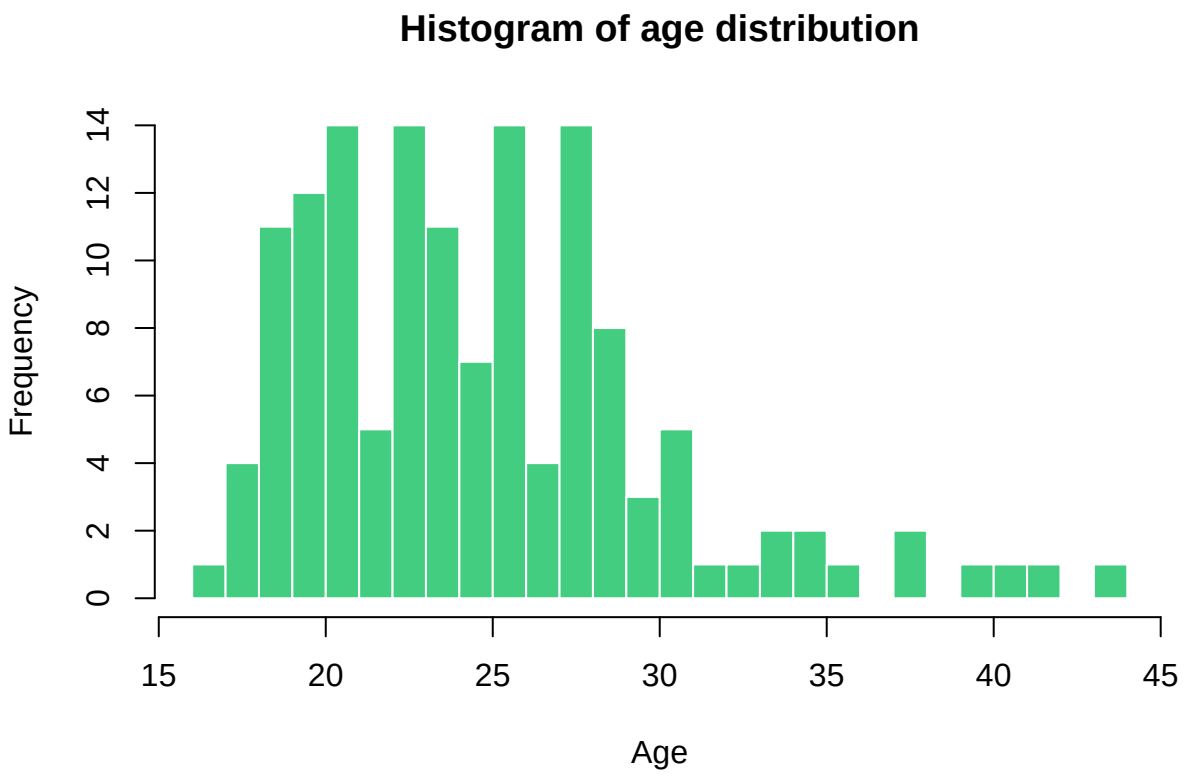


Age

```
summary(data.all[,4])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   16.00   21.00   24.00   25.18   28.00   44.00
```

```
hist(data.all[,4], xlab = "Age", col = "seagreen3", border = "white",
     main = "Histogram of age distribution", breaks = length(unique(data.all[,4])))
```



Age of the participants ranged from 16 to 44. If we look at the distribution of age in the cis- and transgender group we see that the range is similar in both groups.

```
# Cisgender group
summary(data.all[data.all[,2]<3,4])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   19.00   23.00   25.00   25.92   29.00   41.00
```

```
# Transgender group
summary(data.all[data.all[,2]>2,4])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   16.00   20.75   24.00   24.62   26.25   44.00
```

Social-Economic Status

```
table(data.all[,5])
```

```
##
##  1  2  3
## 19 87 34
```

Level of education

```
table(data.all[,6])
```

```
##
##  2  3  4  5
```

```
## 22 76 28 14
```

Handedness

```
table(data.all[,7])
```

```
##
##   1   2
## 129  11
```

Gender identity

```
summary(data.all[,8])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   0.000   0.000   5.000   5.036  10.000  10.000
```

```
table(data.all[,8])
```

```
##
##  0  1  2  3  7  8  9 10
## 49  4 13  4  1  9 16 44
```

```
# Cisgender women
summary(data.all[data.all[,2]==1,8])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   7.000   9.000   9.500   9.267  10.000  10.000
```

```
# Cisgender men
summary(data.all[data.all[,2]==2,8])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##     0.0     0.0     0.0     0.9     2.0     3.0
```

```
# Transgender women
summary(data.all[data.all[,2]==3,8])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   0.000   0.000   0.000   0.375   0.000   3.000
```

```
# Transgender men
summary(data.all[data.all[,2]==4,8])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   8.000   9.000  10.000   9.625  10.000  10.000
```

Sexual orientation

```
summary(data.all[,9])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   0.000   0.000   5.000   4.957  10.000  10.000
```

```
table(data.all[,9])
```

```
##
##  0  1  2  3  7  8  9 10
## 50 12  7  1  1  9 14 46
```

```
# Cisgender women
summary(data.all[data.all[,2]==1,9])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.0000  0.0000  0.0000  0.5333  1.0000  2.0000
```

```
# Cisgender men
summary(data.all[data.all[,2]==2,9])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   7.000   9.250  10.000   9.533  10.000  10.000
```

```
# Transgender women
summary(data.all[data.all[,2]==3,9])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   8.000   9.000  10.000   9.475  10.000  10.000
```

```
# Transgender men
summary(data.all[data.all[,2]==4,9])
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   0.000   0.000   0.000   0.325   0.000   3.000
```

Mental illnesses

There are no available measures for the cisgender group. ####Somatization

```
table(data.all[,22])
```

```
##
## #NULL!      0      1
##     60     67     13
```

Obsessive-compulsive disorder

```
table(data.all[,23])
```

```
##
## #NULL!      0      1
##     60     58     22
```

Among the cisgender participants 1 had a history of obsession.

Interpersonal sensitivity

```
table(data.all[,24])
```

```
##
## #NULL!      0      1
##     60     57     23
```

Depression

```
table(data.all[,25])
```

```
##
## #NULL!      0      1      2
##     60     42     37      1
```

Among the cisgender participants 3 had a history of depression.

Anxiety

```
table(data.all[,26])
```

```
##
## #NULL!      0      1      2
##     60     54     25      1
```

Among the cisgender participants 1 had a history of a general anxiety disorder.

Hostility

```
table(data.all[,27])
```

```
##
## #NULL!      0      1      2
##     60     64     15      1
```

Phobic anxiety

```
table(data.all[,28])
```

```
##
## #NULL!      0      1
##     60     67     13
```

Paranoia

```
table(data.all[,29])
```

```
##
## #NULL!      0      1
##     60     46     34
```

Psychotism

```
table(data.all[,30])
```

```
##
## #NULL!      0      1
##     60     67     13
```

Global severity

```
table(data.all[,31])
```

```
##
## #NULL!      0      1
##     60     59     21
```

Cisgender group

Past psychiatric condition Out of 60 cisgender participants 3 had a history of depression, 1 reported a general anxiety disorder and 1 had a history of obsession.

Past medical condition Out of 60 cisgender participants 3 reported migraine, 1 reported left ear surgery, 1 participant had suffered from heart palpitations, 1 participants reported a history of meningitis, 1 participant reported they had asthma as a child and 1 partcipants reported favism.

Analysis of 1 measurement

```
bg <- 3
nd <- 28
ln <- nd-bg
# Object to save p-values of ANOVA
pan <- array(data=NA, dim = ln)

# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
  tempan <- aov(data.hyp[,i] ~ as.factor(data.hyp[,2]))
  pan[i-bg+1] <- unlist(summary(tempan))[9]
}

# FDR correction on p-values to correct for multiple testing
pancorr <- p.adjust(pan, method = "bonferroni")
round(pancorr,3)
```

```
##  [1] 0.918 1.000 0.000 0.006 0.025 0.746 0.132 0.016 1.000 0.000 0.006
## [12] 0.312 0.029 0.012 0.008 0.000 0.018 0.000 0.000 0.039 0.116 1.000
## [23] 0.000 0.032 0.000 1.000
```

```
sum(pancorr < 0.05)
```

```
## [1] 17
```

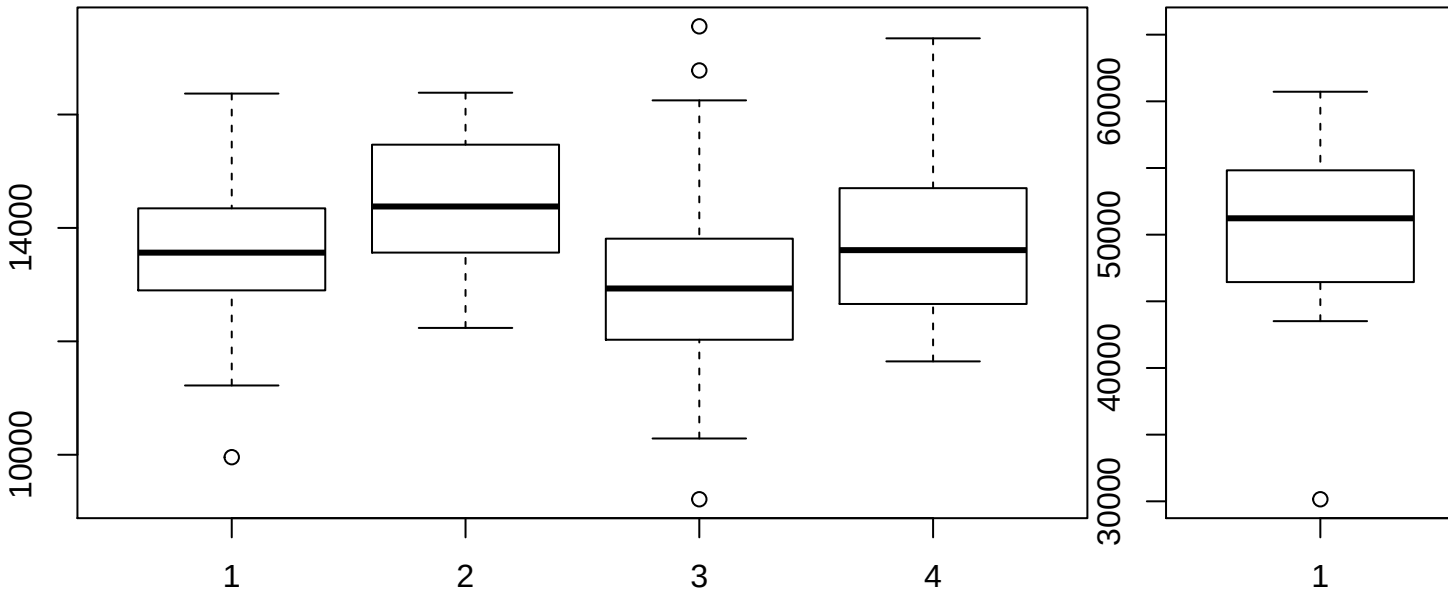
```
names(data.hyp[,which(pancorr < 0.05) + bg - 1])
```

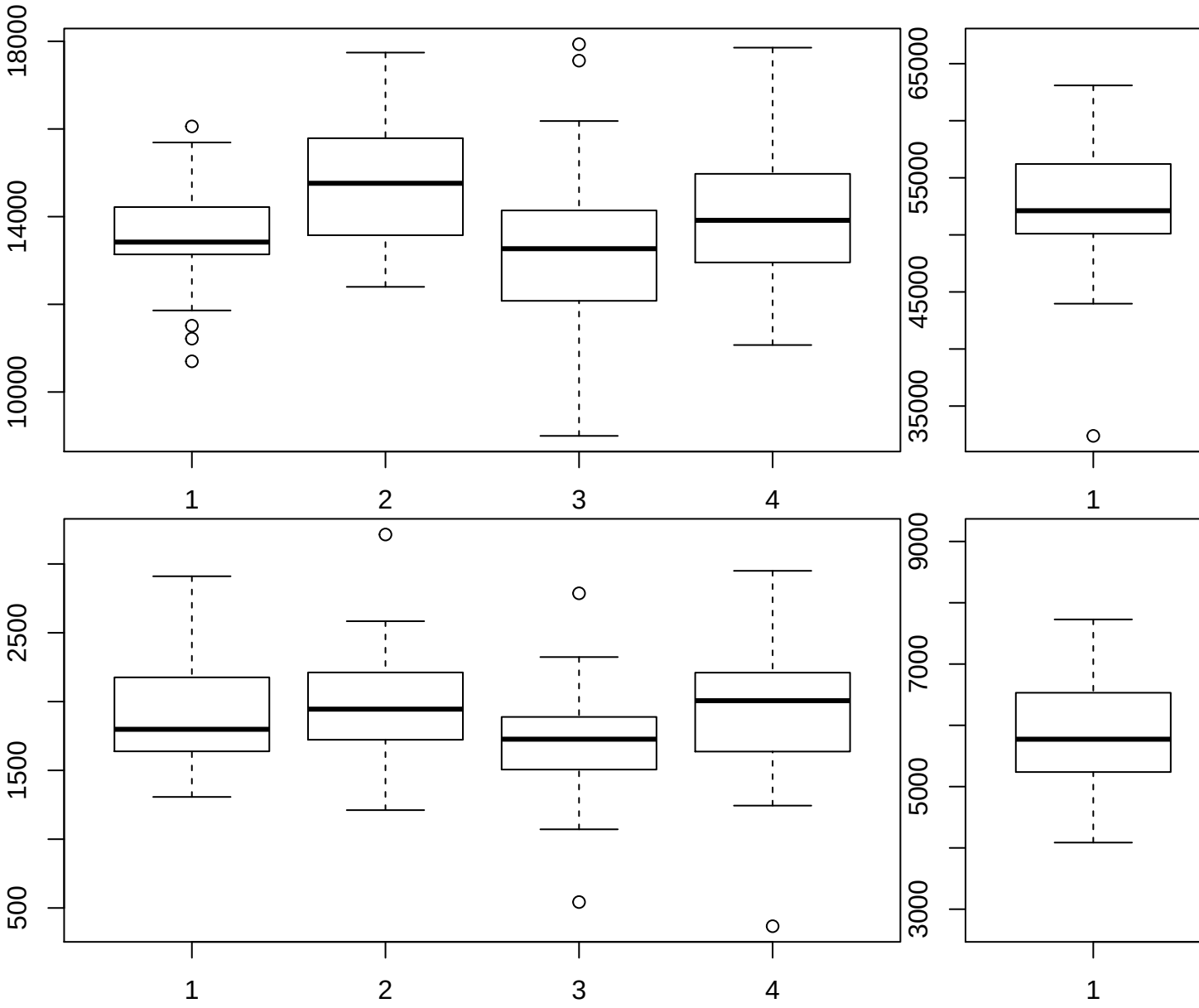
```
##  [1] "T1_L_fusiform_volume"
##  [2] "T1_L_inferiorparietal_volume"
##  [3] "T1_L_postcentral_volume"
##  [4] "T1_R_caudalanteriorcingulate_volume"
##  [5] "T1_R_fusiform_volume"
##  [6] "T1_R_inferiorparietal_volume"
##  [7] "T1_R_precentral_volume"
##  [8] "T1_R_frontalpole_volume"
##  [9] "T1_LeftCerebellumWhiteMatter"
## [10] "T1_LeftCerebellumCortex"
## [11] "T1_RightCerebellumWhiteMatter"
## [12] "T1_RightCerebellumCortex"
## [13] "T1_LeftThalamusProper"
## [14] "T1_LeftCaudate"
```

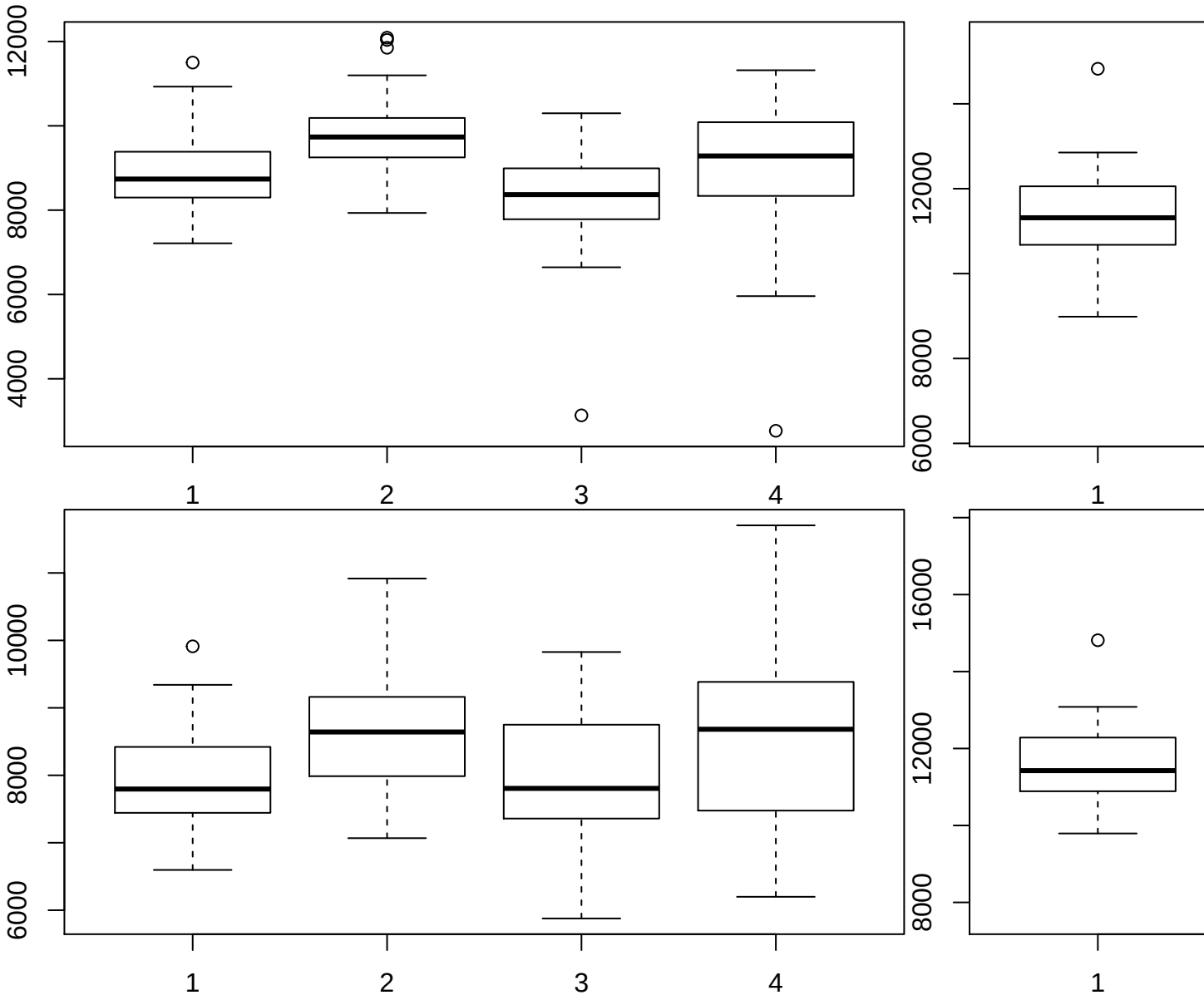
```
## [15] "T1_RightThalamusProper"
## [16] "T1_RightCaudate"
## [17] "T1_RightPutamen"
```

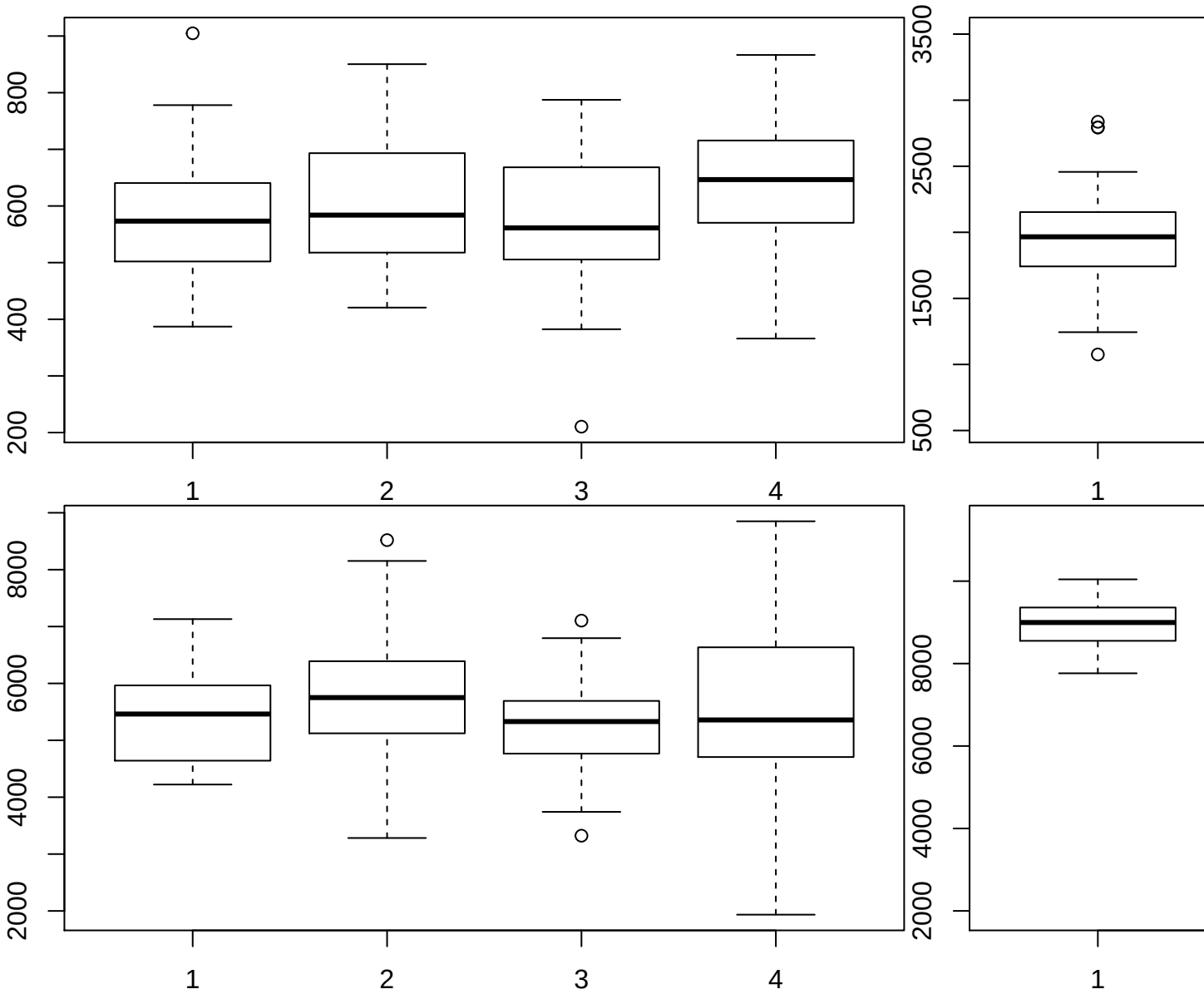
Analysis of the average

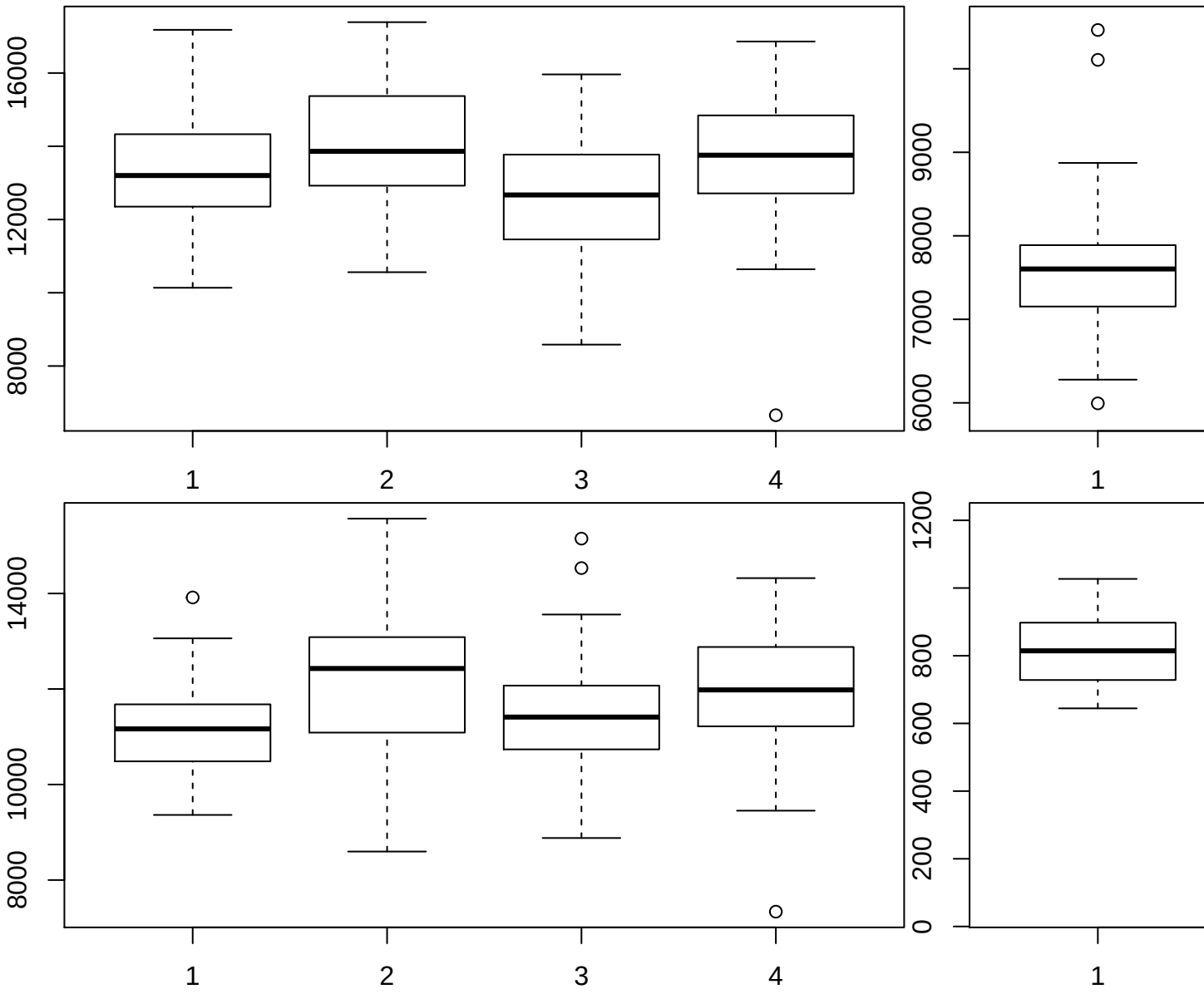
```
bg <- 55
nd <- 80
ln <- nd-bg+1

# Object to save p-values of ANOVA
pan <- array(data=NA, dim = ln)

# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
  tempan <- aov(data.hyp[,i] ~ as.factor(data.hyp[,2]))
  pan[i-bg+1] <- unlist(summary(tempan))[9]

  # construct boxplot for every region
  boxplot(data.hyp[,i] ~ as.factor(data.hyp[,2]))
}
```

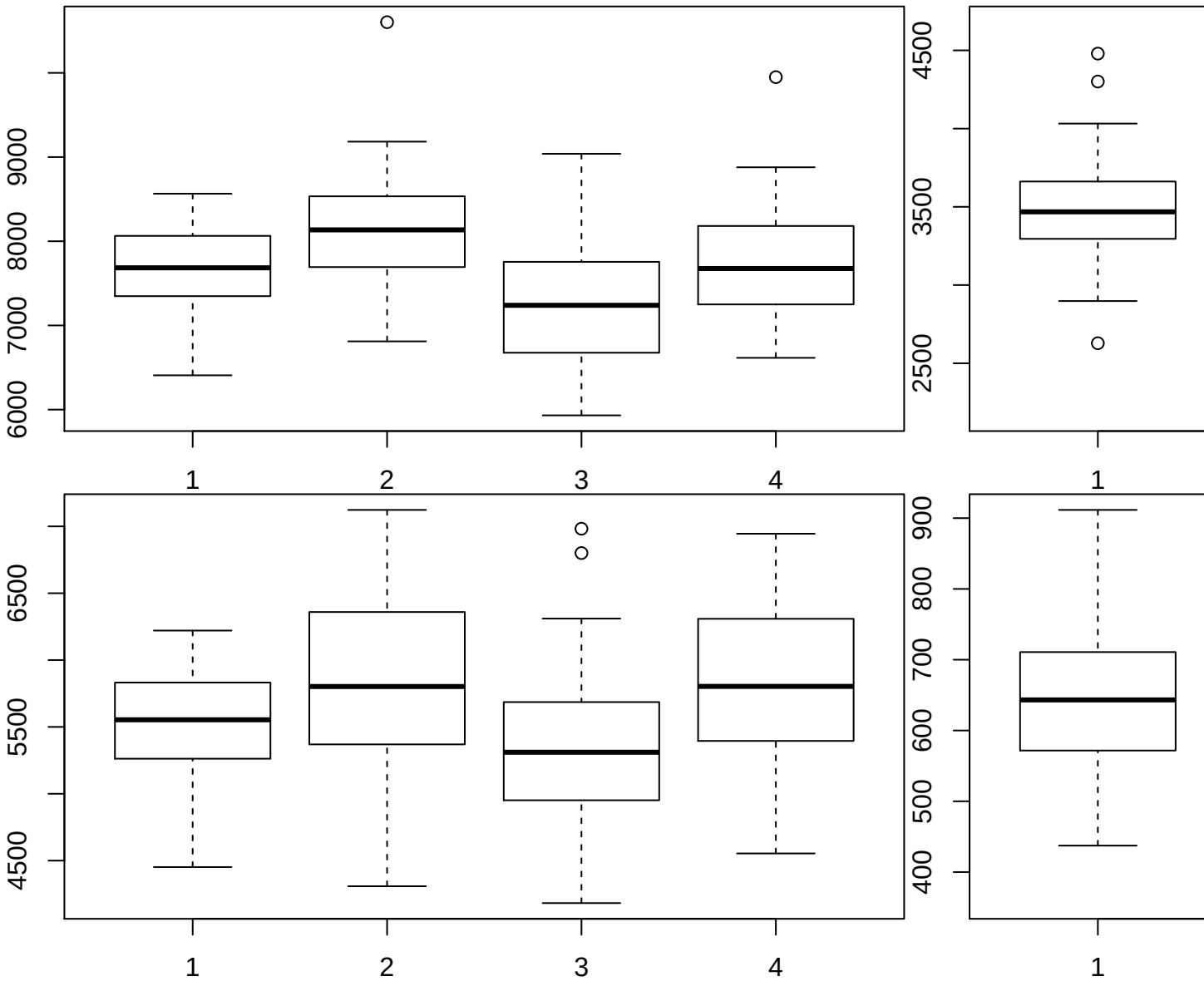


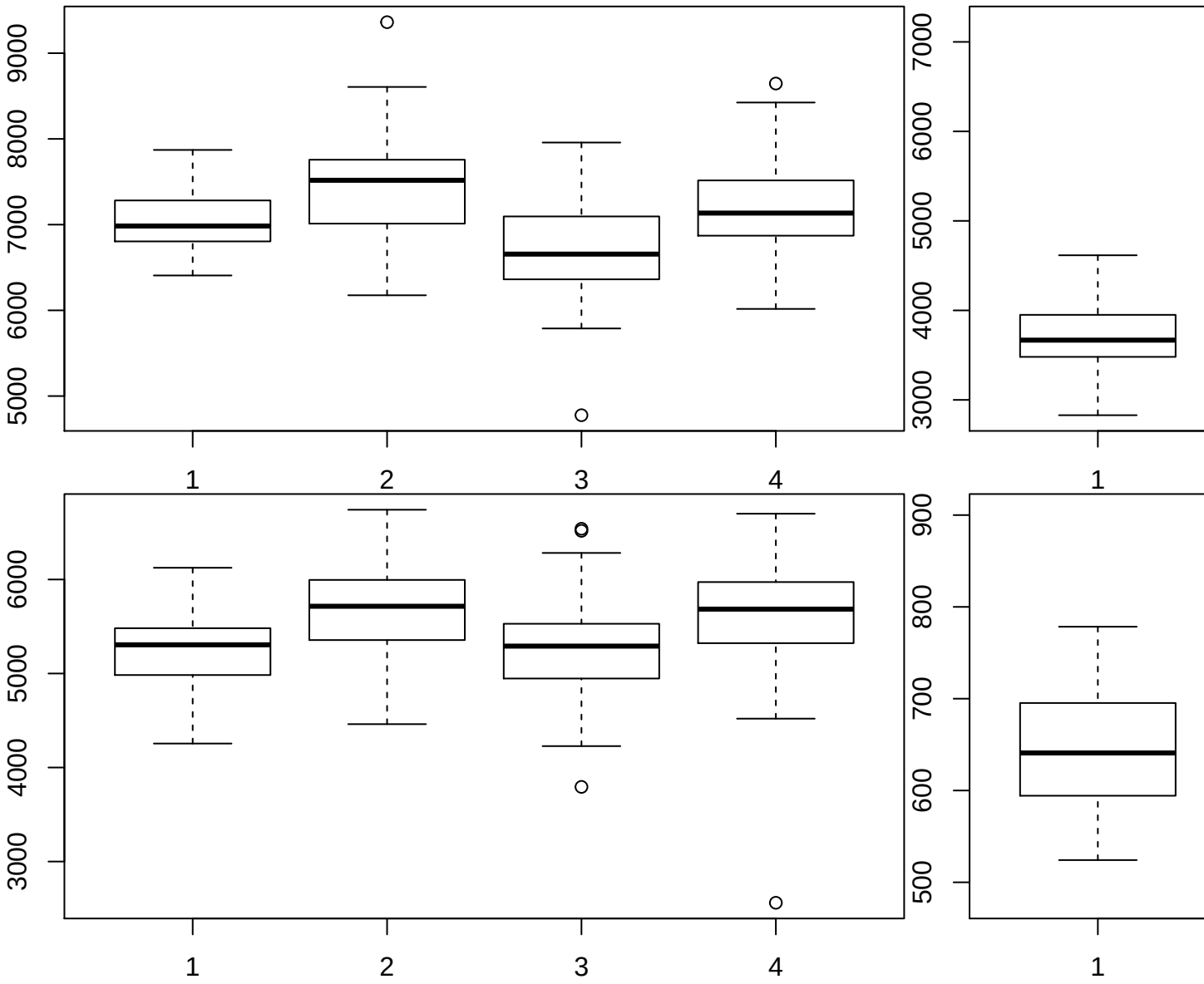

18000
14000
10000
65000
55000
45000
35000
1
2
3
4
1
2500
1500
500
9000
7000
5000
3000
1
2
3
4
1


12000
8000
6000
4000
1
2
3
4
12000
8000
6000
1
10000
8000
6000
1
2
3
4
16000
12000
8000
1


200
400
600
800
1
2
3
4
500
1500
2500
3500
1
2000
4000
6000
8000
1
2
3
4
2000
4000
6000
8000
1


16000
12000
8000
1
2
3
4
9000
8000
7000
6000
1
14000
10000
8000
1
2
3
4
1200
800
600
400
200
0
1


6000
7000
8000
9000
1
2
3
4
2500
3500
4500
1
4500
5500
6500
1
2
3
4
400
500
600
700
800
900
1




```
# FDR correction on p-values to correct for multiple testing
pancorr <- p.adjust(pan, method = "bonferroni")
round(pancorr,3)
```

```
##  [1] 0.049 0.000 0.040 0.000 0.698 1.000 0.001 0.076 0.089 1.000 1.000
## [12] 0.015 1.000 0.009 0.053 1.000 0.193 0.035 0.000 0.073 0.008 1.000
## [23] 0.000 0.146 0.022 0.292
```

```
sum(pancorr < 0.05)
```

```
## [1] 12
```

```
names(data.hyp[,which(pancorr < 0.05) + bg - 1])
```

```
##  [1] "Tavg_LeftCerebellumWhiteMatter"
##  [2] "Tavg_LeftCerebellumCortex"
##  [3] "Tavg_RightCerebellumWhiteMatter"
##  [4] "Tavg_RightCerebellumCortex"
```

```
##  [5] "Tavg_L_fusiform_volume"
##  [6] "Tavg_R_caudalanteriorcingulate_volume"
##  [7] "Tavg_R_fusiform_volume"
##  [8] "Tavg_R_frontalpole_volume"
##  [9] "Tavg_LeftThalamusProper"
## [10] "Tavg_LeftPutamen"
## [11] "Tavg_RightThalamusProper"
## [12] "Tavg_RightPutamen"
```

Why are there less regions for which the difference is statistically significant when the average is used compared to when one measure is used?

Post-hoc tests

We conduct post-hoc t-tests on the statistically significant regions to determine which group differences cause the effect.

Correlation between T1 and T2

```
bg <- 36
nd <- 108
ln <- nd-bg+1

# Object to save correlations
corrall <- array(data=NA, dim = ln)

# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
  corrall[i-bg+1] <- cor(x = data.all[,i], y = data.all[,i + ln + 1])
}

summary(corrall)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.6334  0.7950  0.8243  0.8216  0.8466  0.9985
```

```
bg <- 3
nd <- 28
ln <- nd-bg+1

# Object to save correlations
corrhyp <- array(data=NA, dim = ln)

# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
  corrhyp[i-bg+1] <- cor(x = data.hyp[,i], y = data.hyp[,i + ln])
}

summary(corrhyp)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.7046  0.9050  0.9334  0.9056  0.9498  0.9963
```

Simulations

Intro

Code

First we need to define the parameters of our simulations.

```
# variance/sd epsilon
seps <- 1

# Number of simulations
asim <- 10

# Effect size
delta <- 0.8

# Number of participants
n <- 30
n.1 <- n/2      # in the first group
n.2 <- n/2      # in the second group

# Level of statistical significance
alpha <- 0.05

# Correlation between first and second measurement
rho <- seq(0.01,0.99,0.01)
```

Then we prepare objects to store our results

```
# Number of simulations
pow.mean1<-vector("numeric",length(rho))
pow.mean2<-vector("numeric",length(rho))
pow.mean3<-vector("numeric",length(rho))
pow.mean4<-vector("numeric",length(rho))
```

```
## Loading required package: Matrix
```

```
##
## Attaching package: 'lmerTest'
```

```
## The following object is masked from 'package:lme4':
##
##     lmer
```

```
## The following object is masked from 'package:stats':
##
##     step
```

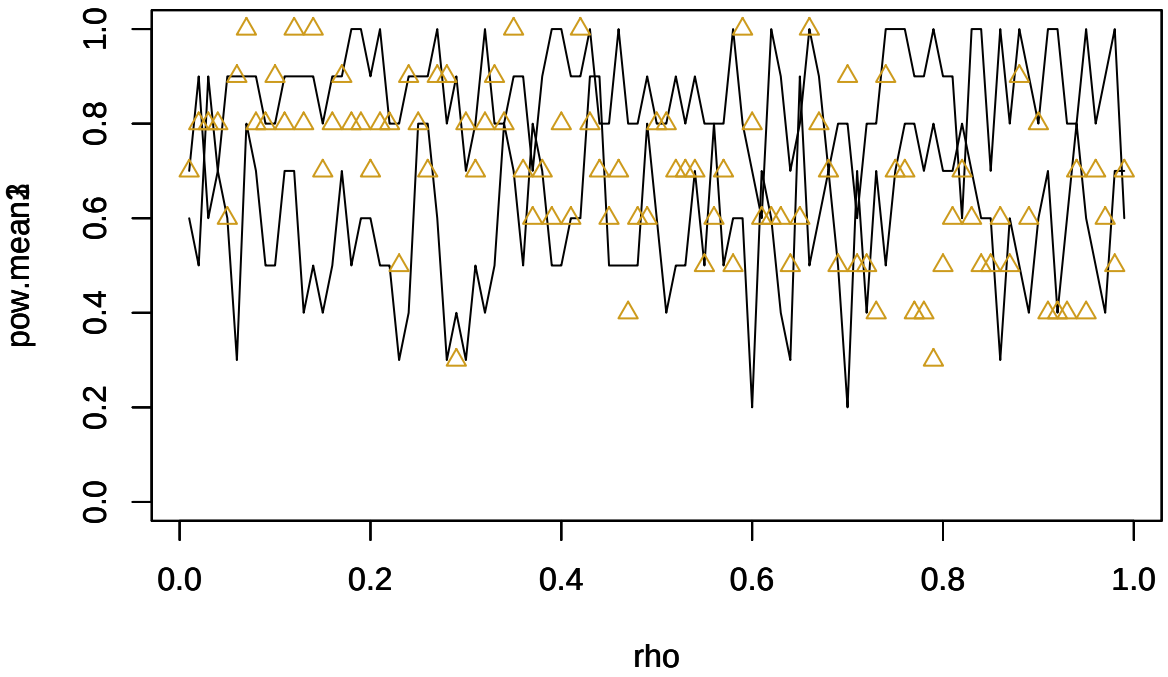
```
# Loop over preset correlations between measure 1 and measure 2
for(i in 1:length(rho)){
  # Create objects to store power in for every simulations
  pow.1<-vector("numeric",asim)
  pow.2<-vector("numeric",asim)
  pow.3<-vector("numeric",asim)
  pow.4<-vector("numeric",asim)
```

```
for(k in 1:asim){
  # Scenario 1: lower bound of power curve
  # two groups with equal amount of subjects, groups differ with an effect size delta
  # Construct a vector that determines in which group each subject falls
  x<-c(rep(1,n.1),rep(0,n.2))

  # Vector with observations in the set of participants
  y<-rnorm(n,0,seps)
  # Add an effect size to the first group
  y[1:n.1]<-y[1:n.1]+delta

  # Boolean of whether an effect is detected, this is later used to compute the power
  pow.1[k]<-summary(lm(y~x))$coef[2,4]<alpha

  # Scenario 2: upper bound of power curve
  # two groups with equal amount of subjects, twice as many as scenario 1, groups differ with an effe
  # Construct a vector that determines in which group each subject falls
  x2<-c(rep(1,(n.1*2)),rep(0,(n.2*2)))

  # Vector with observations in the set of participants
  y2<-rnorm(n*2,0,seps)
  # Add an effect size to the first group
  y2[1:(n.1*2)]<-y2[1:(n.1*2)]+delta

  # Boolean of whether an effect is detected, this is later used to compute the power
  pow.2[k]<-summary(lm(y2~x2))$coef[2,4]<alpha

  # Scenario 3: two measurements for every subject, same amount of subjects as in scenario 1
  # two groups with equal amount of subjects, correlation between measurements, groups differ with an
  # Construct a vector that determines in which group each subject falls
  x3<-c(rep(1,n.1),rep(0,n.2),rep(1,n.1),rep(0,n.2))

  # Vector with first observation of every participant
  y3<-rnorm(n,0,seps)
  # Factor to multiply second set of observations with to obtain results in line with predefined corr
  alpac<-sqrt(rho[i]^2/(1-rho[i]^2)*seps)
  # Construct second set of observations that are correlated with first set (y3)
  y3.2u<-alpac*y3+rnorm(n)
  y3.2<-y3.2u/sqrt(var(y3.2u))
  # Add effect size to the first group of participants
  y3[1:n.1]<-y3[1:n.1]+delta
  y3.2[1:n.1]<-y3.2[1:n.1]+delta
  # Combine both observations in 1 vector
  y3o<-c(y3,y3.2)

  # Define subject numbers
  subject<-rep(1:n,2)
  # Construct mixed model
  mm<-lmer(y3o ~ x3 + (1 | subject))
  # Boolean of whether an effect is detected, this is later used to compute the power
  pow.3[k]<-summary(mm)$coef[2,5]<alpha

  # Scenario 4: What if we work with the average?
```

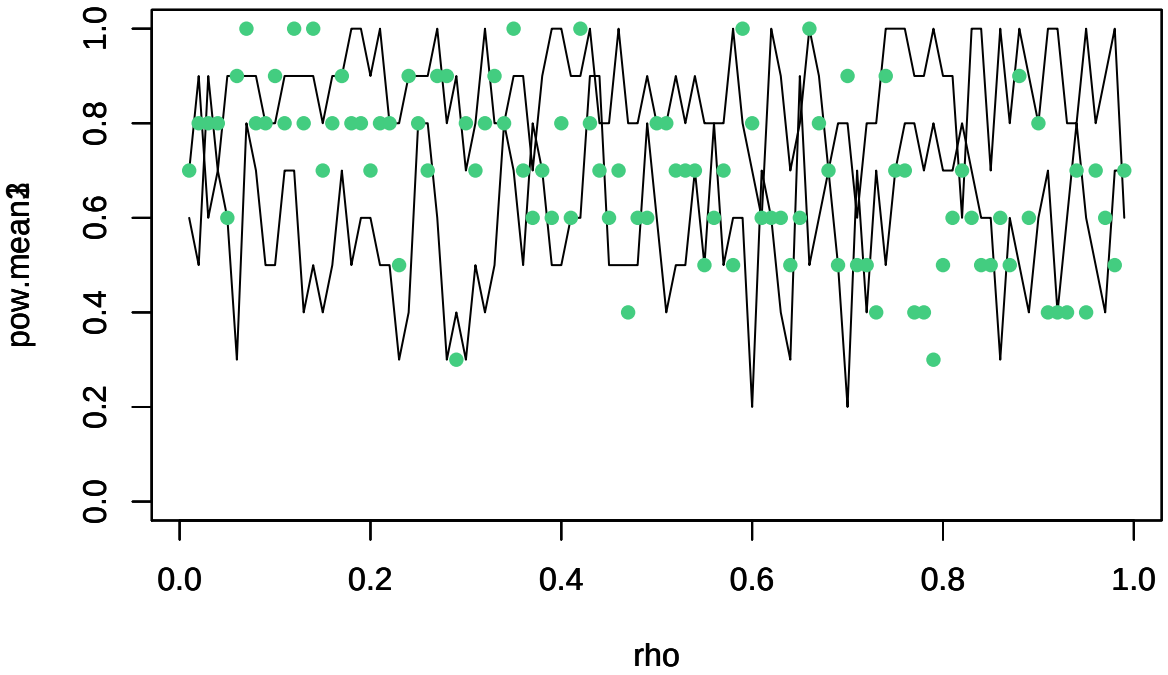
```
    y3m<-(y3+y3.2)/2
    # Boolean of whether an effect is detected, this is later used to compute the power
    pow.4[k]<-summary(lm(y3m~x))$coef[2,4]<alpha
  }
  pow.mean1[i]<-mean(pow.1)
  pow.mean2[i]<-mean(pow.2)
  pow.mean3[i]<-mean(pow.3)
  pow.mean4[i]<-mean(pow.4)
}
```

Results

```
# power of taking both measures into account
plot(rho,pow.mean1,ylim=c(0,1), type="l")
par(new = TRUE)
plot(rho,pow.mean2,ylim=c(0,1), type="l")
par(new = TRUE)
plot(rho,pow.mean3,ylim=c(0,1), type="p", col = "goldenrod3", pch = 2)
```




```
# power of using the average
plot(rho,pow.mean1,ylim=c(0,1), type="l")
par(new = TRUE)
plot(rho,pow.mean2,ylim=c(0,1), type="l")
par(new = TRUE)
plot(rho,pow.mean3,ylim=c(0,1), type="p", col = "seagreen3", pch = 16)
```

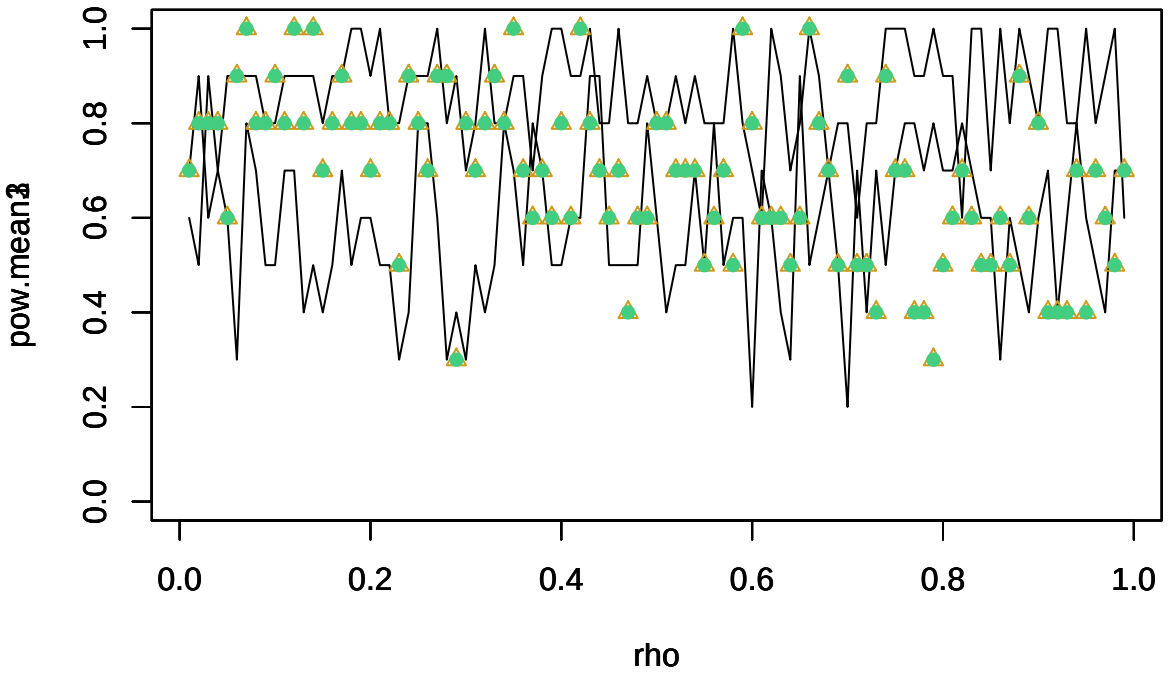


If we overlay both plots we see that there is a lot of overlap. This can also be demonstrated by looking at the results that are exactly the same.

```
table(pow.mean3==pow.mean4)
```

```
##
## FALSE  TRUE
##     1    98
```

```
# Overlap of both plots
plot(rho,pow.mean1,ylim=c(0,1), type="l")
par(new = TRUE)
plot(rho,pow.mean2,ylim=c(0,1), type="l")
par(new = TRUE)
plot(rho,pow.mean3,ylim=c(0,1), type="p", col = "goldenrod3", pch = 2)
par(new = TRUE)
plot(rho,pow.mean3,ylim=c(0,1), type="p", col = "seagreen3", pch = 16)
```



Discussion