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 administering 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 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)</pre>
## [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"
##
       "Tavg_RightCerebellumCortex"
       "Tavg L caudalanteriorcingulate volume"
       "Tavg_L_caudalmiddlefrontal_volume"
##
       "Tavg_L_fusiform_volume"
##
    [7]
##
    [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"
```

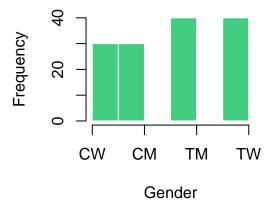
Descriptives

In this section population parameters are presented.

Gender

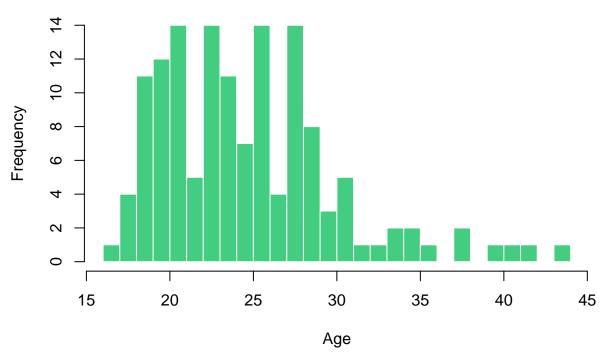
There were 60 cisgender and 80 transgender participants. One participant (P22) was removed from the analysis because no anatomical data was available for this participant.

Frequency of gender



Age

Histogram of age distribution



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])</pre>
      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
```

Level of education

```
table(data.all[,6])
## 2 3 4 5
## 22 76 28 14
Handedness
table(data.all[,7])
##
##
    1
## 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
# Cisqender 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
##
# Cisqender 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
         2 3 7
                  8
                    9 10
## 50 12 7 1 1
                  9 14 46
# Cisgender women
summary(data.all[data.all[,2]==1,9])
                              Mean 3rd Qu.
##
     Min. 1st Qu. Median
                                              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
                             0.325
##
     0.000
            0.000
                                     0.000
                                             3.000
Mental illnesses
```

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

```
table(data.all[,22])
##
## #NULL!
                0
                       1
```

Obsessive-compulsive disorder

67

13

```
table(data.all[,23])
##
## #NULL!
                0
                       1
               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.

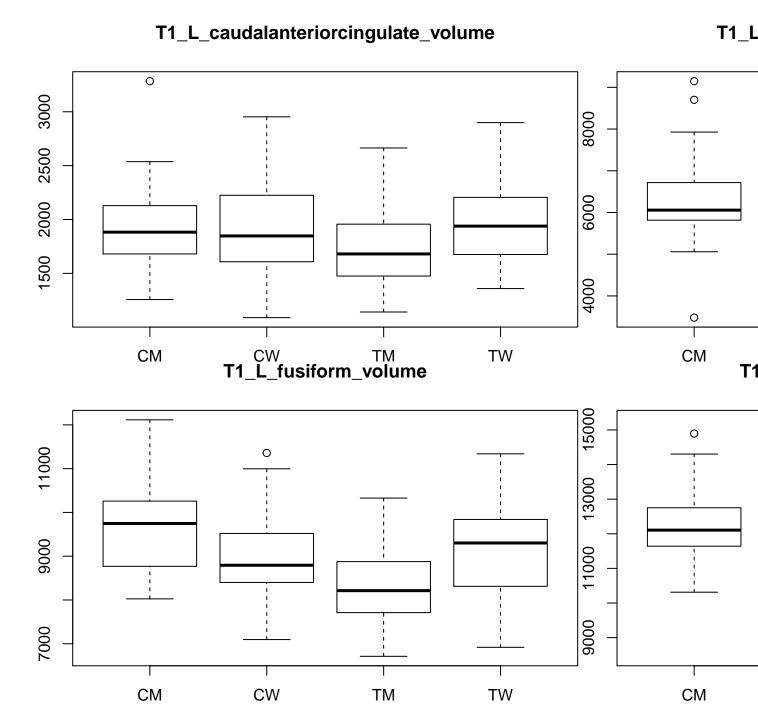
Past medical condition Out of 60 cisgender participants 3 reported migraine, 1 reported left ear surgery, 1 participant had suffered from heart palpitations, 1 participants reported a history of meningitis, 1 participant reported they had asthma as a child and 1 participants reported favism.

Analysis of 1 measurement

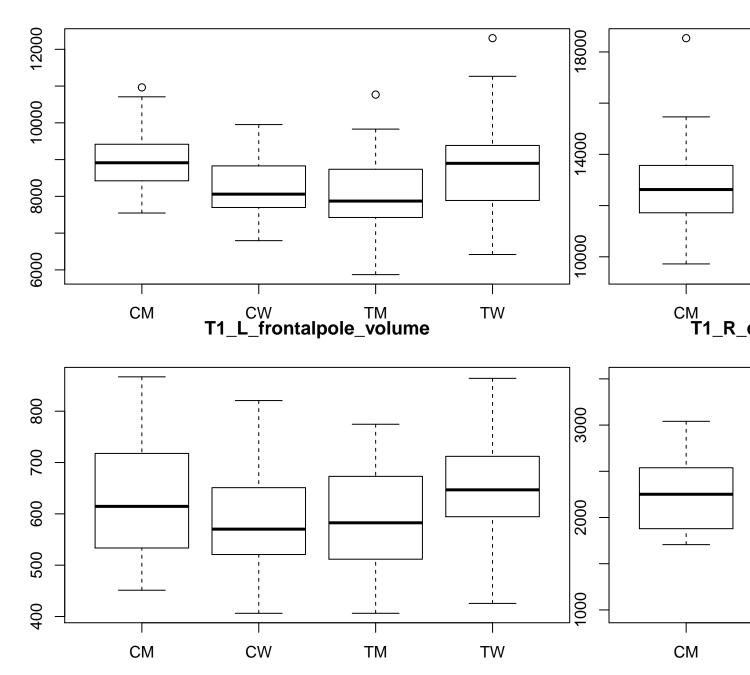
```
bg <- 3
nd <- 28
ln <- nd-bg
fac <- c(rep("CW",30), rep("CM",30), rep("TM",40), rep("TW",40)) # factor for participant group
# Object to save p-values of ANOVA
pan.one <- array(data=NA, dim = ln)

# 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.one[i-bg+1] <- unlist(summary(tempan))[9]

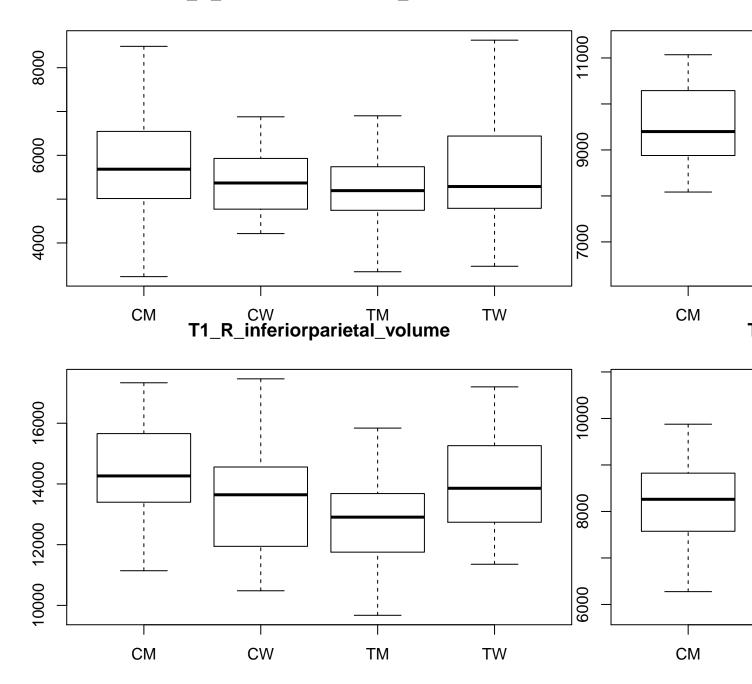
  boxplot(data.hyp[,i] ~ fac, main = names(data.hyp)[i])
}</pre>
```



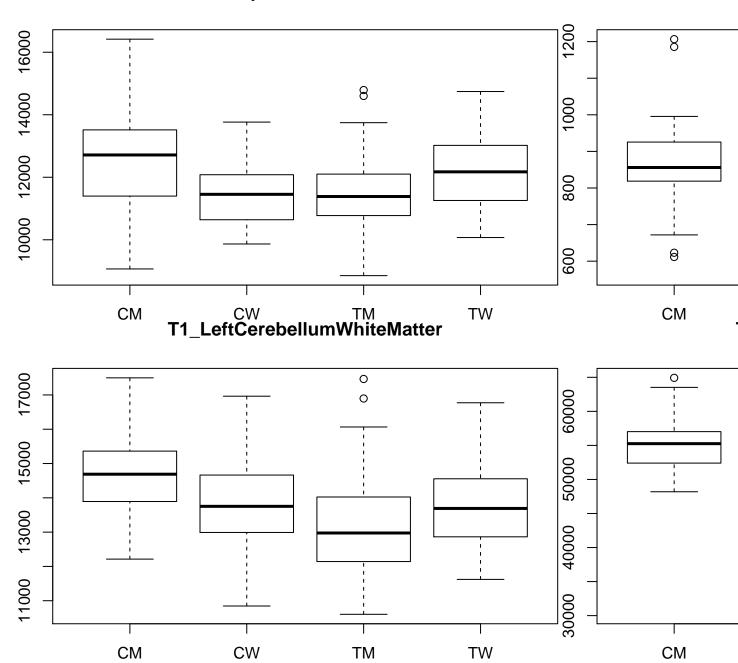
T1_L_postcentral_volume

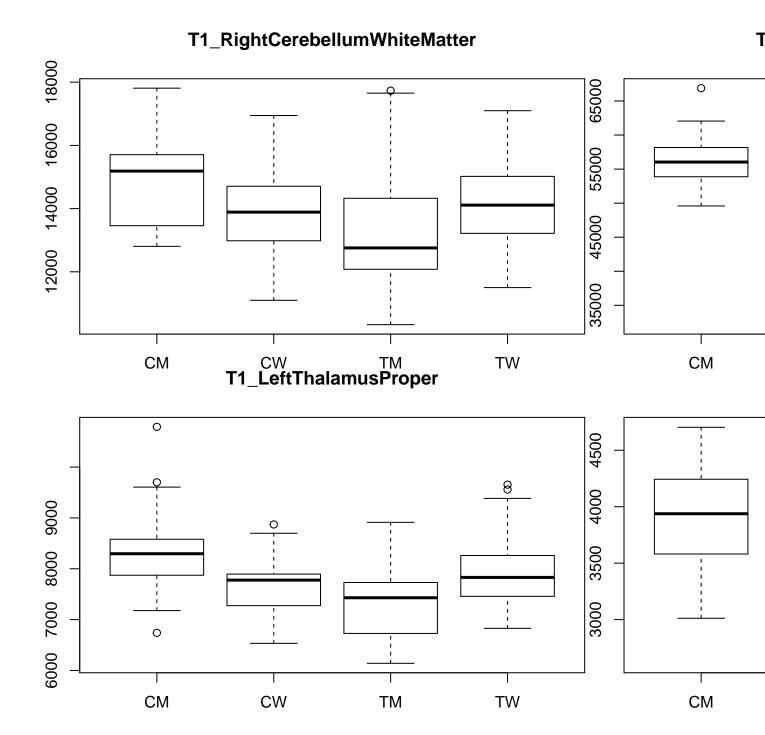


T1_R_caudalmiddlefrontal_volume

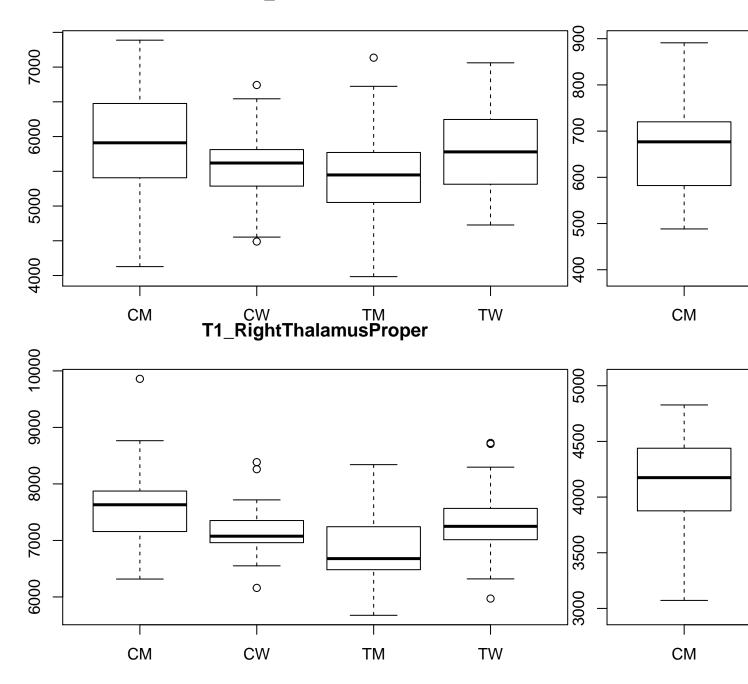




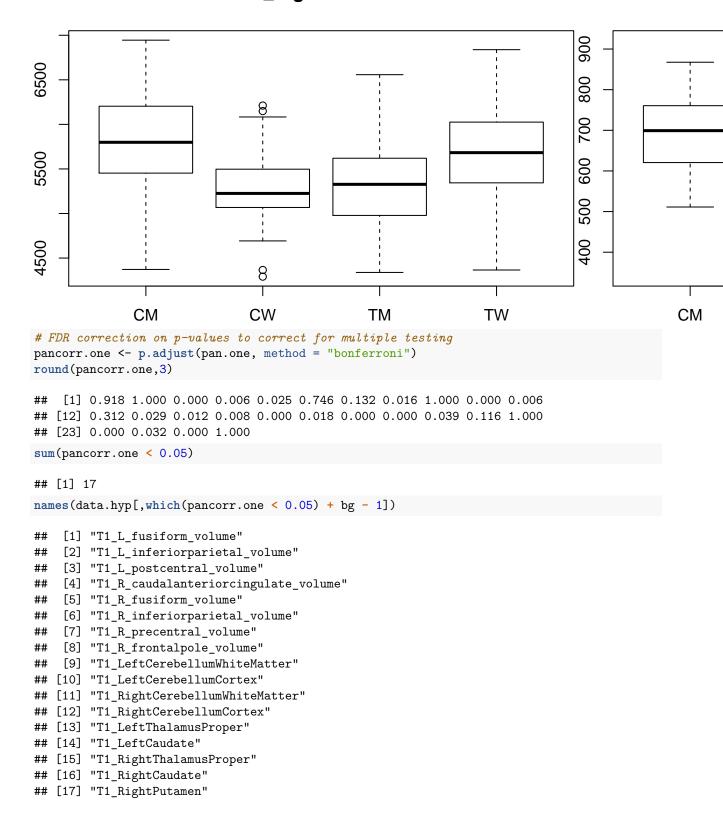




T1_LeftPutamen

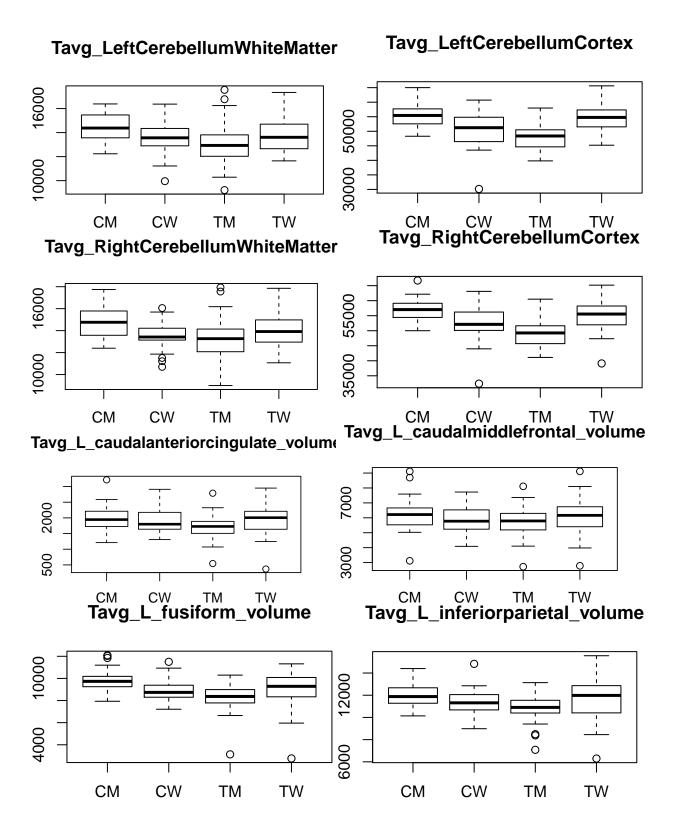


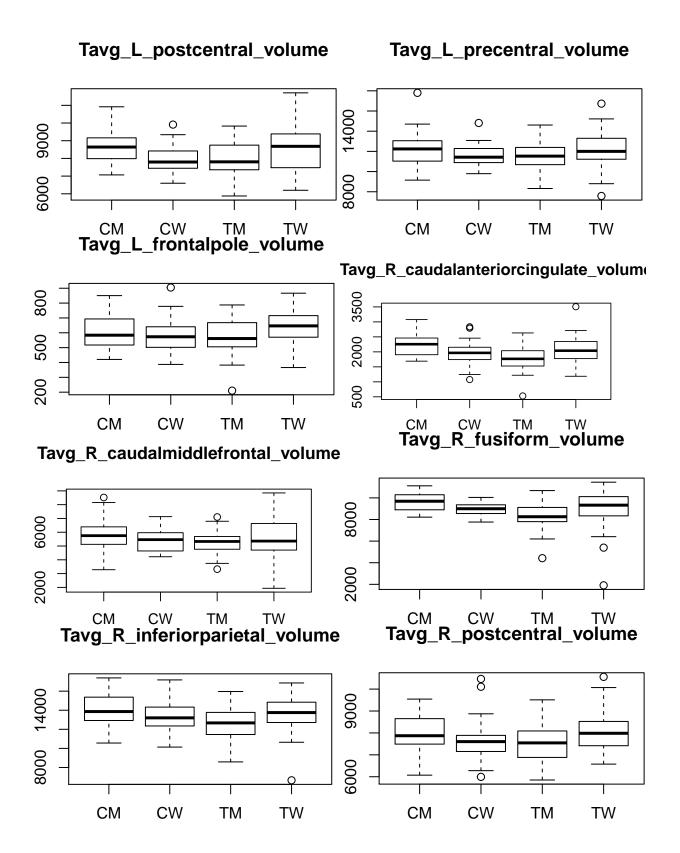
T1_RightPutamen

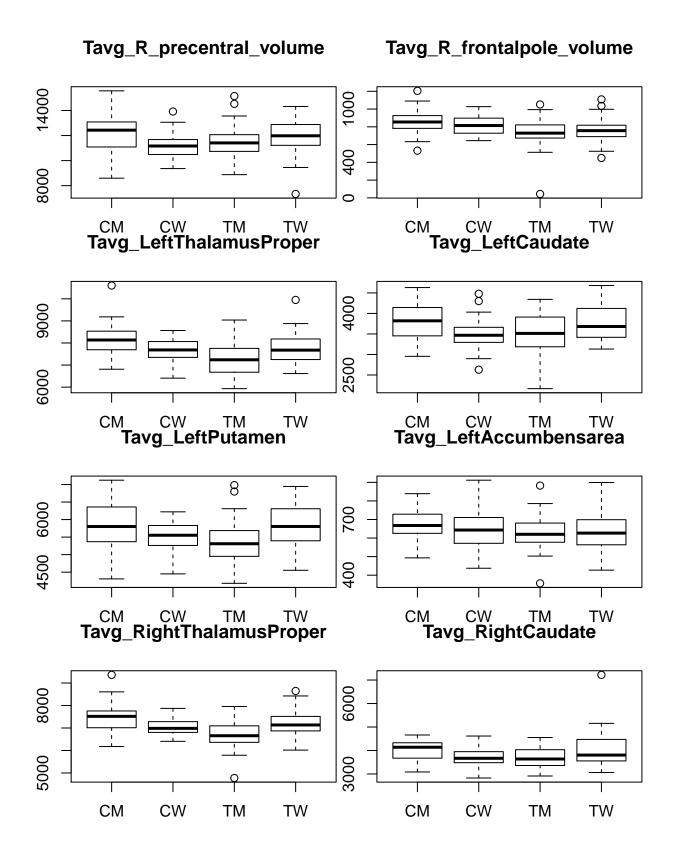


Analysis of the average

```
bg <- 55
nd <- 80
ln \leftarrow nd-bg+1
fac <- c(rep("CW",30), rep("CM",30), rep("TM",40), rep("TW",40)) # factor for participant group
# Object to save p-values of ANOVA
pan.avg <- array(data=NA, dim = ln)</pre>
# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
 tempan <- aov(data.hyp[,i] ~ as.factor(data.hyp[,2]))</pre>
  pan.avg[i-bg+1] <- unlist(summary(tempan))[9]</pre>
 # construct boxplot for every region
  boxplot(data.hyp[,i] ~ fac, main = names(data.hyp)[i])
# FDR correction on p-values to correct for multiple testing
pancorr.avg <- p.adjust(pan.avg, method = "bonferroni")</pre>
round(pancorr.avg,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.avg < 0.05)</pre>
## [1] 12
names(data.hyp[,which(pancorr.avg < 0.05) + bg - 1])</pre>
## [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"
```

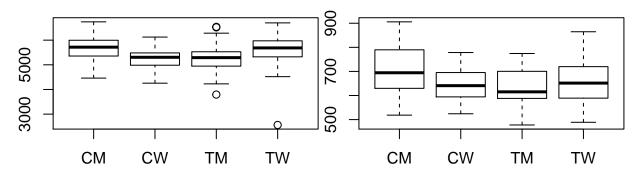






Tavg_RightPutamen

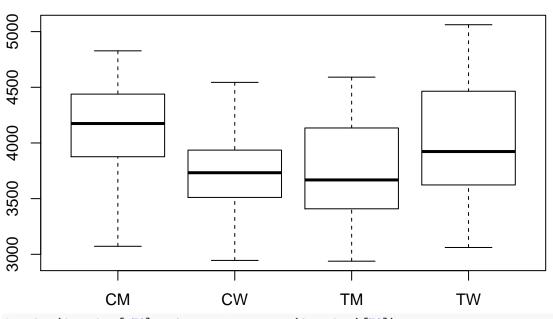
Tavg_RightAccumbensarea



Why are there less regions for which the difference is statistically significant when the average is used compared to when one measure is used? To investigate this we look at the difference between the boxplots for one statistically significant region.

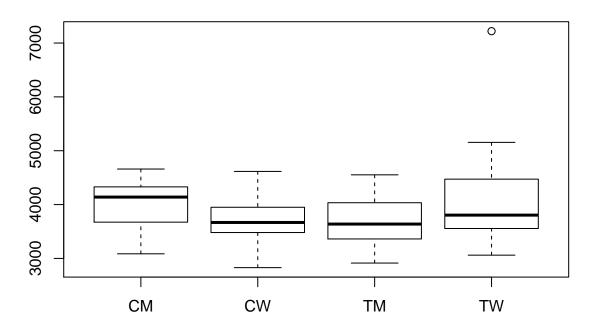
boxplot(data.hyp[,26] ~ fac, main = names(data.hyp)[26])

T1_RightCaudate



boxplot(data.hyp[,78] ~ fac, main = names(data.hyp)[78])

Tavg_RightCaudate



Post-hoc tests

We conduct post-hoc t-tests on the statistically significant regions to determine which group differences cause the effect. The p-values are uncorrected at this point and I computed them for every region.

```
# create an object with all possible combinations
allcomb <- combn(c(1:4),2)

# create object to save results
pt.one <- array(data = NA, dim = c(length(pan.one),dim(allcomb)[2]))
pt.avg <- array(data = NA, dim = c(length(pan.avg),dim(allcomb)[2]))

# Left Cerebellum White Matter
# 1 measure
bg <- 3
nd <- 28
for(r in bg:nd)
for(i in 1:dim(allcomb)[2]){
   pt.one[r-bg+1,i] <- unlist(t.test(data.hyp[data.hyp[,2]==allcomb[1,i],r], data.hyp[data.hyp[,2]==
   }
   round(pt.one,3)</pre>
```

```
## [,1] [,2] [,3] [,4] [,5] [,6]
## [1,] 0.812 0.028 0.980 0.040 0.762 0.007
## [2,] 0.149 0.507 0.291 0.029 0.599 0.057
## [3,] 0.002 0.008 0.289 0.000 0.034 0.000
## [4,] 0.023 0.026 0.469 0.000 0.158 0.004
## [5,] 0.002 0.504 0.039 0.000 0.386 0.010
## [6,] 0.047 0.524 0.135 0.015 0.515 0.040
## [7,] 0.155 0.887 0.003 0.166 0.178 0.002
## [8,] 0.012 0.142 0.449 0.000 0.066 0.017
## [9,] 0.099 0.430 0.261 0.027 0.576 0.079
```

```
## [10,] 0.002 0.003 0.258 0.000 0.130 0.001
## [11,] 0.027 0.095 0.178 0.000 0.255 0.001
## [12,] 0.145 0.371 0.089 0.011 0.891 0.003
## [13,] 0.002 0.830 0.004 0.006 0.369 0.015
## [14,] 0.001 0.938 0.104 0.001 0.029 0.121
## [15,] 0.006 0.129 0.934 0.000 0.002 0.113
## [16,] 0.001 0.098 0.002 0.000 0.686 0.000
## [17,] 0.007 0.174 0.490 0.000 0.022 0.037
## [18,] 0.001 0.038 0.010 0.000 0.251 0.000
## [19,] 0.001 0.033 0.102 0.000 0.029 0.000
## [20,] 0.004 0.973 0.012 0.003 0.481 0.011
## [21,] 0.023 0.467 0.070 0.005 0.361 0.011
## [22,] 0.196 0.874 0.912 0.135 0.183 0.973
## [23,] 0.021 0.008 0.310 0.000 0.129 0.001
## [24,] 0.001 0.858 0.021 0.001 0.254 0.034
## [25,] 0.000 0.401 0.000 0.000 0.179 0.005
## [26,] 0.531 0.051 0.540 0.014 0.247 0.283
  # Average
  bg <- 55
 nd <- 80
 for(r in bg:nd)
   for(i in 1:dim(allcomb)[2]){
      pt.avg[r-bg+1,i] <- unlist(t.test(data.hyp[data.hyp[,2]==allcomb[1,i],r], data.hyp[data.hyp[,2]==
 round(pt.avg,3)
          [,1] [,2] [,3] [,4] [,5]
   [1,] 0.015 0.153 0.471 0.000 0.058 0.029
   [2,] 0.001 0.047 0.005 0.000 0.363 0.000
  [3,] 0.001 0.373 0.195 0.000 0.055 0.047
## [4,] 0.000 0.022 0.016 0.000 0.162 0.000
   [5,] 0.769 0.021 0.894 0.011 0.868 0.013
   [6,] 0.233 0.423 0.352 0.054 0.759 0.087
## [7,] 0.002 0.023 0.651 0.000 0.025 0.017
## [8,] 0.024 0.065 0.308 0.000 0.443 0.012
## [9,] 0.001 0.894 0.024 0.002 0.497 0.031
## [10,] 0.080 0.946 0.085 0.093 0.835 0.102
## [11,] 0.446 0.686 0.073 0.223 0.315 0.018
## [12,] 0.012 0.100 0.559 0.000 0.046 0.023
## [13,] 0.131 0.461 0.279 0.035 0.679 0.088
## [14,] 0.001 0.004 0.845 0.000 0.065 0.037
## [15,] 0.059 0.100 0.184 0.001 0.529 0.003
## [16,] 0.200 0.920 0.036 0.122 0.406 0.012
## [17,] 0.004 0.198 0.002 0.068 0.766 0.075
## [18,] 0.260 0.010 0.039 0.001 0.005 0.443
## [19,] 0.006 0.015 0.580 0.000 0.024 0.004
## [20,] 0.008 0.753 0.003 0.017 0.939 0.009
## [21,] 0.007 0.418 0.007 0.002 0.568 0.001
## [22,] 0.346 0.483 0.915 0.068 0.261 0.521
## [23,] 0.004 0.012 0.082 0.000 0.152 0.001
## [24,] 0.002 0.685 0.015 0.004 0.972 0.028
## [25,] 0.001 0.710 0.005 0.003 0.588 0.014
## [26,] 0.030 0.349 0.699 0.003 0.066 0.187
```

Correlation between T1 and T2

```
bg <- 36
nd <- 108
ln \leftarrow nd-bg+1
# Object to save correlations
corrall <- array(data=NA, dim = ln)</pre>
# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
  corrall[i-bg+1] \leftarrow 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 \leftarrow nd-bg+1
# Object to save correlations
corrhyp <- array(data=NA, dim = ln)</pre>
# Compute ANOVA for every predictor and save p-value
for(i in bg:nd){
  corrhyp[i-bg+1] \leftarrow 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
# plot with correlations? Which region lies where?
```

Simulations

RESULTS OF THE SIMULATIONS STILL NEED TO FINISH, these take a long time to run. ## Intro ## Code

First we need to define the parameters of our simulations.

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

# Number of simulations
asim <- 10

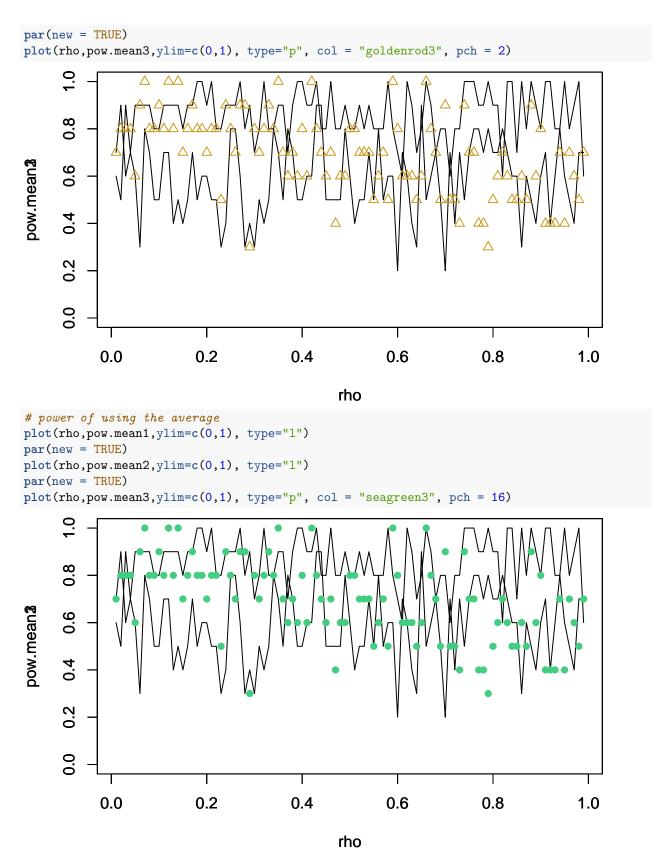
# Effect size
delta <- 0.8</pre>
```

```
# Number of participants
n <- 30
n.1 < - n/2
               # in the first group
               # in the second group
n.2 < - n/2
# Level of statistical significance
alpha \leftarrow 0.05
# Correlation between first and second measurement
rho \leftarrow seq(0.01, 0.99, 0.01)
Then we prepare objects to store our results
# Number of simulations
pow.mean1<-vector("numeric",length(rho))</pre>
pow.mean2<-vector("numeric",length(rho))</pre>
pow.mean3<-vector("numeric",length(rho))</pre>
pow.mean4<-vector("numeric",length(rho))</pre>
## 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)</pre>
  pow.2<-vector("numeric",asim)</pre>
  pow.3<-vector("numeric",asim)</pre>
  pow.4<-vector("numeric",asim)</pre>
  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)</pre>
  # Construct mixed model
 mm < -lmer(y3o \sim x3 + (1 \mid subject))
  # Boolean of whether an effect is detected, this is later used to compute the power
 pow.3[k] <-summary(mm) $coef[2,5] <alpha</pre>
  # Scenario 4: What if we work with the average?
 y3m<-(y3+y3.2)/2
  # Boolean of whether an effect is detected, this is later used to compute the power
 pow.4[k] < -summary(lm(y3m-x))$coef[2,4] <alpha
pow.mean1[i]<-mean(pow.1)</pre>
pow.mean2[i] <-mean(pow.2)</pre>
pow.mean3[i] <-mean(pow.3)</pre>
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")
```



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
            98
##
       1
# 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)
     0.8
pow.mean3
     9.0
     0.4
     0.2
     0.0
           0.0
                         0.2
                                        0.4
                                                                    8.0
                                                                                   1.0
                                                      0.6
                                               rho
```

Discussion