Reanalysis of 30-Hasan

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Contents

Reference

Hasan, A., Wobrock, T., Guse, B., Langguth, B., Landgrebe, M., Eichhammer, P., Frank, E., Cordes, J., Wölwer, W., Musso, F., Winterer, G., Gaebel, W., Hajak, G., Ohmann, C., Verde, P. E., Rietschel, M., Ahmed, R., Honer, W. G., Dechent, P., … Koutsouleris, N. (2017). Structural brain changes are associated with response of negative symptoms to prefrontal repetitive transcranial magnetic stimulation in patients with schizophrenia. Molecular Psychiatry, 22(6), 857–864. https://doi.org/10.1038/mp.2016.161

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Notes from reading methods section

The aim of the study was to determine whether negative symptom improvement in schizophrenia patients receiving rTMS to the left dorsolateral prefrontal cortex (DLPFC) was related to brain volume changes. A total of 73 patients with schizophrenia and predominant negative symptoms were randomized to an active (n = 34) or sham (n = 39) rTMS intervention applied 5 days per week for 3 weeks to the left DLPFC.

- Dependant variable: D_V_REL_Cluster1 or "brain volume changes"
- Independent variable: Treatment_Group, active (n = 34) vs. sham (n = 39)
- Covariate: "PANSS-NS%" (relative negative symptom improvement)

Reading data

Data is loaded, reshaped if necessary, and factors are specified.

```
##  Subject_Number Site   Treatment_Group D_PANSS_NS_REL    D_V_REL_Cluster1
##  1      : 1     1:30   Verum:34        Min.   :-64.706   Min.   :-4.4755
##  2      : 1     3:43   Sham :39        1st Qu.:-29.630   1st Qu.: 0.0086
##  3      : 1                            Median :-14.286   Median : 1.0903
##  4      : 1                            Mean   :-16.332   Mean   : 1.3647
##  5      : 1                            3rd Qu.: -4.545   3rd Qu.: 2.6918
##  6      : 1                            Max.   : 64.706   Max.   : 8.3032
##  (Other):67
##  D_V_REL_Cluster2  D_V_REL_Cluster3
##  Min.   :-2.3698   Min.   :-1.4315
##  1st Qu.:-0.0010   1st Qu.: 0.5623
##  Median : 0.8640   Median : 1.3192
##  Mean   : 0.7614   Mean   : 1.2982
##  3rd Qu.: 1.3195   3rd Qu.: 1.8729
##  Max.   : 4.0782   Max.   : 5.0302
##
```

Descriptives

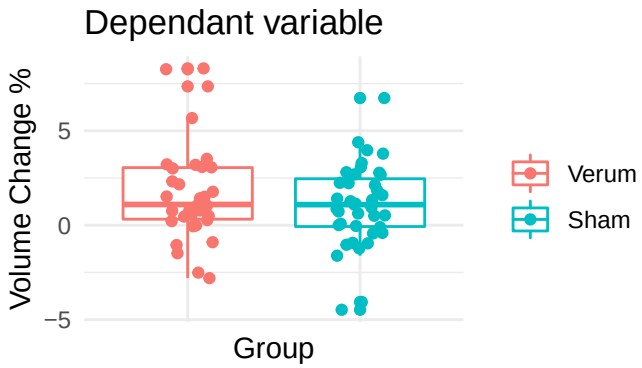
Dependant variable

The relationship between DV and IV.

```
# idx = c(1, 3, 2, 4) # sorting as in publication
tab.dv = array(NA, dim=c(2,3))
tab.dv[,1] = levels(data$Treatment_Group)
tab.dv[,2] = summary(data$Treatment_Group)
tab.dv[,3] = tapply(data$D_V_REL_Cluster1, data$Treatment_Group,
                    function (x) sprintf("%0.2f (%0.2f)", mean(x), sd(x)))
colnames(tab.dv) = c("group", "n", "mean (SD)") # large SD noted and manually checked to be correct
print(tab.dv)
```

```
##      group   n    mean (SD)
## [1,] "Verum" "34" "1.71 (2.63)"
## [2,] "Sham"  "39" "1.06 (2.15)"
```

```
ggplot(data, aes(y=D_V_REL_Cluster1, x=Treatment_Group, color=Treatment_Group)) +
  geom_boxplot() +
  geom_point(position = position_jitter(width = 0.15, height = 0)) +
  theme_minimal() +
  theme(axis.text.x = element_blank(), legend.title = element_blank()) +
  xlab("Group") + ylab("Volume Change %") + ggtitle("Dependant variable")
```

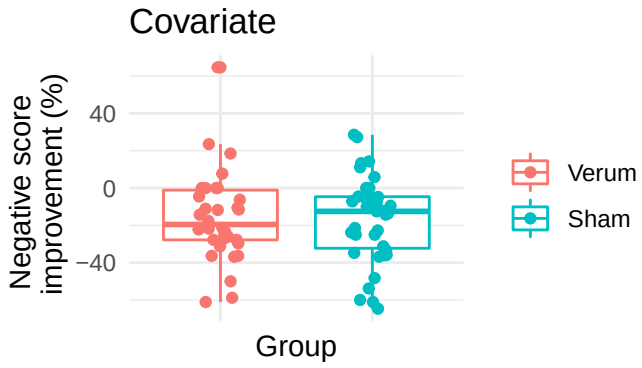


Covariate(s)

```
# idx = c(1, 3, 2, 4) # sorting as in publication
tab.cv = array(NA, dim=c(2,3))
tab.cv[,1] = levels(data$Treatment_Group)
tab.cv[,2] = summary(data$Treatment_Group)
tab.cv[,3] = tapply(data$D_PANSS_NS_REL, data$Treatment_Group,
                    function (x) sprintf("%0.1f (%0.1f)", mean(x), sd(x)))
colnames(tab.cv) = c("group", "n", "mean (SD)")
print(tab.cv) # large SD noted and manually checked to be correct
```

```
##      group   n    mean (SD)
## [1,] "Verum" "34" "-15.8 (23.9)"
## [2,] "Sham"  "39" "-16.8 (22.7)"
```

```
ggplot(data, aes(y=D_PANSS_NS_REL, x=Treatment_Group, color=Treatment_Group)) +
  geom_boxplot() +
  geom_point(position = position_jitter(width = 0.15, height = 0)) +
  theme_minimal() +
  theme(axis.text.x = element_blank(), legend.title = element_blank()) +
  xlab("Group") + ylab("Negative score \n improvement (%)") + ggtitle("Covariate")
```



Main analysis ANCOVA

```
contrasts(data$Treatment_Group) = contr.helmert(2)

fit.ancova = manova(cbind(D_V_REL_Cluster1, D_V_REL_Cluster2, D_V_REL_Cluster3) ~ Treatment_Group * D_PA

result = Anova(fit.ancova, type=3) # Type III
print(result)
```

```
##
## Type III MANOVA Tests: Pillai test statistic
##                                Df test stat approx F num Df den Df    Pr(>F)
## (Intercept)                     1   0.48155  20.7438      3     67  1.29e-09
## Treatment_Group                 1   0.00091   0.0204      3     67 0.9960000
## D_PANSS_NS_REL                  1   0.20777   5.8572      3     67 0.0012952
## Treatment_Group:D_PANSS_NS_REL  1   0.24469   7.2350      3     67 0.0002816
##
## (Intercept)                    ***
## Treatment_Group
## D_PANSS_NS_REL                 **
## Treatment_Group:D_PANSS_NS_REL ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Comparing ANCOVA in original study with reanalysis

Independant variable

```
tab.IV = rbind(stats.orig.IV, stats.rep.IV)
rownames(tab.IV) = c("original Study", "reanalysis")
print(t(tab.IV))
```

```
##        original Study reanalysis
## Fvalue "0.02"         "0.020"
## df1    "3"            "3"
## df2    "67"           "67"
## pvalue "0.996"        "0.996"
```

Covariate

```
tab.CV = rbind(stats.orig.CV, stats.rep.CV)
rownames(tab.CV) = c("original Study", "reanalysis")
print(t(tab.CV))
```

```
##        original Study reanalysis
## Fvalue "5.86"         "5.86"
## df1    "3"            "3"
## df2    "67"           "67"
## pvalue "0.001"        "0.001"
```

Interaction

```
tab.CV = rbind(stats.orig.int, stats.rep.inter)
rownames(tab.CV) = c("original Study", "reanalysis")
print(t(tab.CV))
```

```
##        original Study reanalysis
## Fvalue "7.24"         "7.24"
## df1    "3"            "3"
## df2    "67"           "67"
## pvalue "< 0.0005"     "0.0003"
```

Assumptions

1. Homogeneity of variance

- ANOVA/ANCOVA is fairly robust in terms of the error rate when sample sizes are equal.
- When groups with larger sample sizes have larger variances than the groups with smaller sample sizes, the resulting F-ratio tends to be conservative. That is, it's more likely to produce a non-significant result when a genuine difference does exist in the population.
- Conversely, when the groups with larger sample sizes have smaller variances than the groups with smaller samples sizes, the resulting F-ratio tends to be liberal and can inflate the false positive rate.

```
tapply(data$D_V_REL_Cluster1, data$Treatment_Group, sd)
```

```
##    Verum     Sham
## 2.634741 2.153220
```

```
leveneTest(D_V_REL_Cluster1 ~ data$Treatment_Group, data = data)
```

```
## Levene's Test for Homogeneity of Variance (center = median)
##       Df F value Pr(>F)
## group  1  0.4015 0.5283
##       71
```

2. Independence between covariate and IV

When the covariate and the experimental effect (independent variable) are not independent the treatment effect is obscured, spurious treatment effects can arise and the interpretation of the ANCOVA is seriously compromised.

We test whether our groups differ on the CV. If the groups do not significantly differ then is appropriate to use the covariate.

In this reanalysis, there is independence between CV and IV

```
fit.cv = aov(data$D_PANSS_NS_REL ~ data$Treatment_Group, data = data)
Anova(fit.cv, type=3)
```

```
## Anova Table (Type III tests)
##
## Response: data$D_PANSS_NS_REL
##                      Sum Sq Df F value   Pr(>F)
## (Intercept)           19292  1 35.5833 8.68e-08 ***
```

```
## data$Treatment_Group     21  1  0.0384   0.8453
## Residuals             38495 71
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

3. Homogeneity of regression slopes

In the current study, the covariate was included as an interaction term, and not as a "global" covariate. This is exactly, how one would test HRS. Therefore, to test HRS is not necessary here and it is fair to say the assumption was met.

Notes

- The study reported a MANCOVA as there were three outcome variables
- The MANCOVA results (effect of treatment, covariate and interaction) were fully reproduced.
- Assumptions were all met. Homogeneity of regression slopes was not required to assess as the covariate was included as an interaction term with the treatment.
- The authors provided SPSS analysis script code, which helped to understand that the covariate was used in an interaction term and not a a global covariate.

Data was analyzed according to recommendations by Field, Miles, & Field (2012).