# Parametric and non-parametric multivariate test statistics for high-dimensional fMRI data

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COMPSTAT
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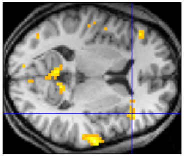
# Characteristics of fMRI data

fMRI = functional magnetic resonance imaging

→ detection of activated voxels in the brain

- number of variables (voxels) exceeds the number of measurements extremely
- spatial dependence
- temporal dependence in each voxel (assuming a first-order autoregressive model)



Hollmann et al. (2010)

first-level analyses mostly done by using a univariate general linear model for each voxel including an adjustment for temporal correlation

Yielding higher power via multivariate statistics in fMRI data?!

# General linear model

signal is measured as time series in $n$ time points over $p$ voxels ($n < p$) $\rightarrow$ presentable in a GLM

$$\mathbf{Y} = \mathbf{X}\mathrm{B} + \mathbf{E} \qquad \mathbf{E} \sim \mathrm{N}(\mathbf{0}, \mathbf{I} \otimes \mathbf{\Sigma})$$

$$\begin{pmatrix} y_{11} & \cdots & y_{1p} \\ \vdots & \ddots & \vdots \\ y_{n1} & \cdots & y_{np} \end{pmatrix} = \begin{pmatrix} x_{11} & \cdots & x_{1s} \\ \vdots & \ddots & \vdots \\ x_{n1} & \cdots & x_{ns} \end{pmatrix} \begin{pmatrix} \beta_{11} & \cdots & \beta_{1p} \\ \vdots & \ddots & \vdots \\ \beta_{s1} & \cdots & \beta_{sp} \end{pmatrix} + \begin{pmatrix} \epsilon_{11} & \cdots & \epsilon_{1p} \\ \vdots & \ddots & \vdots \\ \epsilon_{n1} & \cdots & \epsilon_{np} \end{pmatrix}$$

hypothesis: $\mathrm{H}_0 : \mathbf{C}'\mathrm{B} = \mathbf{0}$

$\Rightarrow$ multivariate analysis is possible by means of so-called stabilized multivariate test statistics (Läuter et al., 1996 and 1998)

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$\Rightarrow$ multivariate analysis is possible by means of so-called stabilized multivariate test statistics (Läuter et al., 1996 and 1998) but adjustment for temporal correlation necessary: aim of our research

# Standardized Sum and Principal Component Test

creating $q$ $(1 \leq q < \min(p,\ n-s))$ summary variables (scores) by means of a $p \times q$-dimensional weight matrix $\mathbf{D}$, that is any function of the total sums of squares and cross products matrix $\mathbf{W}$ $(\mathbf{W} = \mathrm{SSQ}_{\mathrm{hypothesis}} + \mathrm{SSQ}_{\mathrm{residuals}})$

$$\mathbf{Z}_{(n\times q)} = \mathbf{Y}_{(n\times p)}\mathbf{D}_{(p\times q)}$$

$\Rightarrow$ using these low-dimensional scores in classical analyses then

- Standardized Sum Test: $\mathbf{d} = \mathrm{Diag}(\mathbf{W})^{-\frac{1}{2}}\mathbf{1}_p$
- Principal Component Test: $\mathbf{D}$: computed by means of the eigenvalue problem of $\mathbf{W}$
  - scale dependent: $\mathbf{W}\mathbf{D} = \mathbf{D}\mathbf{\Lambda}$, $\mathbf{D}'\mathbf{D} = \mathbf{I}_q$
  - scale invariant: $\mathbf{W}\mathbf{D} = \mathrm{Diag}(\mathbf{W})\mathbf{D}\mathbf{\Lambda}$, $\mathbf{D}'\mathrm{Diag}(\mathbf{W})\mathbf{D} = \mathbf{I}_q$

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# Parametric adjustment for temporal correlation

**Satterthwaite** approximation

temporal correlation is taken into account within the test statistic

$\rightarrow$ adjusting the variance estimation and the degrees of freedom

**Prewhitening**

$\mathbf{Y} = \mathbf{X}\mathrm{B} + \mathbf{E}\;,\;\mathbf{E} \sim \mathrm{N}(\mathbf{0}, \mathbf{V} \otimes \mathbf{\Sigma})$

$\rightarrow$ classical model: $\mathbf{Y}^\star = \mathbf{X}^\star\mathrm{B} + \mathbf{E}^\star,\;\; \mathbf{E}^\star \sim \mathrm{N}(\mathbf{0}, \mathbf{I}_n \otimes \mathbf{\Sigma})$ via

$\mathbf{Y}^\star = \mathbf{V}^{-\frac{1}{2}}\mathbf{Y},\quad \mathbf{X}^\star = \mathbf{V}^{-\frac{1}{2}}\mathbf{X},\quad \mathbf{E}^\star = \mathbf{V}^{-\frac{1}{2}}\mathbf{E}$

$\rightarrow$ yields an exact test when $\mathbf{V}$ is known

$\Rightarrow$ **problem**:

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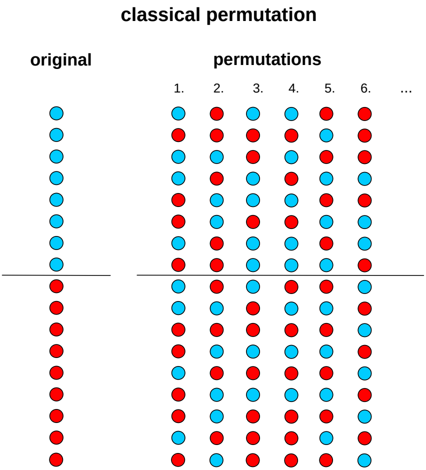
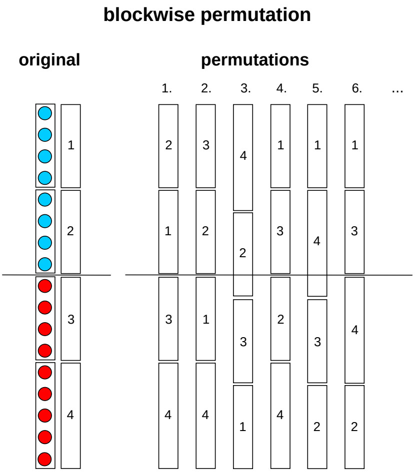
# Non-parametric adjustment for temporal correlation



# Non-parametric adjustment for temporal correlation

**blockwise permutation** of adjacent elements to account for temporal correlation



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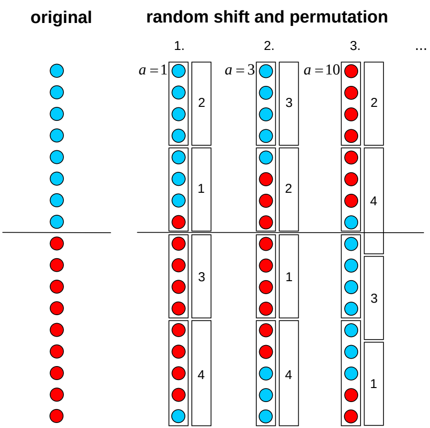
**blockwise permutation including a random shift**



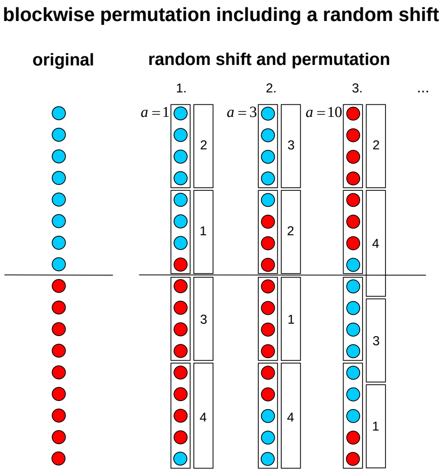
# Non-parametric adjustment for temporal correlation

**blockwise permutation** of adjacent elements to account for temporal correlation

**including a random shift** in order to increase the number of possible blockwise permutations

$\longrightarrow$ in each permutation step:

- random removal of $a$ $(0 \leq a < n)$ elements on top, adding them at the end
- block arrangement and permutation
- calculation of the permuted test statistic



# Simulation studies for multivariate adjustments

. . . to control the empirical type I error

- prewhitening holds the nominal test level (for at least a few hundreds of measurements, which is a common sample size in fMRI studies)
- Satterthwaite approximation partly exceeds the test level
- blockwise permutation including a random shift holds the nominal test level (for a block length of at least 40 even when there are just two blocks left)

# Application on fMRI data: Ultimatum Game

Ultimatum Game: socio-economic application in fMRI
$\longrightarrow$ subject gets an offer for division of an amount of money

$\longrightarrow$ the **difference in activation for unfair and fair offers** in the anterior insula is hard to detect by univariate test statistics – better using multivariate tests?

$\Rightarrow$ analyzing this small homogeneous region as well as a larger heterogeneous region including the anterior insula to compare the different test statistics and adjustments

# Application on fMRI data: Ultimatum Game

exemplary results of one subject

| region | correction method | univariate test statistics: unadjusted | univariate test statistics: Bonferroni-adjusted | multivariate test statistics: Standard. Sum Test | multivariate test statistics: scale variant PC Test | multivariate test statistics: scale invariant PC Test |
|---|---|---|---|---|---|---|
| anterior insula $p = 48$ | Satterthwaite | 0.002 | 0.105 | <0.001 | 0.099 | 0.123 |
| | prewhitening | 0.006 | 0.283 | <0.001 | 0.086 | 0.073 |
| | blockwise permutation including a random shift | <0.001 | 0.048 | 0.005 | 0.070 | 0.071 |
| region including anterior insula $p = 900$ | Satterthwaite | <0.001 | 0.234 | 0.162 | 0.035 | 0.361 |
| | prewhitening | 0.001 | 1.000 | 0.169 | 0.018 | 0.237 |
| | blockwise permutation including a random shift | <0.001 | 0.090 | 0.236 | 0.004 | 0.009 |

*P*-values for testing the difference of unfair to fair offers within the anterior insula as well as within a larger heterogenous region containing the anterior insula;
univariate: the minimale *P*-value is given; permutations done with block length 50

# Summary

⇒ stabilized multivariate tests are applicable and advantageous in fMRI analyses using adjustments for temporal correlation

- prewhitening works well for large sample sizes
- Satterthwaite approximation partly fails
- blockwise permutation including a random shift turns out to be an applicable and powerful alternative method (also in the univariate case)

# References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Thank you for your attention.

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