Second level analysis of fMRI

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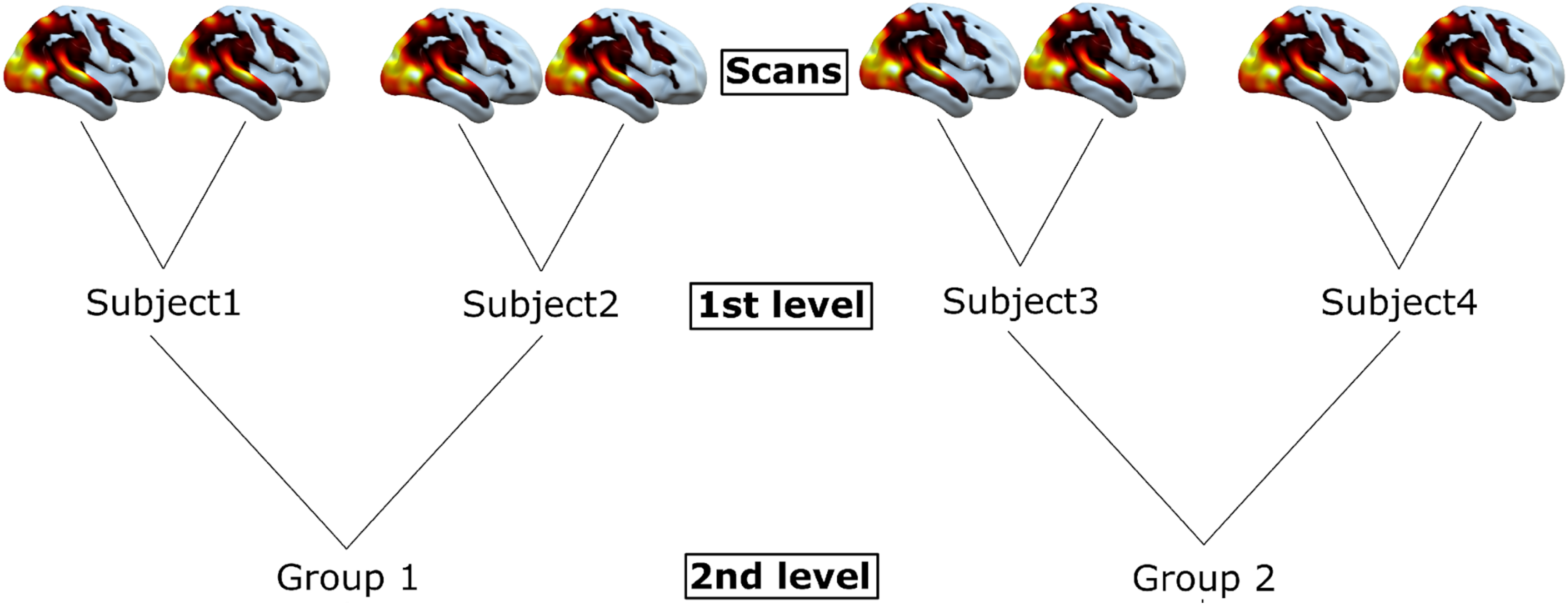
Topics

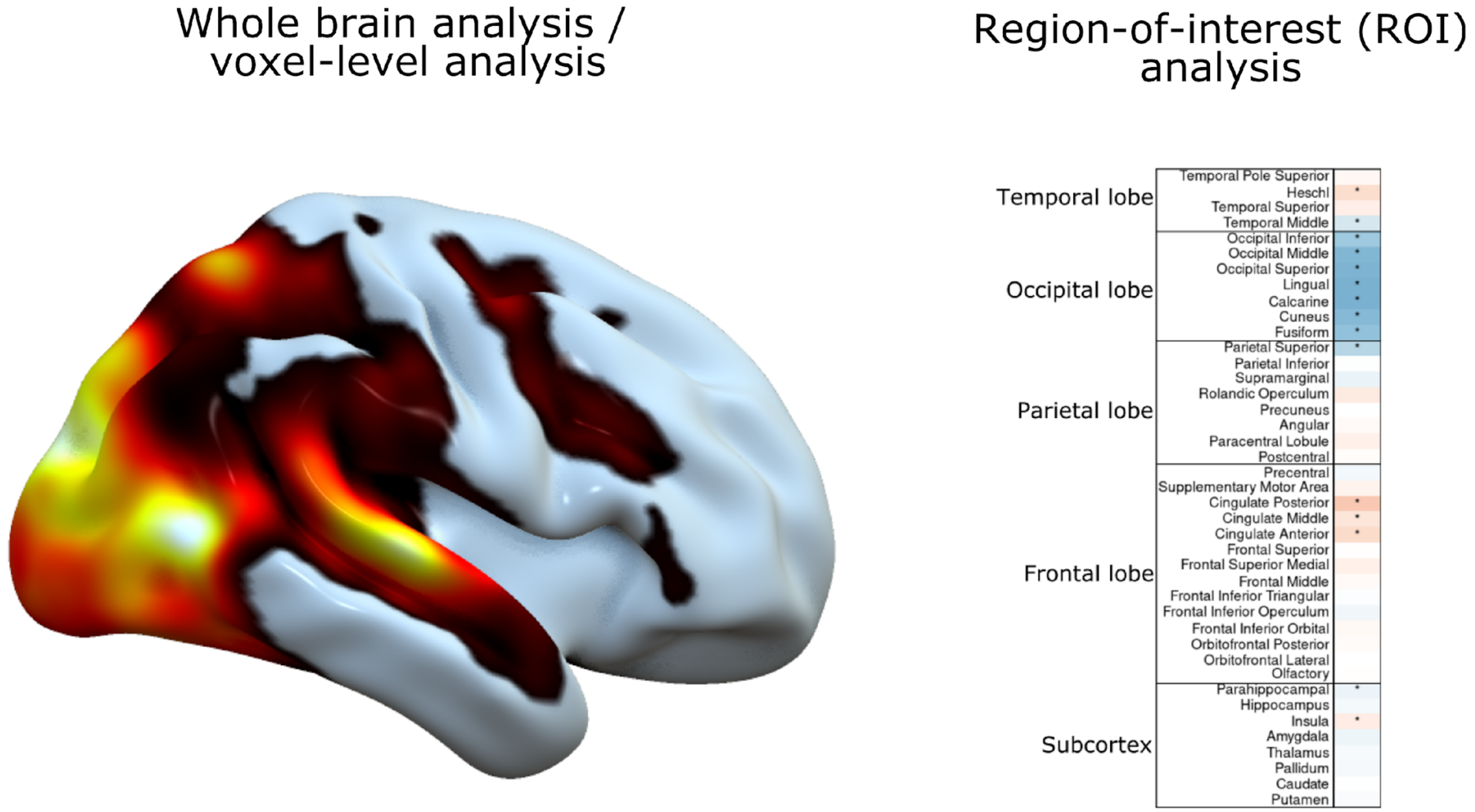
Introduction to the second level analysis

Theoretical framework of the group analysis

Multiple comparisons problem

Non-parametric tests


Scans
Subject1
Subject2
1st level
Subject3
Subject4
Group 1
2nd level
Group 2


Whole brain analysis /
voxel-level analysis
Region-of-interest (ROI)
analysis
Temporal lobe
Temporal Pole Superior
Heschl *
Temporal Superior
Temporal Middle *
Occipital lobe
Occipital Inferior *
Occipital Middle *
Occipital Superior *
Lingual *
Calcarine *
Cuneus *
Fusiform *
Parietal lobe
Parietal Superior *
Parietal Inferior
Supramarginal
Rolandic Operculum
Precuneus
Angular
Paracentral Lobule
Postcentral
Frontal lobe
Precentral
Supplementary Motor Area
Cingulate Posterior *
Cingulate Middle *
Cingulate Anterior *
Frontal Superior
Frontal Superior Medial
Frontal Middle
Frontal Inferior Triangular
Frontal Inferior Operculum
Frontal Inferior Orbital
Orbitofrontal Posterior
Orbitofrontal Lateral
Olfactory
Subcortex
Parahippocampal *
Hippocampus
Insula *
Amygdala
Thalamus
Pallidum
Caudate
Putamen

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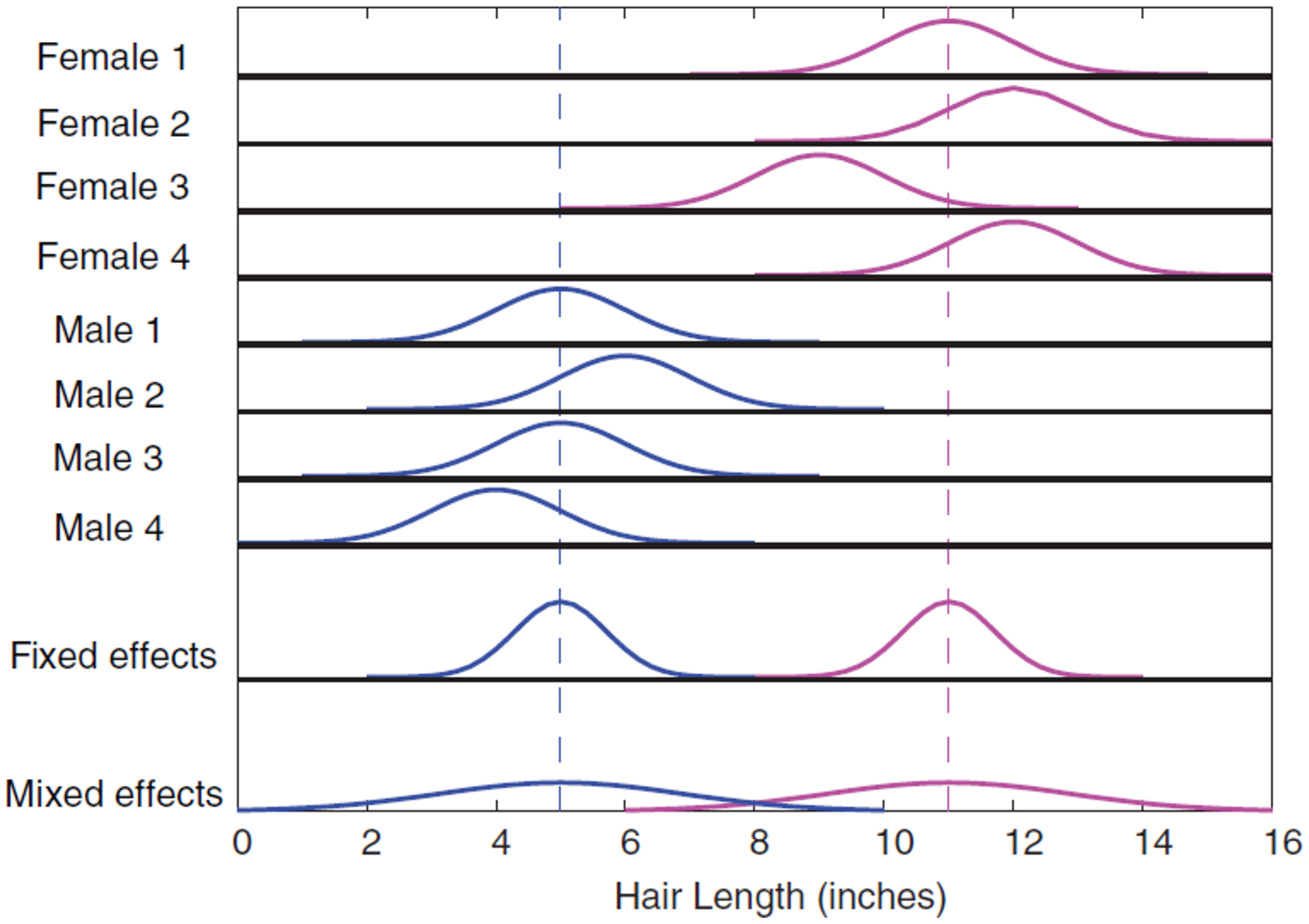
One sample *t*-test

$$t = \frac{\beta - 0}{\sigma/\sqrt{n}}$$

$$\beta = \text{mean beta coefficient ober subjects}$$

$$\sigma = SD\ (\sqrt{Var})$$

$$n = sample\ size$$



Sources of variation in fMRI (or hair length)

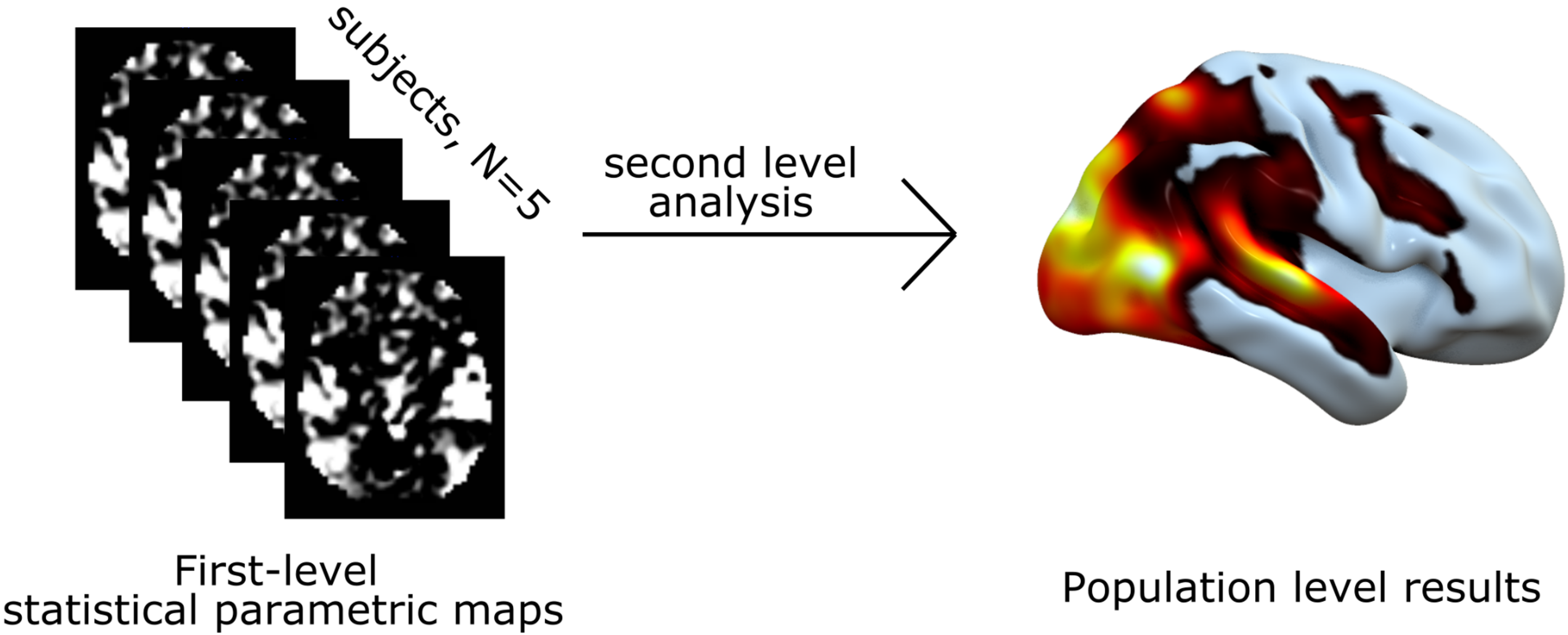
Var^W = within-subject variance

Var^B = between-subject variance

(Poldrack, Nichols, & Mumford, 2011)

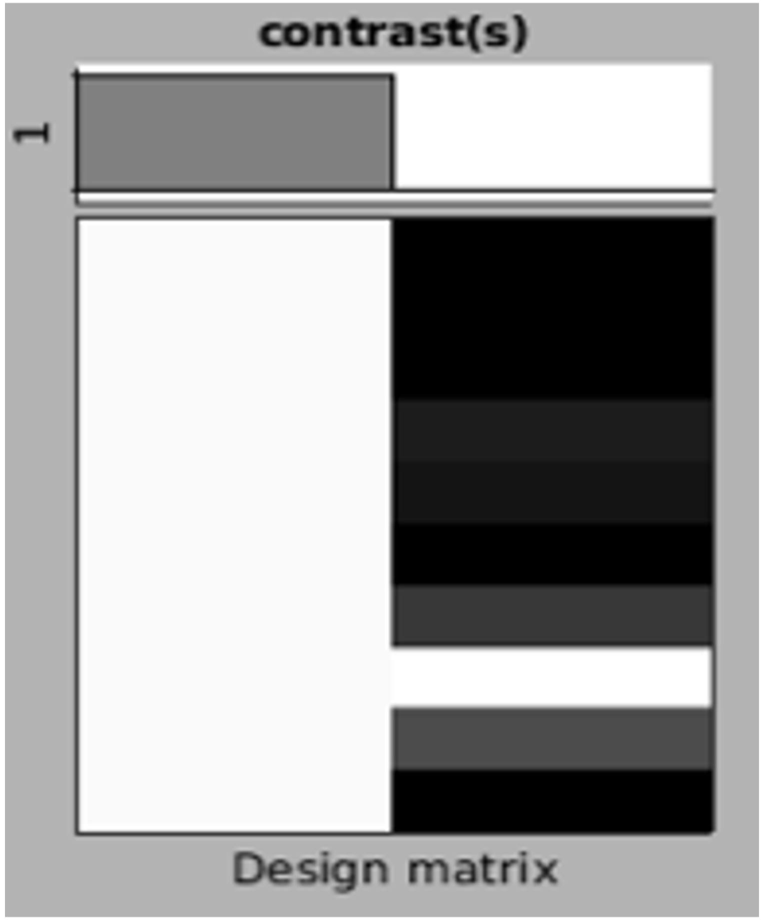
Fixed effects model		Mixed effects model
Var^W	Variance used in the analysis	$Var^W + Var^B$
Describe study sample only	Results	Generalize to population
Combine repeated measures within subjects	Application	Group analysis of fMRI

Summary statistics approach (mixed effect model)



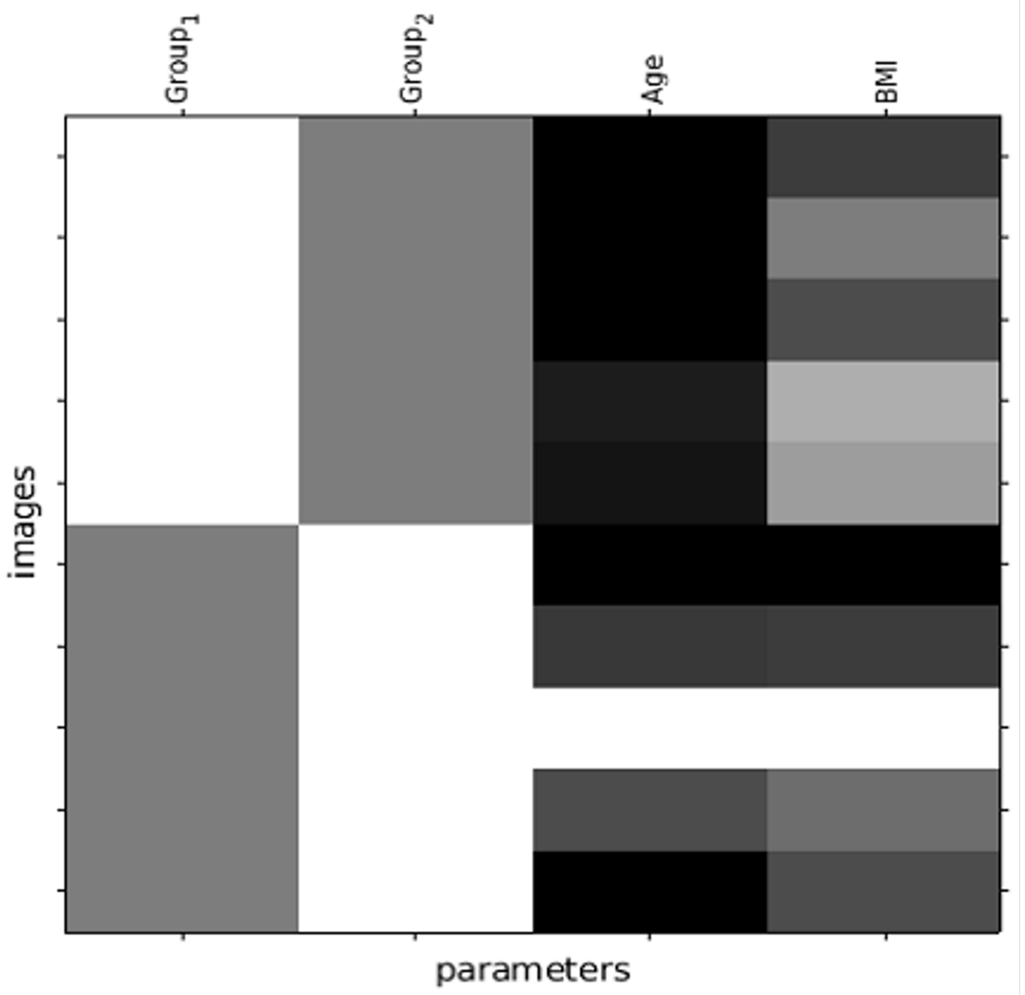
One sample t-test

- H: Brain activity is associated with the study condition somewhere in the brain, (beta /= 0)
- Significance of each voxel is tested independently
- Contrast
  - Main effect
  - Condition1 – Condition2
- Covariates of interest [0 1] or [0 -1]
- Nuisance covariates [1 0]



Two sample t-test

- H: Brain activity different bewteen two groups of subjects (beta1 /= beta2)
- Group1 > Group2 with nuisances
  - [1 -1 0 0]
  - “Whether males have increased brain response for the condition when we control age and BMI of the subjects”



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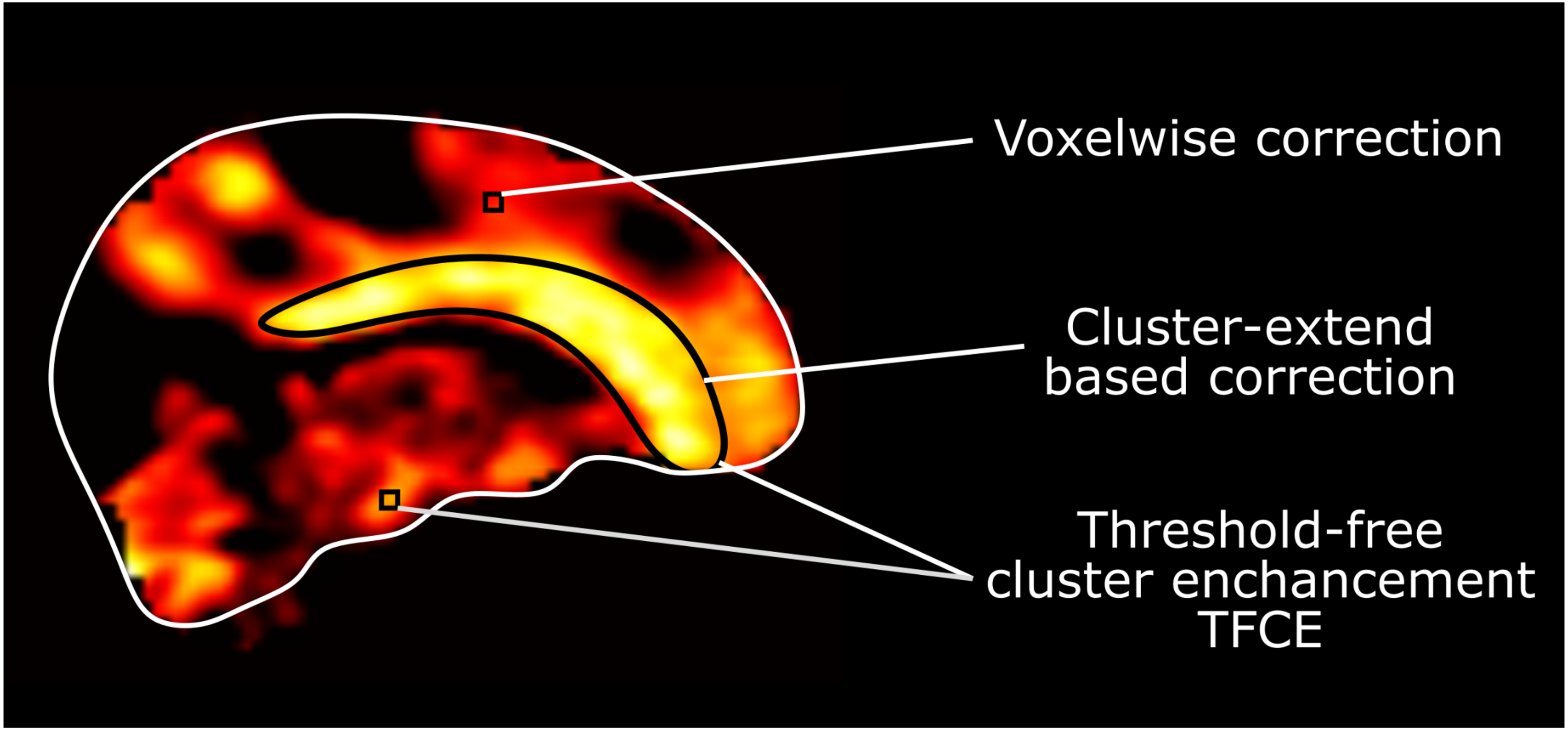
Multiple comparisons correction methods



(Review: Lindquist & Mejia, 2015)

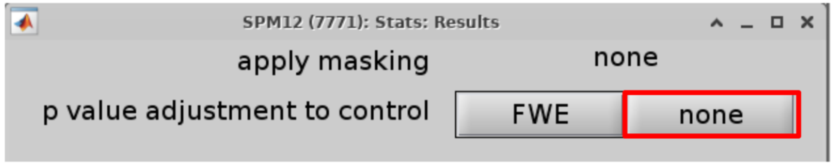
Voxelwise multiple comparisons correction

- Family-wise error rate (FWER) (Lindquist & Mejia, 2015)
  - Probability of making one or more false positives
  - Bonferroni correction
    - “There is a 5% propability of making **at least one** false positive finding”
    - 0.05 / number of tests = corrected p-value threshold
- False discovery rate (Benjamini & Hochberg, 1995)
  - “**No more than 5%** of our findings are false positives”

Cluster-extend based correction (Lindquist & Mejia, 2015)

- Accounts for the spatial dependency between voxels
- “What is the probability to observe a activating cluster of this size under the null hypothesis of no activation”
- Three-step procedure
  1. Choose primary voxel-level threshold
     e.g. $p < 0.001$
  2. Choose minimum size of the cluster
     e.g. 50
  3. Control for FWER on a cluster level
- The approach may be problematic

1


2


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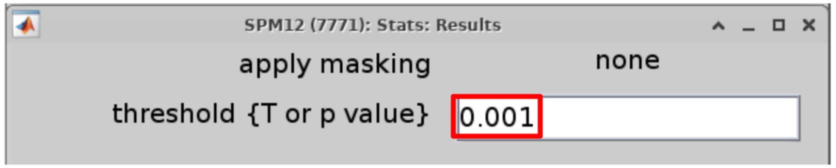

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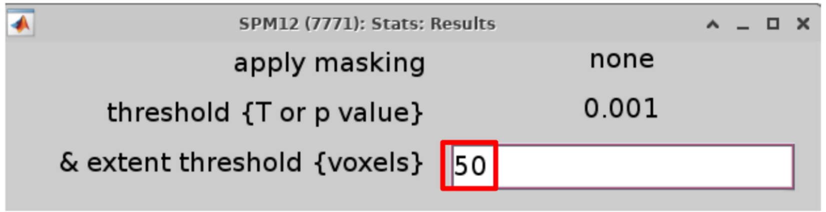
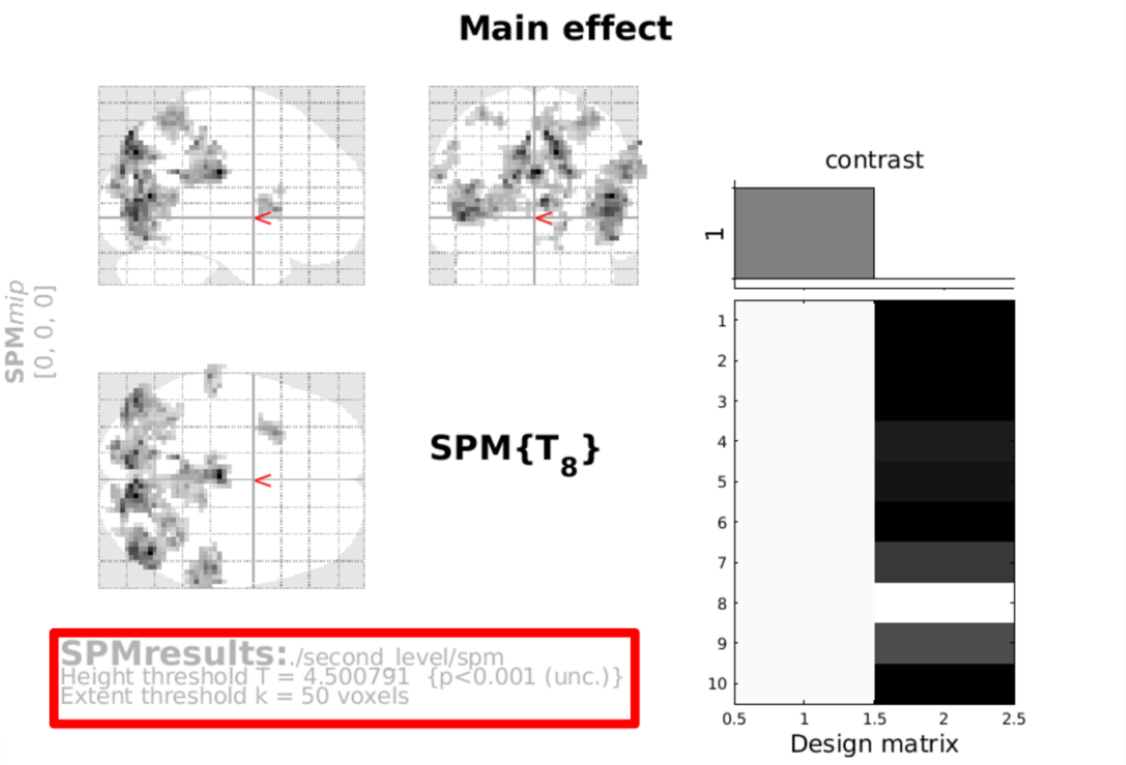
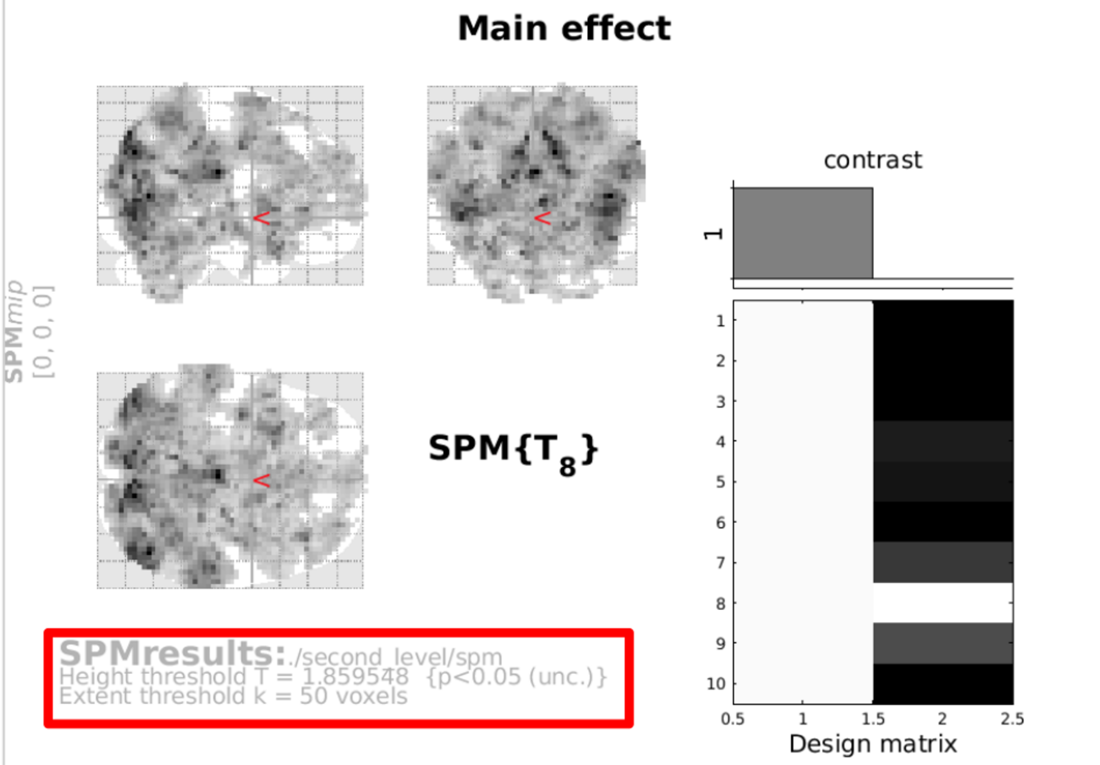




Statistics: ***p-values adjusted for search volume***

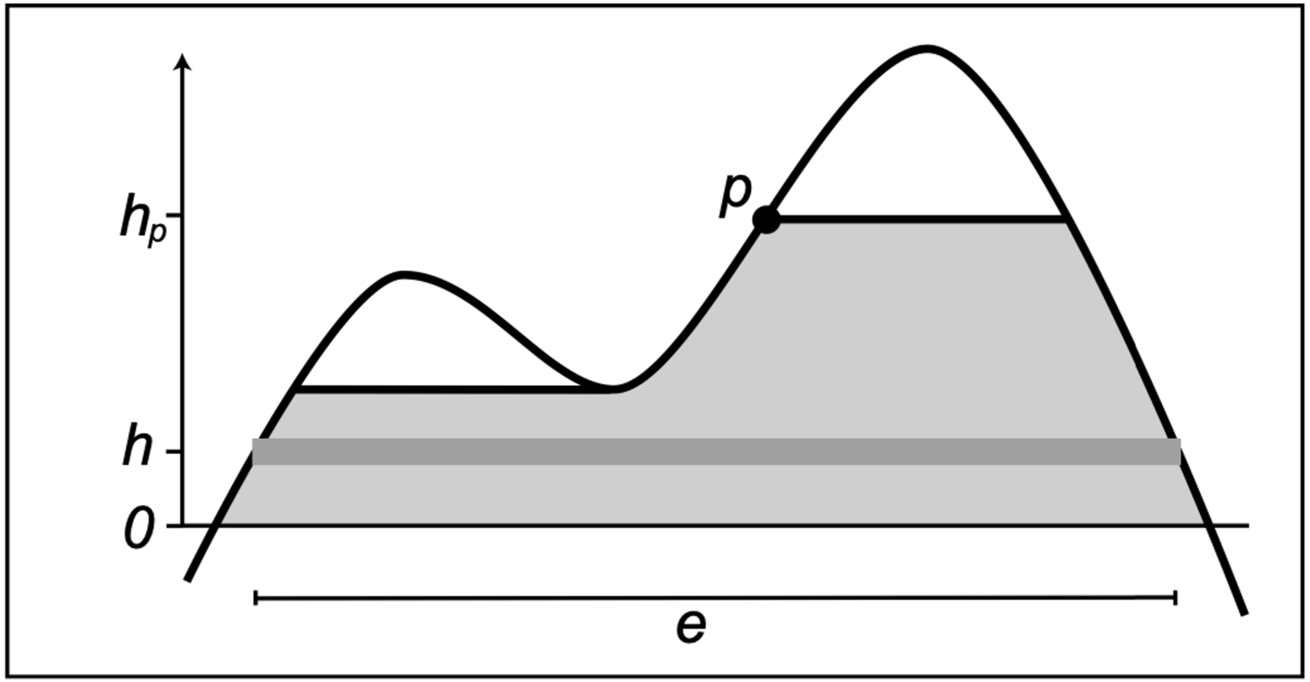
set-level		cluster-level				peak-level							
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_E)	p_{uncorr}	mm	mm	mm
0.000	10	0.000	0.000	453	0.000	0.014	0.507	14.69	5.04	0.000	48	-69	12
						0.099	0.507	11.33	4.65	0.000	45	-78	3
						0.188	0.581	10.40	4.52	0.000	48	-72	-15
		0.000	0.000	166	0.000	0.016	0.507	14.39	5.01	0.000	0	-24	27
						0.242	0.581	10.06	4.46	0.000	-12	-51	27
						0.593	0.581	8.91	4.27	0.000	0	-33	24
		0.000	0.000	1011	0.000	0.019	0.507	14.10	4.98	0.000	12	-78	39
						0.040	0.507	12.77	4.83	0.000	6	-81	51
						0.061	0.507	12.06	4.75	0.000	3	-78	9
		0.000	0.000	202	0.000	0.296	0.581	9.79	4.42	0.000	66	-39	45
						0.296	0.581	9.79	4.42	0.000	57	-27	24
						0.425	0.581	9.32	4.34	0.000	57	-33	30
		0.000	0.000	57	0.000	0.536	0.581	9.03	4.29	0.000	-63	-30	24
						0.999	0.606	7.34	3.94	0.000	-54	-27	45
						1.000	0.824	5.45	3.43	0.000	-57	-33	33
		0.000	0.000	68	0.000	0.764	0.581	8.61	4.21	0.000	-27	12	3
						1.000	0.641	6.70	3.79	0.000	-30	3	3
						1.000	0.719	6.05	3.61	0.000	-21	15	15
		0.000	0.000	55	0.000	0.831	0.591	8.51	4.19	0.000	18	-66	-6
						1.000	0.694	6.24	3.66	0.000	18	-60	0
						1.000	0.705	6.20	3.65	0.000	12	-72	-9
		0.000	0.000	130	0.000	0.991	0.606	8.17	4.12	0.000	30	-60	57

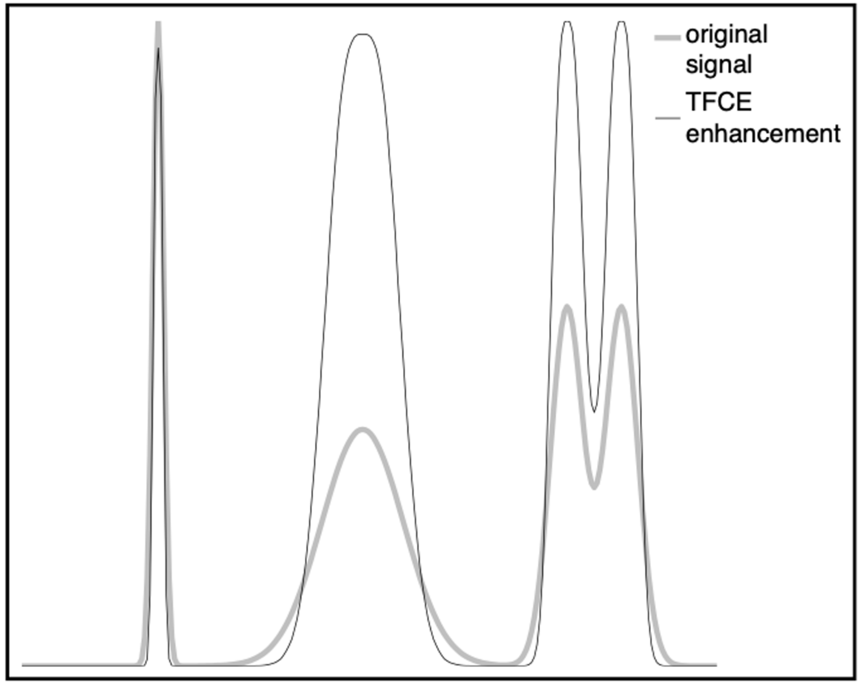


Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level							
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_E)	p_{uncorr}	mm	mm	mm
1.000	3	0.000	0.000	18190	0.000	0.014	0.309	14.69	5.04	0.000	48	-69	12
						0.016	0.309	14.39	5.01	0.000	0	-24	27
						0.019	0.309	14.10	4.98	0.000	12	-78	39
		0.003	0.000	668	0.000	0.536	0.355	9.03	4.29	0.000	-63	-30	24
						0.999	0.370	7.34	3.94	0.000	-54	-27	45
						1.000	0.503	5.45	3.43	0.000	-57	-33	33
		0.893	0.253	163	0.013	1.000	0.490	5.60	3.48	0.000	-36	39	24
						1.000	0.503	5.34	3.39	0.000	-39	45	33
						1.000	0.658	4.22	2.98	0.001	-24	42	33

Threshold-free cluster enchancement (TFCE)



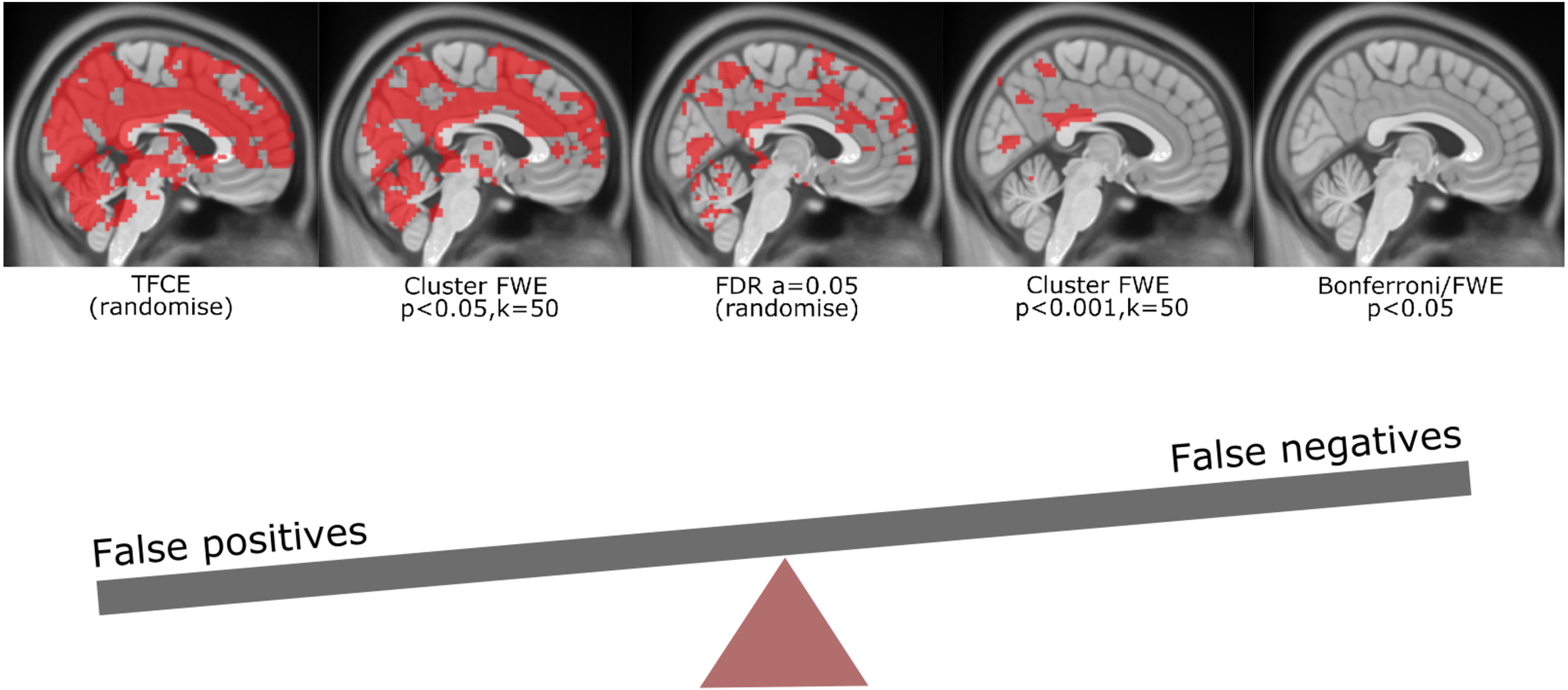


TFCE = h_p (voxelwise t-value) * e (amount of suporting voxels)

 The voxelwise significance is adjusted by the amount supporting voxels

 Significance of each voxel is assessed with permutations and then corrected for multiple comparisons

(Smith & Nichols, 2009)



Conservative correction inflates effect size estimates

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Non-parametric tests

- Motivation for non-parametric tests in group analyses (Eklund, Nichols, & Knutsson, 2016)
    1. Parametric tests may produce false positive findings in group level analyses after multiple comparisons corrections
    2. Voxelwise multiple comparisons methods may produce too conservative findings and cluster-based methods false positives
    3. Non-parametric tests have been shown to correct better for multiple comparisons.
- Tools for non-parametric tests
    - SnPM (Doc: https://warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/software/snpm)
    - FSL Randomise (Winkler, Ridgway, Webster, Smith & Nichols, 2014)
        - One and two sample (unpaired/paired) T-tests, repeated measures anova
        - Easy to output statsitical result maps with variuous differend multiple comparisons methods
            - Included TFCE method
        - Doc: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise

References

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B-Statistical Methodology, 57*(1), 289-300. doi:DOI 10.1111/j.2517-6161.1995.tb02031.x

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Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage, 92*, 381-397. doi:10.1016/j.neuroimage.2014.01.060