Smooth logistic mass univariate inference for MS lesion data using sign-flipping

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Example Lesion Images

We have Lesion data from 238 subjects with MS

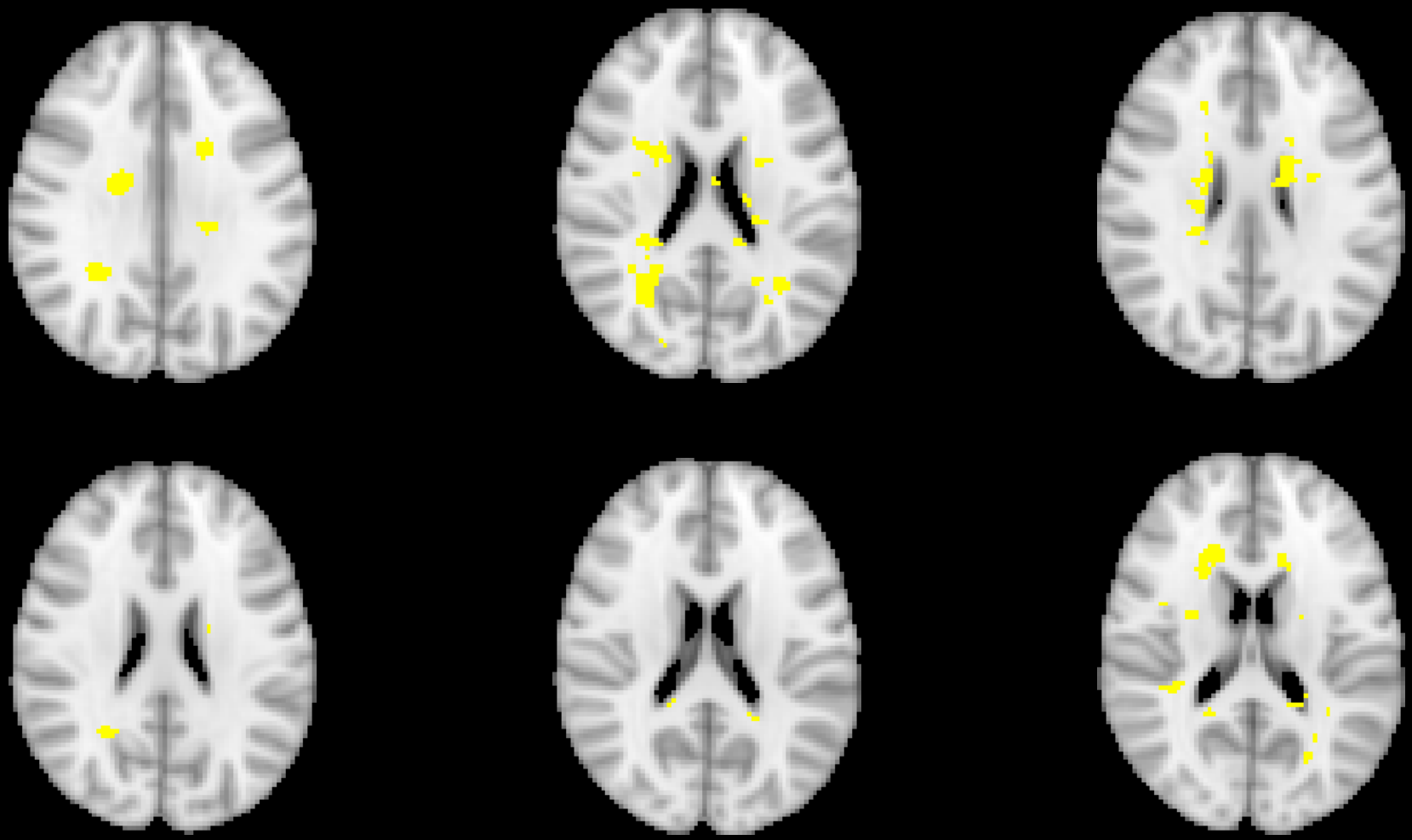
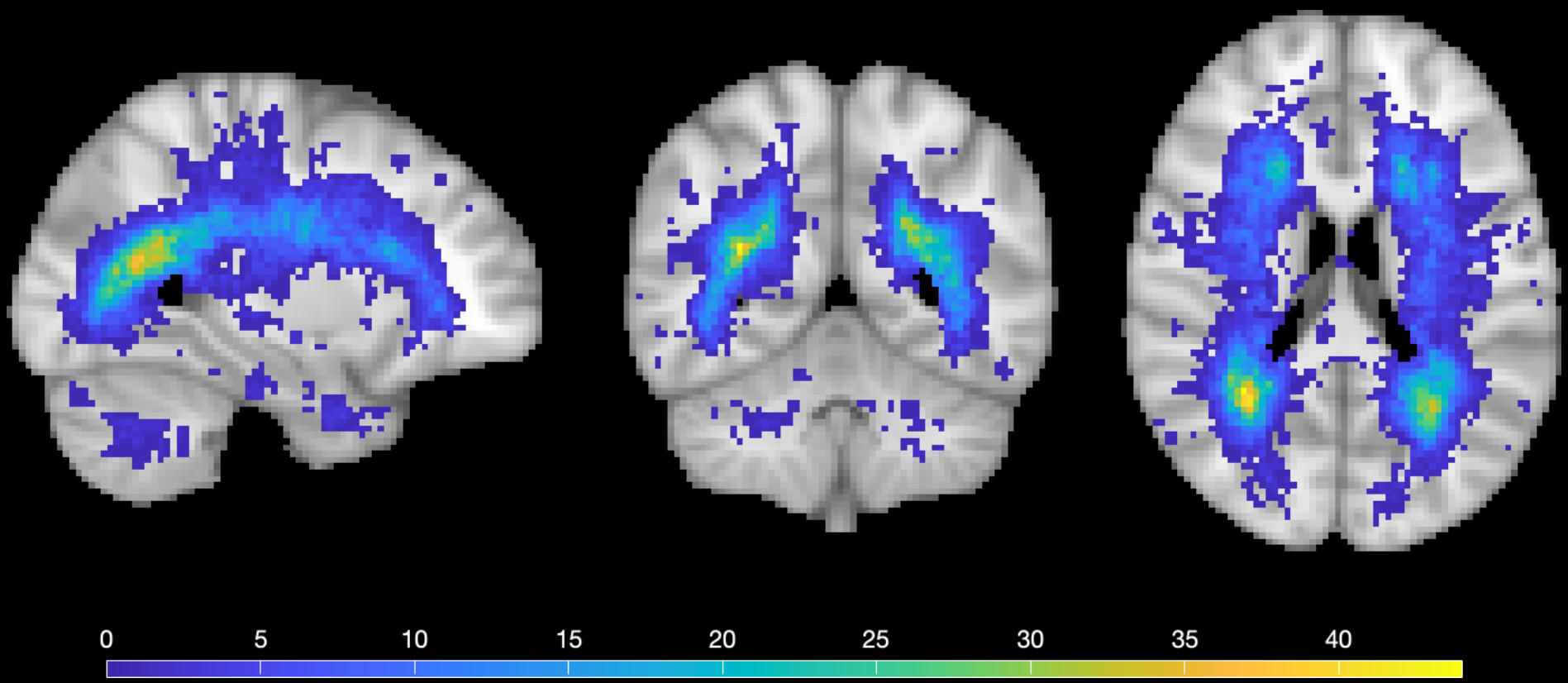


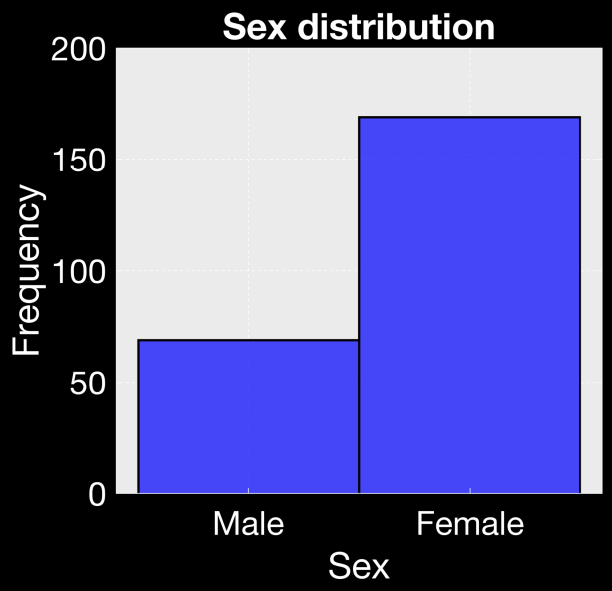
Figure 1: Brain lesions from 6 example subjects

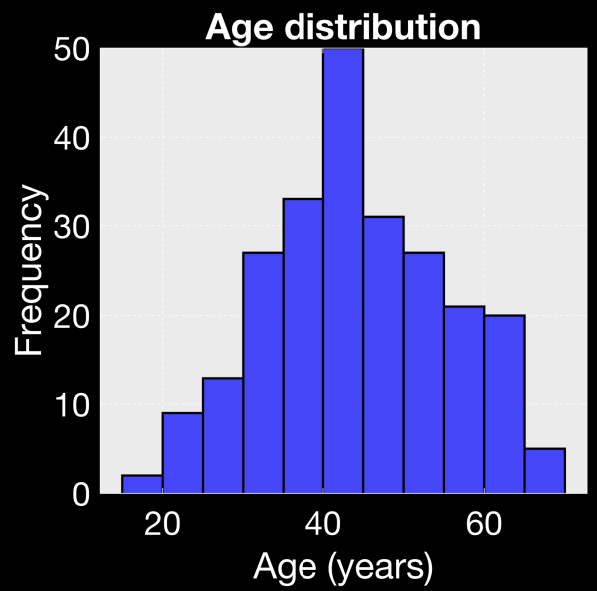
Lesion distribution over all 238 subjects

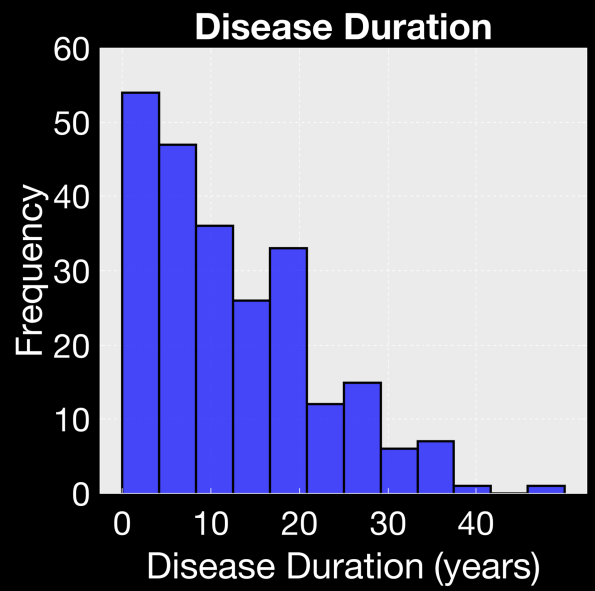


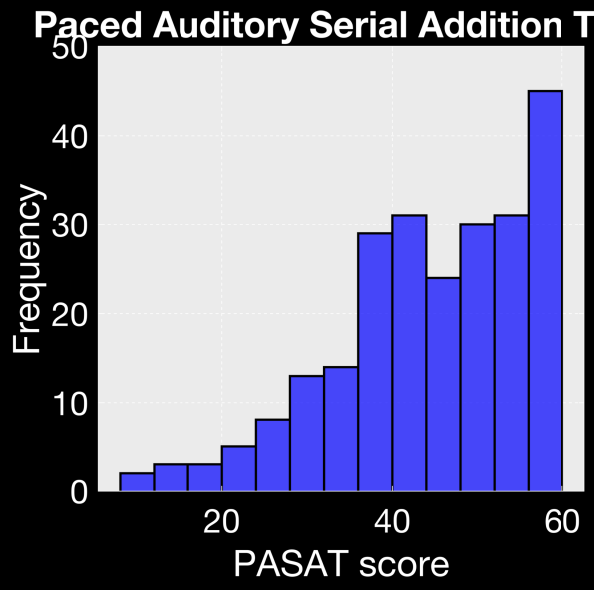
We shall fit lesion count against some covariates of interest.

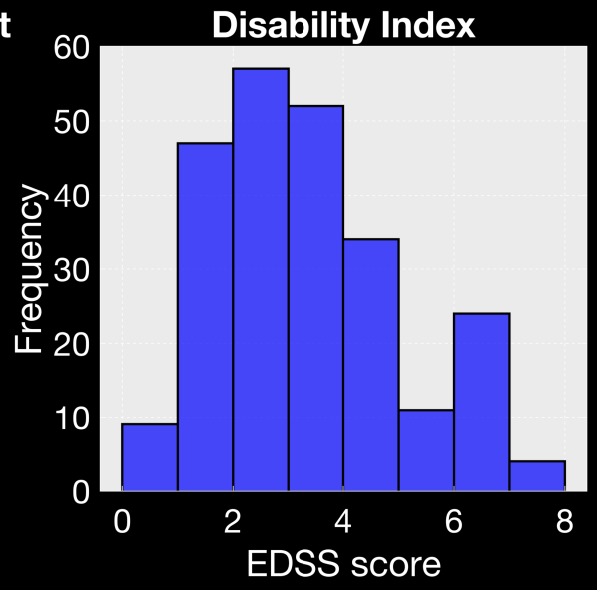
Covariates

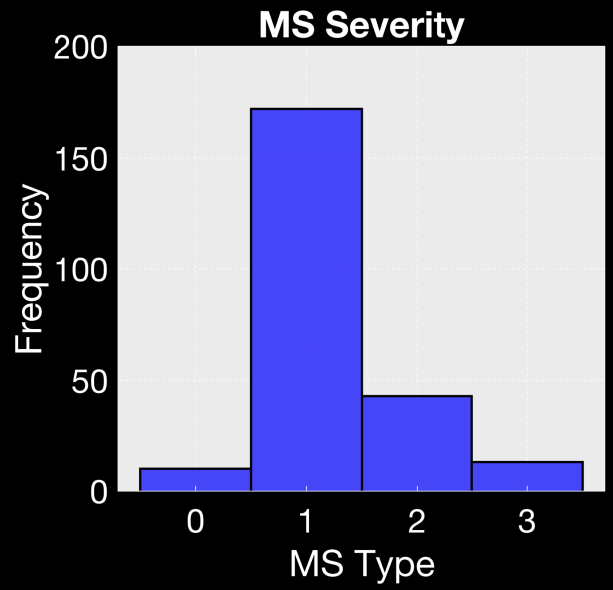

Sex distribution
Frequency
200
150
100
50
0
Male
Female
Sex


Age distribution
Frequency
50
40
30
20
10
0
20
40
60
Age (years)


Disease Duration
Frequency
60
50
40
30
20
10
0
0
10
20
30
40
Disease Duration (years)


Paced Auditory Serial Addition Test
Frequency
50
40
30
20
10
0
20
40
60
PASAT score


Disability Index
Frequency
60
50
40
30
20
10
0
0
2
4
6
8
EDSS score


MS Severity
Frequency
200
150
100
50
0
0
1
2
3
MS Type

Model set up

Let $\mathcal{L}$ be the set of voxels and assume $Y_i(l) \sim \text{Binomial}(q_i(l))$ where $q_i : \mathcal{L} \to \mathbb{R}$ and

$$\log\left(\frac{q_i(l)}{1-q_i(l)}\right) = x_i^T\beta(l) + z_i^T\gamma(l) \tag{1}$$

At each voxel $l \in \mathcal{L}$, we will want to test the null hypothesis

$$H_0(l) : \beta(l) = 0.$$

This results in a very large multiple testing problem and so we shall seek to control the FWER over voxels.

Calculating the effective scores

At each $l \in \mathcal{L}$ let $S_n(l)$ be the effective score at voxel l. Then it turns out that we can write

$$S_n(l) = n^{-1/2} \sum_{i=1}^{n} \nu_i(l).$$

as the sum of score contributions for each subject. Importantly, under the null hypothesis that $\beta(l) = 0$,

$$\{S_n(l)\}_{l \in \mathcal{L}}$$

converges in distribution.

Smoothing the effective scores

In order to increase SNR, we can apply smoothing to the effective scores. Given a smoothing kernel K, let

$$\tilde{\nu}_i(l) = \sum_{l' \in \mathcal{L}} K(l - l')\nu_i(l).$$

We then consider the test-statistic:

$$T_n(l) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \tilde{\nu}_i(l).$$

Sign-flipping the effective scores

It is possible to show that $\{T_n(l)\}_{l\in\mathcal{L}} \overset{d}{\Longrightarrow} N(0, G)$, some unknown G. In order to infer on the limiting distribution we use sign-flipping. In particular let

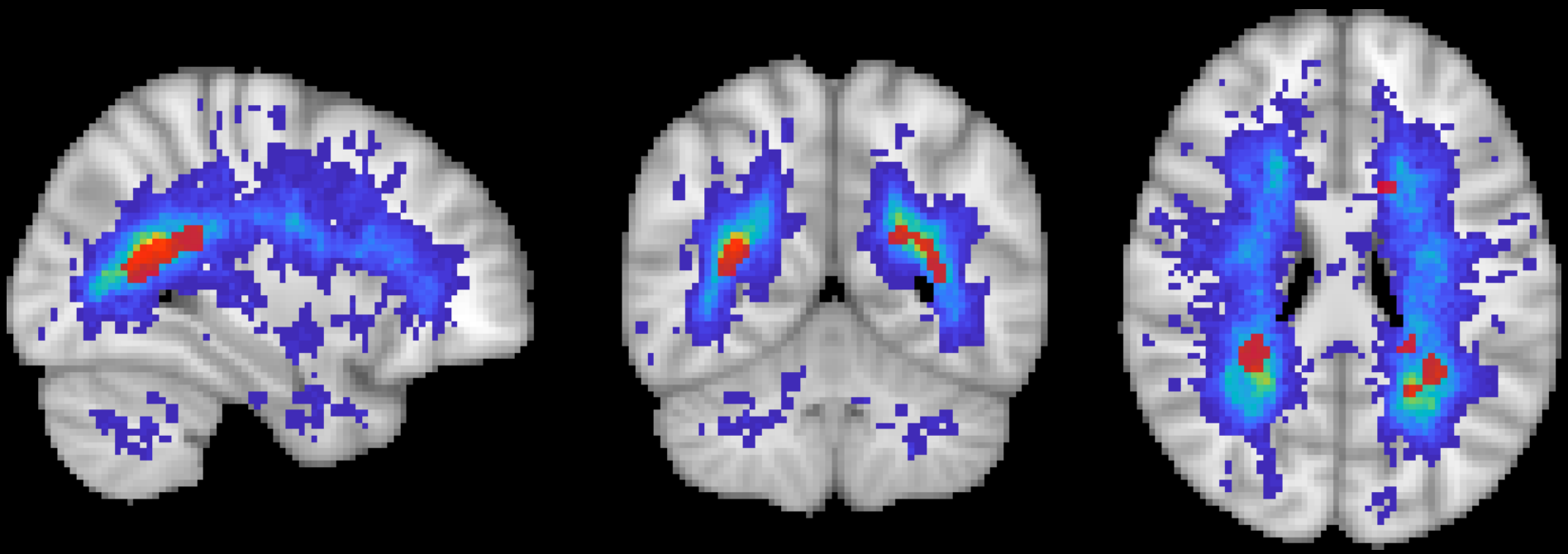
$$T_n^b(l) = n^{-1/2} \sum_{i=1}^{n} g_{bi} \tilde{\nu}_i(l),$$

Where g_{bi}, $1 \leq b \leq B, 1 \leq i \leq n$ are i.i.d. from $\{-1, 1\}$. We show that

Theorem: $\{T_n^b(l)\}_{l\in\mathcal{L}} \overset{d}{\Longrightarrow} N(0, G)$.

Application to the MS lesion dataset - FWHM 4 voxels

Let Q be the 95% quantile of the sign-flipped distribution of $\max_{l \in \mathcal{L}} T_n$ to control the FWER, rejecting $H_0(l)$ if $T_n(l) > Q$.



Conclusions

- Our approach allows resampling in the context of multiple generalized linear models. Further methodological details are available in the SIS submission and in our other paper *Permutation-based multiple testing when fitting many generalized linear models* available on arxiv and at `sjdavenport.github.io/research/`.

-In particular allows smoothing to be combined into the framework which helps to increase detection power.

- Slides for this talk are available on my website: `sjdavenport.github.io/talks`

- Code to implement these methods are available in the flipscores R package, the pyperm python package and the matperm matlab package.

Further theory

Theorem: Let $\mathcal{N}(K)$ be the null set up to the support of the kernel K. Then

$$\lim_{n \to \infty} \mathbb{P}\left(|\mathcal{R}_n \cap \mathcal{N}(K)| > 0\right) \leq \alpha.$$

False Positive Rate Comparison

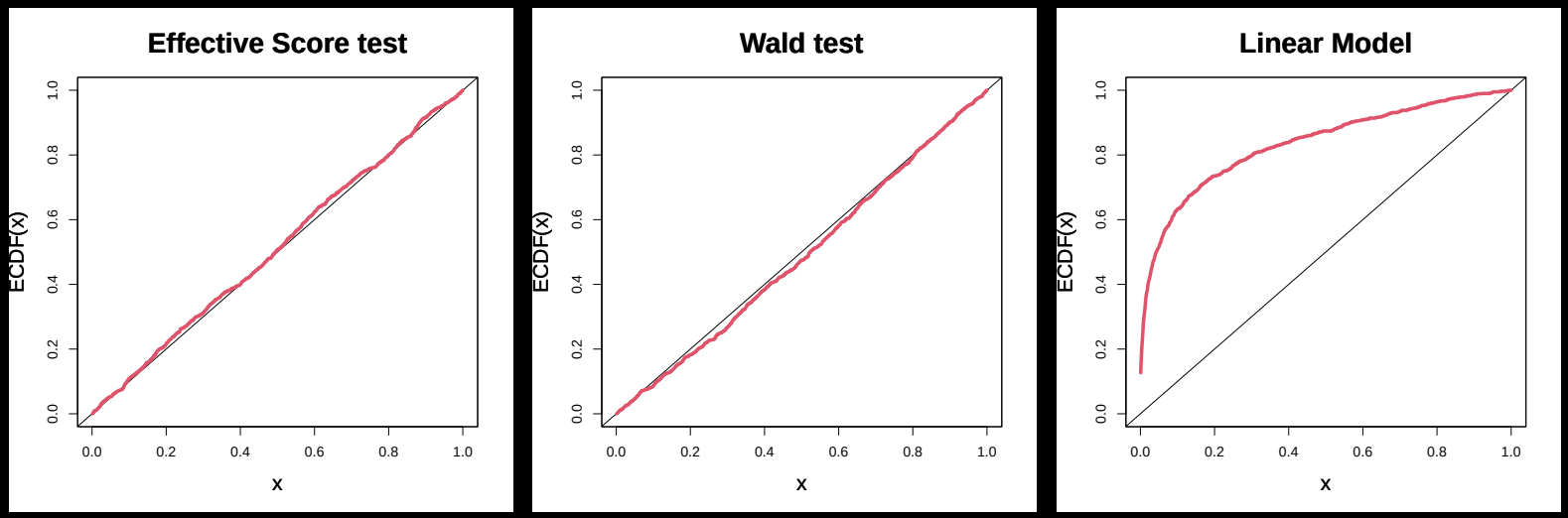
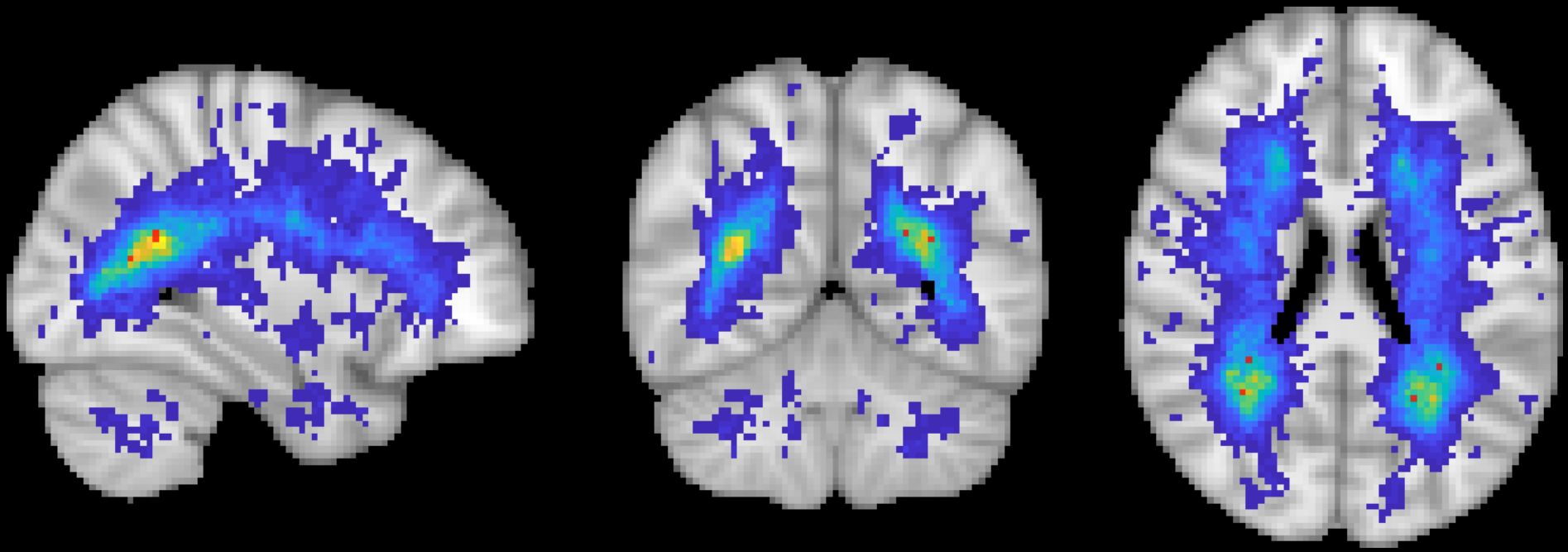
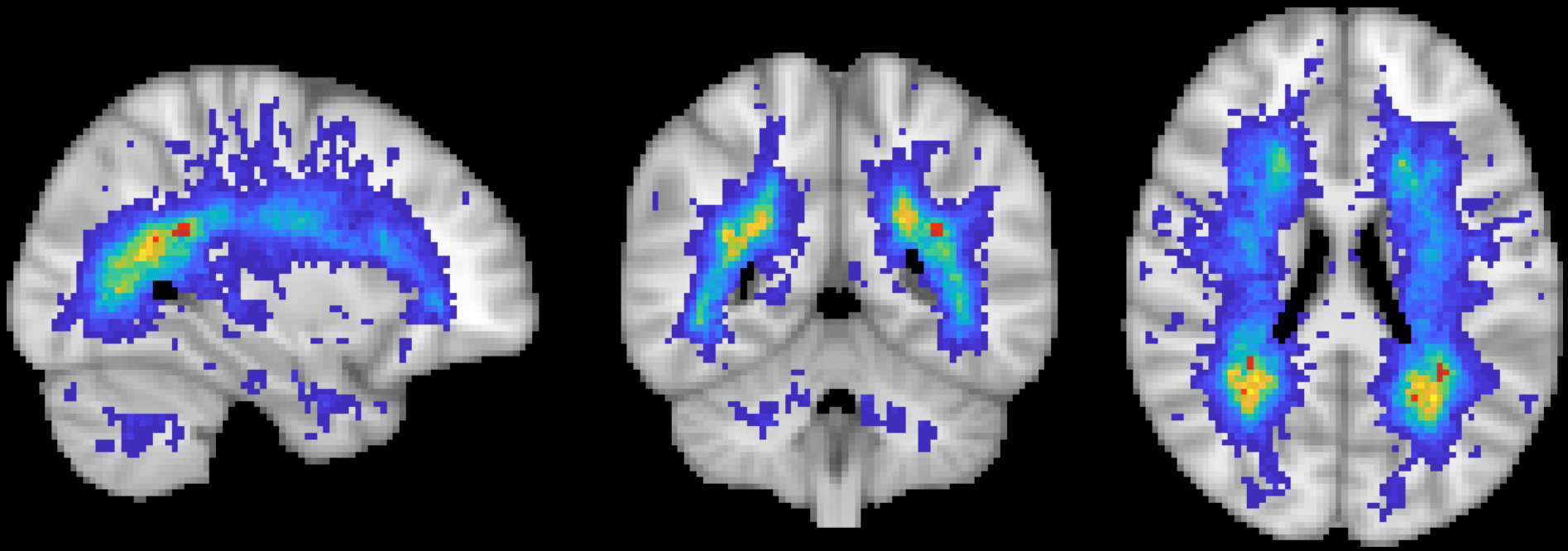


Figure 2: Empircal CDF of the simulated p-values. Fitting a linear model to the data results in high levels of false positives. Instead the sign-flipped effective score test and Wald test control to the nominal rate.

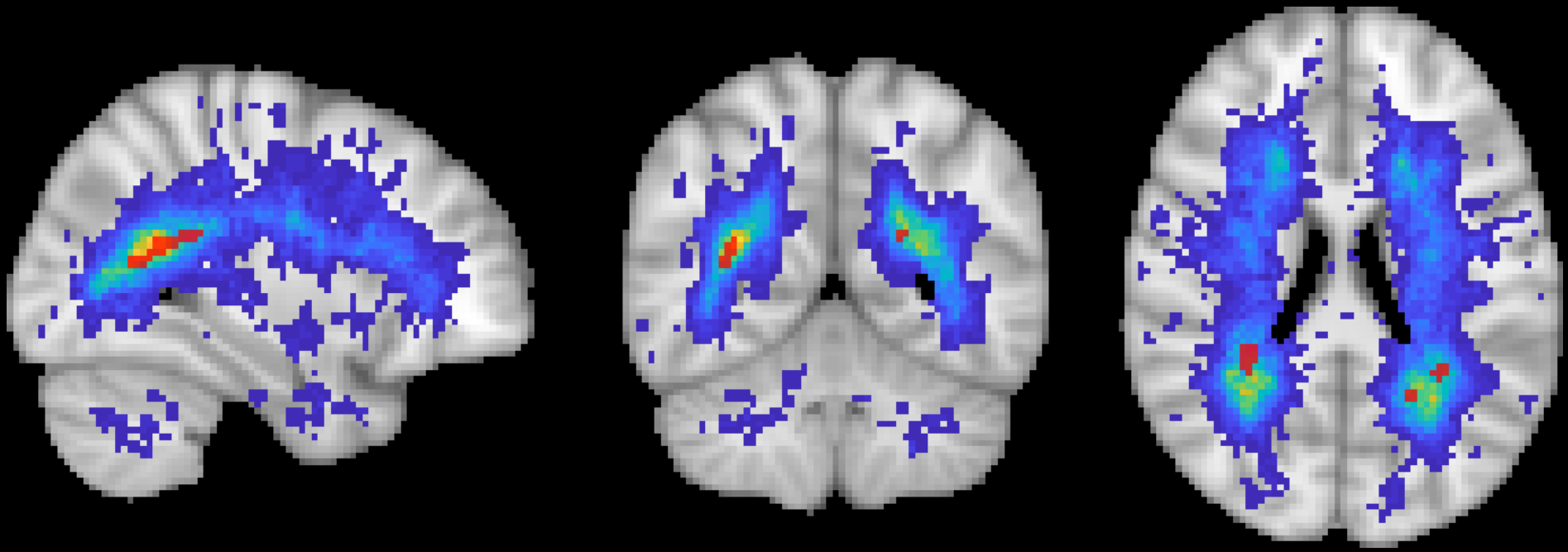
Application to the MS lesion dataset - FWHM 0 voxels



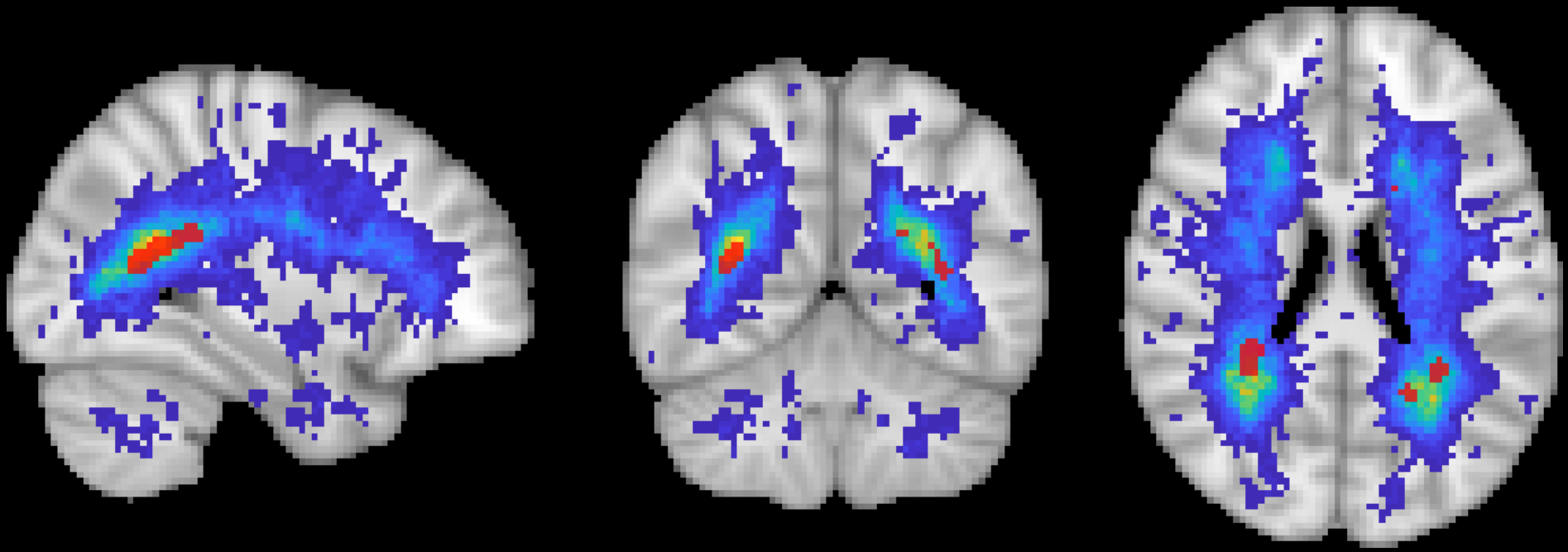
Application to the MS lesion dataset - FWHM 1 voxels



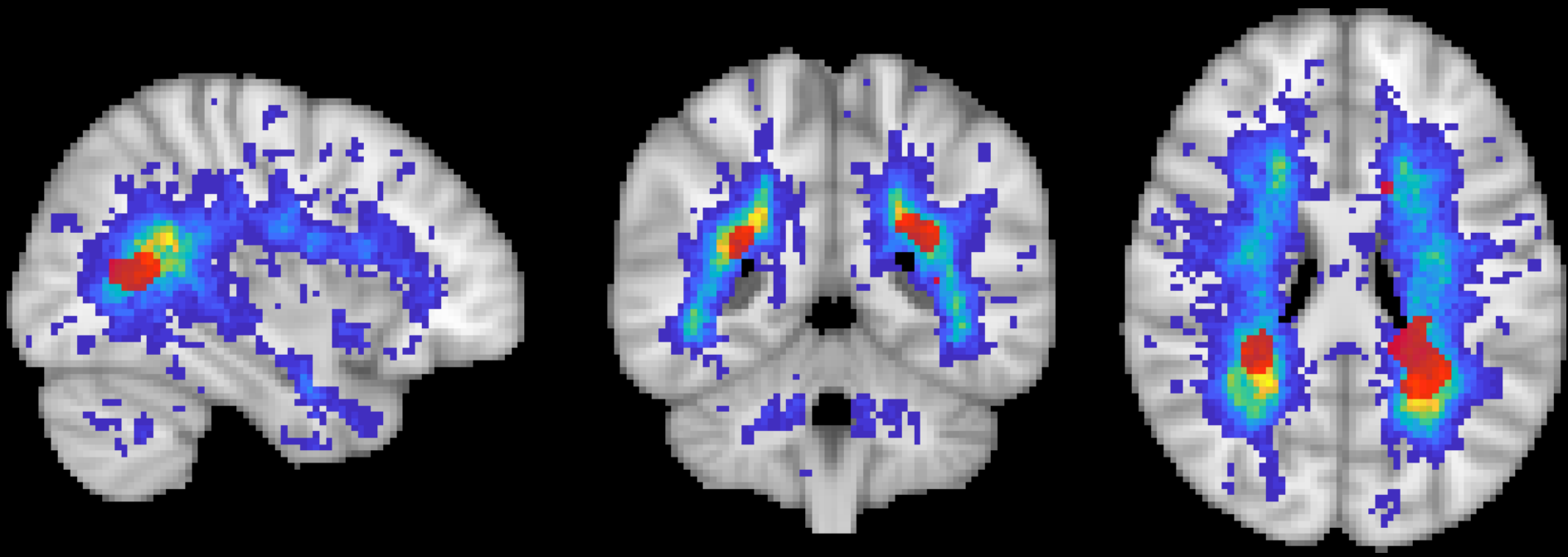
Application to the MS lesion dataset - FWHM 2 voxels



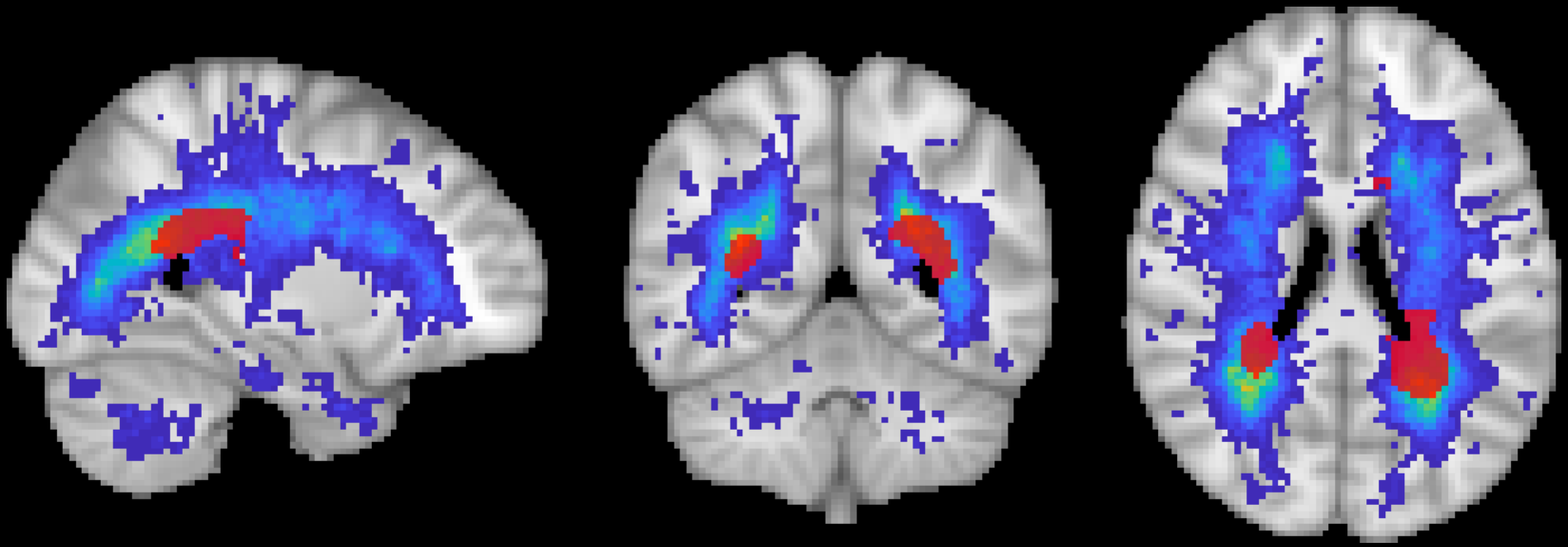
Application to the MS lesion dataset - FWHM 3 voxels



Application to the MS lesion dataset - FWHM 5 voxels



Application to the MS lesion dataset - FWHM 6 voxels



Application to the MS lesion dataset - FWHM 7 voxels