

Medical Image Analysis

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Lecture 2.

Voxel-based Morphometry (VBM)

January 25, 2007

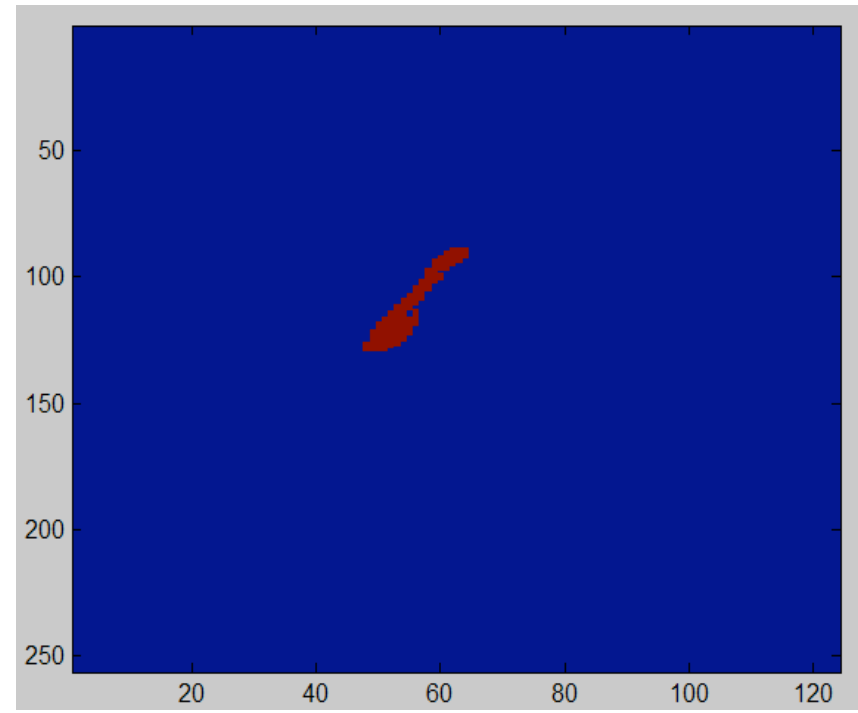
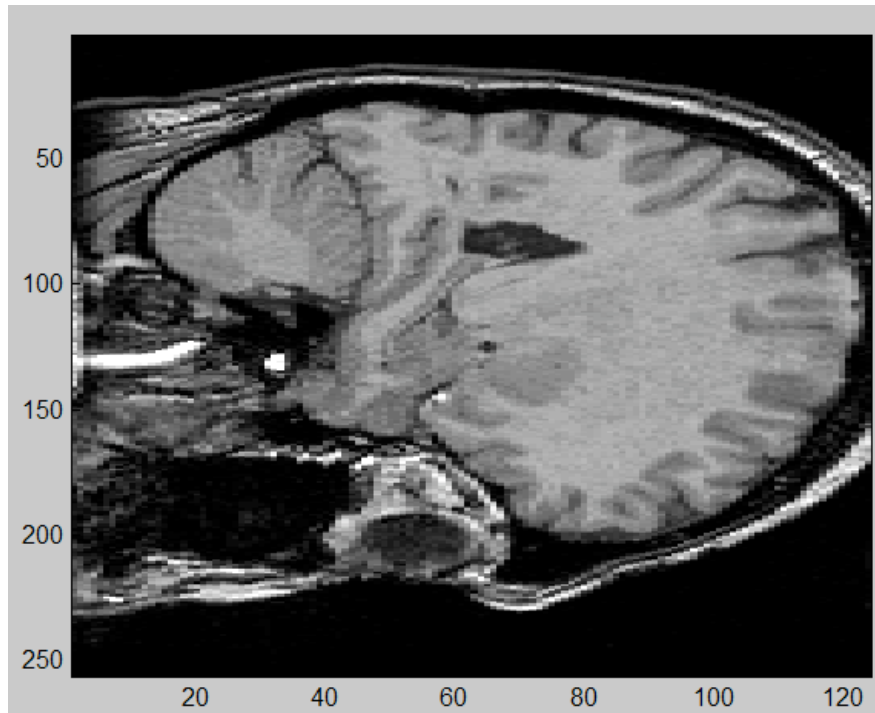
Occam's razor

- When given two equally valid explanations (model) for a phenomenon, one should embrace the less complicated formulation (model).
- All thing being equal, the simplest solution tends to be the best one.
- If you want to try complicated modeling, do the simplest model first.

ROI volumetry

- This is a traditional approach
- ROI volumetry measures volume of a segmented region region of interest (ROI). It provides a single scalar measure of the ROI.

Example: Hippocampal volumetry



1. Manually segment hippocampus
2. Count the number of masked voxels
3. #number of voxel x volume of voxel

Voxel-based morphometry (VBM)

- A new approach (Ashburner & Friston, 2000)
- No ROI segmentation required.
- Anatomical difference is characterized at each voxel.

Advantages of VBM

- It does not require *a priori* knowledge of the ROI to perform the morphological analysis (Davatzikos, 1999; Ashburner and Friston, 2000; Chung et al., 2001).
- No need for time consuming either manual or automatic segmentation of ROI.
- Anatomical differences can be detected at a voxel level within ROI itself giving additional localization power that ROI-based approaches lack.

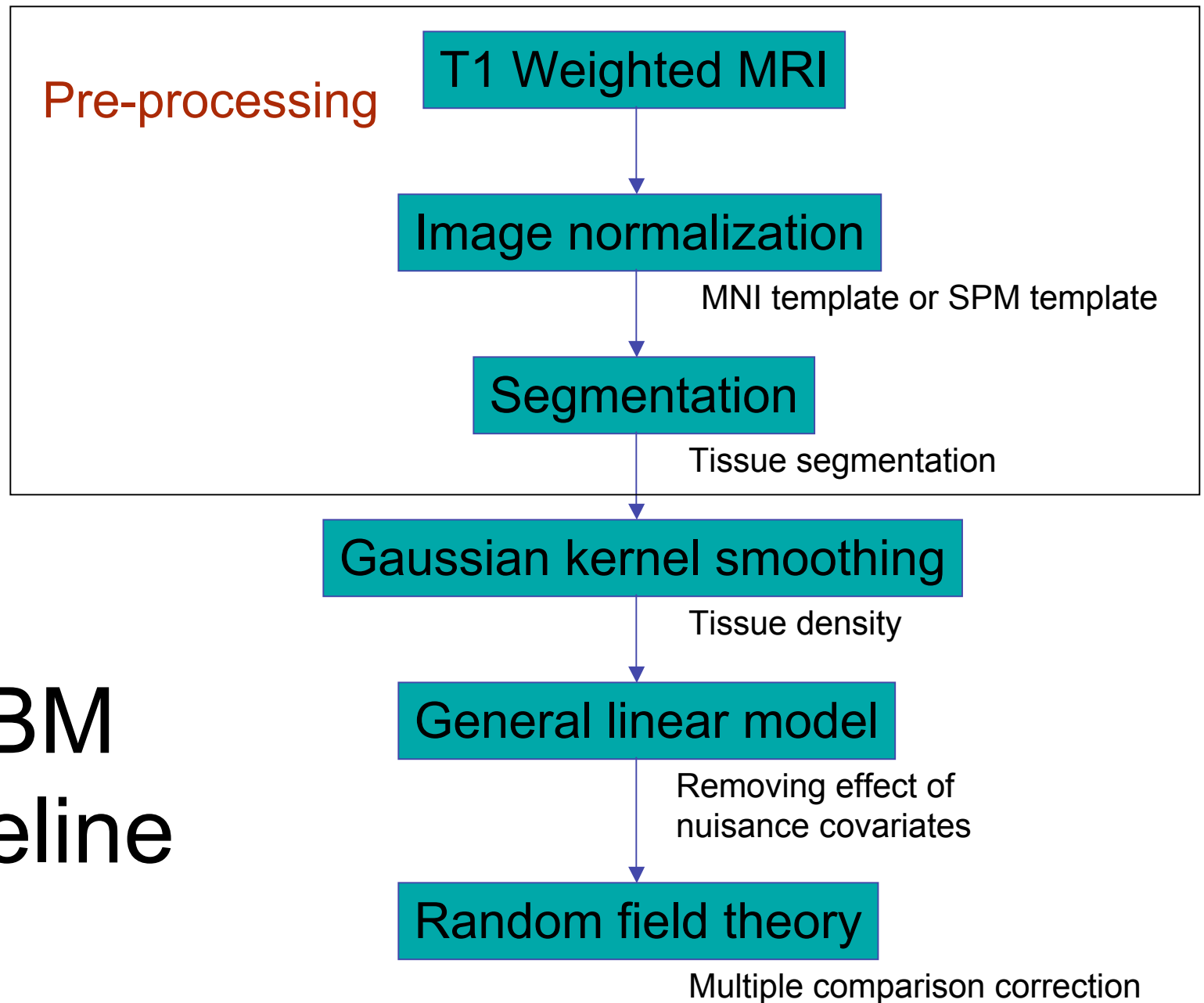
Introduction to VBM

- Fully automated image analysis technique allowing identification of regional differences in gray matter (GM) and white matter (WM) between populations without a prior ROI.
- Implemented in the SPM package (Wellcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>)

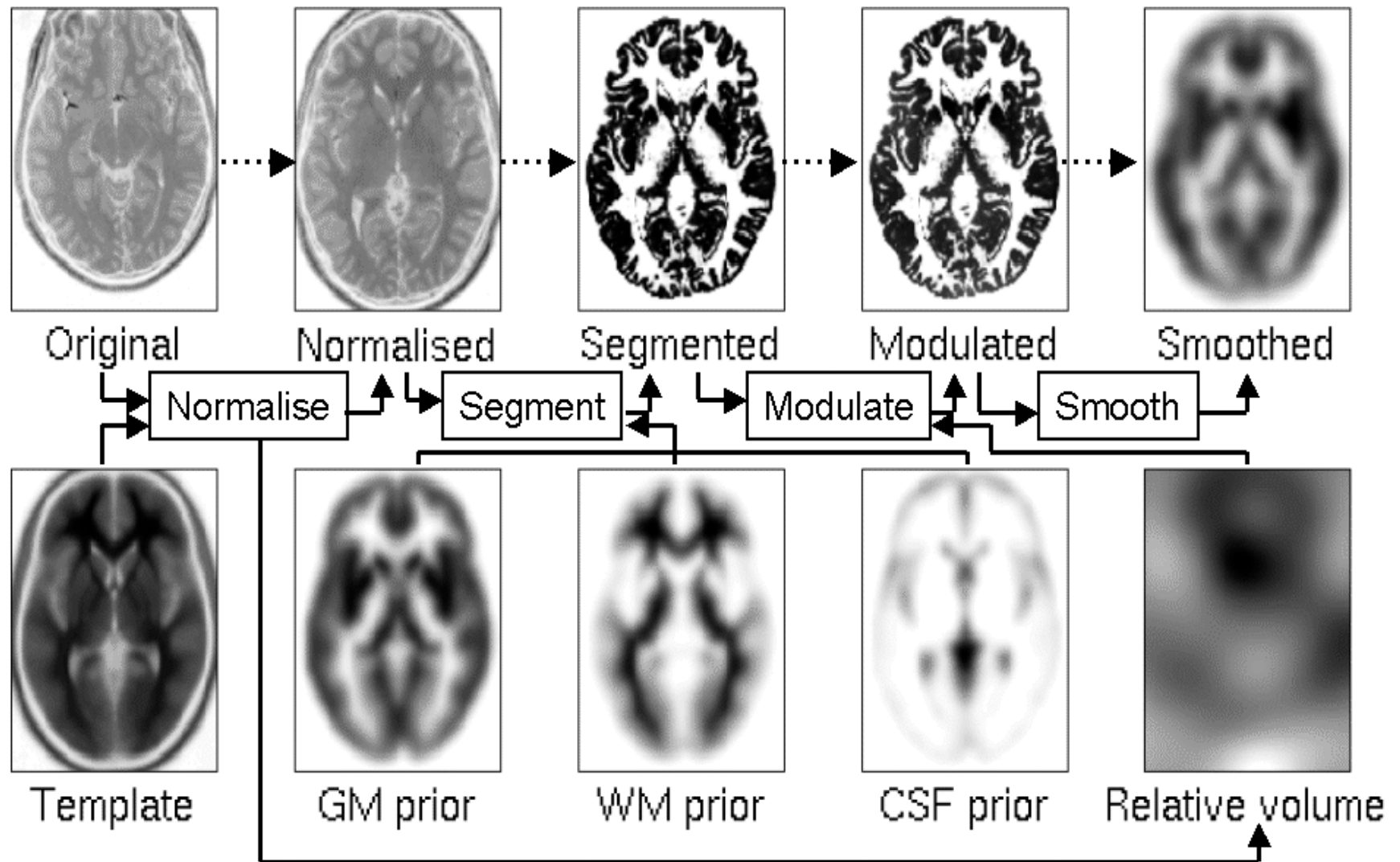
VBM procedures

- Normalize structural MRIs to the standard SPM template
- Segment the normalized images into white and gray matter and cerebrospinal fluid (CSF) based on a Gaussian mixture model (Ashburner and Friston, 1997, 2000).
- The final output: the probability of each voxel belonging to a particular tissue type. This probability is usually referred to as the *gray/white matter density*.

VBM pipeline



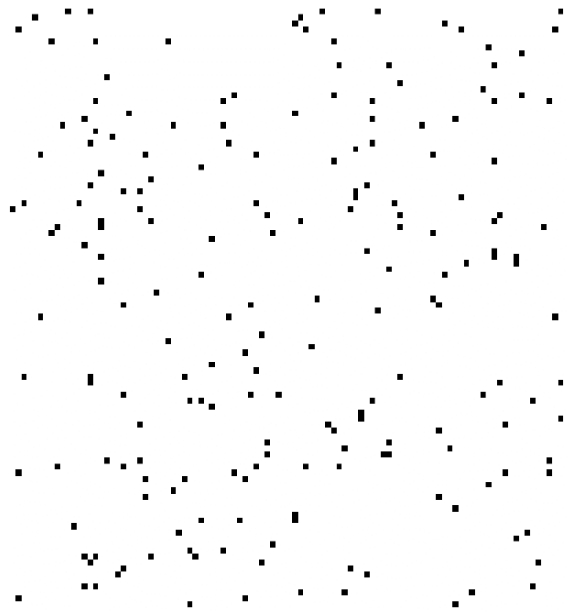
Pre-processing for VBM



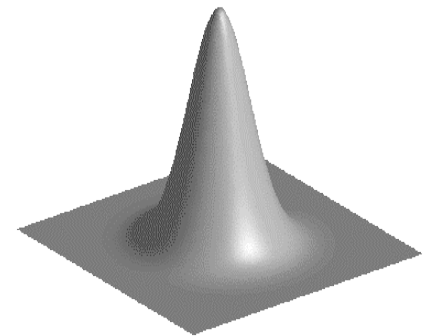
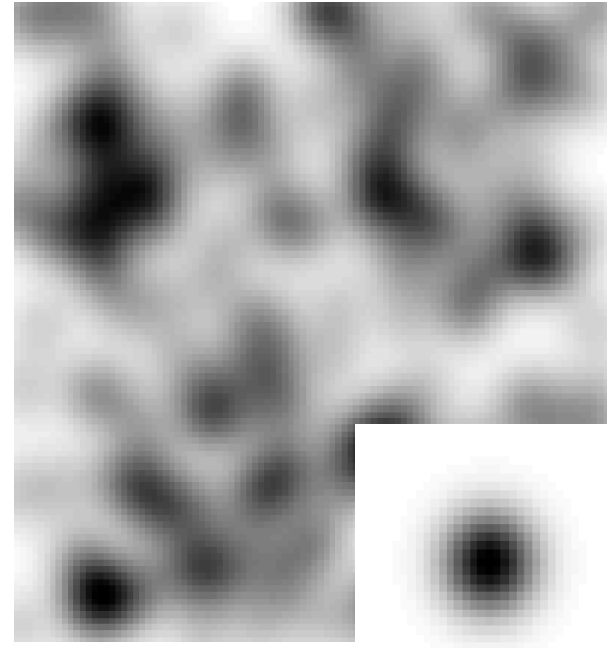
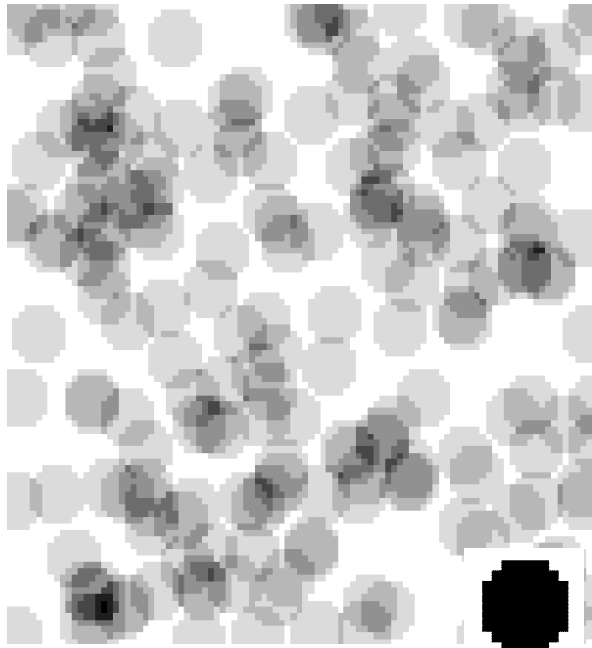
Source: John Ashburner

Smoothing

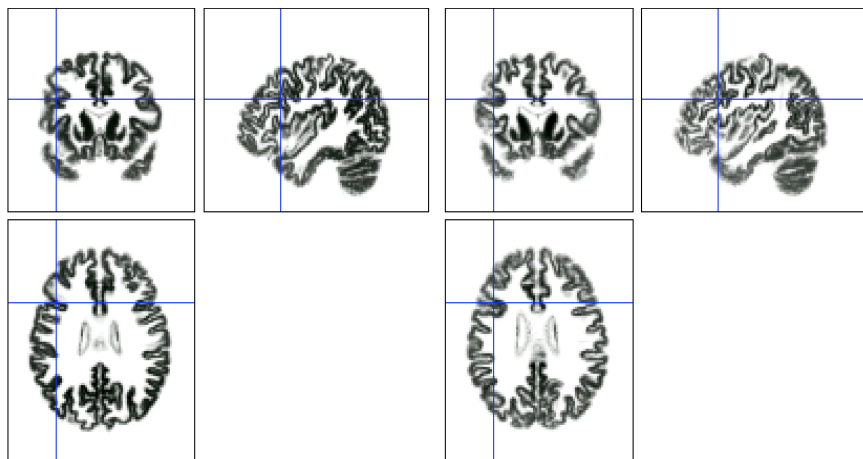
Before convolution



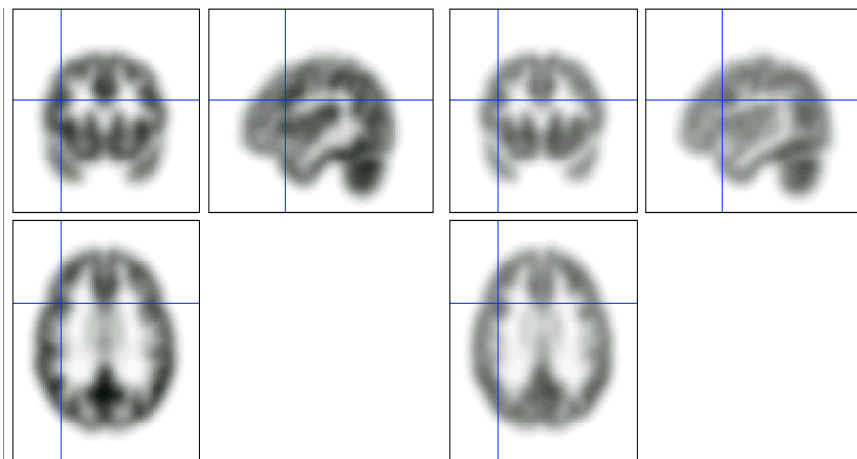
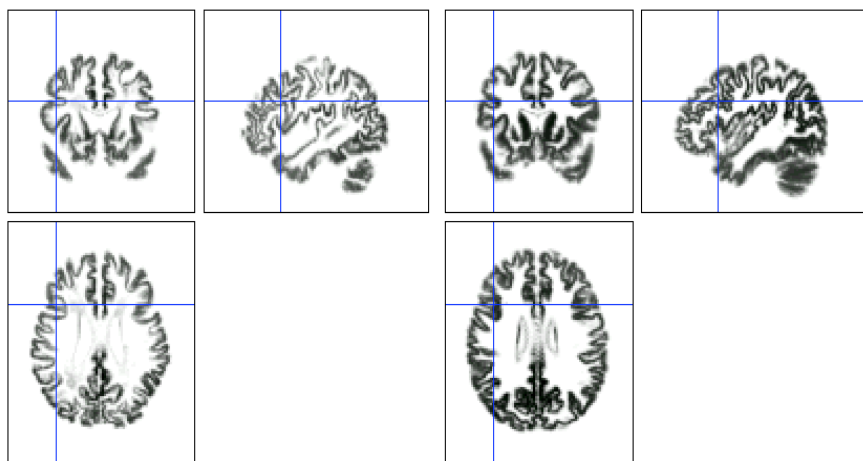
Convolved with a circle



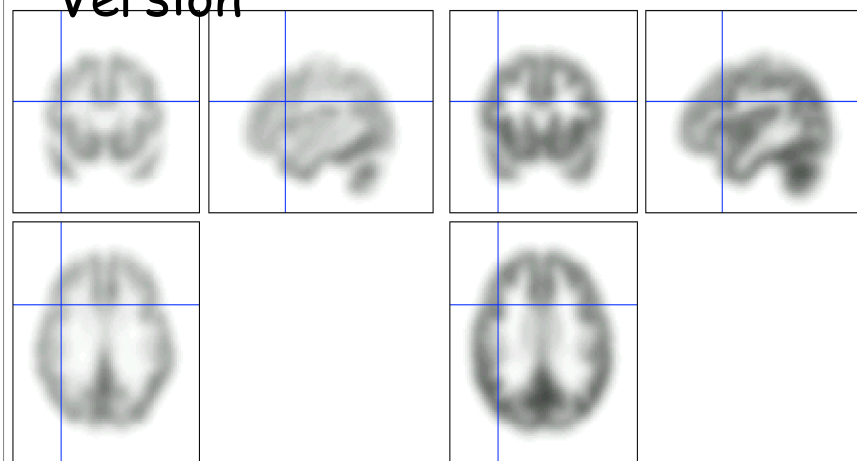
Examples of four subjects



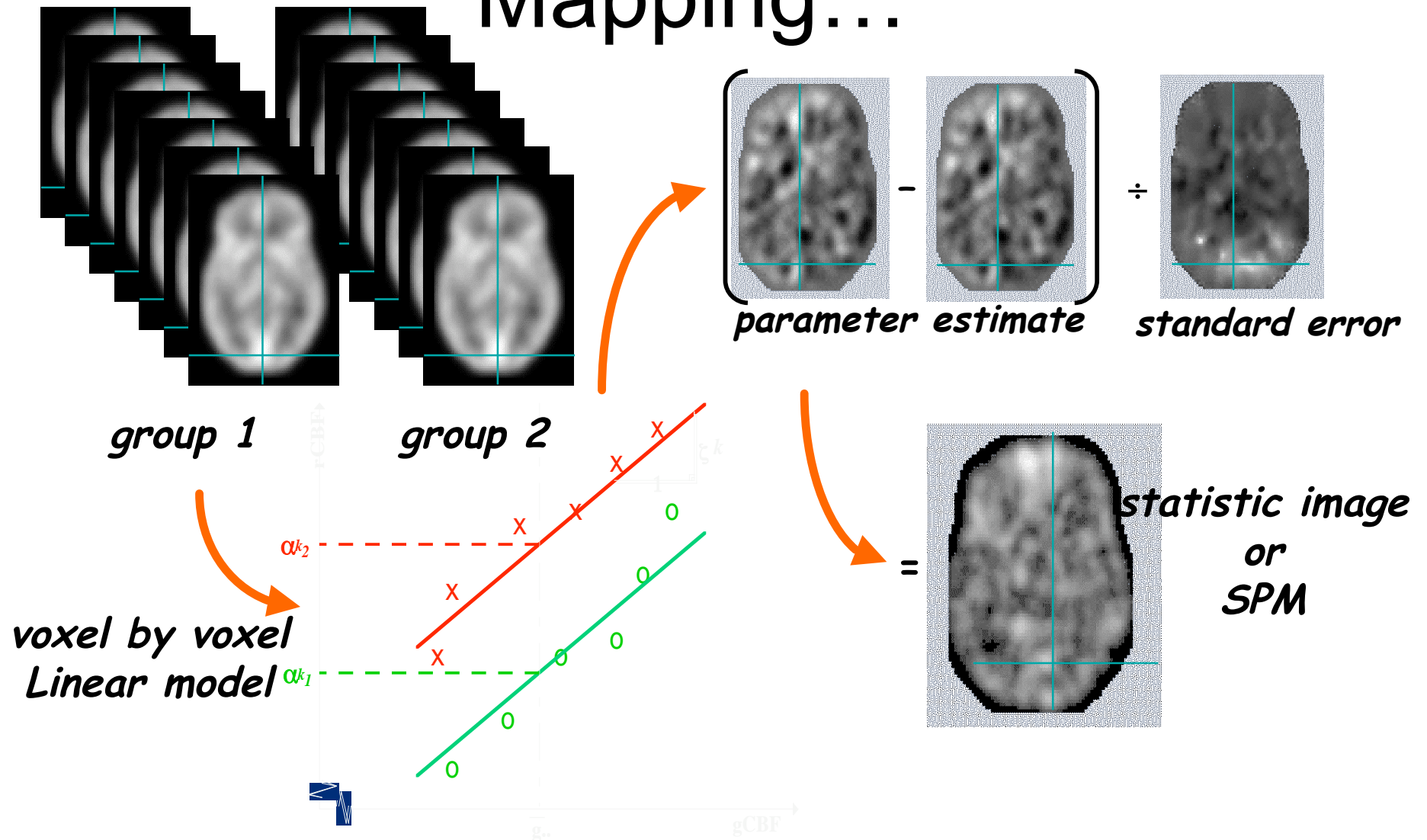
Warped Grey Matter Density



12mm FWHM Smoothed
Version

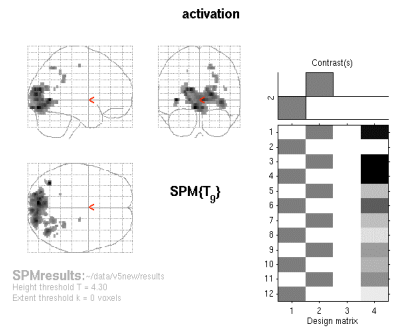


Statistical Parametric Mapping...



SPM results

activation



Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level			x,y,z (mm)
p	c	p _{corrected}	k	p _{uncorrected}	p _{corrected}	T	(Z _e)	
0.964	11	0.000	1285	0.000	0.109	12.51	(5.01)	-8 -82 -12
					0.269	10.43	(4.71)	20 -86 8
					0.272	10.40	(4.70)	-14 -80 16
		0.411	17	0.030	0.168	11.51	(4.87)	-38 -64 0
		0.000	125	0.000	0.465	9.16	(4.48)	36 -66 -4
					0.997	5.74	(3.63)	28 -52 -4
		0.100	26	0.010	0.369	6.46	(3.85)	20 -58 -48
		0.375	25	0.011	0.393	5.98	(3.73)	26 -58 36
		0.976	5	0.112	0.958	5.05	(3.59)	18 -54 52
		0.990	4	0.263	1.000	4.82	(3.38)	-40 -70 -8
		1.000	2	0.401	1.000	4.81	(3.38)	44 -50 50
		1.000	2	0.401	1.000	4.71	(3.26)	-20 -46 44
		1.000	1	0.585	1.000	4.57	(3.20)	40 -52 20
		1.000	2	0.401	1.000	4.38	(3.13)	22 -46 40

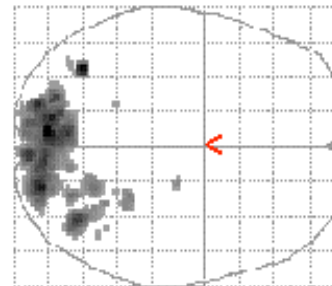
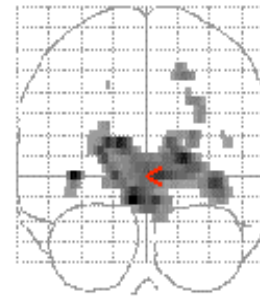
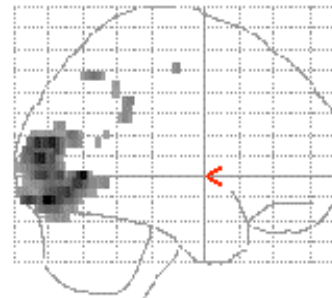
table shows at most 5 subsidiary maxima > 6.0mm apart per cluster

Height threshold: T = 4.30, p = 0.001 (1.000 corrected) Degrees of freedom = (1, 9, 0)

Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected) Smoothness P(FWHM) = 10.9 (2.1 9.2 mm) = 5.5 (0.2 3.3 voxels)

Expected voxels per cluster, (vc) = 1.443 Search volume: 5 = 971856 mm³ = 82741 voxels = 803.8 voxels

Expected number of clusters, (nc) = 17.64 Voxel size: (2.0, 2.0, 4.0) mm (1 voxel = 75.37 voxels)

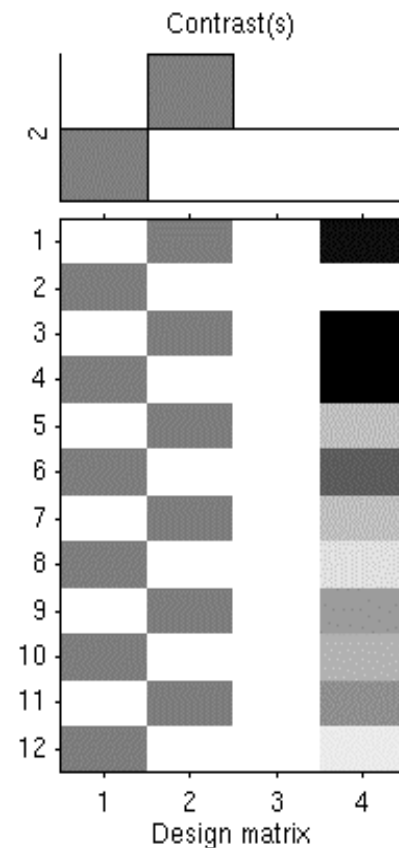


SPM(T₉)

SPMresults: ~/data/v5new/results

Height threshold T = 4.30

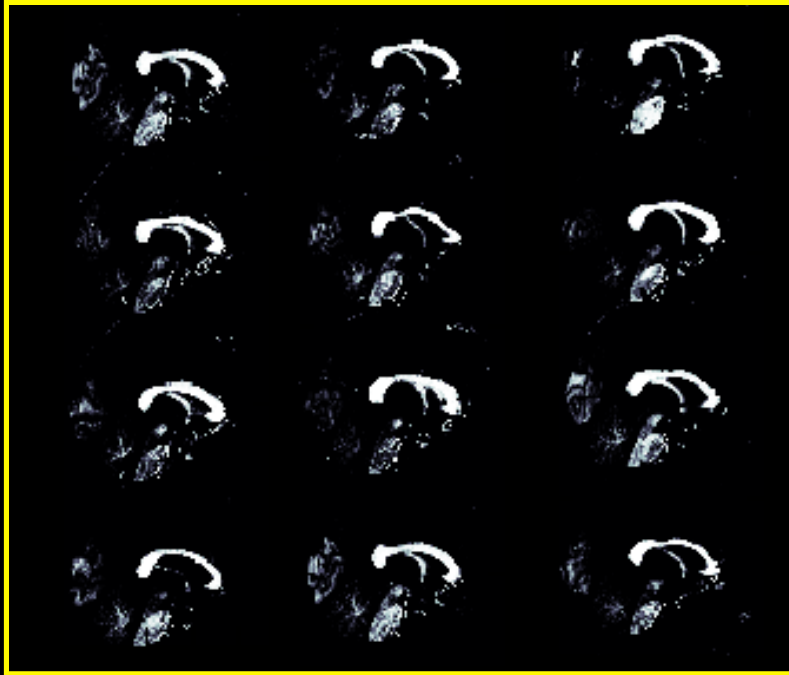
Extent threshold k = 0 voxels



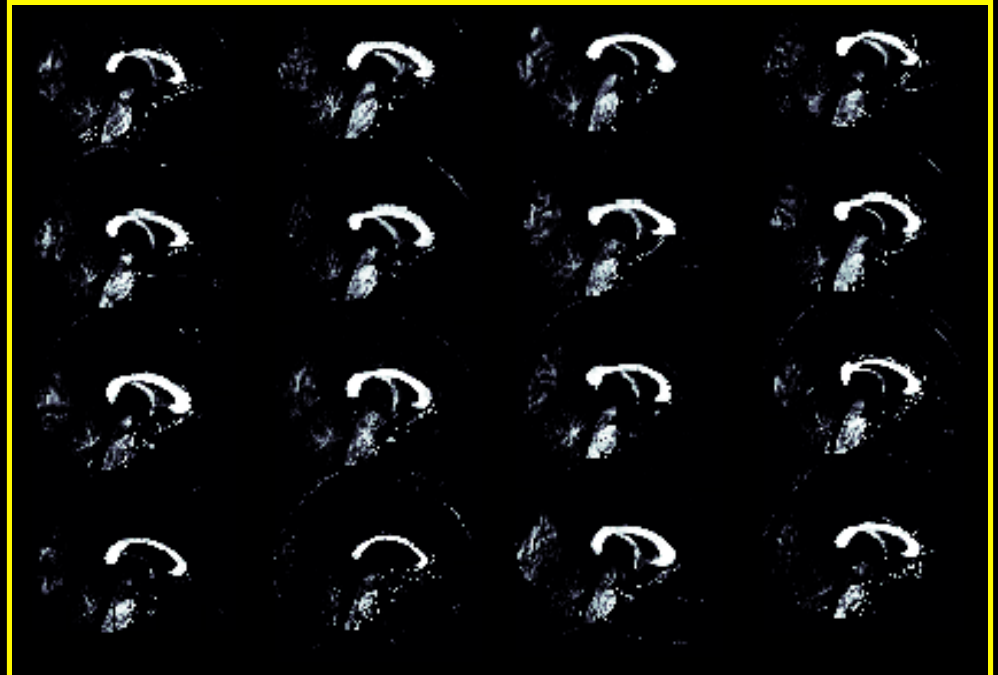
Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level			x,y,z (mm)
p	c	p _{corrected}	k	p _{uncorrected}	p _{corrected}	T	(Z _e)	
0.964	11	0.000	1285	0.000	0.109	12.51	(5.01)	-8 -82 -12
					0.269	10.43	(4.71)	20 -86 8
					0.272	10.40	(4.70)	-14 -80 16
		0.411	17	0.030	0.168	11.51	(4.87)	-38 -64 0
		0.000	125	0.000	0.465	9.16	(4.48)	36 -66 -4
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		0.990	4	0.263	1.000	4.82	(3.38)	-40 -70 -8
		1.000	2	0.401	1.000	4.81	(3.38)	44 -50 50
		1.000	2	0.401	1.000	4.71	(3.26)	-20 -46 44
		1.000	1	0.585	1.000	4.57	(3.20)	40 -52 20
		1.000	2	0.401	1.000	4.38	(3.13)	22 -46 40

Real Example: 2D version of VBM



m=12 normal controls



n=16 autistic subjects

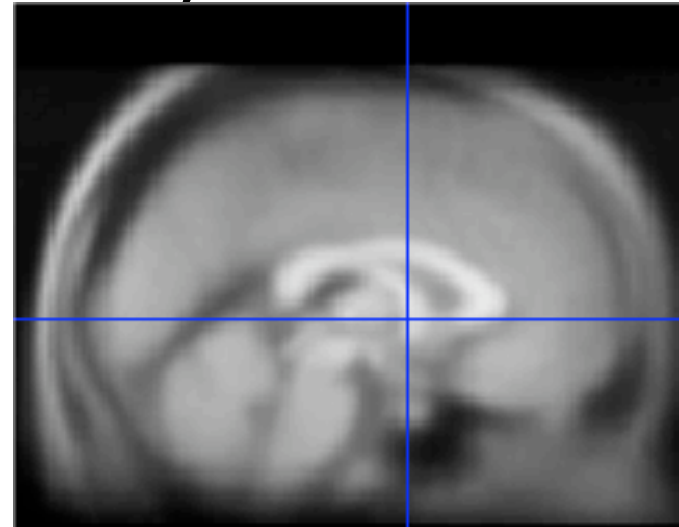
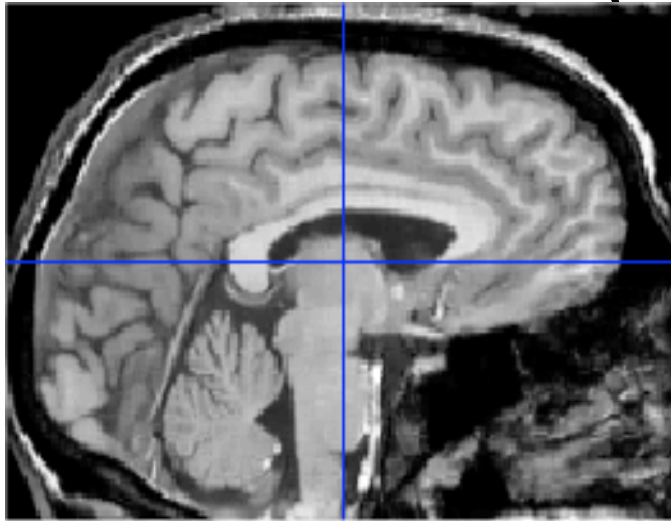
Possible Research Project. See me if you want this project.

Available data associated with MRI

SUBID	GROUP	EYE_M	MOUTH_M	FACE_M	CORRECT	AGE	IQ	NEUT_STRT	NEUT_SIDE	EMO_STRT	EMO_SIDE	NEUTRAL	EMOTION
Subject1	Control	1127.188	0	1399	38	15		1838.25	1971.142857	1576.416667	1366.583333	1904.69643	1471.5
Subject2	Control	1124.706	697.71429	3548.15	40	18		1181	1067.375	1047.083333	997.3333333	1124.1875	1022.20833
Subject5	Control	411.0985	522.4	1459.10526	40	18		1326.625	1233.125	1329.833333	1425.583333	1279.875	1377.70833
Subject8	Control	625.6333	246.16667	1403.66667	40	16		1356.25	1334.375	1131.666667	933.8333333	1345.3125	1032.75
Subject9	Control	374.869	513.16667	2181.45	38	15		1107.875	1336.75	1101.666667	1068.833333	1222.3125	1085.25
Subject10	Control	486.6639	254.33333	1415.625	40	13		1925.125	2266.5	1103	1548.5	2095.8125	1325.75
Subject11	Control	716.2167	523.66667	1522.93548	40	18		727	916.625	863.1666667	826.1666667	821.8125	844.666667
Subject12	Control	498.6923	182	1251.4375	39	21		1320.625	1048.375	1086.5	1008.083333	1184.5	1047.29167
Subject13	Control	66	0	144	39	14		1320.625	1048.375	1086.5	1008.083333	1184.5	1047.29167
Subject14	Control	263.373	322.8	577.15625	39	16		1092	1286	1072.5	1051.833333	1189	1062.16667
Subject15	Control				40	17		1251.125	1125.5	970.5833333	1004.833333	1188.3125	987.708333
Subject16	Control	726.8444	399.83333	1630.85	40	23		883	1007.375	961	1092.416667	945.1875	1026.70833
Subject103	Autism	236.3167	275.8	759.642857	40	17	103	1462.875	1472.25	1080.416667	1090.75	1467.5625	1085.58333
Subject104	Autism	395.9688	217.5	1326.18421	40	14	122	1154.375	965.625	1137.583333	1363.666667	1060	1250.625
Subject105	Autism	503.64	509.14815	1650.35	37	12		1588.875	1942.5	1549.25	1418.416667	1765.6875	1483.83333
Subject106	Autism	315.6232	294.25	820.46875	24	15	84	1992.625	1182.5	1114.583333	1370.333333	1587.5625	1242.45833
Subject107	Autism	433.5313	455	1550.575	36	25	101	1984.625	1667.75	1247.583333	1215	1826.1875	1231.29167
Subject108	Autism	991.7925	550.53846	2420.8	40	14	93	963.5	1279.5	898.8333333	876.6666667	1121.5	887.75
Subject109	Autism	0	0	83	0	15	35						
Subject110	Autism	0	0	0	5	14	67	584.875	767.75	1694.916667	1208.75	676.3125	1451.83333
Subject111	Autism	58.5	298	186.5	36	24	117	1436	1235.875	1307.25	1399.166667	1335.9375	1353.20833
Subject113	Autism	344.25	347.8	1042.5	0	18	53						
Subject114	Autism	268.7455	262.7	793.65625	39	10	88	1606.875	1647.375	1743.5	1584.833333	1627.125	1664.16667
Subject116	Autism				39	12	117	1339.375	1276.875	1559.75	1186.5	1308.125	1373.125
Subject117	Autism	0	344.33333	628.4	23	22	79	2128	1313.5	1367.75	1604.583333	1720.75	1486.16667
Subject118	Autism	224.0972	687.44444	1350.94444	21	12	74	1345.5	1697.75	1625.583333	1270.083333	1521.625	1447.83333

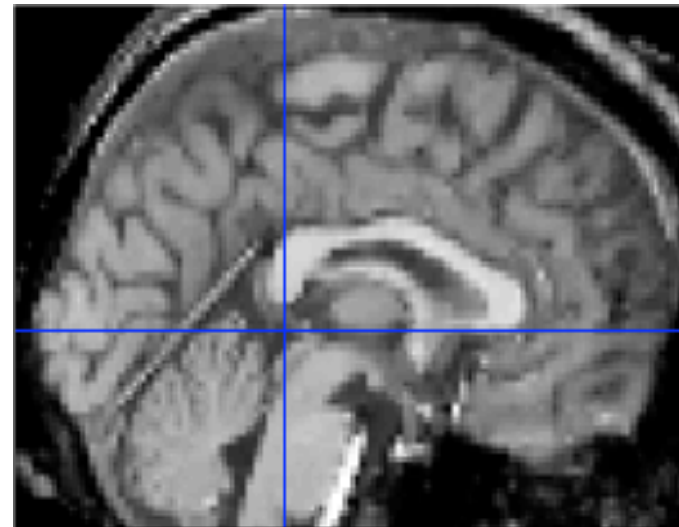
- Group dummy variable for autistic (0) and control (1)
- Age
- Facial emotion discrimination task accuracy (max score 40) and its response time (ms)
- Gaze fixation durations (ms) on eyes and faces

**Pre-processing
Nonlinear image registration
(Normalization)**

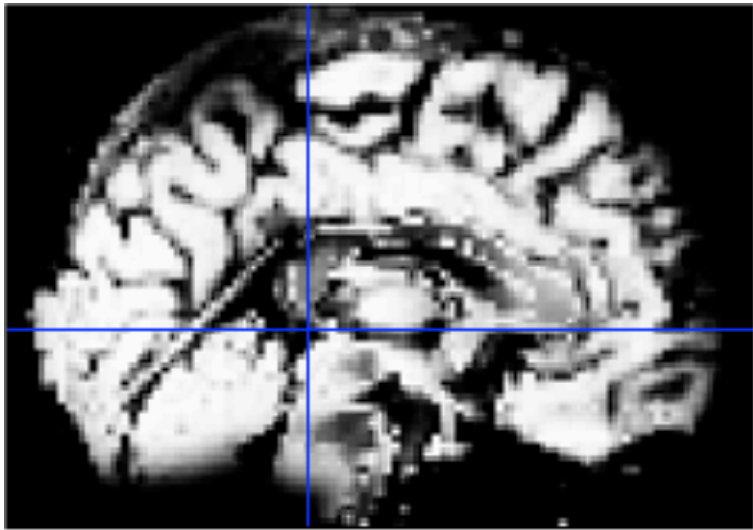


300 subjects MNI template

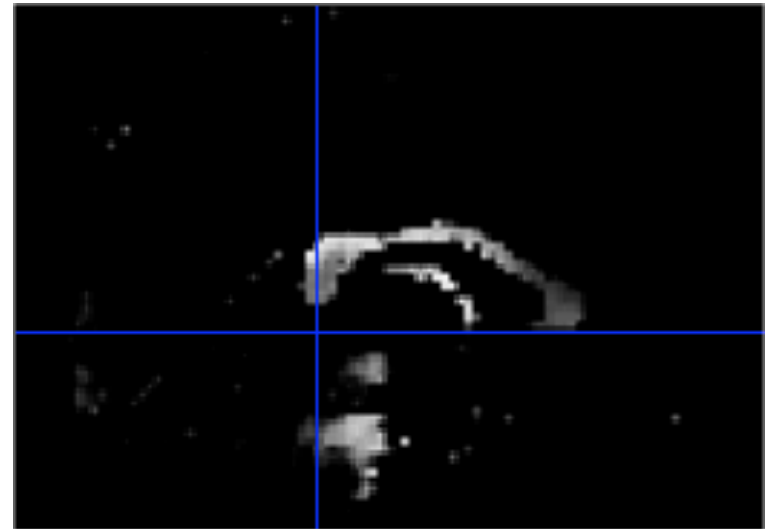
**Each subject undergoes
this process to reduce
positional variability.**



White matter segmentation

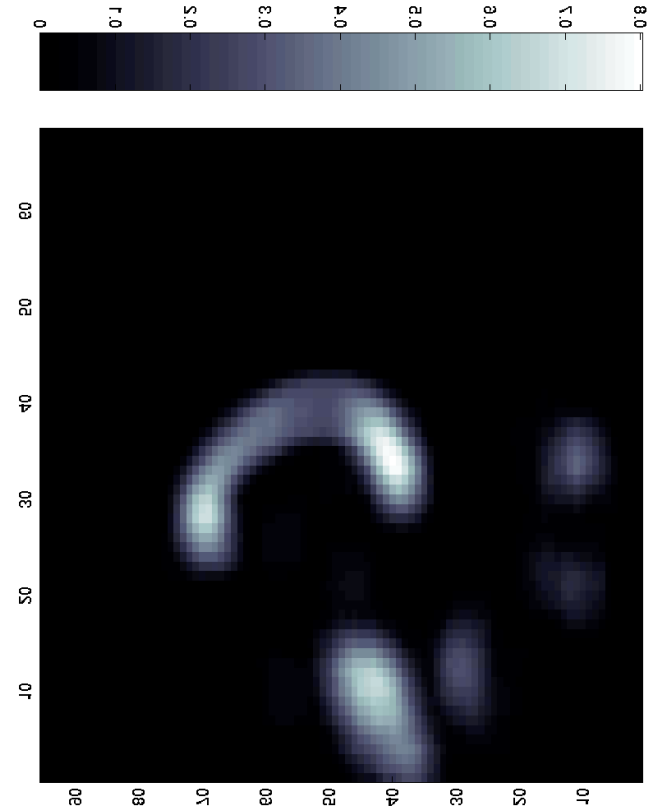
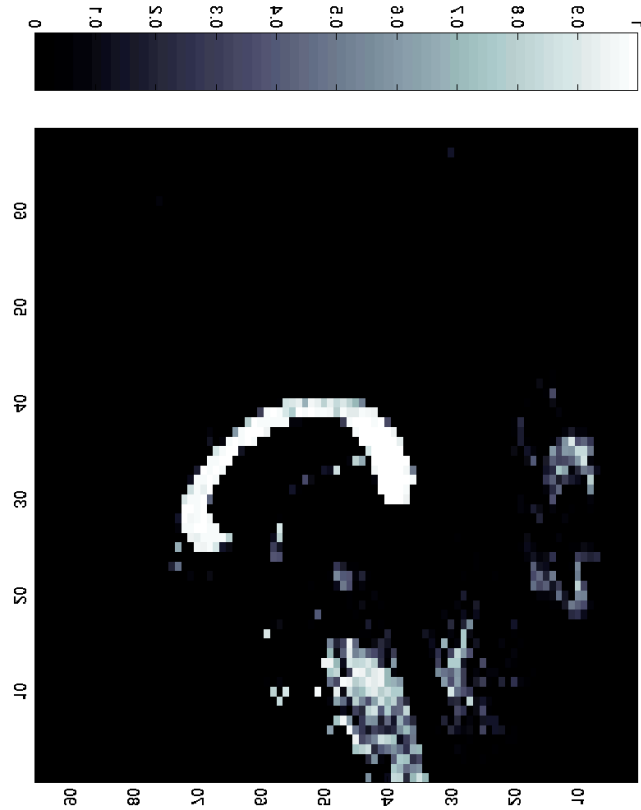


Normalized image



**Segmentation of
midsagittal corpus
callosum region**

We will study the underlying Gaussian mixture model later.



2D Gaussian kernel smoothing on white matter density map.

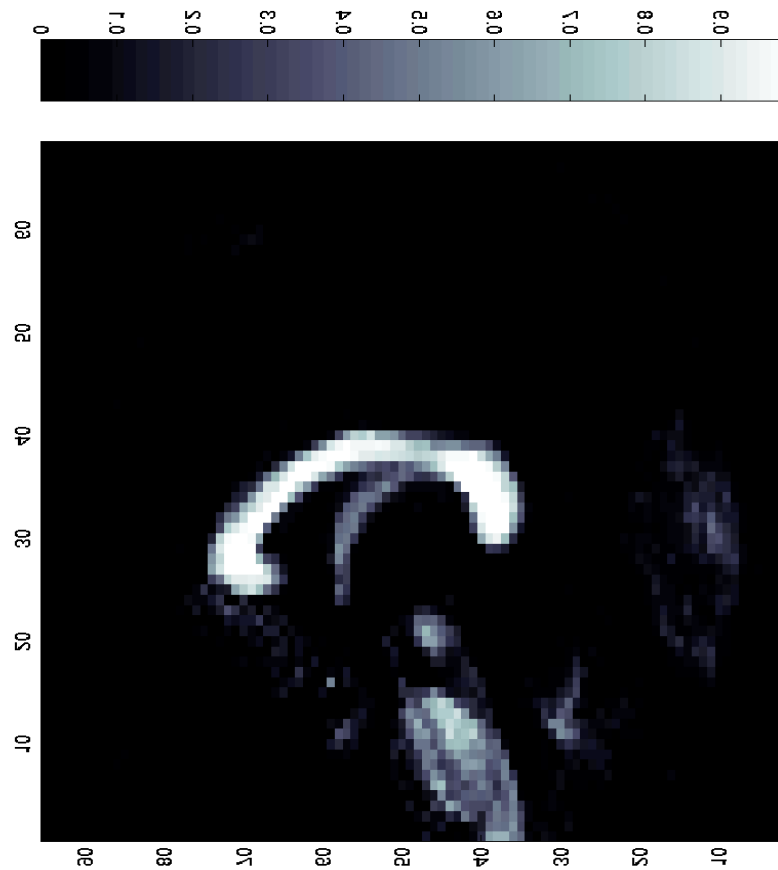
Is *logit* transform necessary?

$$\text{logit}(p) : p \rightarrow \frac{1}{2} \log\left(\frac{p}{1-p}\right)$$

It is not necessary since Gaussian kernel smoothing will make data more Gaussian.

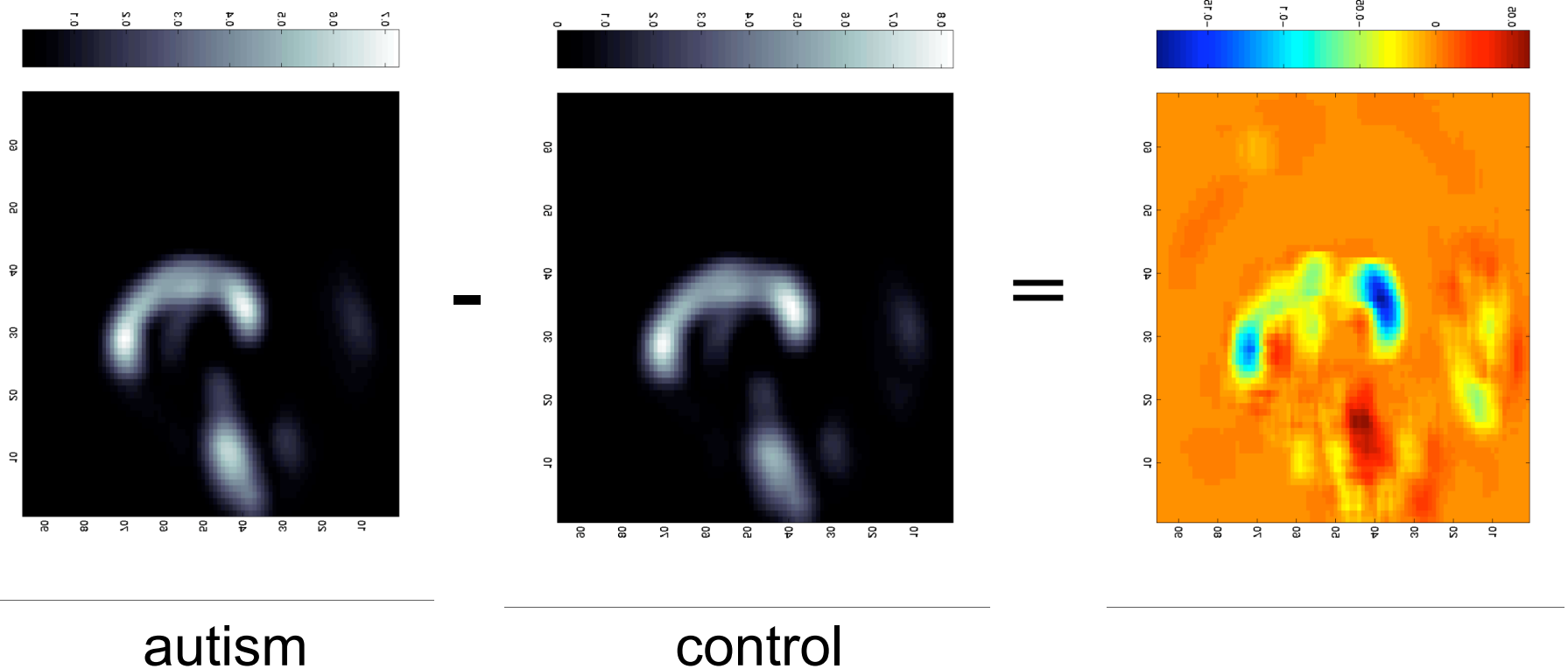
Selfstudy: can you prove this statement?

Mid-sagittal section of brain



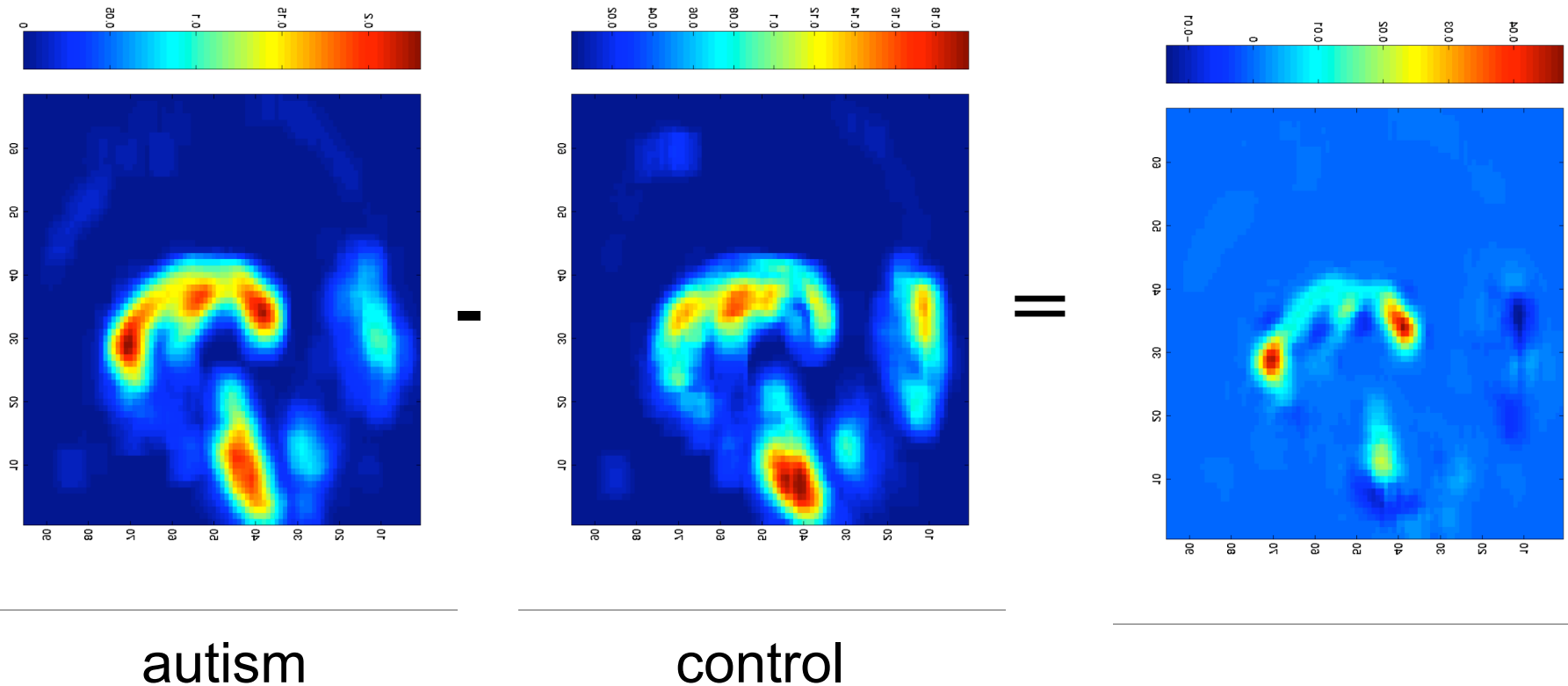
Average of 12 normalized mid sagittal segmented images showing well defined corpus callosum.
This is our template.

White matter concentration difference

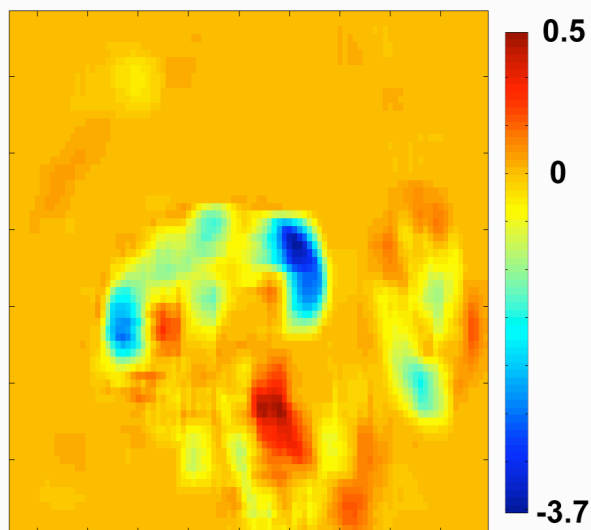


- Compute the sample mean at each voxel.
- Is the density difference statistically significant ?

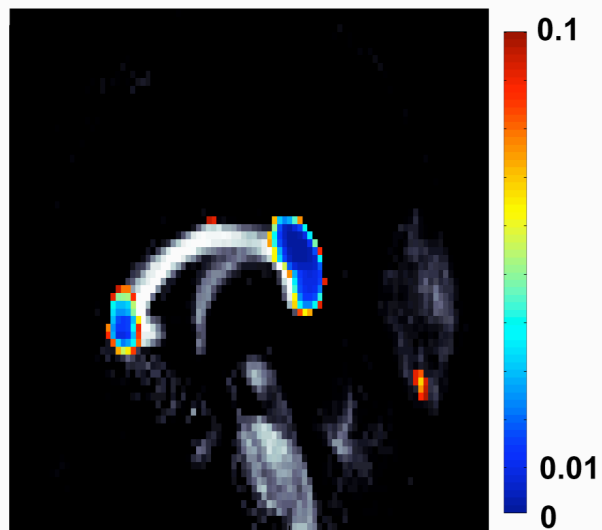
White matter variability difference



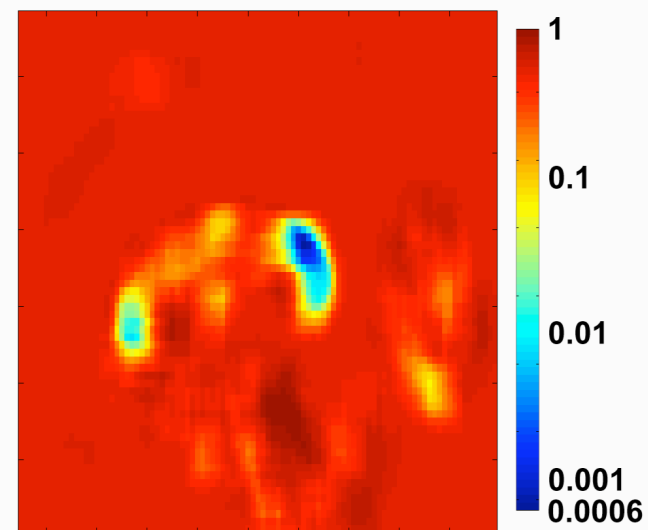
- Compute the sample variance
- Even though the difference shows unequal variance, you used *two sample t-statistic with equal variance assumption*. **Why? It gives us the exact *t* random field.**



t -statistic



P -value



P -value in logscale

But the two sample t test doesn't seem to be right. There may be possible age effect so it is necessary to remove the age effect. How?

General linear model (GLM)

$$density = \lambda_1 + \lambda_2 age + \beta_1 group + e$$

$$H_0 : \beta_1 = 0 \text{ vs. } H_1 : \beta_1 \neq 0$$

Generalize this model

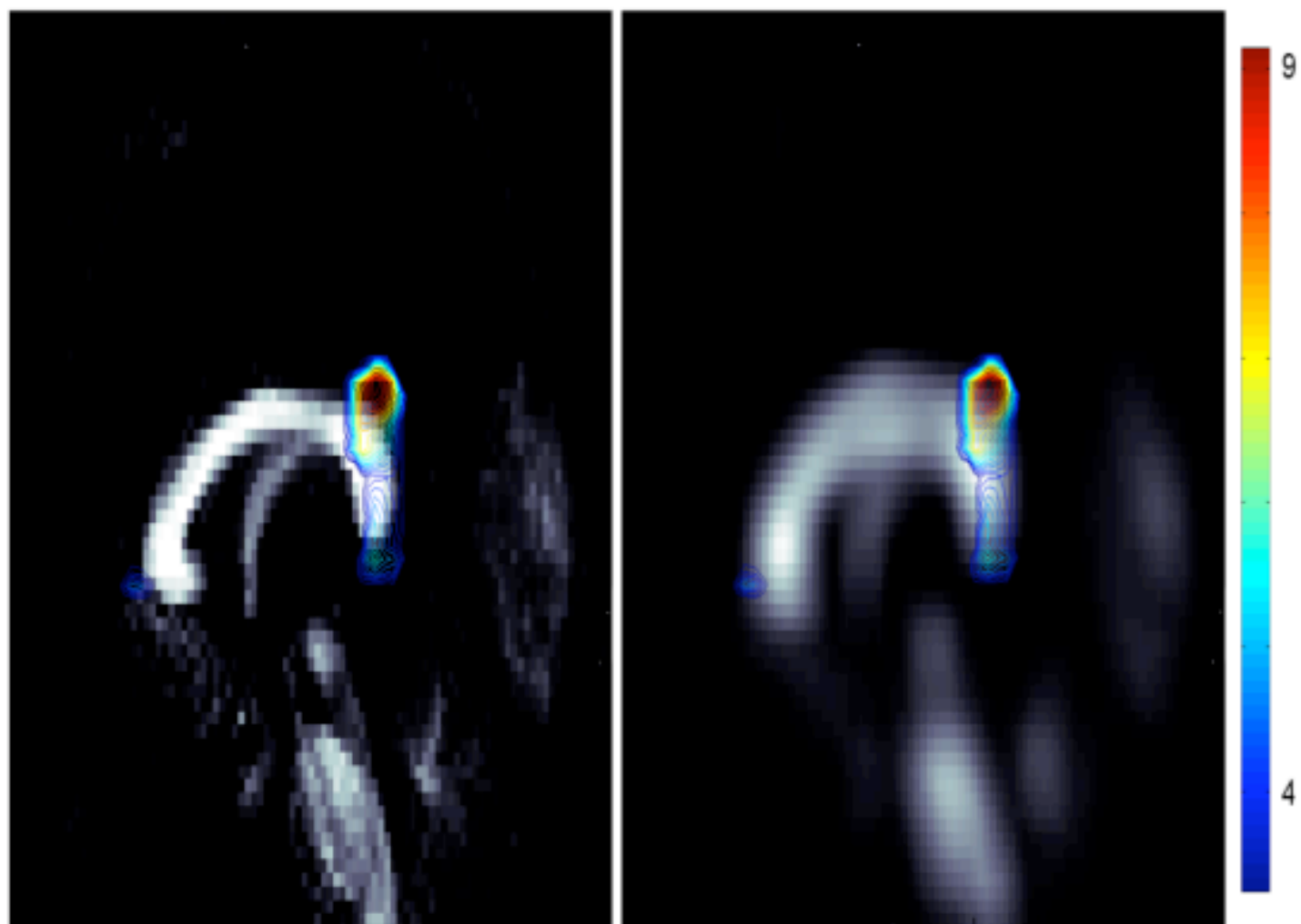
$$Y = \mathbf{z}\lambda + \mathbf{x}\beta + e$$

$$\mathbf{x} = (x_1, \dots, x_p) \quad \text{Variables of interest}$$

$$\mathbf{z} = (z_1, \dots, z_k) \quad \text{Nuisance covariates}$$

$$F = \frac{(SSE_0 - SSE_1)/p}{SSE_0/(m + n - p - k)} \sim F_{p, m+n-p-k}$$

Computing the sum of squared errors (residuals) requires the least squares estimation (LSE) of unknown parameters.



after removing age effect

Effect of age

Age distribution for autistic subjects:

16.1 (s.d. 4.5)

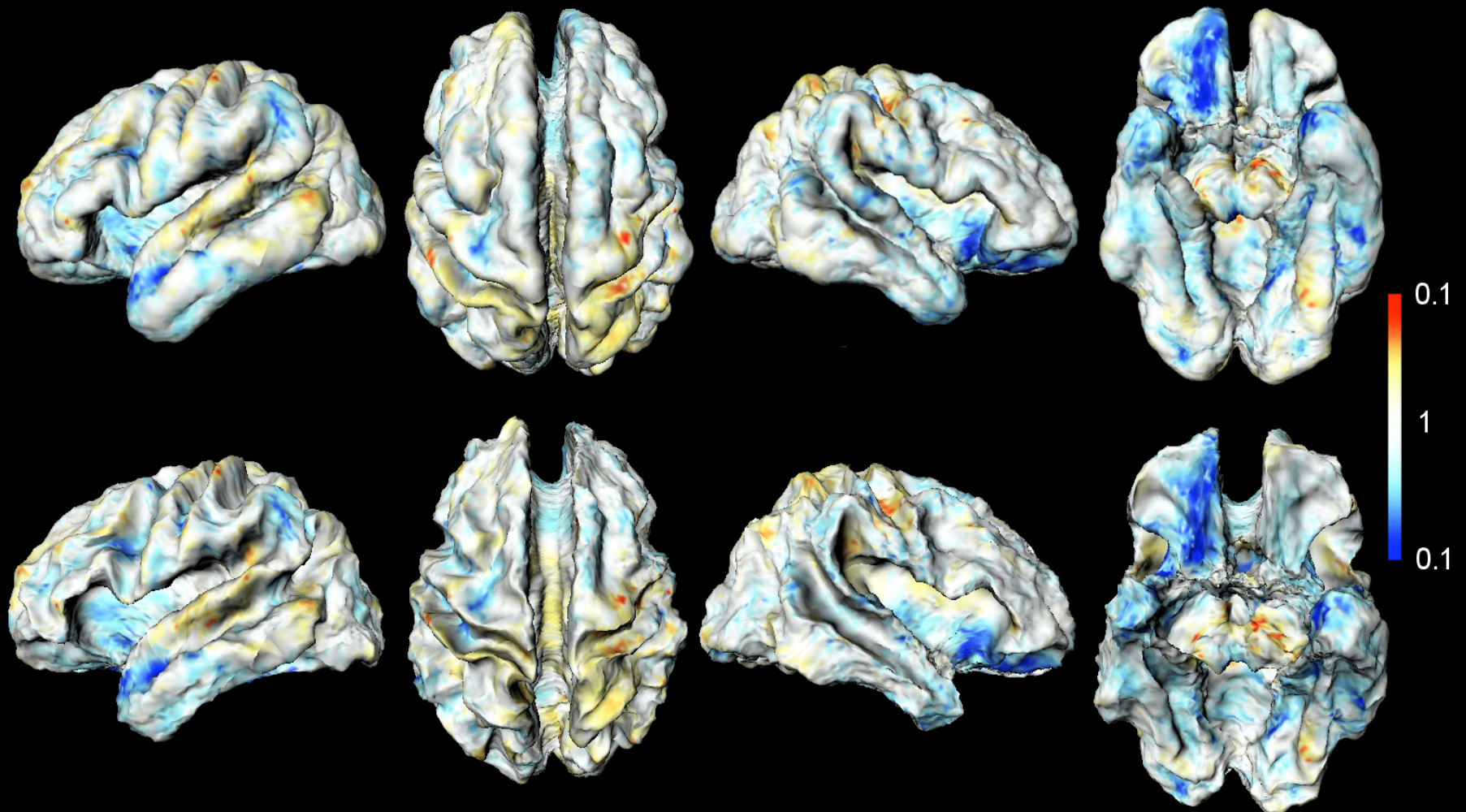
Age distribution for control subjects:

17.1 (s.d. 2.8)

In this study, there is no visible age effect.

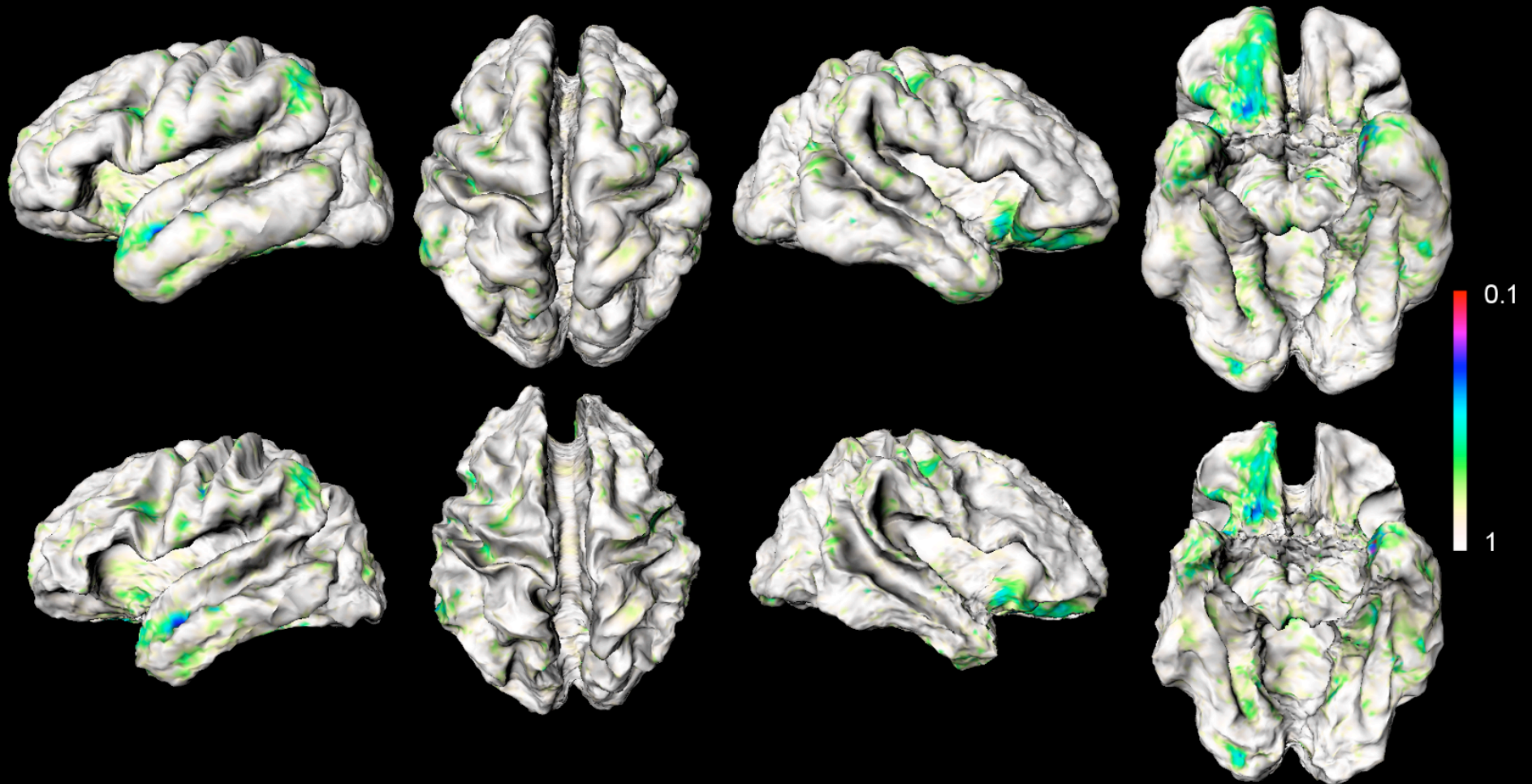
However, a different study on the same data set shows significant age effect.

p -value map for t -test on cortical thickness difference



Decrease: left superior temporal sulcus, left occipital-temporal gyrus, right orbital prefrontal
Increase: left superior temporal gyrus, left middle temporal gyrus, left and right postcentral sulci

p -value map for F -test removing age effect



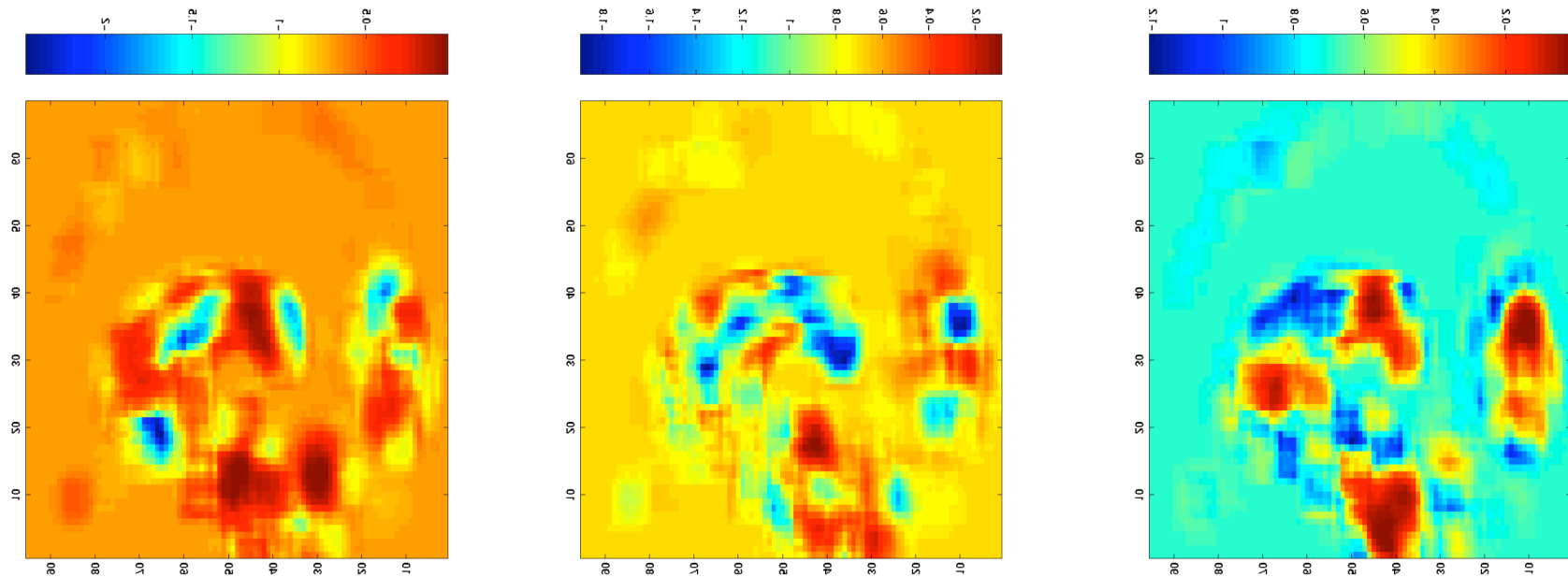
Decrease: left superior temporal sulcus
left occipital-temporal gyrus
right orbital prefrontal

It is better to remove the age effect in anatomical data especially for developmental age range (10-20 years).

How to validate VBM framework ?

This is not a permutation test although it looks like it.

Randomly permute 16 autism and 12 controls to generate 14 autism and 14 controls. Our two sample t-test should not detect anything except possible random occurrences.



Above all three random permutations, $p\text{-value} > 0.3679$

Issue of image registration in VBM

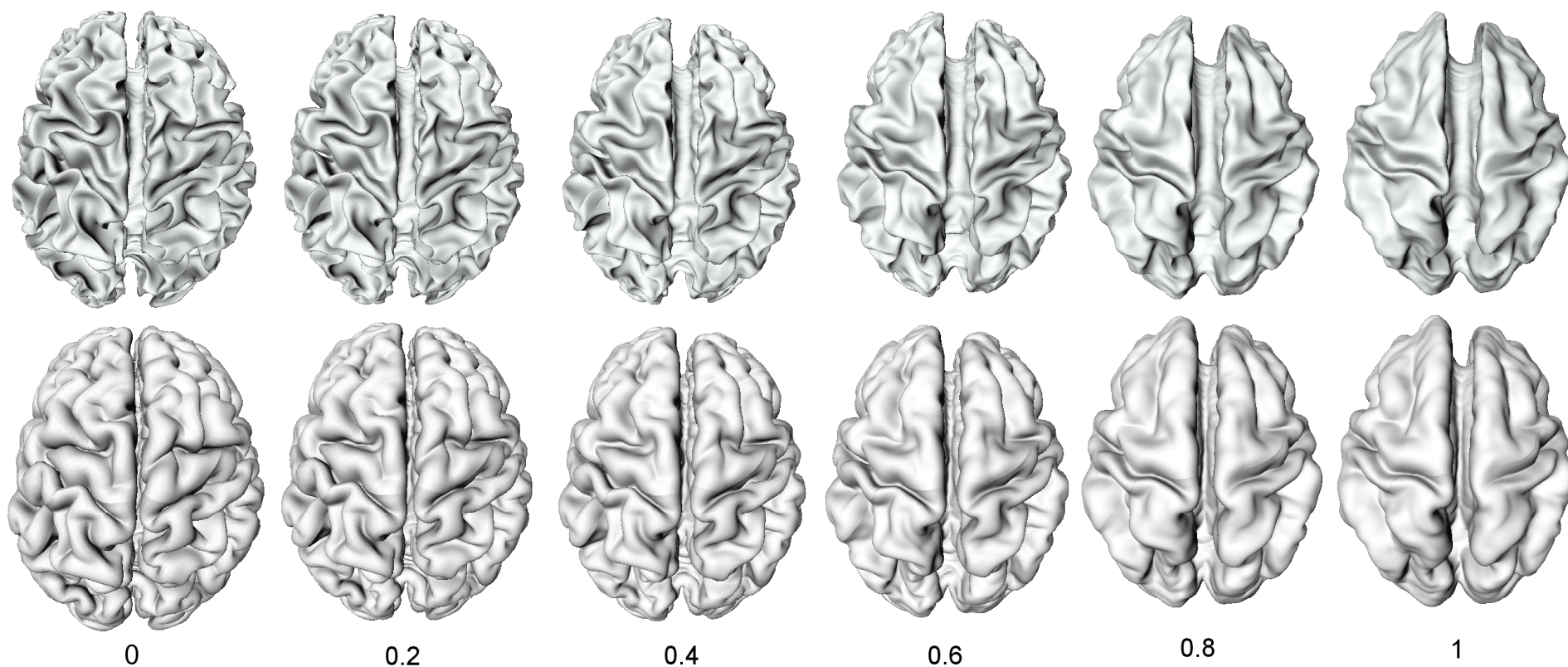
- If the registration is perfect, every parts of CC matches perfectly. It will result in similar gray matter density maps.
- Similar measures make differentiating populations difficult. Why? It reduces between-group variability.
- If the registration is coarse, most part of CC will not match and it will result in large within-group variability.
- In order for VBM to work, coarse registration seems to be sufficient.

Modulated VBM:

- There is a way to incorporate the amount of registration into VBM. *We will talk about this after tensor-based morphometry.*

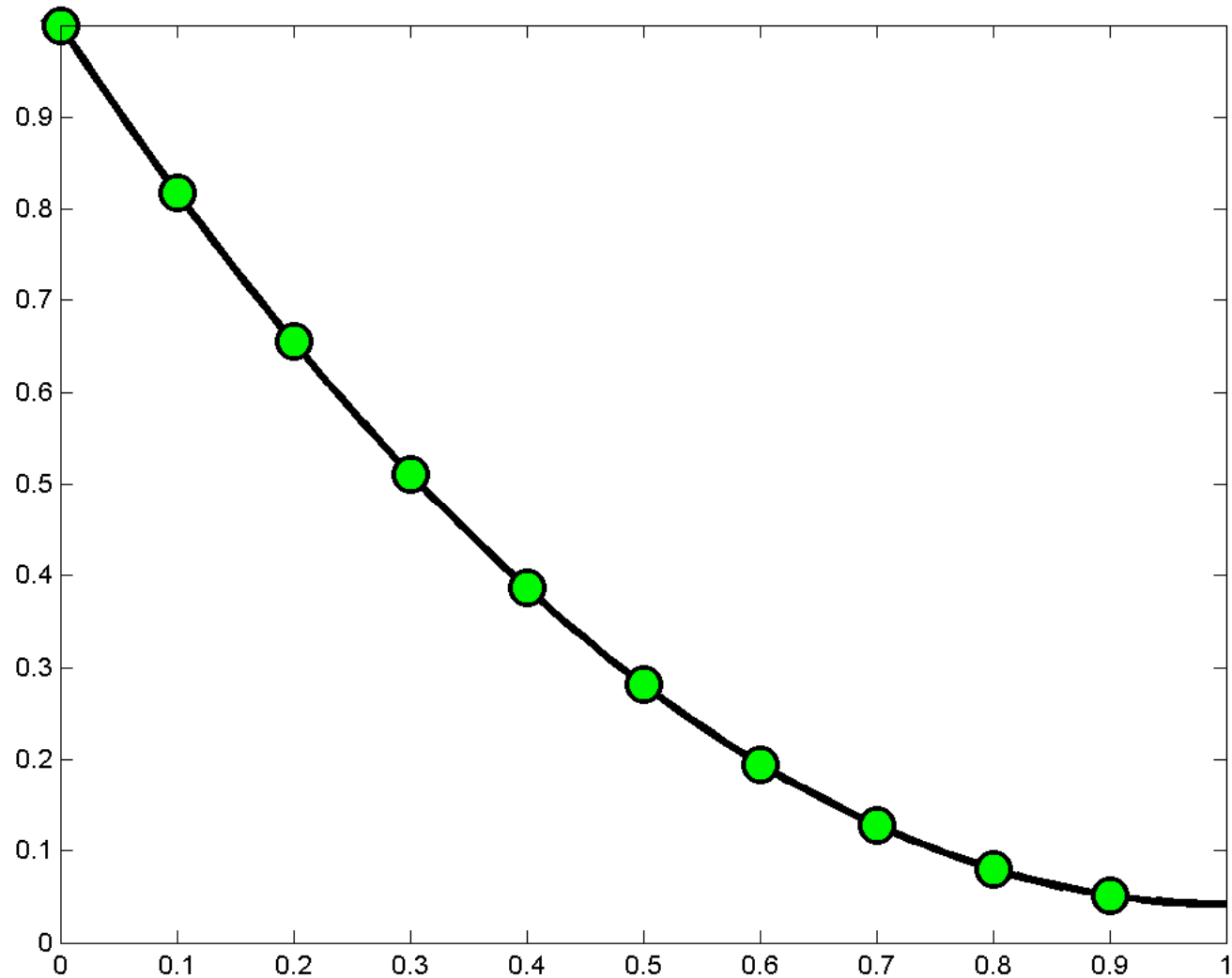
single
subject

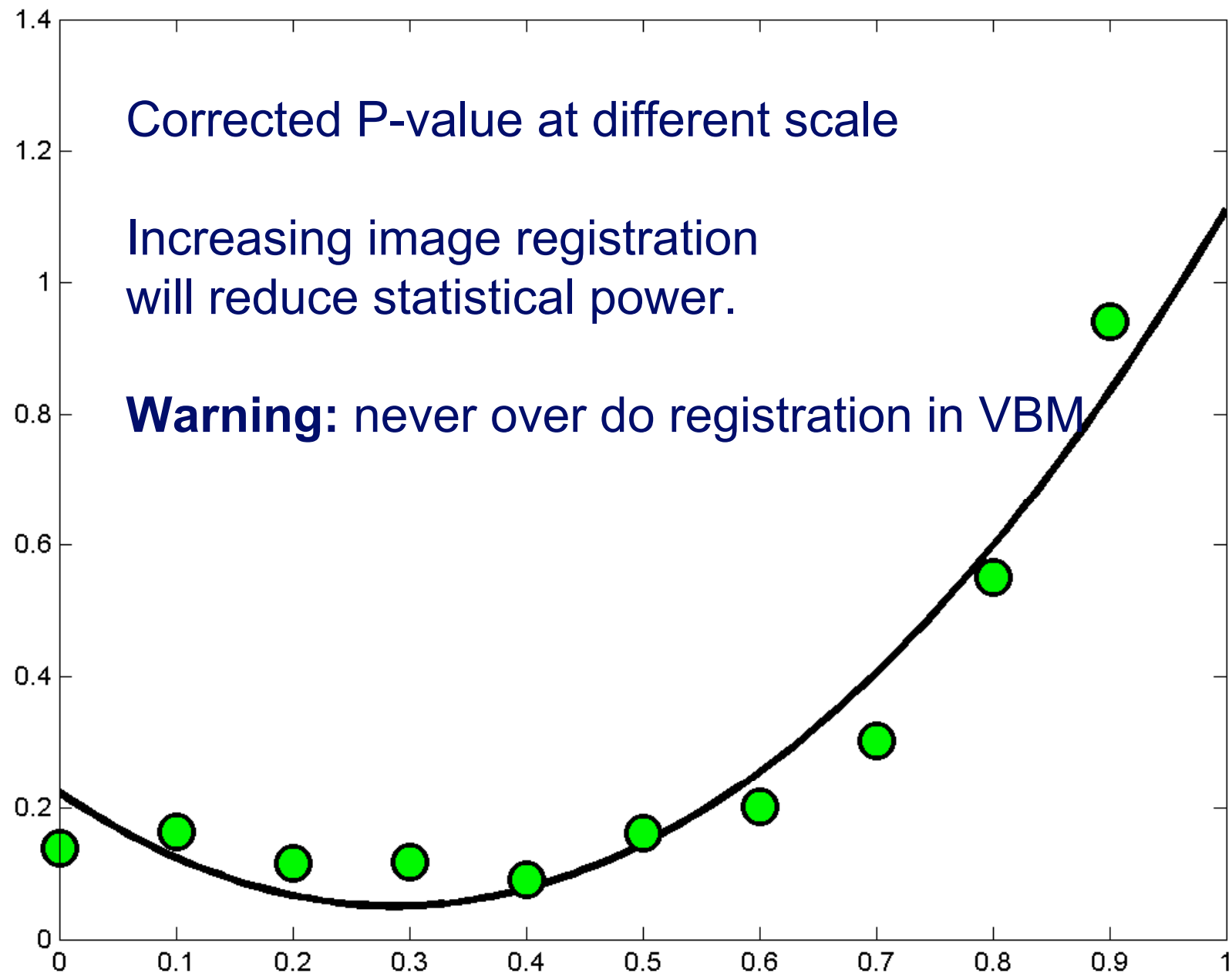
average
template



The trajectory of nonlinear image registration.

Decreasing normalization variability





Lecture 3 topics

Deformation based Morphometry
(DBM) and
Hotelling's T^2 statistic