The challenges of high-resolution fMRI: facing the broken assumptions at lower resolutions

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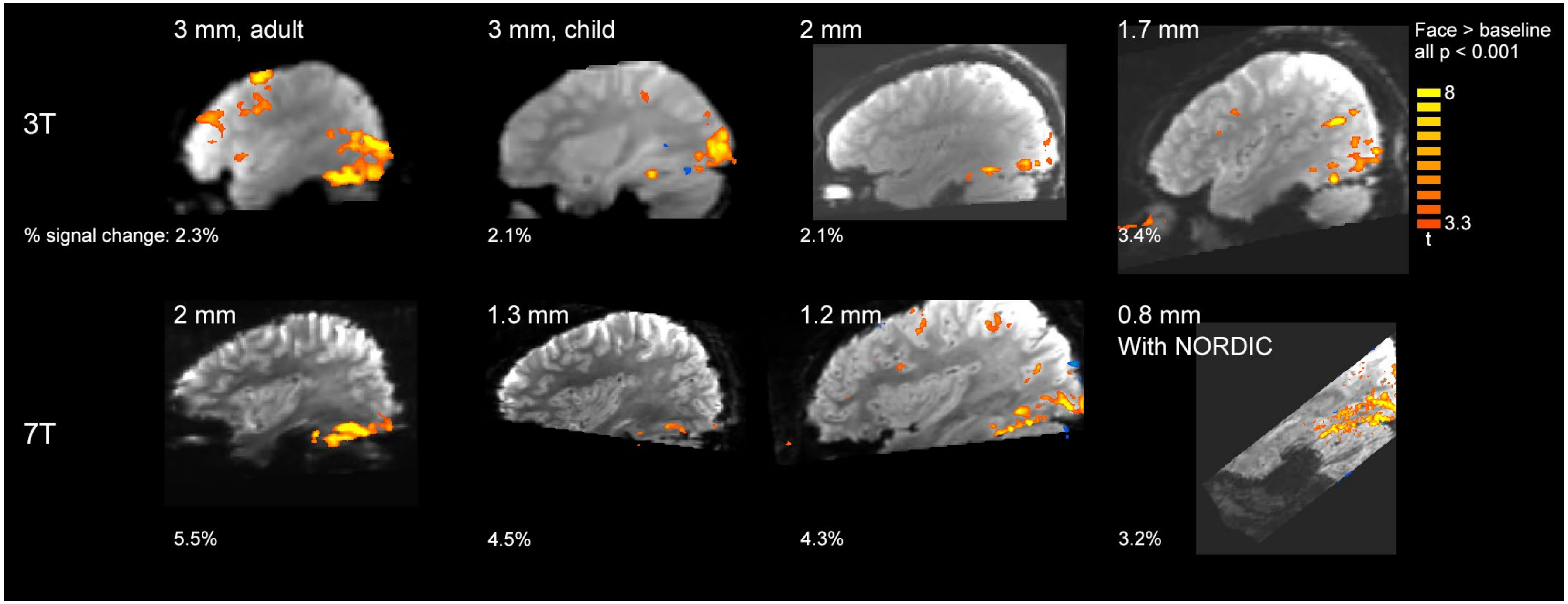


Fondation Bettencourt Schueller
Reconnue d'utilité publique depuis 1987

CENIR Institut du Cerveau

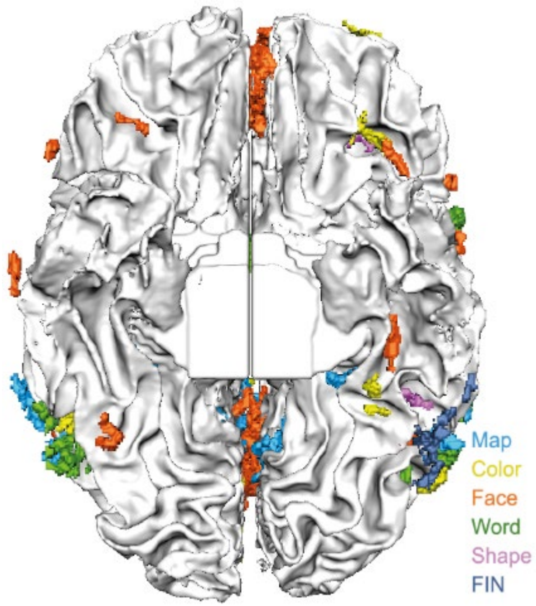
Paris Brain Institute ICM

NeuroSpin

My research directions

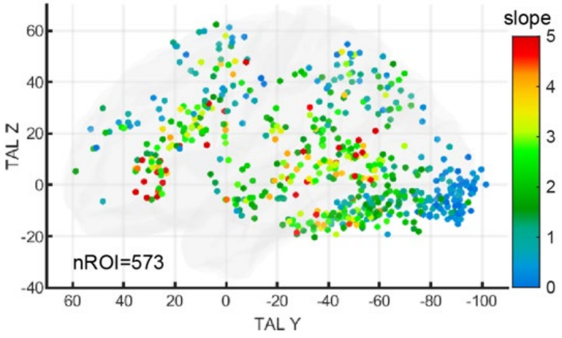
- High-level vision: category-specific areas
- Cortical plasticity and reorganization
- Top-down bottom-up interactions in cortical layers

Category-specific areas



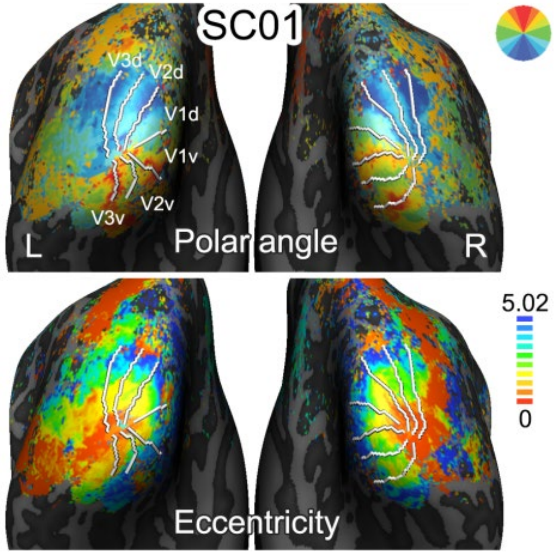
Liu et al. (2025)

Word-similarity gradient



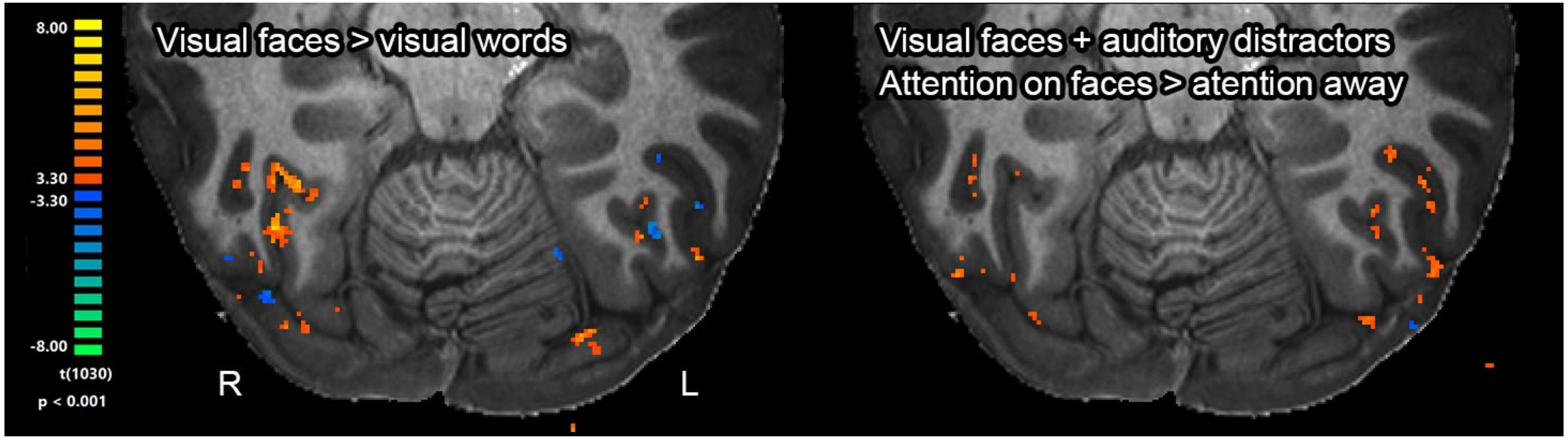
Zhan et al. (2023)

Retinotopy



Heitmann et al. (2023)

Modulation of layer activity by attention



Zhan et al. (in prep)

The 7T fMRI: high resolution

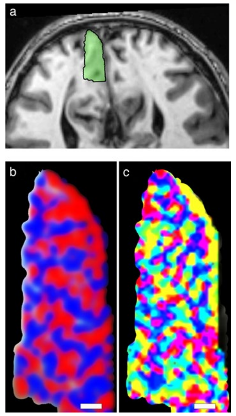
7T fMRI: high resolution

Macroscale			Mesoscale		Microscale
Brain lobes	**Brain areas**	**Activation clusters**	**Columns**	**Layers**	**Neurons**
10 cm	A few cm	?	0.5-1 mm	< 1 mm	< 0.1 mm

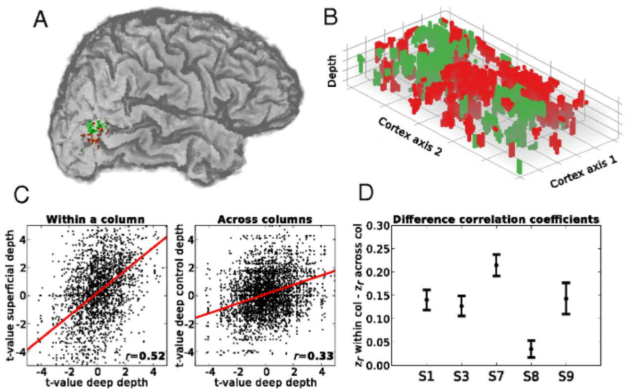
Individual-subject analysis
No smoothing

- Gray-matter segmentation
- Column/layer analysis

Column fMRI

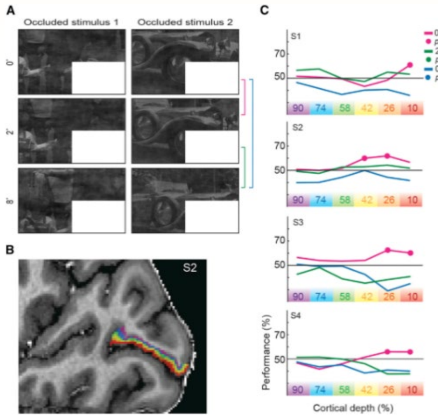


Yacoub, Harel, Ugurbil (2008)

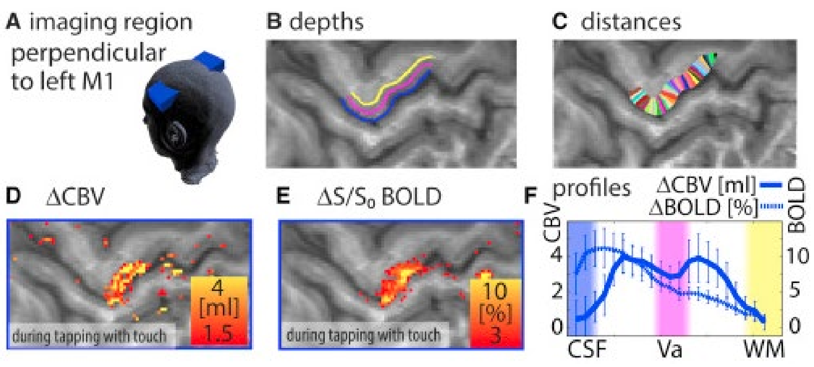


Schneider et al. (2019)

Layer fMRI



Muckli et al. (2015)



Huber, …, Poser, Bandettini (2017)

7T fMRI: high contrast, high SNR, high statistical power

Macroscale → **Mesoscale** → **Microscale**

Brain lobes
10 cm

Brain areas
A few cm

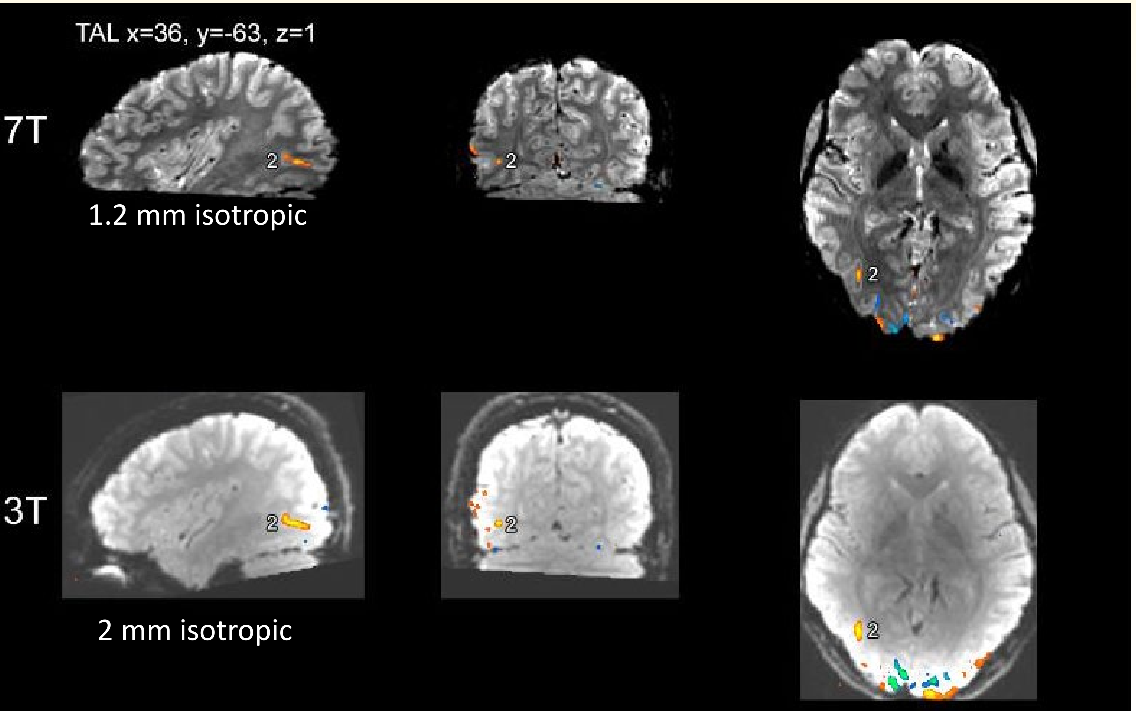
Activation clusters
?

Columns
0.5-1 mm

Layers
< 1 mm

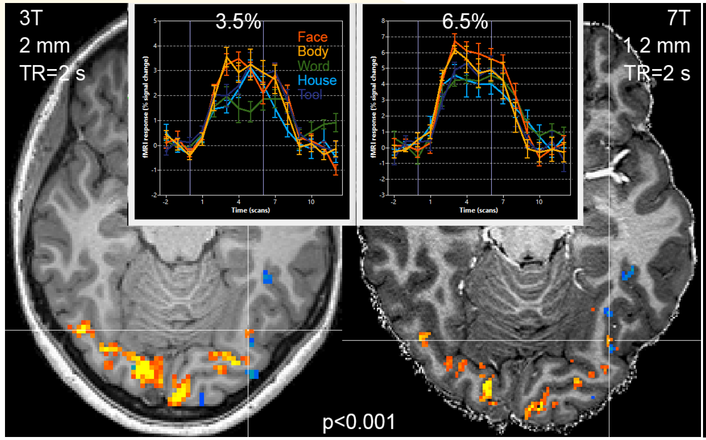
Neurons
< 0.1 mm

Similar to 3T analysis
Can do smoothing
Group-level statistics



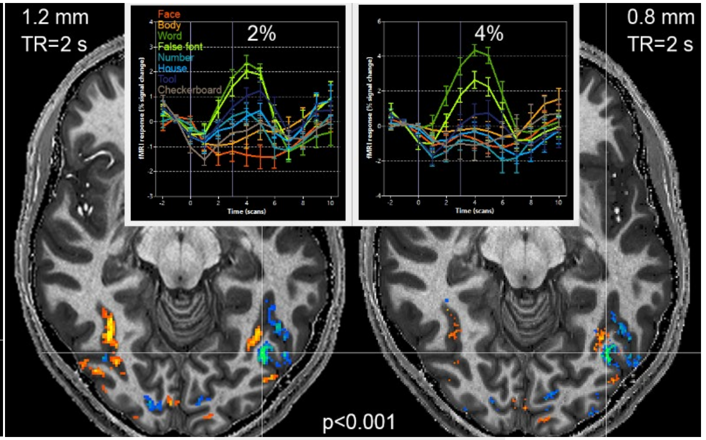
Field and resolution increase

Same subject, same task, 3T vs 7T

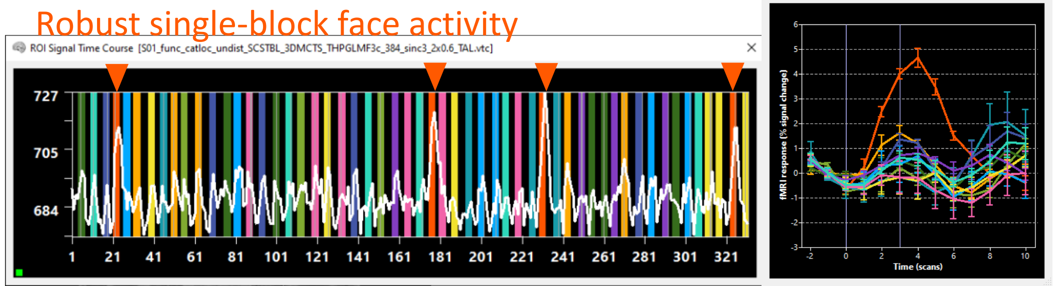


Resolution increase

Same subject, same task, 7T, 1.2 vs 0.8 mm with NORDIC

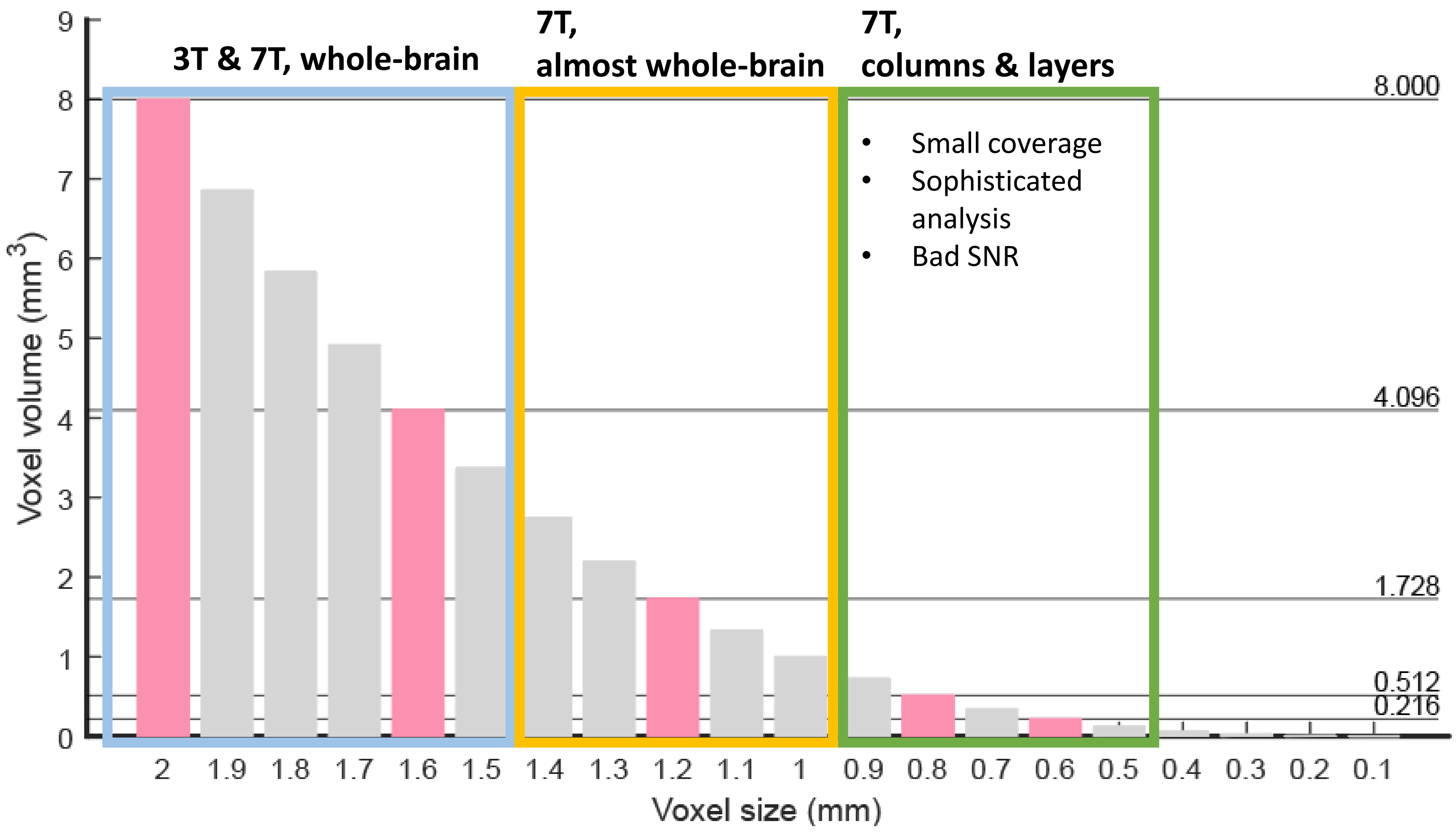


Robust single-block face activity



Higher resolution suffers from lower (t)SNR

At the same field strength: SNR drops with **voxel volume**, bad SNR below 1 mm resolution



Good for routine use for functional localization

- High contrast
- High spatial resolution
- High SNR & tSNR
- Shorter scanning time

- 3T analysis methods still work

?

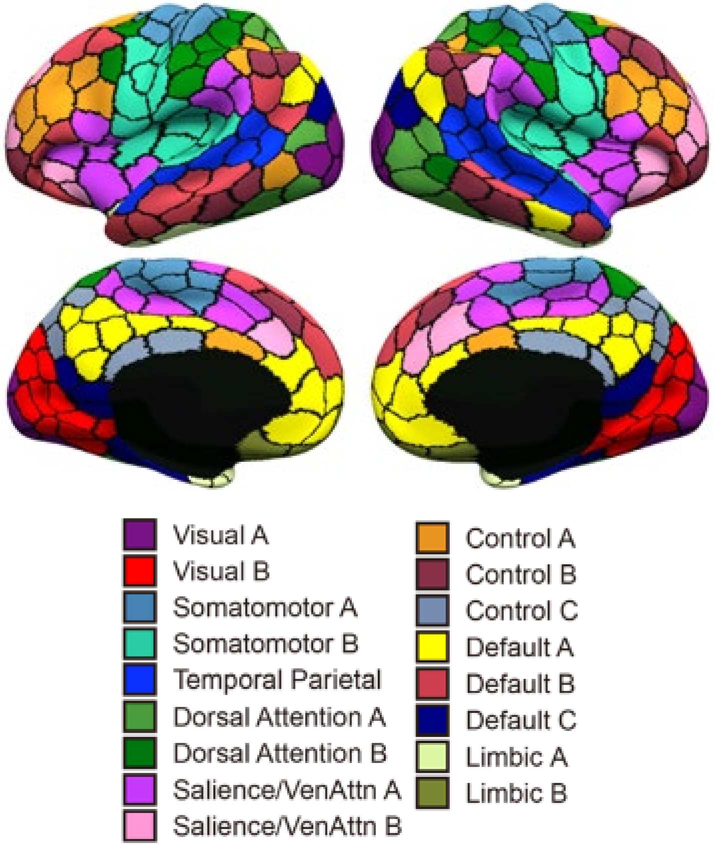
Multiple 3T assumptions are broken

Spatial scales, and their data

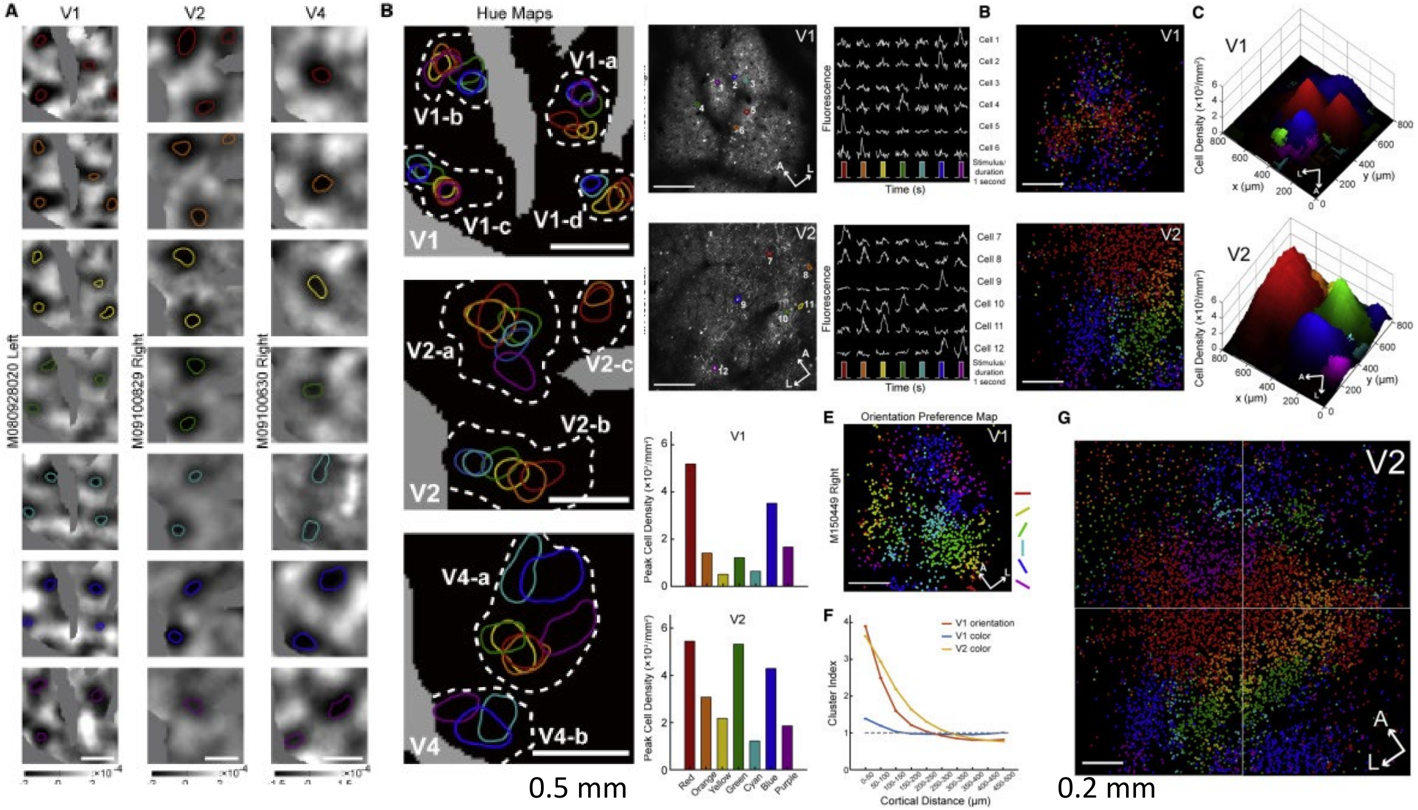
Macroscale → **Mesoscale** → **Microscale**

Brain lobes	Brain areas	Activation clusters	Columns	Layers	Neurons
10 cm	A few cm	?	0.5-1 mm	< 1 mm	< 0.1 mm

Low-resolution low-SNR scheme



High-resolution High-SNR scheme



Liu, ..., Tang, Wang (2020)

7T fMRI: transition between two schemes

Macroscale — **Mesoscale** — **Microscale**

Brain lobes	Brain areas	Activation clusters	Columns	Layers	Neurons
10 cm	A few cm	?	0.5-1 mm	< 1 mm	< 0.1 mm

Low-resolution low-SNR scheme — **High-resolution High-SNR scheme**

Human Methodologies

Brain lesions, PET, 3T traditional fMRI, 3T precision fMRI, 7T column/layer fMRI, 7T supra-millimeter fMRI, Intracranial recordings, NeuroPixels

Nonhuman Methodologies

Brain lesions, Nonhuman primate fMRI, Intrinsic signal optical imaging, Electrophysiology, NeuroPixels, Multi-photon imaging

- Low signal-to-noise ratio (SNR)
- A few experimental conditions
- Small amount of data per subject
- Large sample size
- Unit of statistical inference: group
- Lots of averaging

→

- High signal-to-noise ratio (SNR)
- Lots of experimental conditions
- Large amount of data per subject
- Small sample size
- Unit of statistical inference: cells, columns, areas, subjects
- Single-trial analysis

Assumptions in low-resolution (e.g. 3T) functional analysis

Derived from **traditions** of the low-resolution low-SNR scheme

Traditions

Tradition of analysis: from PET studies

- Low signal-to-noise ratio
- Needs smoothing, and averaging across participants
- Doesn’t allow inference at single-subject level

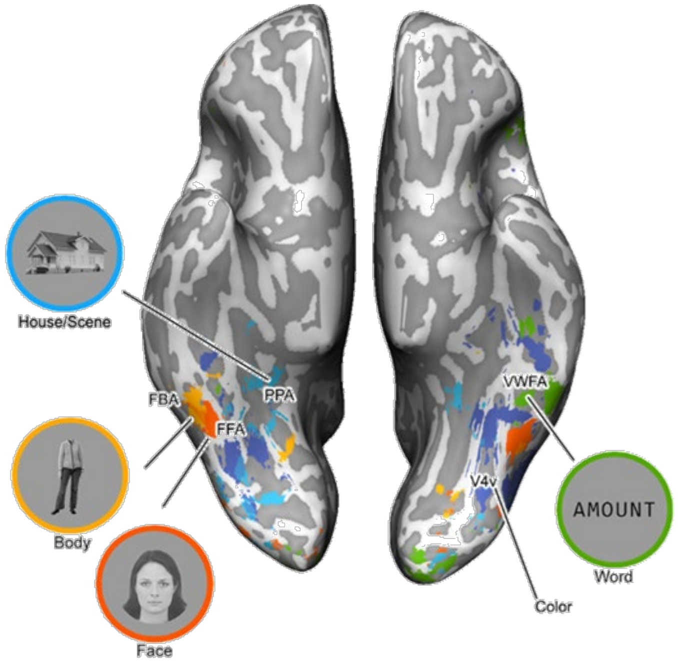
Tradition to map brain functions: **Cognitive subtraction and pure insertion**

- **Assumption: cognitive components can be cleanly separated by subtraction of brain measures**
    - Dates back to the Donders reaction time studies
    - Critique: Friston et al. (1996)

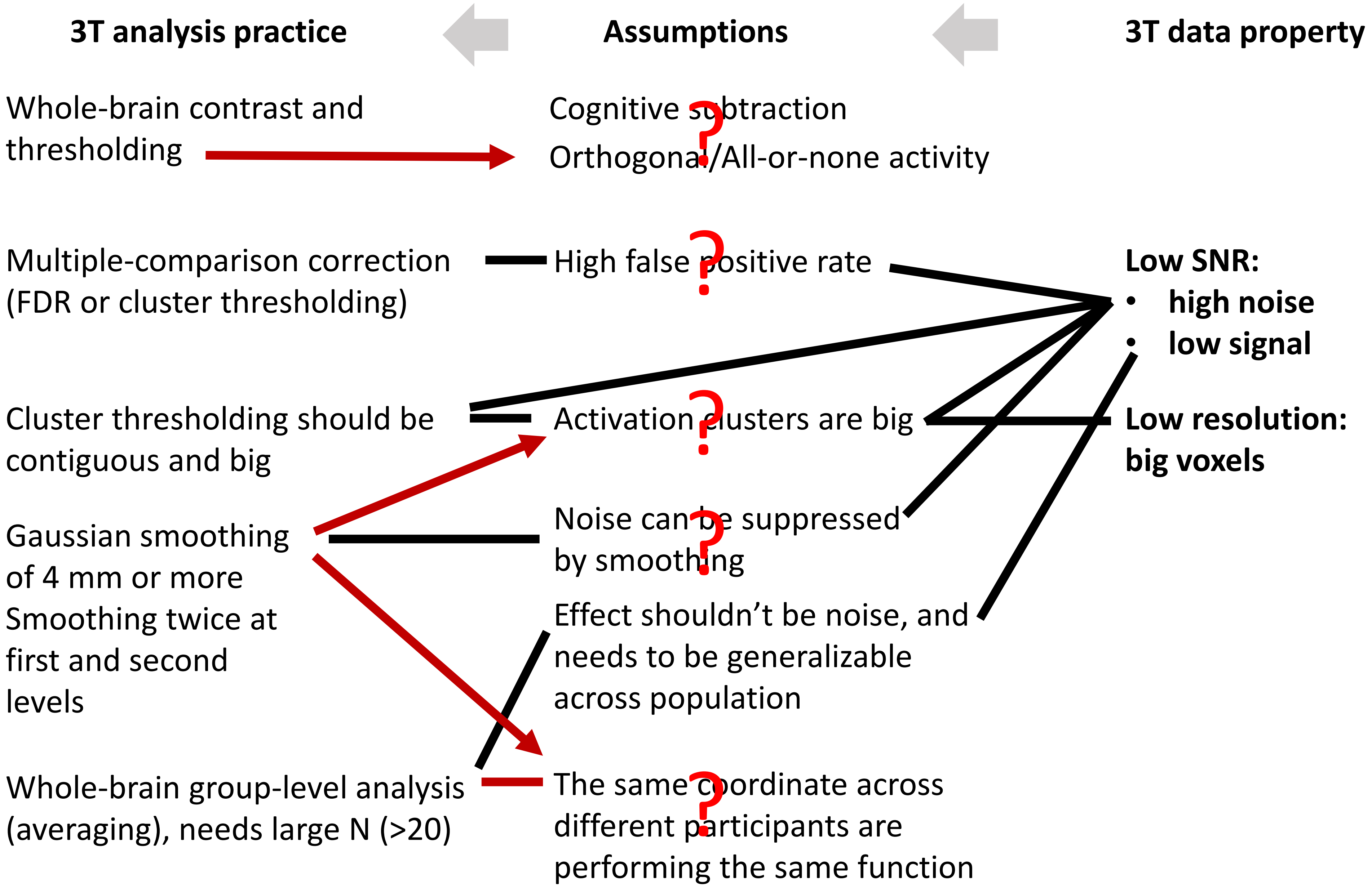
Low-resolution low-SNR scheme

3T fMRI analysis in practice: **big voxel, smoothing, univariate contrasts, whole-brain group-level statistics, multiple-comparison correction**

- Has led to successful brain-mapping (localization) findings
- Including multiple category-specific areas in the ventral pathway



Practice and assumptions in 3T functional analysis



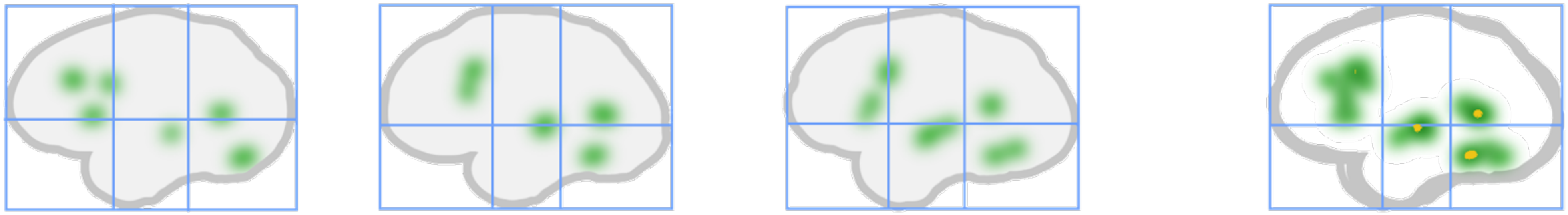
Assumptions in 3T functional analysis

1. **The same coordinate across different participants are performing the same function**
   - **Aim: get one value per participant.** More of a convenience for statistical inference
   - **Problem: inter-individual anatomical/functional variability → not fully solved**

Whole-brain group-level analysis

- Same function in the voxel at the same location per participant ← Smoothing

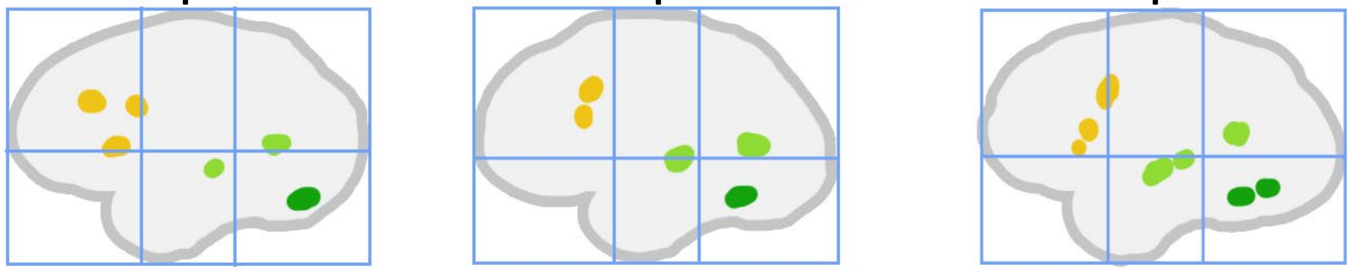
Participant 1 **Participant 2** **Participant 3** **Group-level statistical test**



Functional localizer (partially individual-subject analysis)

- Same function in the same set of ROIs per participant

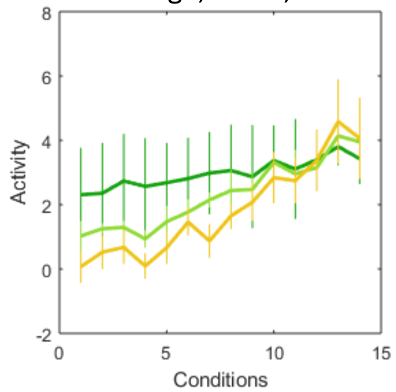
Participant 1 **Participant 2** **Participant 3**



Extract data per ROI

Group-level statistical test

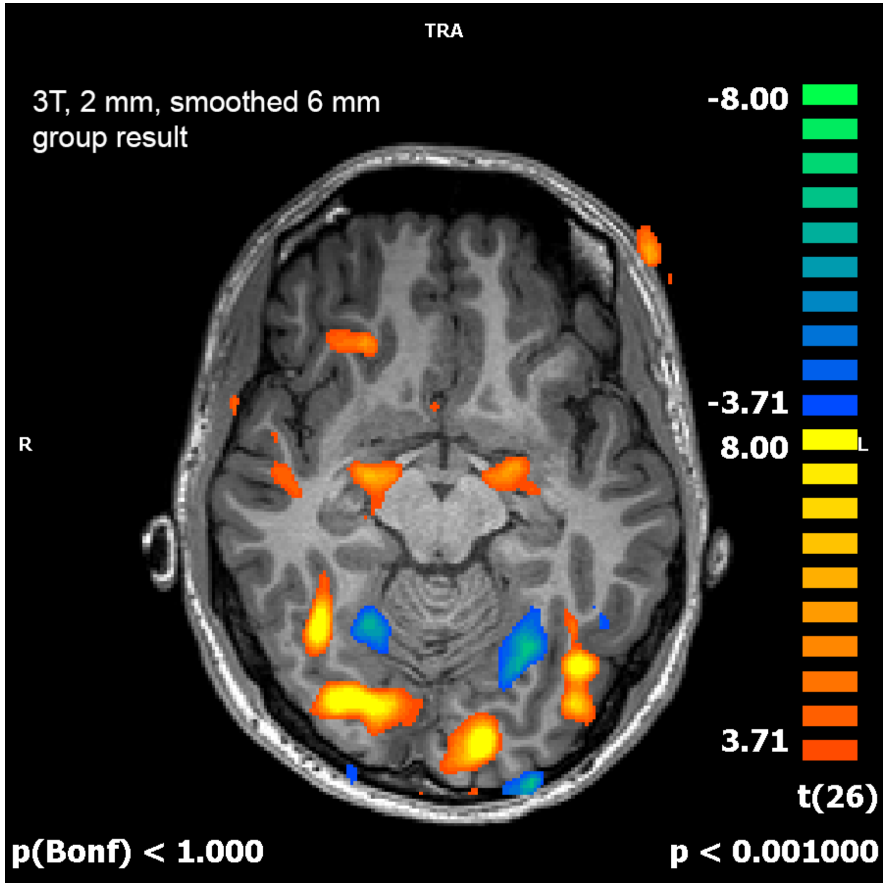
Average, t-test, etc.

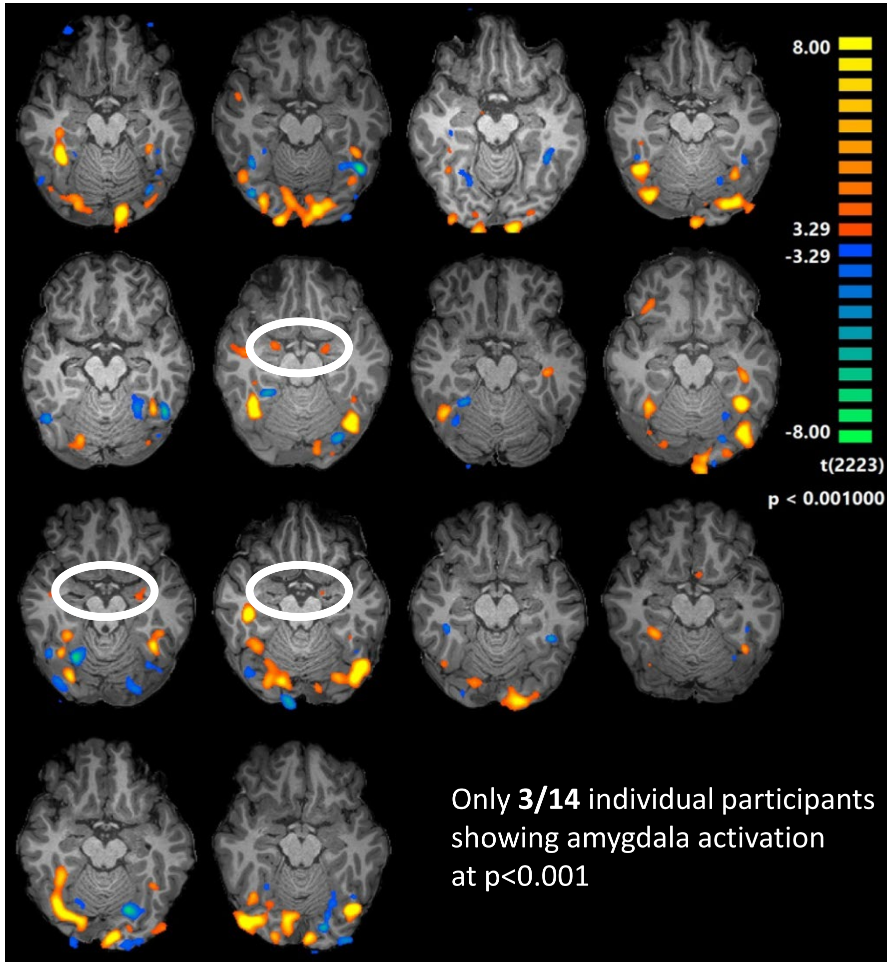


Assumptions in 3T functional analysis

1. **The same coordinate across different participants are performing the same function**
   - **Clash between group-level and individual analyses**
     - Group-level analysis **relatively lenient**: effect > 0 across participants, can have participants without an effect. **Effect size usually small or moderate**
     - Individual-level analysis **relatively stringent**: replication per individual. **Big effect size**

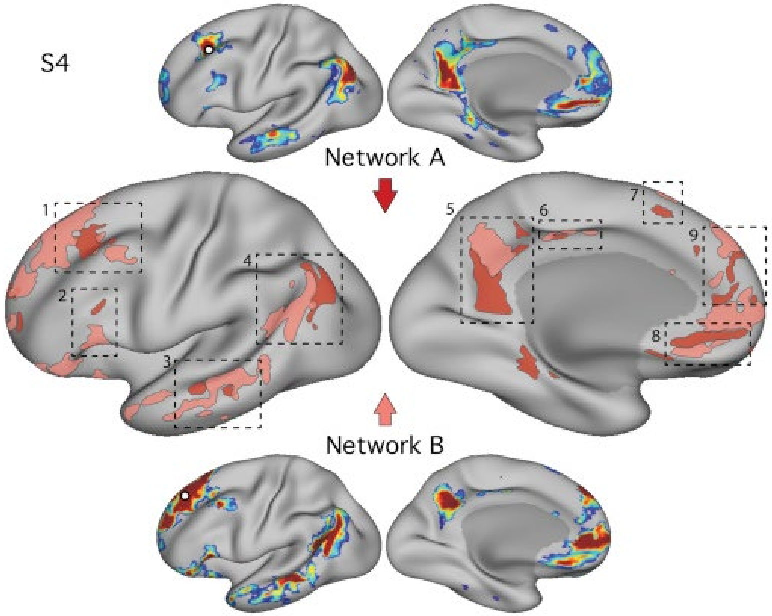
Face > body: significant amygdala activation at group level





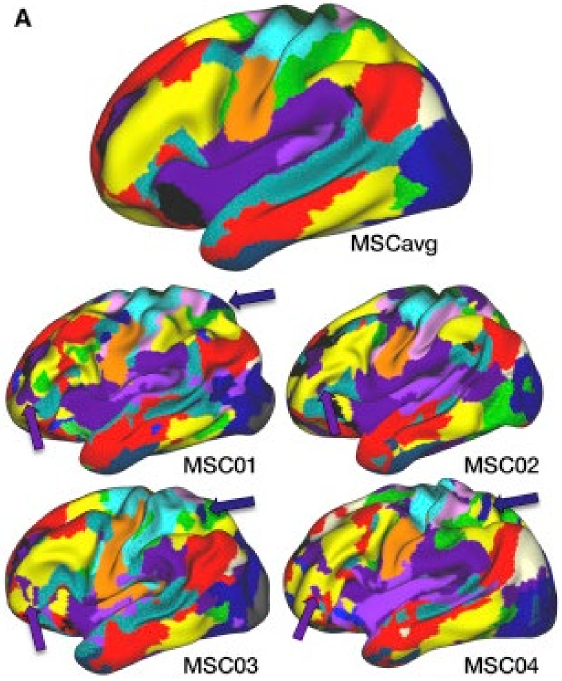
Assumptions in 3T functional analysis

1. **The same coordinate across different participants are performing the same function**
   - **Clash between group-level and individual analyses**
     - **Precision functional mapping with small N: large amount of data per individual**
     - **Individual activation hidden by whole-brain group-level analysis**



Braga & Buckner (2017)

4 participants
7 min 2 sec x 24 runs resting-state



Gordon et al. (2017)

10 participants
30 min x 10 runs resting-state

Assumptions in 3T functional analysis

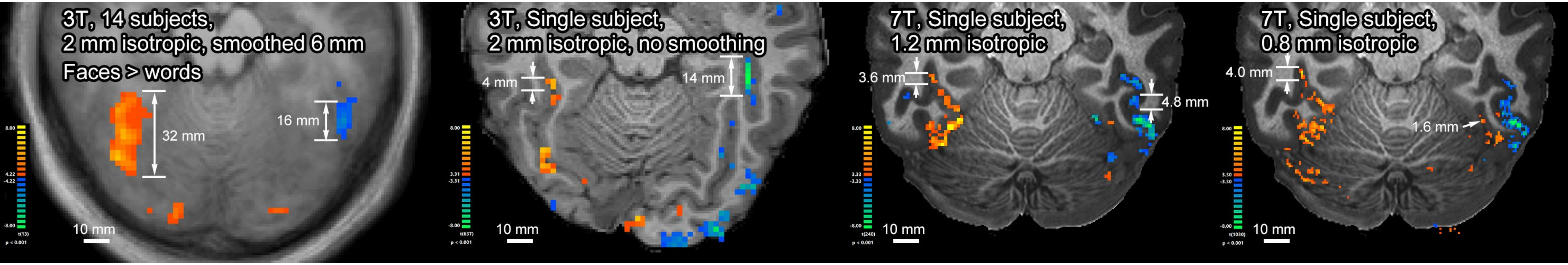
Activation cluster size doesn't change that much across fields and resolutions, usually < 10 mm

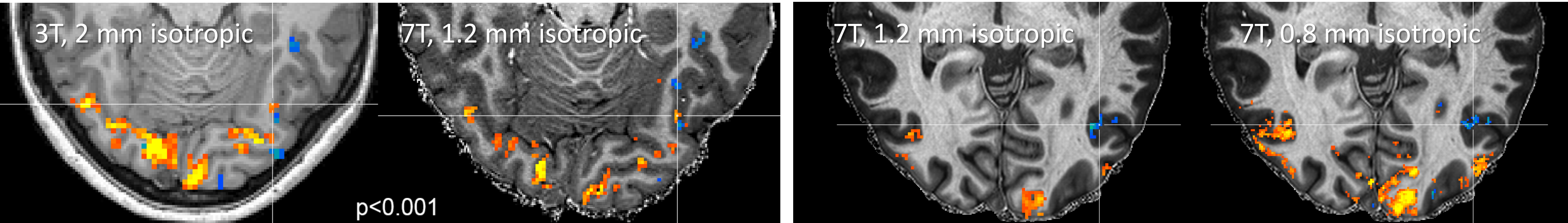
2. Activation clusters are big

- **How big are real functional units in the brain?**

Macroscale → **Mesoscale** → **Microscale**

Brain lobes	Brain areas	Activation clusters	Columns	Layers	Neurons
10 cm	A few cm	?	0.5-1 mm	< 1 mm	



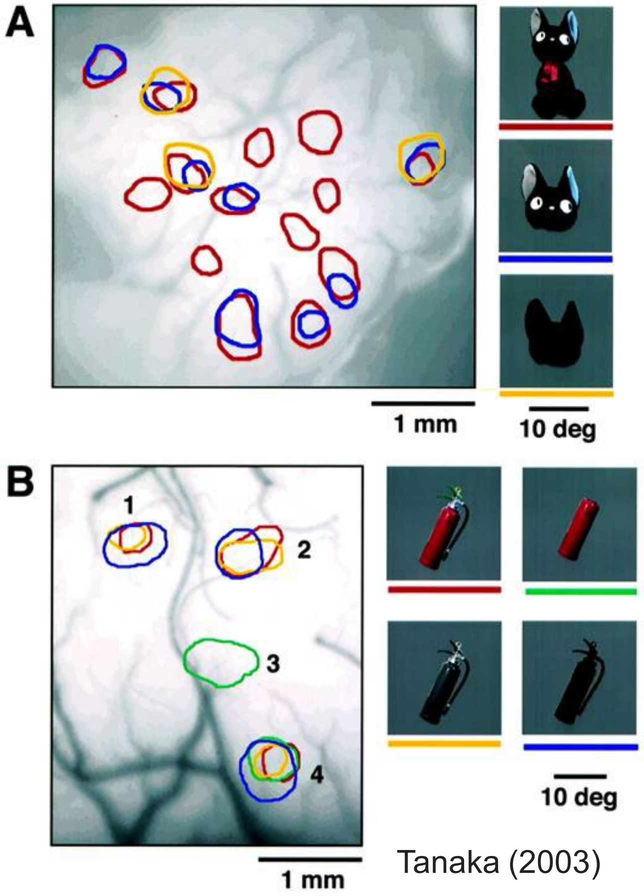


Assumptions in 3T functional analysis

3. Cognitive subtraction

- Works well if the **cognitive processes** and the **involved brain areas** are very different
  - E.g. across different object categories

Differences within categories?
Within local brain area – at mesoscale?



Tanaka (2003)

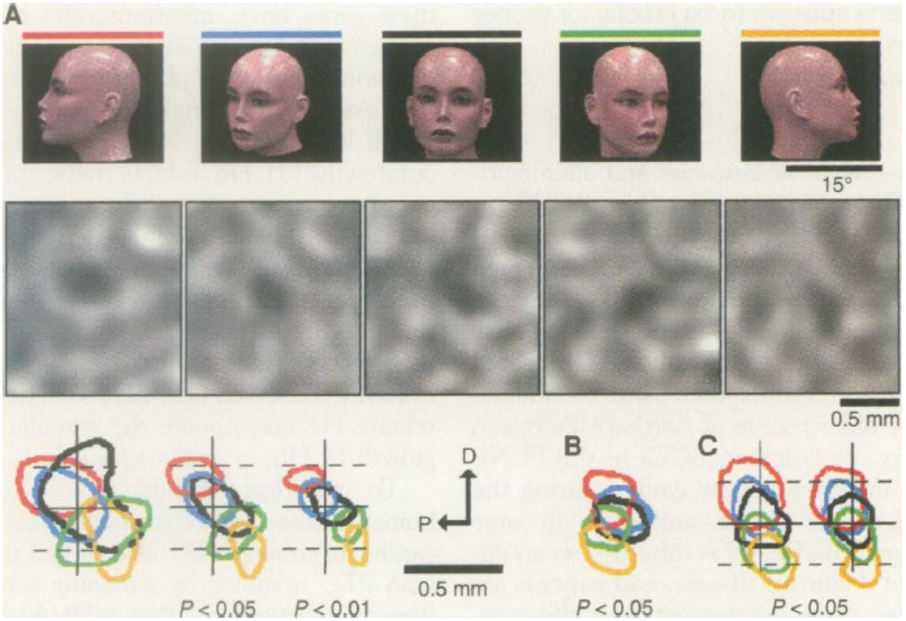
Different categories/conditions to contrast with?
Latent features for each condition are not orthogonal/independent

- E.g. words versus
  - Scrambled words
  - Checkerboards
  - Other categories (which ones?)
- Passive/active task modulation?

- Example for faces & FFA: Berman et al. (2010)
- Example for words: Li, Hiersche, Saygin (2023)

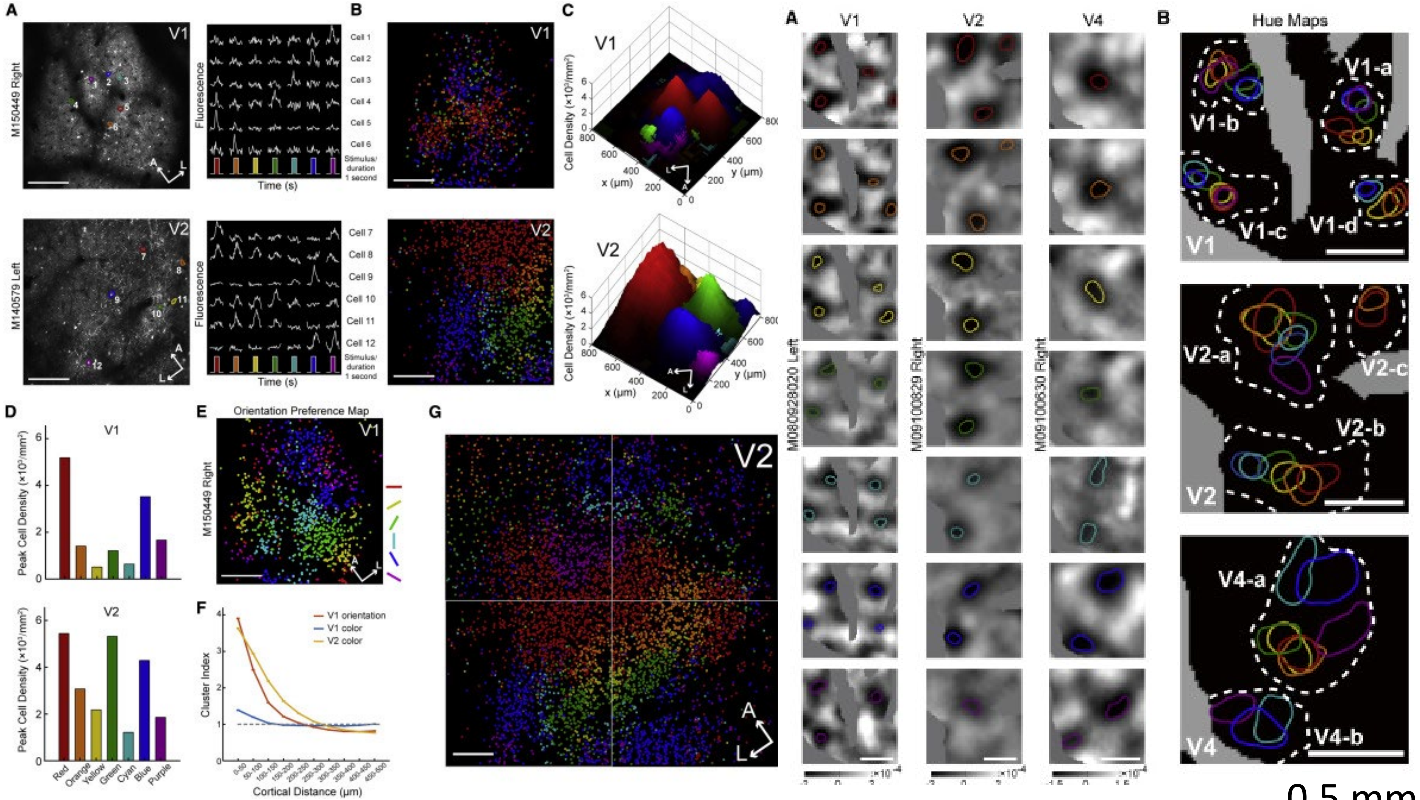
Actual columns in macaques: systematic **"moving"** of columns → continuous maps of similar features within patches

Face columns in IT:
optical imaging guided by electrophysiology



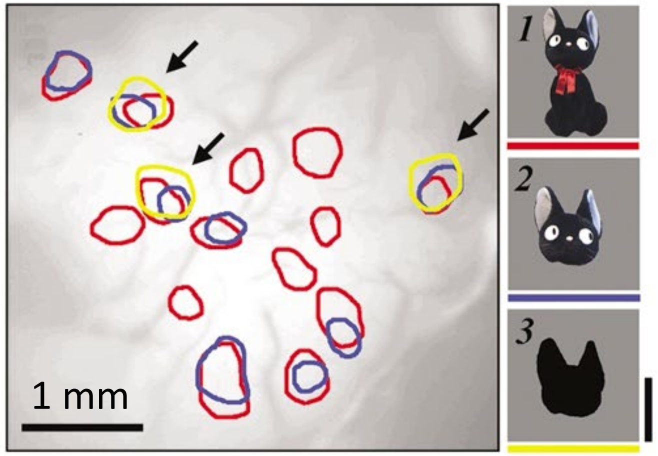
Wang, Tanaka, Tanifuji (1996)

Color columns in V1, V2, V4:
simultaneous optical imaging, electrophysiology, 2-photon imaging



0.5 mm

Liu, …, Tang, Wang (2020)



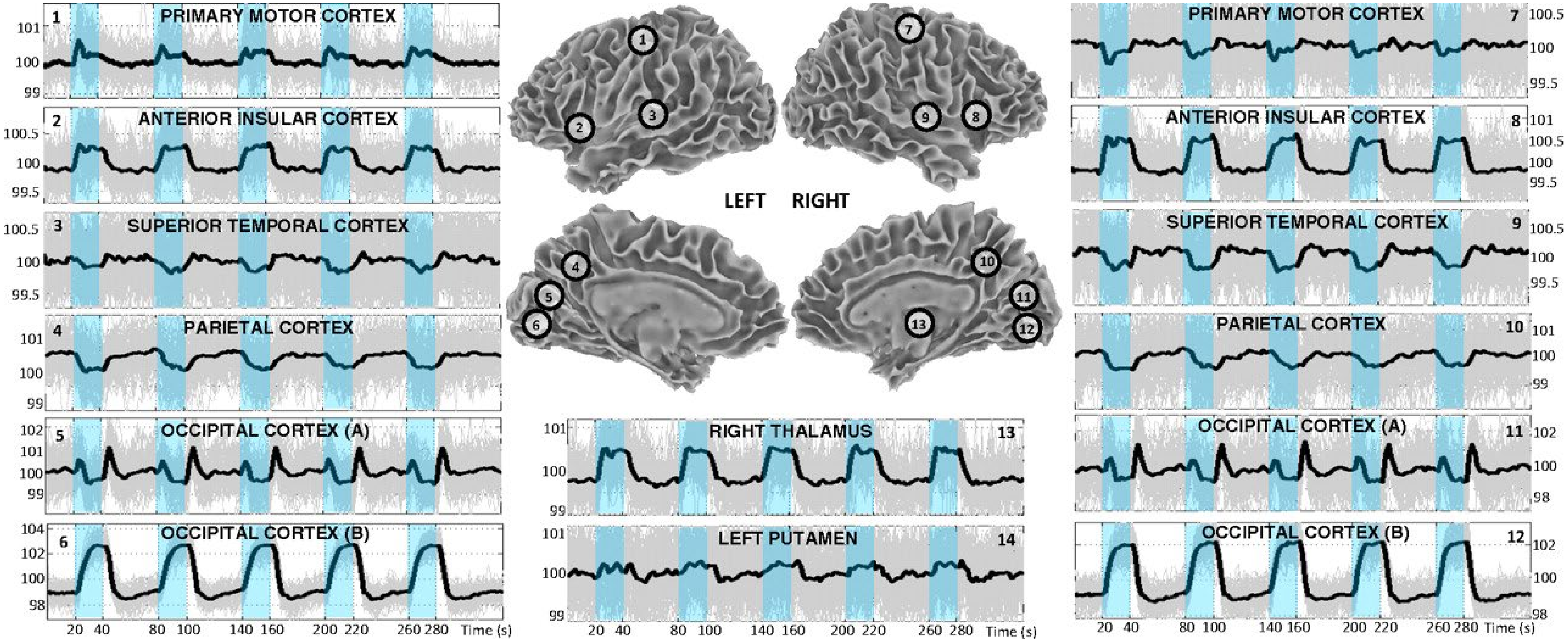
Columns for complex objects in IT:
optical imaging, electrophysiology

Tsunoda, Yamane, Nishizaki, Tanifuji (2001)

Assumptions in 3T functional analysis

4. High false positive rate

- **Eklund, Nichols, Knutsson (2006): "Cluster failure"**
- **What about false negatives?**



Gonzalez-Castillo et al. (2012)

3 participants, 100 runs per participant

- Flickering checkerboard, or letter/number discrimination tasks

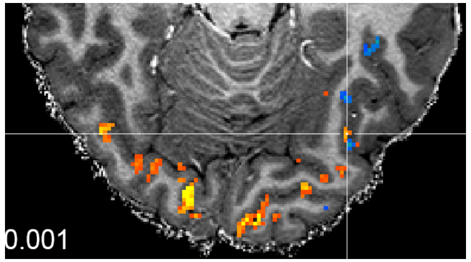
Over 90% brain areas time-locked to stimulation (activated)

- Signal change as small as 0.2%
- Different HRF shapes

Assumptions in 3T functional analysis

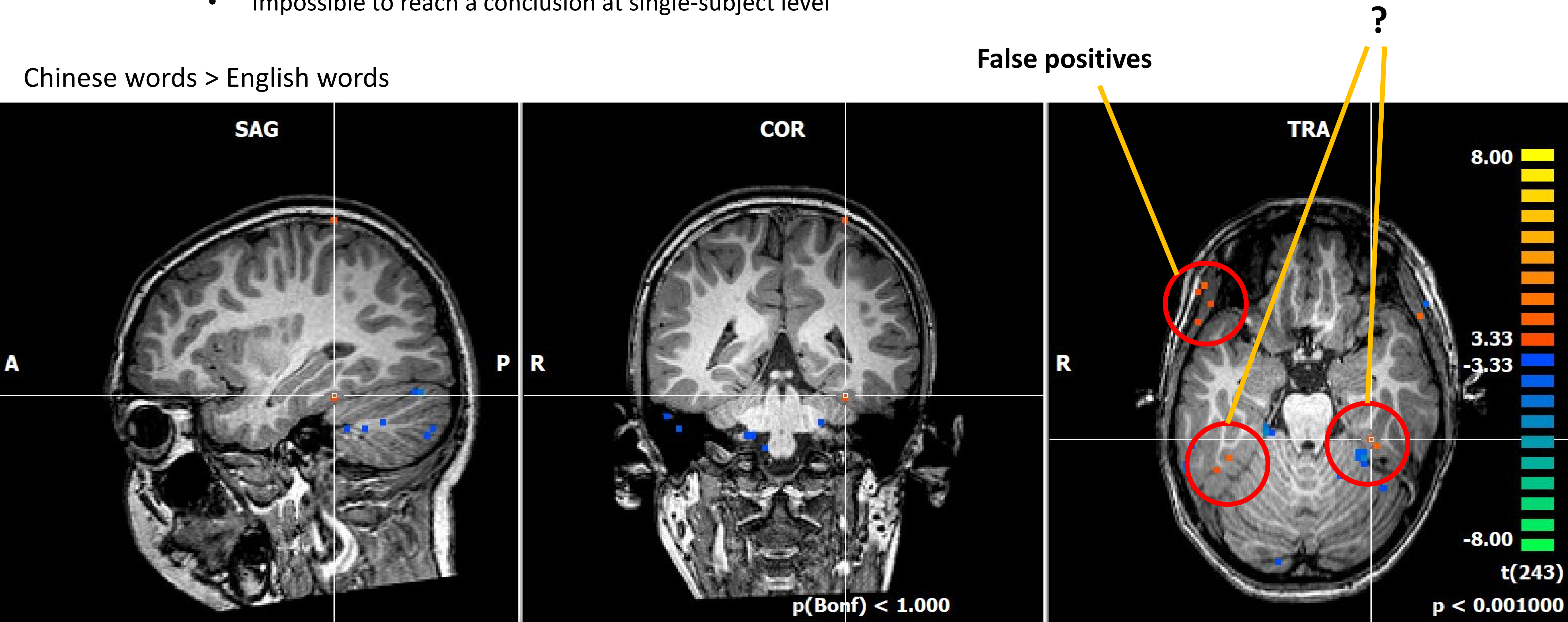
4. High false positive rate

- **What about when an activation cluster is smaller than a single voxel?**



- Example: child data, 3 mm isotropic resolution (27 mm^3 per voxel), no smoothing
  - Impossible to reach a conclusion at single-subject level

Chinese words > English words



Assumptions in 3T functional analysis

5. **Noise can be suppressed by smoothing**
    - Then it’s a pity to do 7T high-resolution fMRI while wasting the resolution
    - Need different ways to remove noise, according to the origin of the noise
        - Submillimeter resolution within thermal regime: NORDIC denoising for removing thermal noise (Vizioli et al. 2021)

Example of broken 3T assumptions: the 7T bilingual study

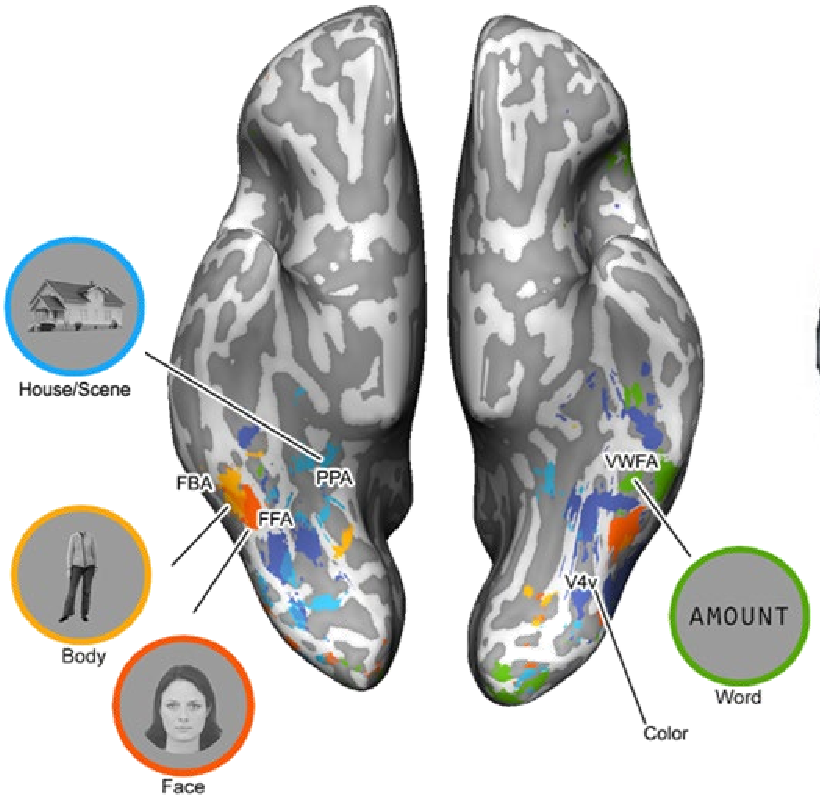
Zhan, M., Pallier, C., Agrawal, A., Dehaene, S., & Cohen, L. (2023). Does the visual word form area split in bilingual readers? A millimeter-scale 7-T fMRI study. Science Advances, 9(14), eadf6140.

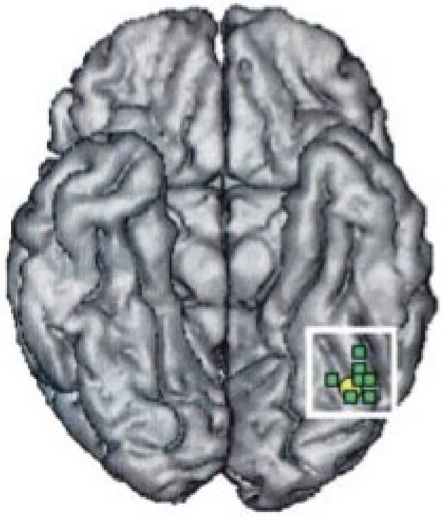
Christophe Pallier   Aakash Agrawal   Stanislas Dehaene   Laurent Cohen

The visual word form area (VWFA)

The ventral occipito-temporal cortex (VOTC)

- Multiple category-specific areas
- VWFA: activated by visual words





$x = -42$ $y = -57$ $z = -15$

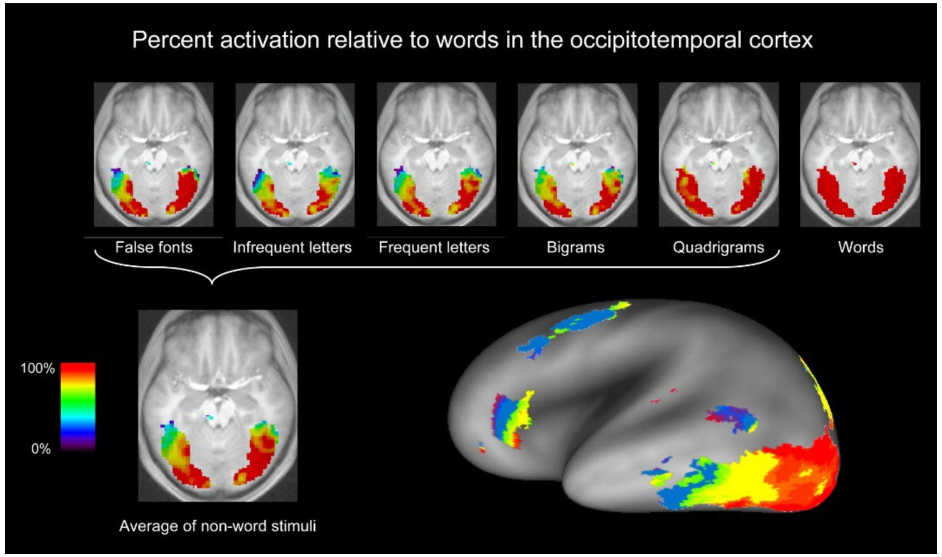
Cohen et al. (2002)

Word-similarity gradient across the VOTC

Activity is higher when the stimuli are more similar to words

Types of stimuli

Components	False font	Infrequent Letters	Frequent Letters	Frequent Bigrams	Frequent Quadrigrams	Words
Strings	0	0	0	0	0	high
Quadrigrams	0	low	low	low	high	high
Bigrams	0	low	low	high	high	high
Letters	0	low	high	high	high	high
Features	high	high	high	high	high	high
Examples	[illegible]	JZWYWK	QOADTQ	QUMBSS	AVONIL	MOUTON



Vinckier et al. (2007)

The bilingual experiment

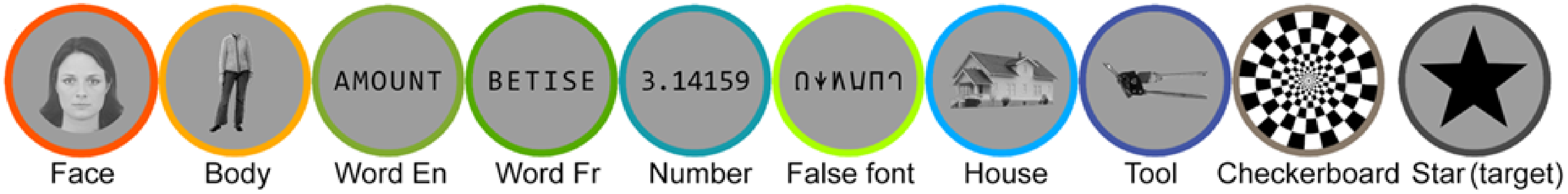
Research questions

- How does the VWFA in bilingual participants process two different languages?
- Are there (additional) cortical patches specialized for each single language?

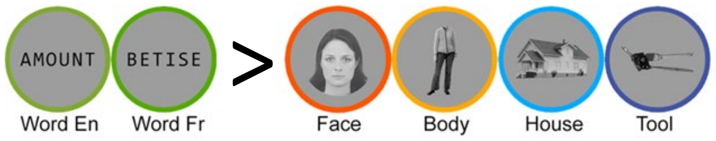
Experiment 1: English-French bilinguals

- 3 sub-groups: n=7 each
  - ● balanced bilingual ● English-dominant ● French-dominant
- Block design, fast stimuli presentation → to maximize bottom-up effects and minimize top-down effects

Object category functional localizer



Define word-specific ROIs



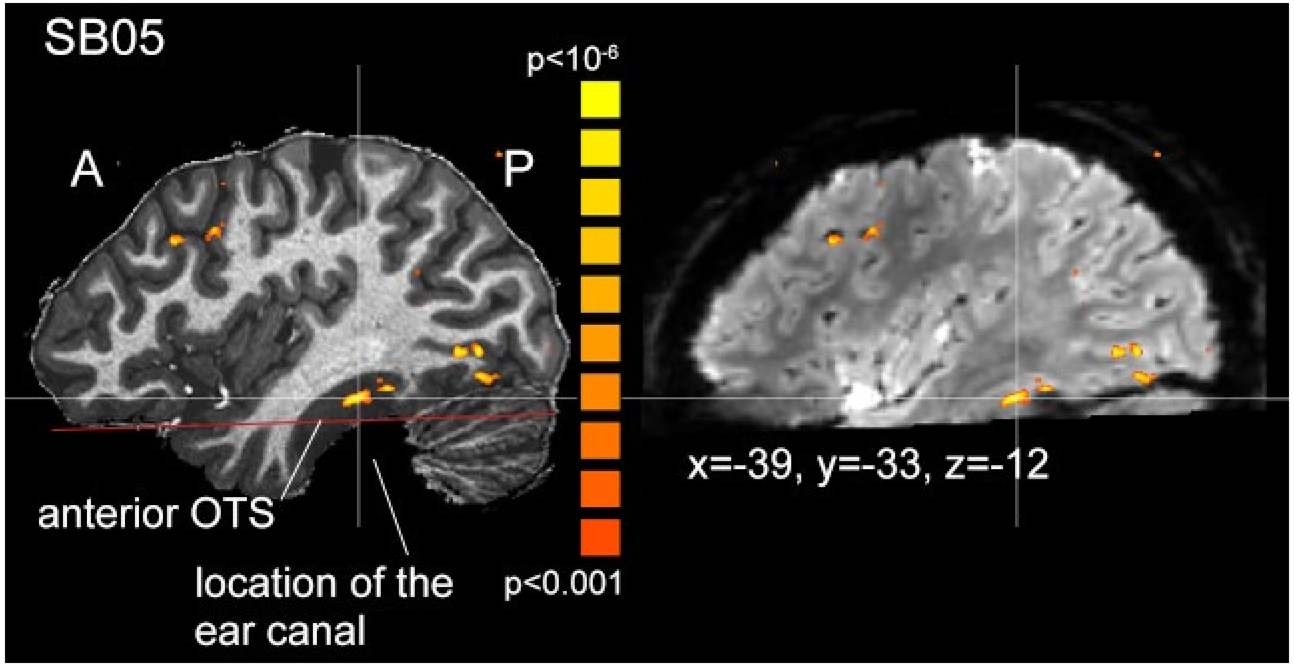
Main fMRI runs

Examine activity profiles in ROIs

7T fMRI data peculiarities

Big ear-canal signal dropout due to stronger B0 inhomogeneity

Conventional group-level inference doesn't work anymore: assumption broken

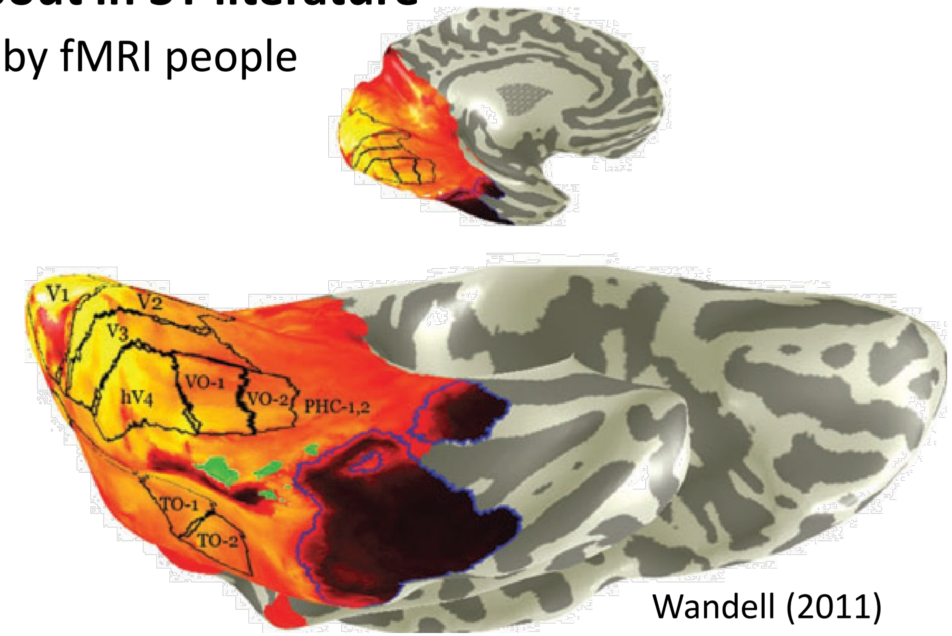


Partial brain coverage (but almost whole-brain)
1.2 mm isotropic
TR=2 s

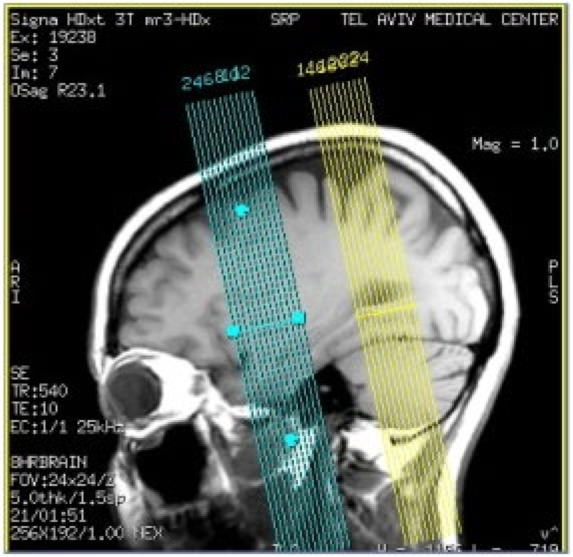
7T fMRI data peculiarities

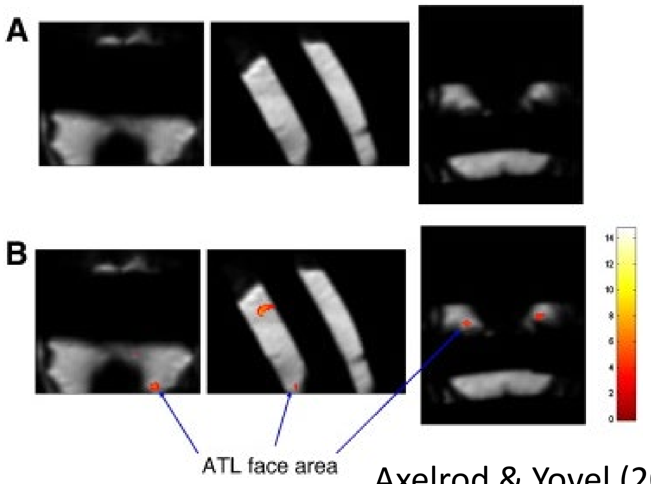
Ear-canal signal dropout in 3T literature

- Largely ignored by fMRI people

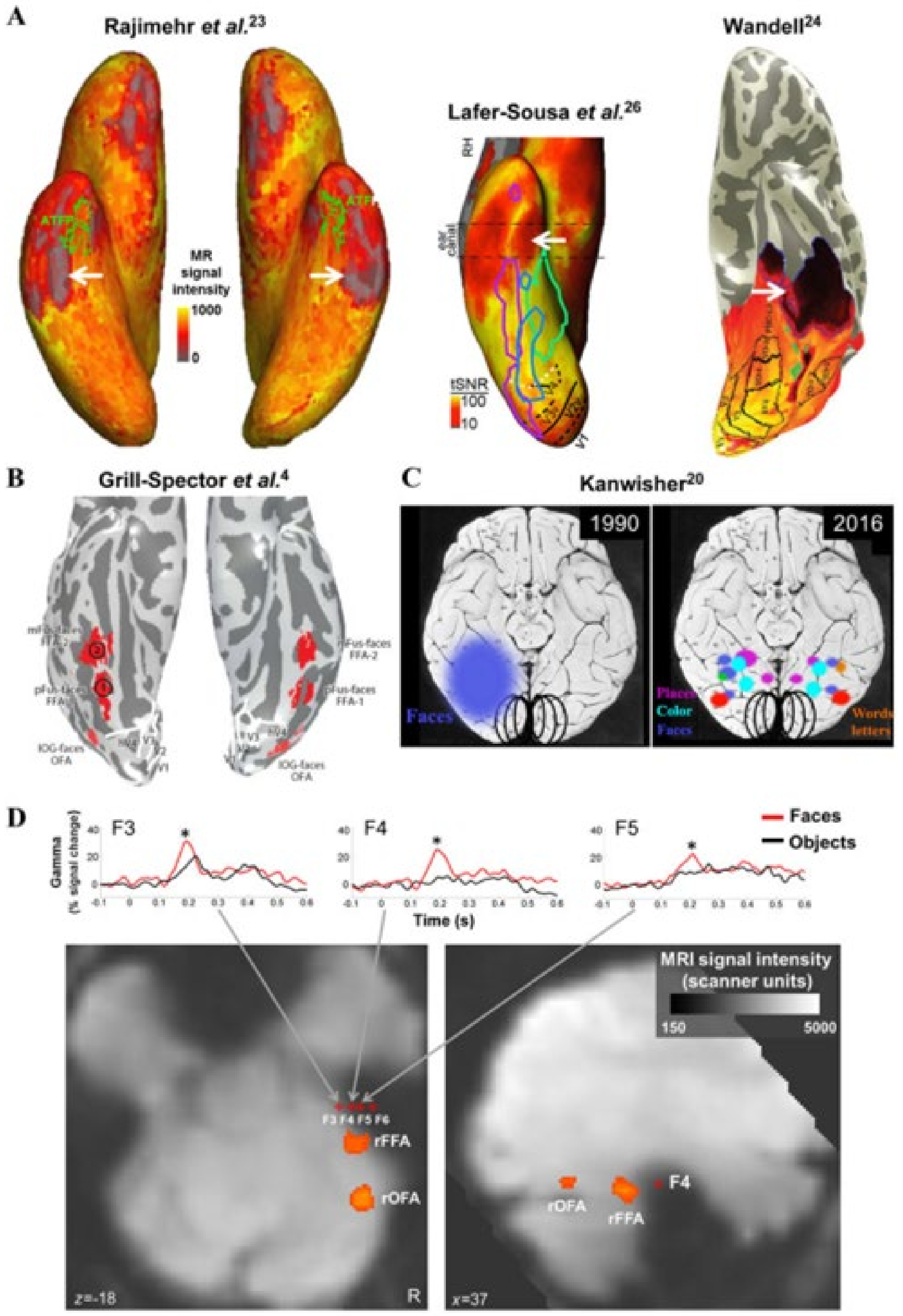


Wandell (2011)





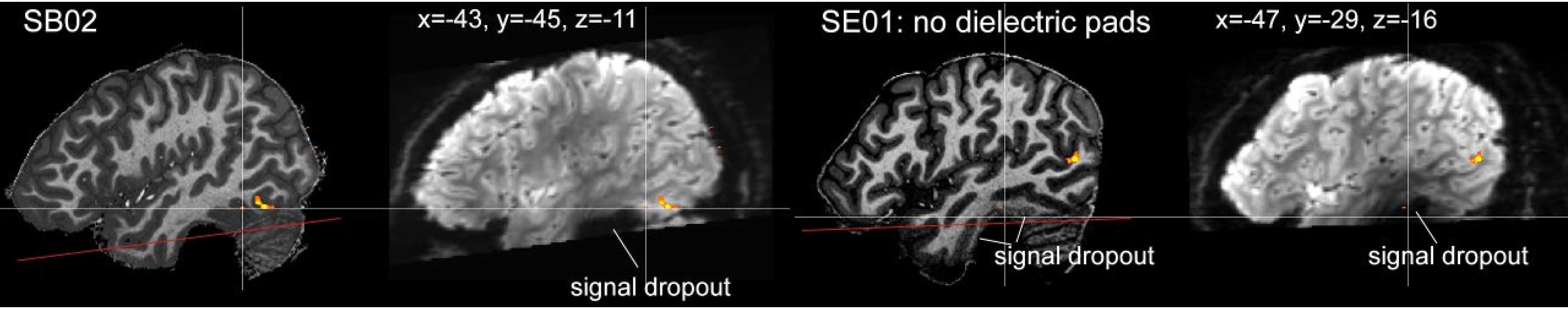
Axelrod & Yovel (2013)

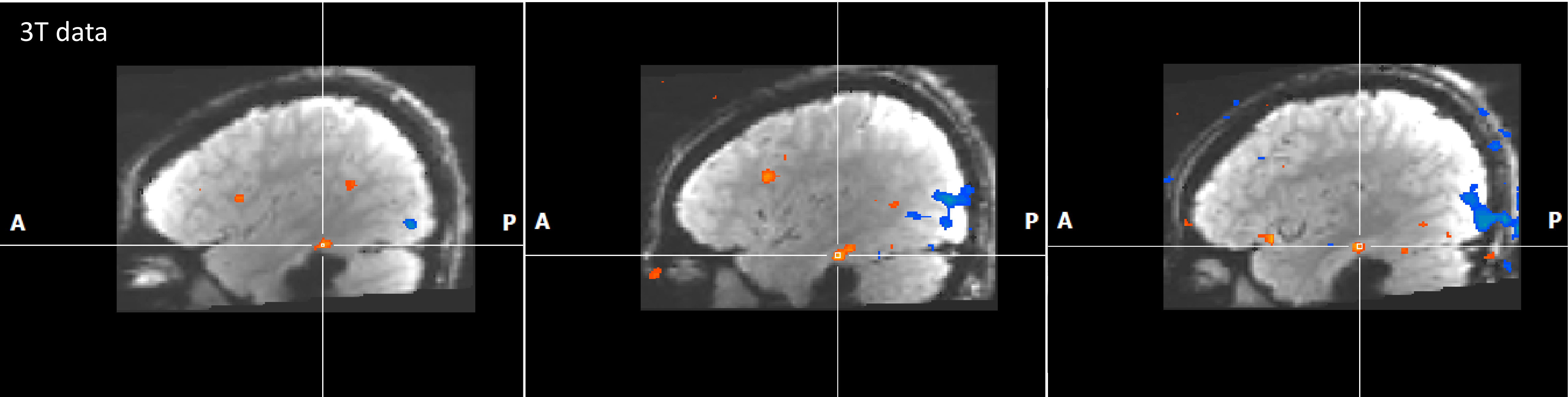


Rossion, Jacques, Jonas (2018)

7T fMRI data peculiarities

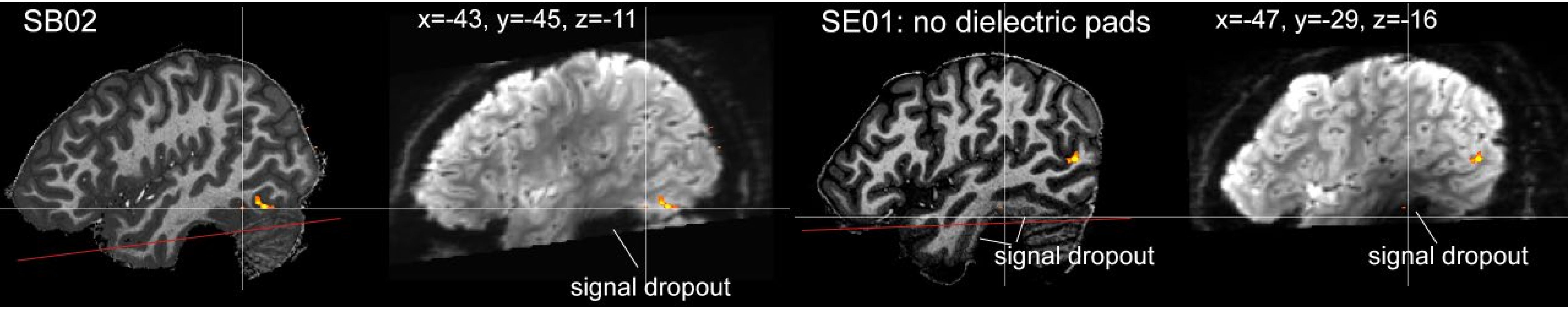
7T: Big ear-canal signal dropout n=3



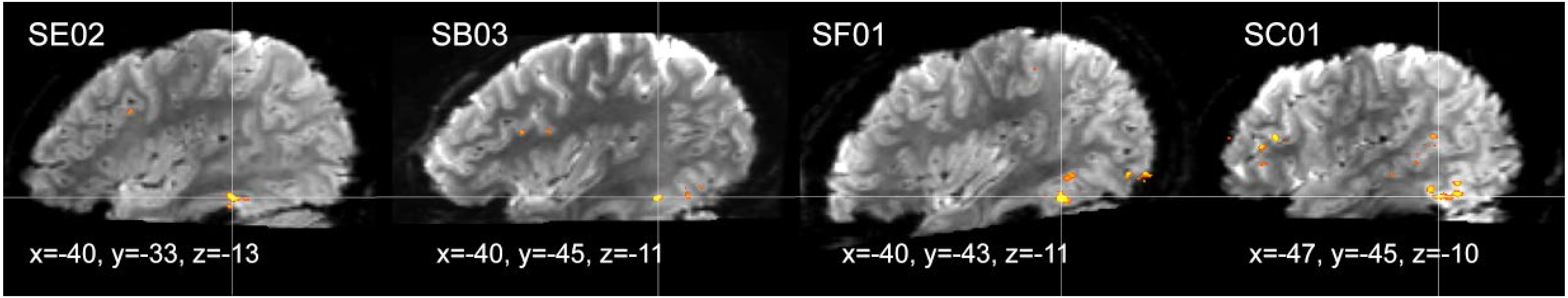


7T fMRI data peculiarities

7T: Big ear-canal signal dropout n=3



Optimized slab positioning n=28



7T fMRI data peculiarities

Conventional group-level inference at 3T: one value per participant

- **Whole-brain contrasts + smoothing**:

  Same function in the voxel at the same location per participant

- **Functional localizer**:

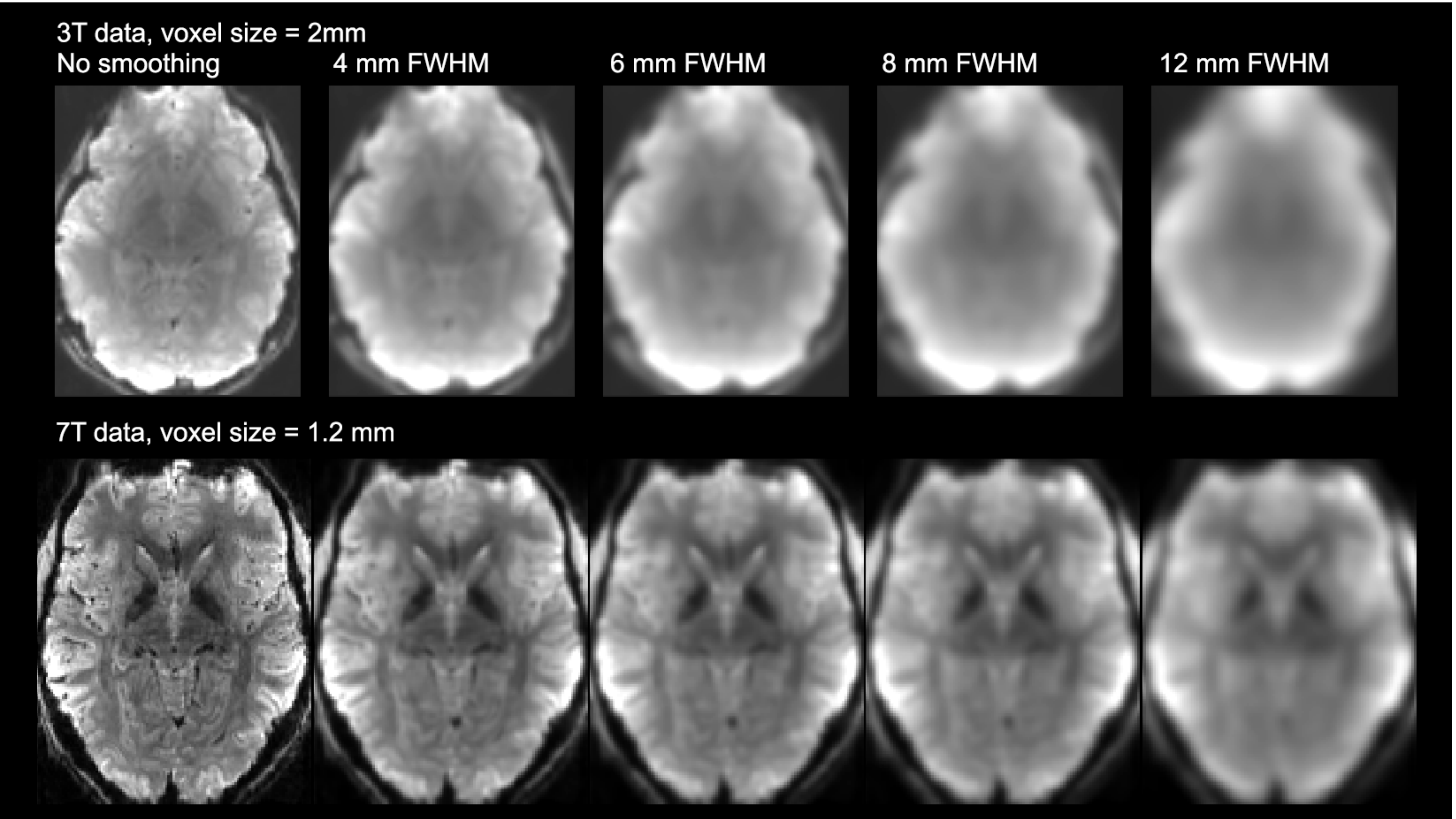
  Same function in the same set of ROIs per participant

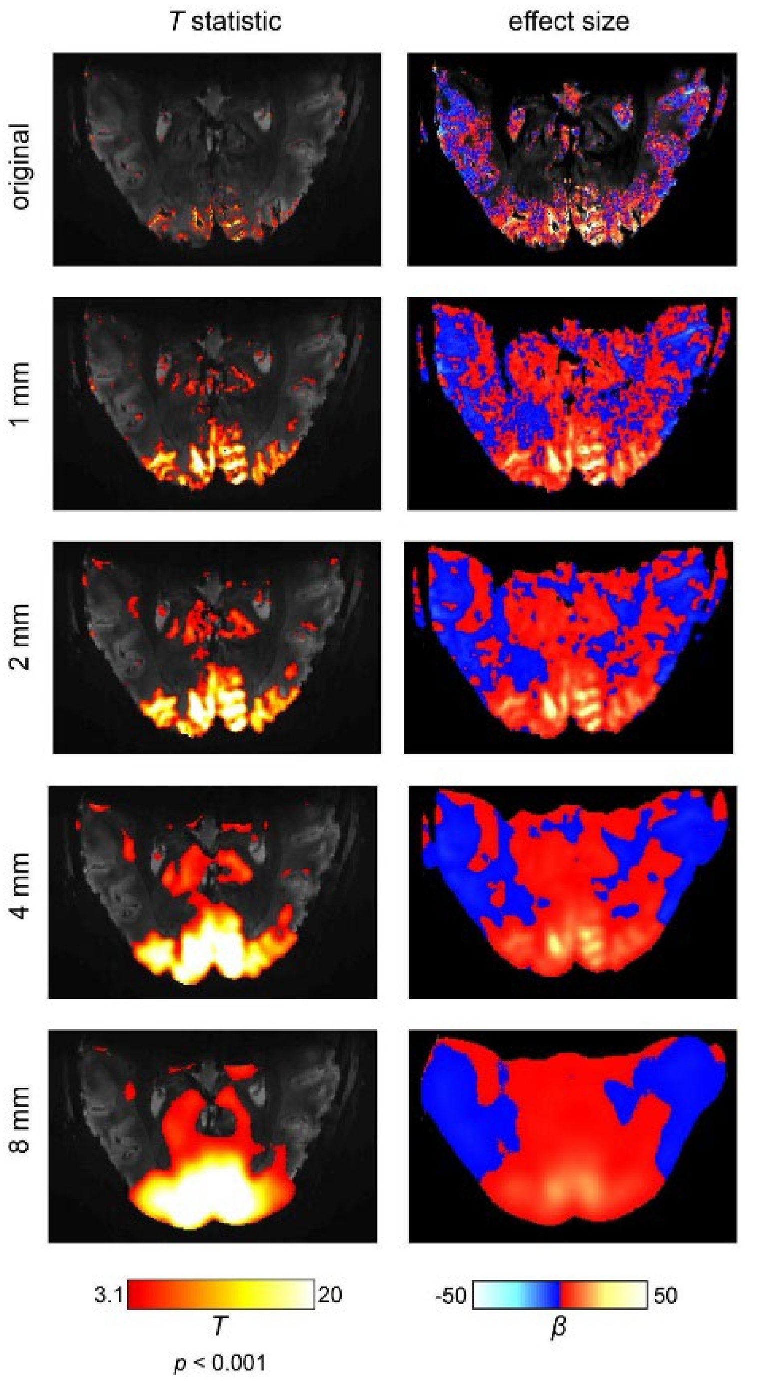
These assumptions don't work any more at 7T

7T fMRI data peculiarities

Whole-brain

- **Smoothing doesn't work** due to high contrast
- **Diluted effect size**





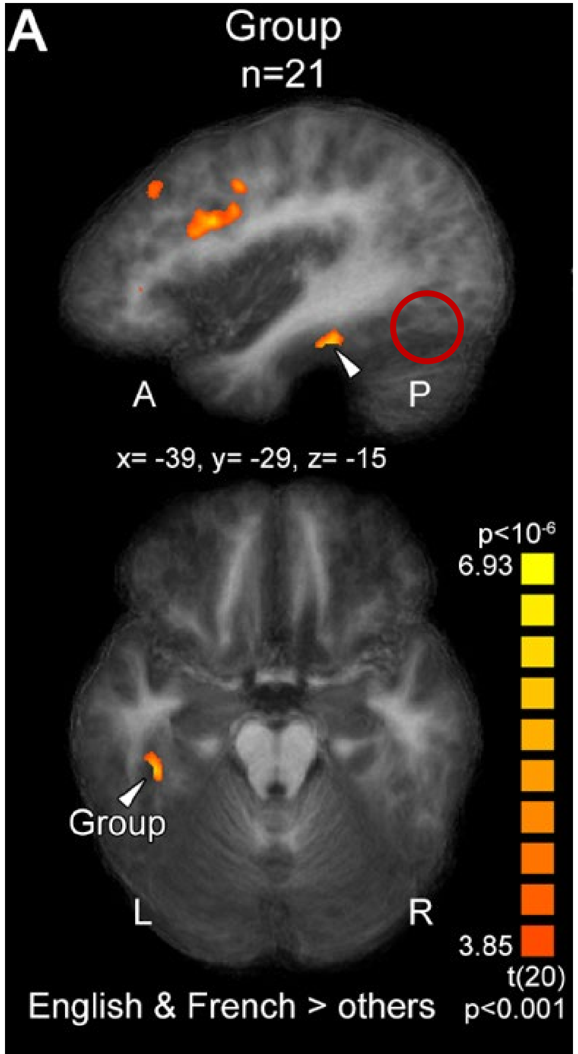
Stelzer, Lohmann, Mueller, Buschmann, Turner (2014)

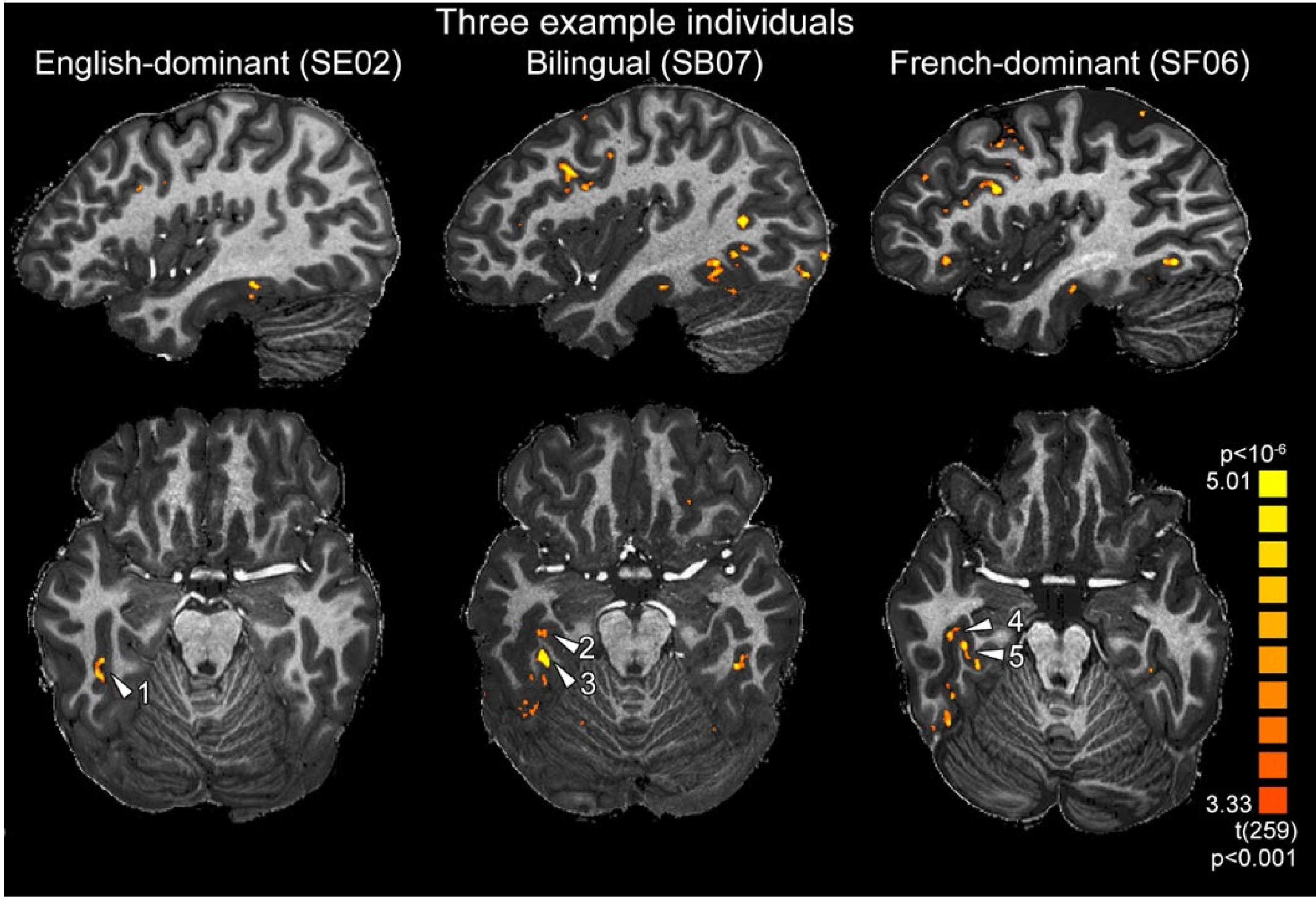
7T fMRI data peculiarities

Whole-brain

- **Smoothing doesn't work**
- VWFA missing in group-level results at TAL Y = -56

- Robust chains of word-specific patches in all individual participants: Not "one" VWFA, but multiple
- Median size: 47 mm³; 25% patches are smaller than 27 mm³

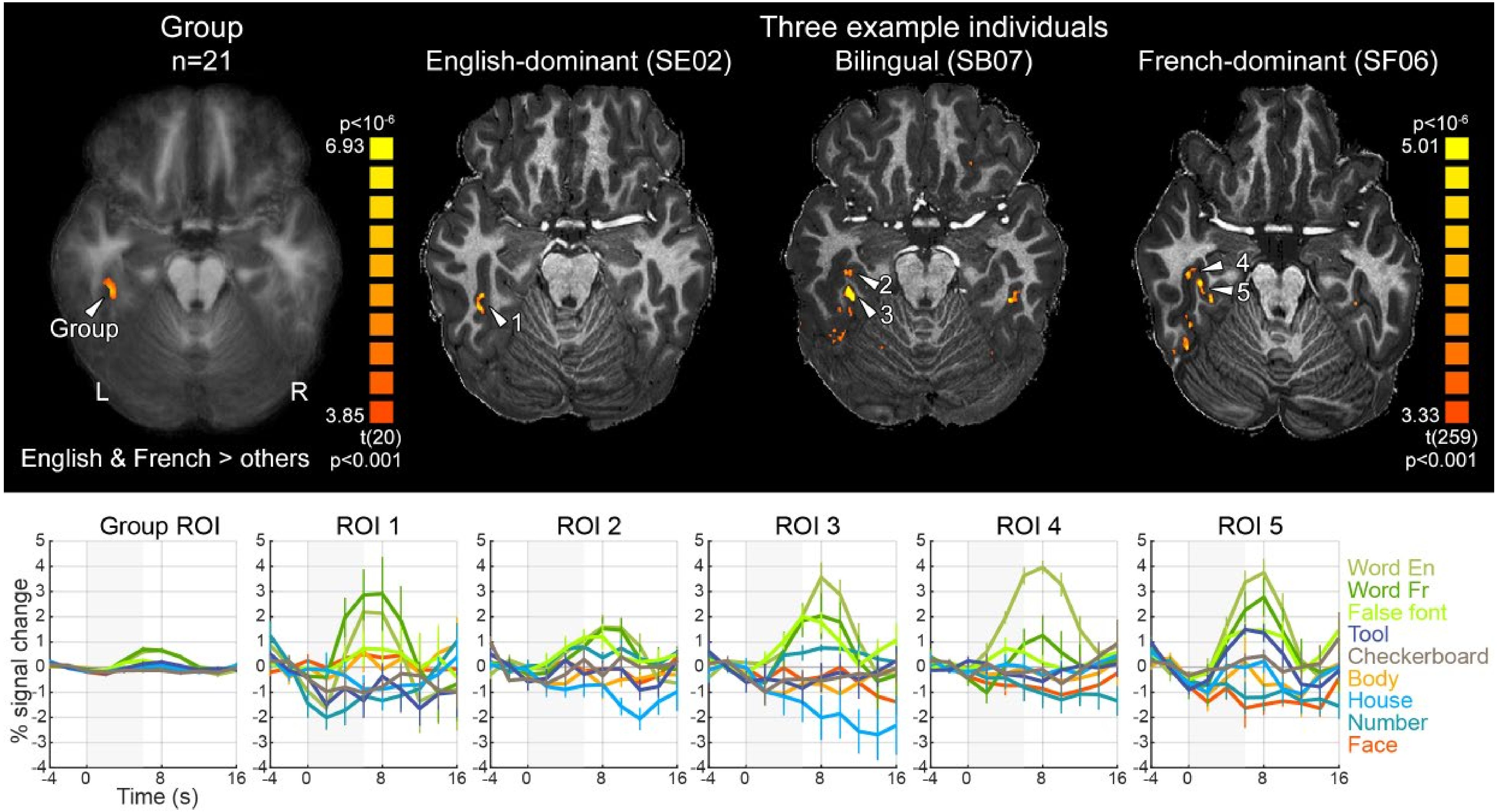




7T fMRI data peculiarities

Whole-brain

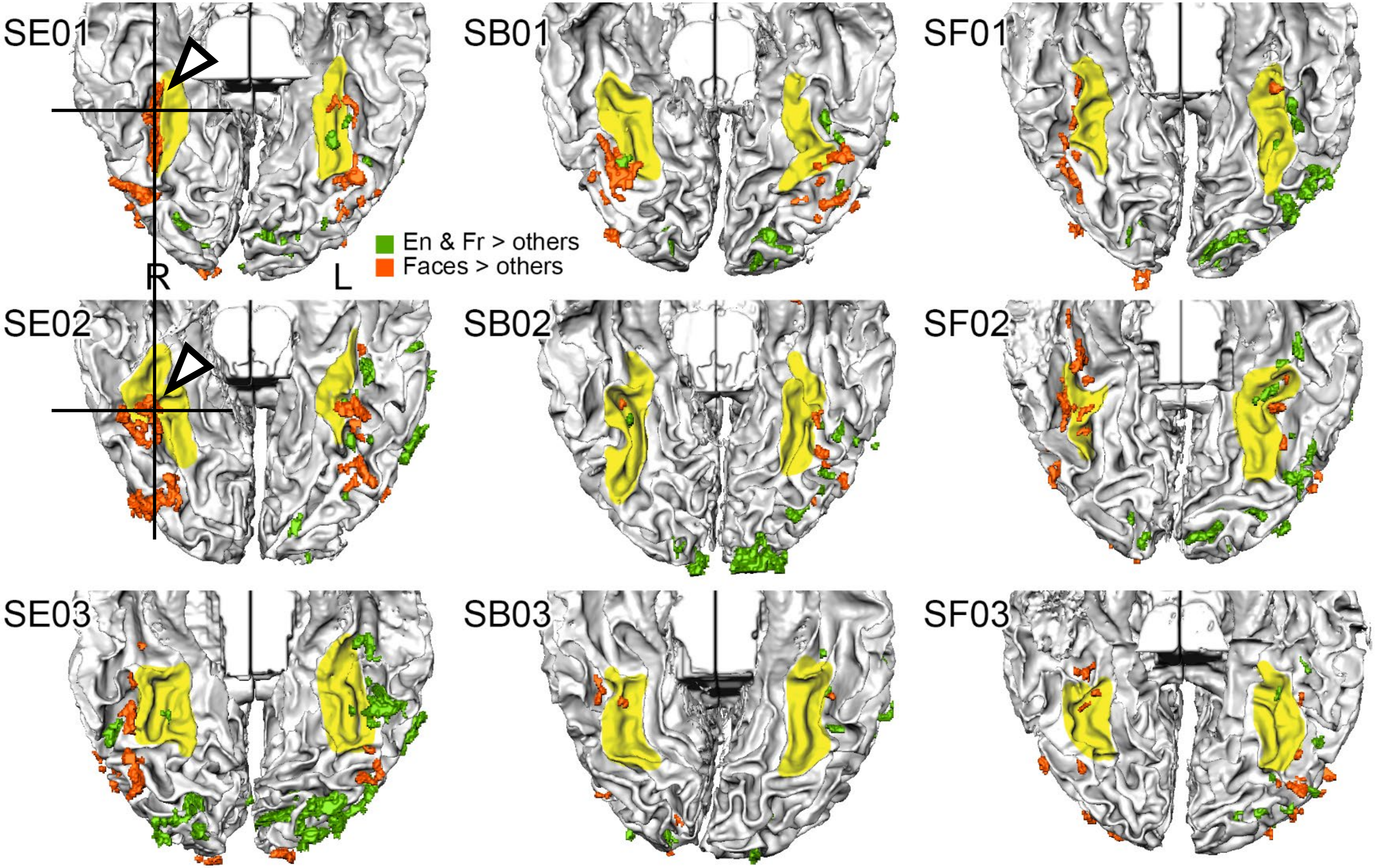
- **Diluted effect size**



7T fMRI data peculiarities

Whole-brain

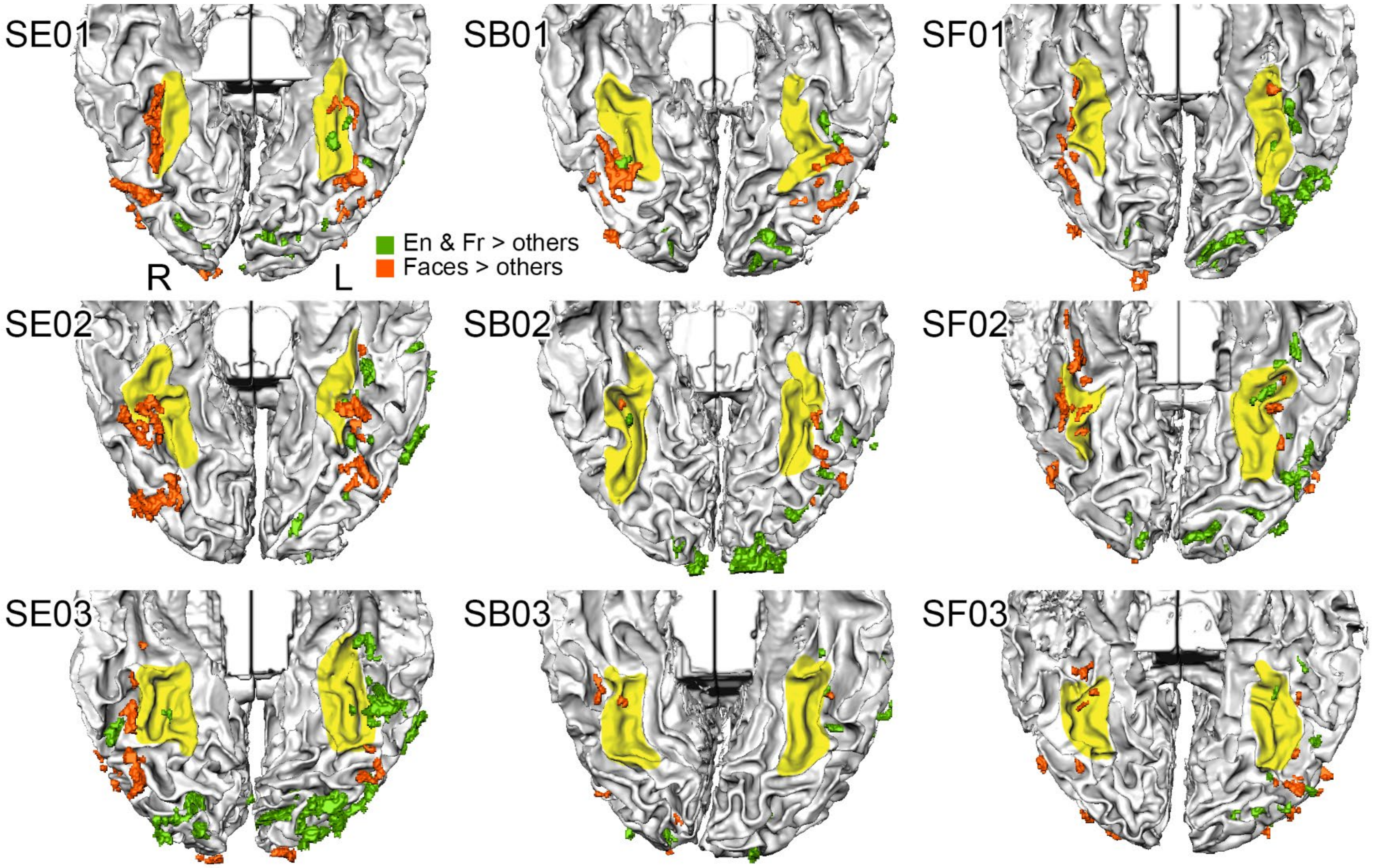
- **Assumption broken: The same coordinate across different participants are performing the same function**



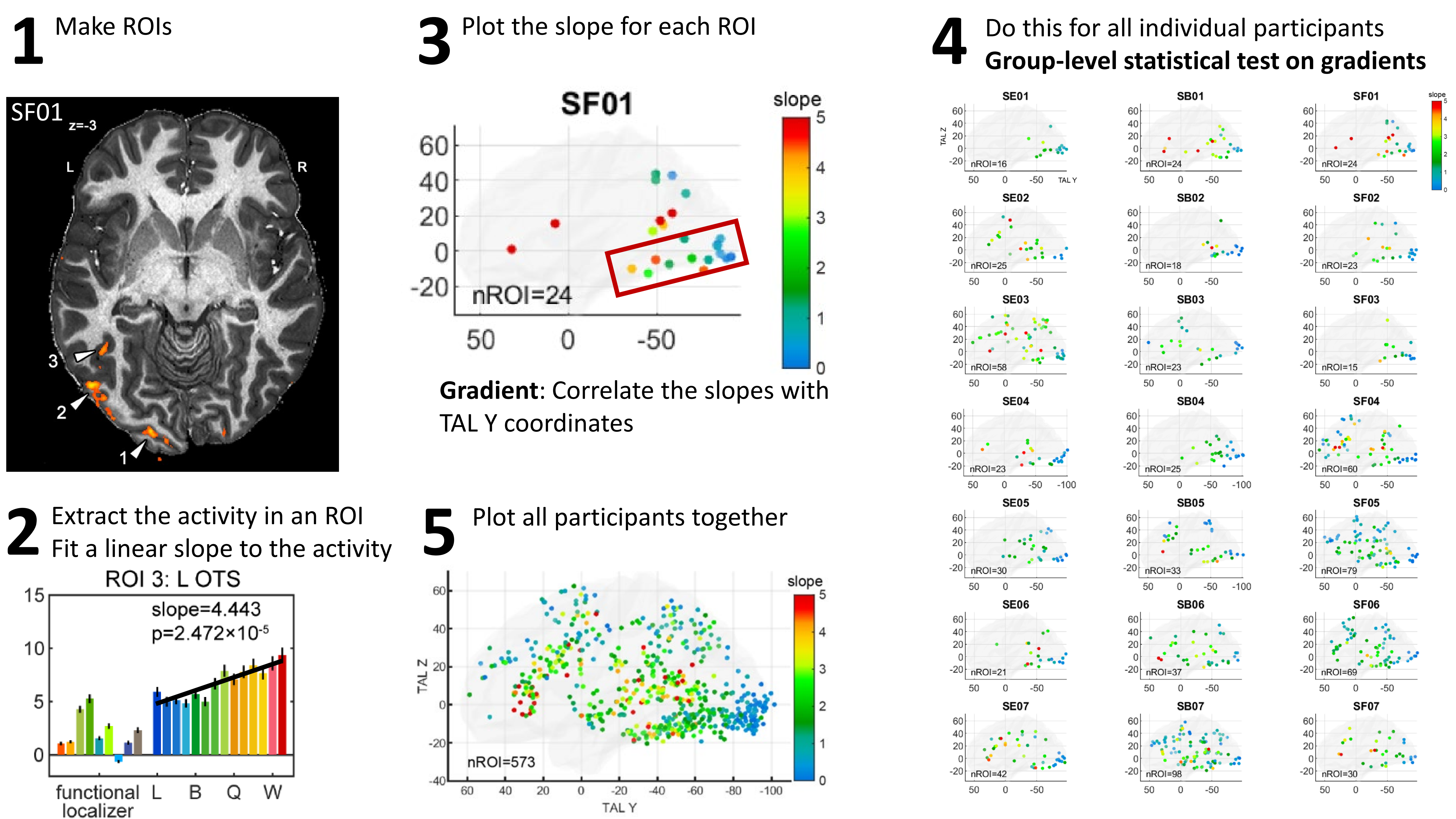
7T fMRI data peculiarities

Functional localizer

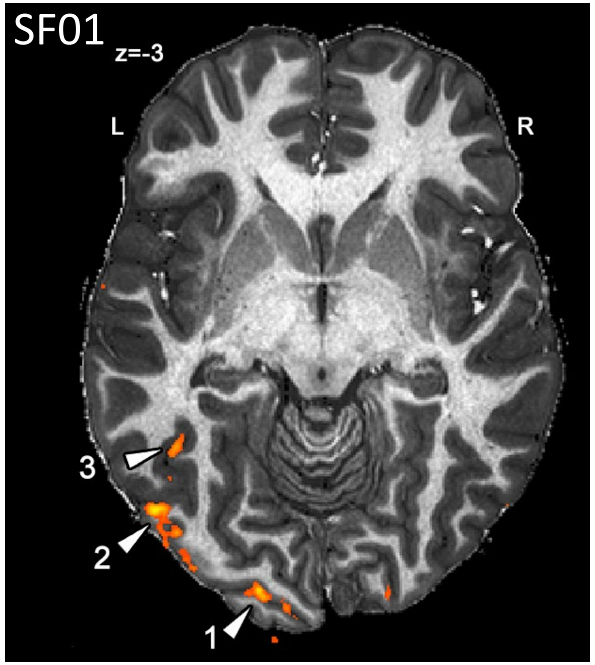
- **Different numbers of ROIs per participant**



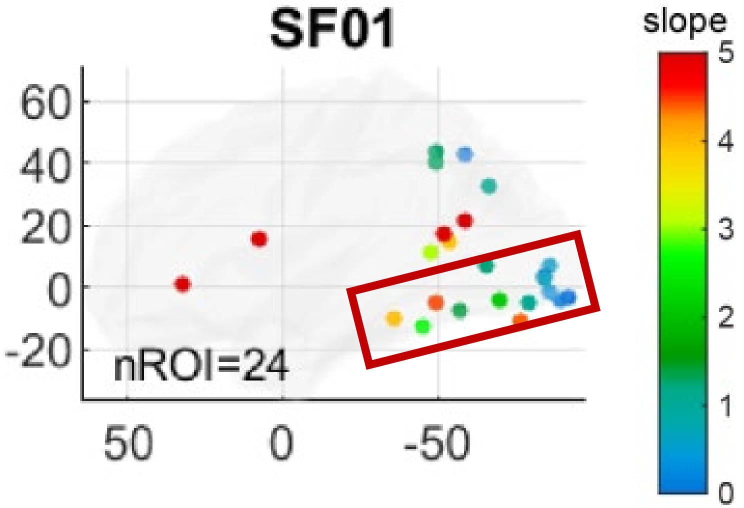
- This forced us to do analysis in individual-subject & ROIs
  - Manually selected 1596 ROIs
    - Labeled anatomical locations
    - Rejected artifacts (e.g. vessels)
  - Examined activity profiles within each ROI
  - **Alternative group-level summary statistics** to get one value per participant


1 Make ROIs
SF01 z=-3
L
R
3
2
1
2 Extract the activity in an ROI
Fit a linear slope to the activity
ROI 3: L OTS
slope=4.443
p=2.472×10-5
functional localizer
L
B
Q
W
3 Plot the slope for each ROI
SF01
slope
nROI=24
Gradient: Correlate the slopes with TAL Y coordinates
4 Do this for all individual participants
Group-level statistical test on gradients
SE01
SB01
SF01
TAL Z
TAL Y
nROI=16
nROI=24
nROI=24
SE02
SB02
SF02
nROI=25
nROI=18
nROI=23
SE03
SB03
SF03
nROI=58
nROI=23
nROI=15
SE04
SB04
SF04
nROI=23
nROI=25
nROI=60
SE05
SB05
SF05
nROI=30
nROI=33
nROI=79
SE06
SB06
SF06
nROI=21
nROI=37
nROI=69
SE07
SB07
SF07
nROI=42
nROI=98
nROI=30
5 Plot all participants together
slope
TAL Z
TAL Y
nROI=573

1 Make ROIs

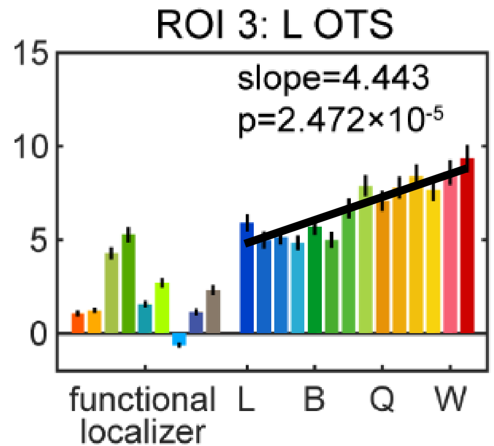


3 Plot the slope for each ROI

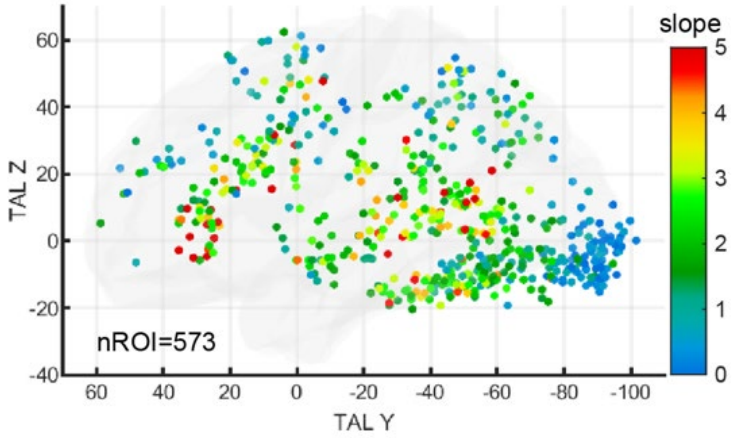


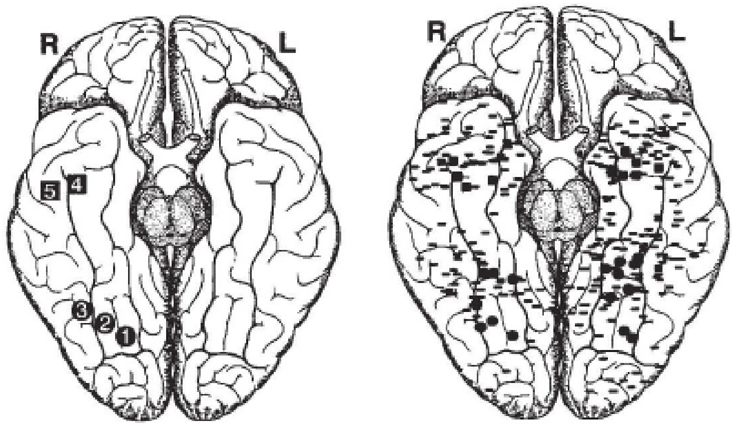
Gradient: Correlate the slopes with TAL Y coordinates

2 Extract the activity in an ROI
Fit a linear slope to the activity

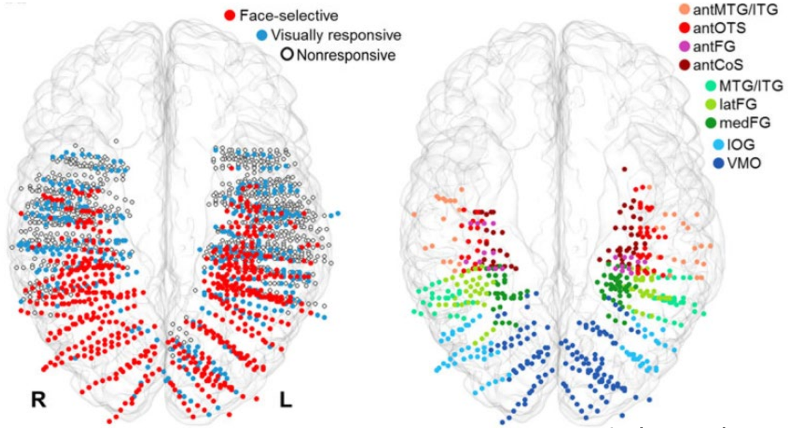


5 Plot all participants together

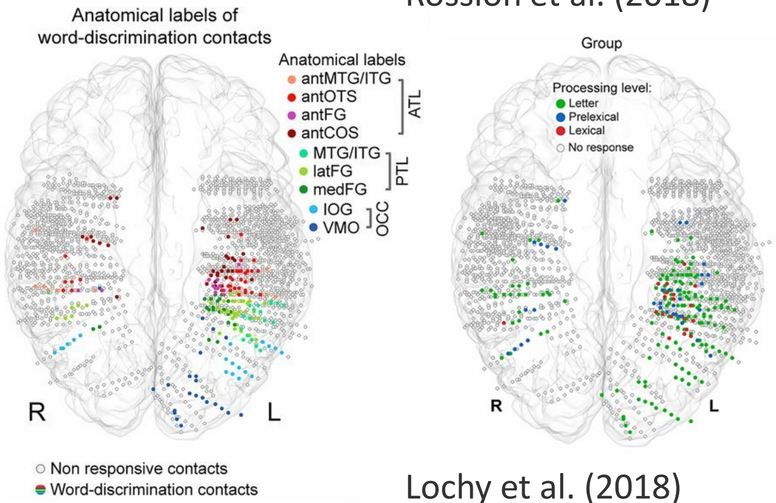




Nobre et al. (1994)

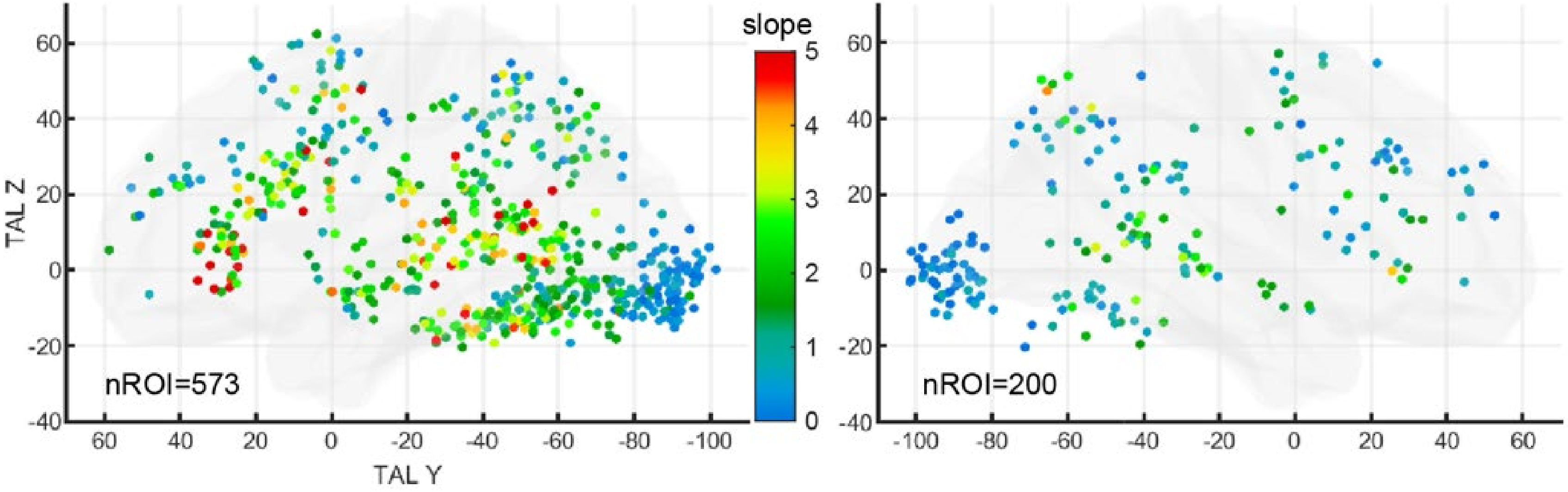


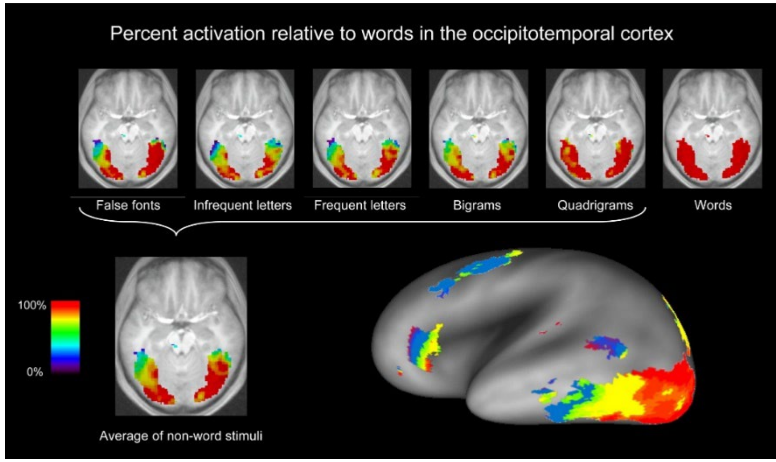
Rossion et al. (2018)



Lochy et al. (2018)

Word-similarity gradients across the VOTC

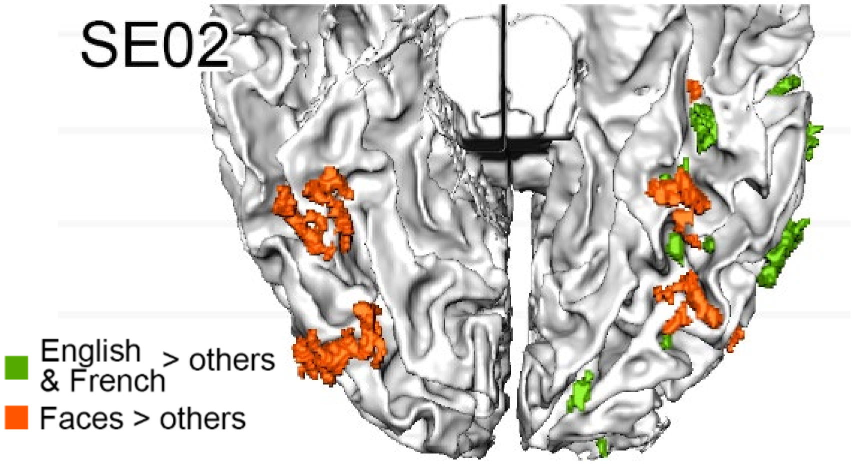




Vinckier et al. (2007)

Present in each individual

- Increasingly high in anterior VOTC (above the ear canal)



The VOTC word-similarity effect is mostly limited in word-specific patches

- Control analysis: Not present in 90% of the face-specific patches
- Present in 10% : left-lateralized, in vicinity to word-specific patches

English-French bilinguals

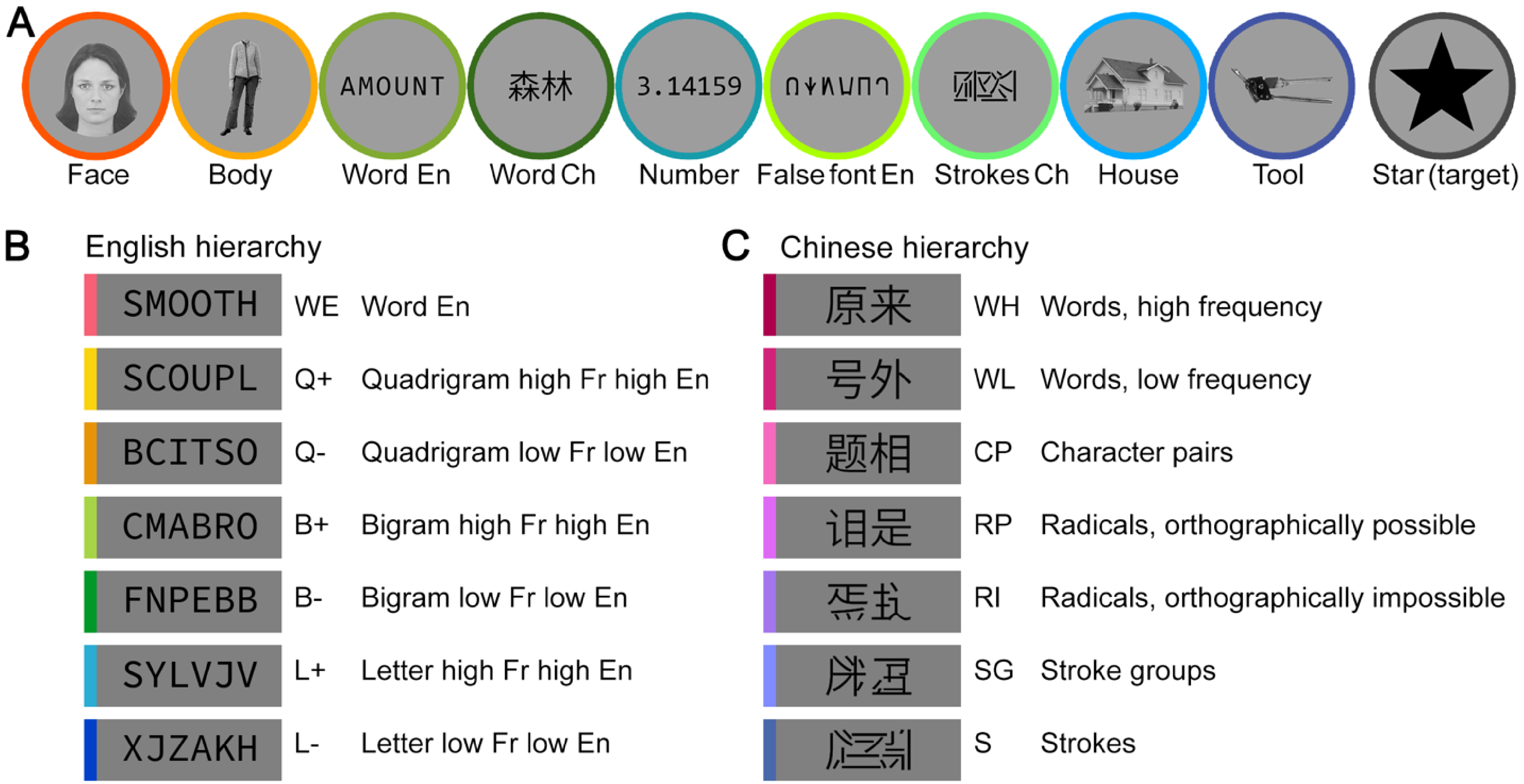
No consistent language-specific activation

- Neither in the localizer nor in the main fMRI runs

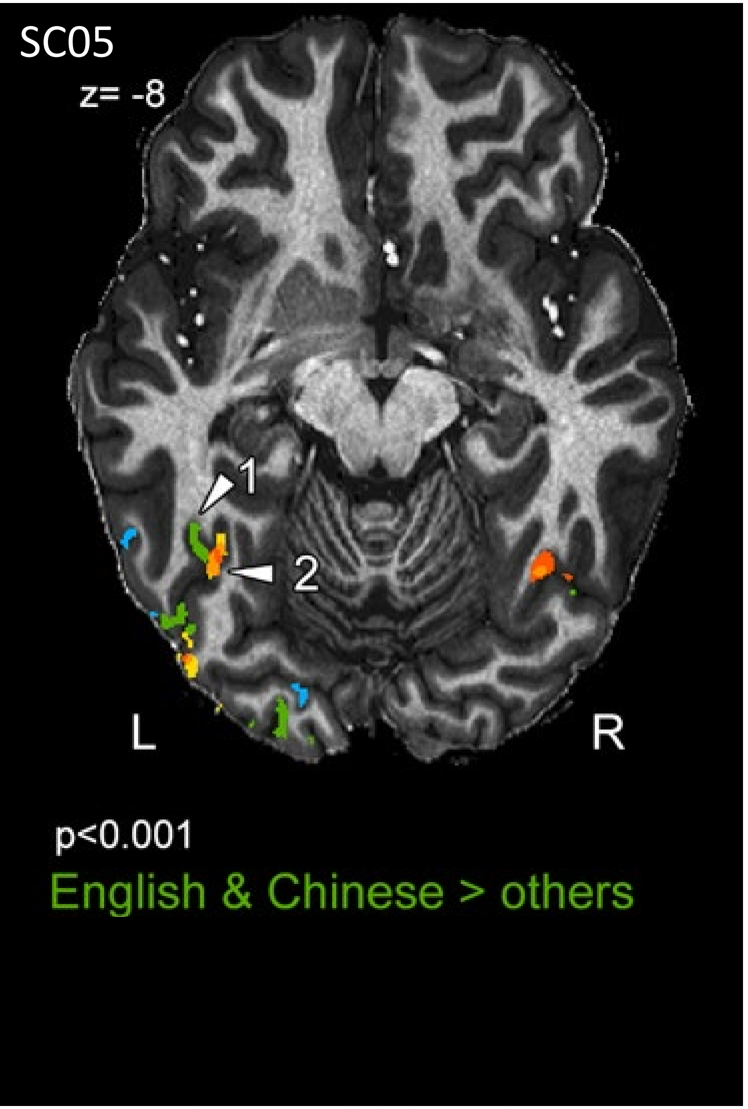
Is it because that the English and French scripts are too similar?

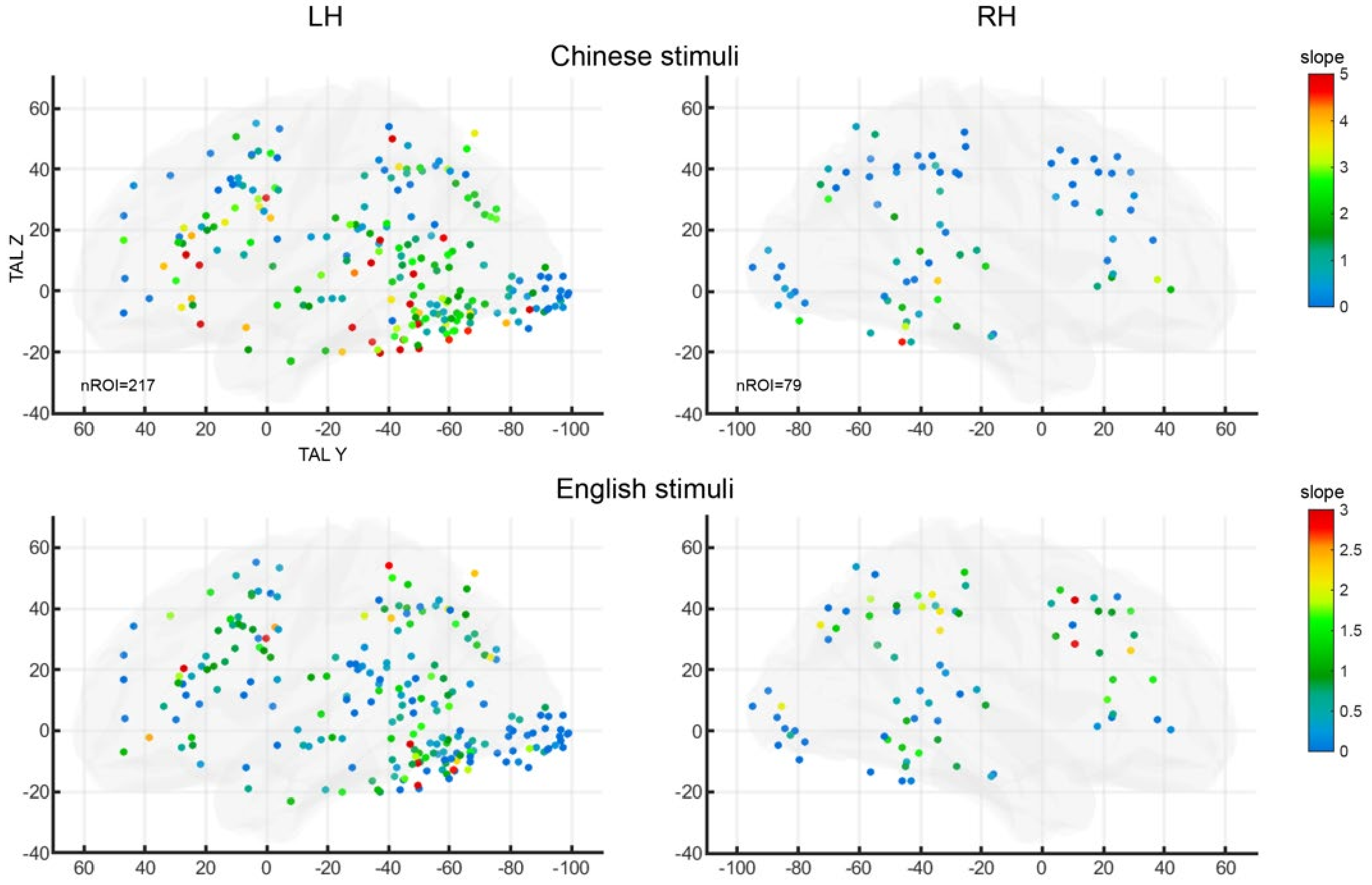
Try more different scripts: English vs. Chinese

Experiment 2: English-Chinese bilinguals n=10

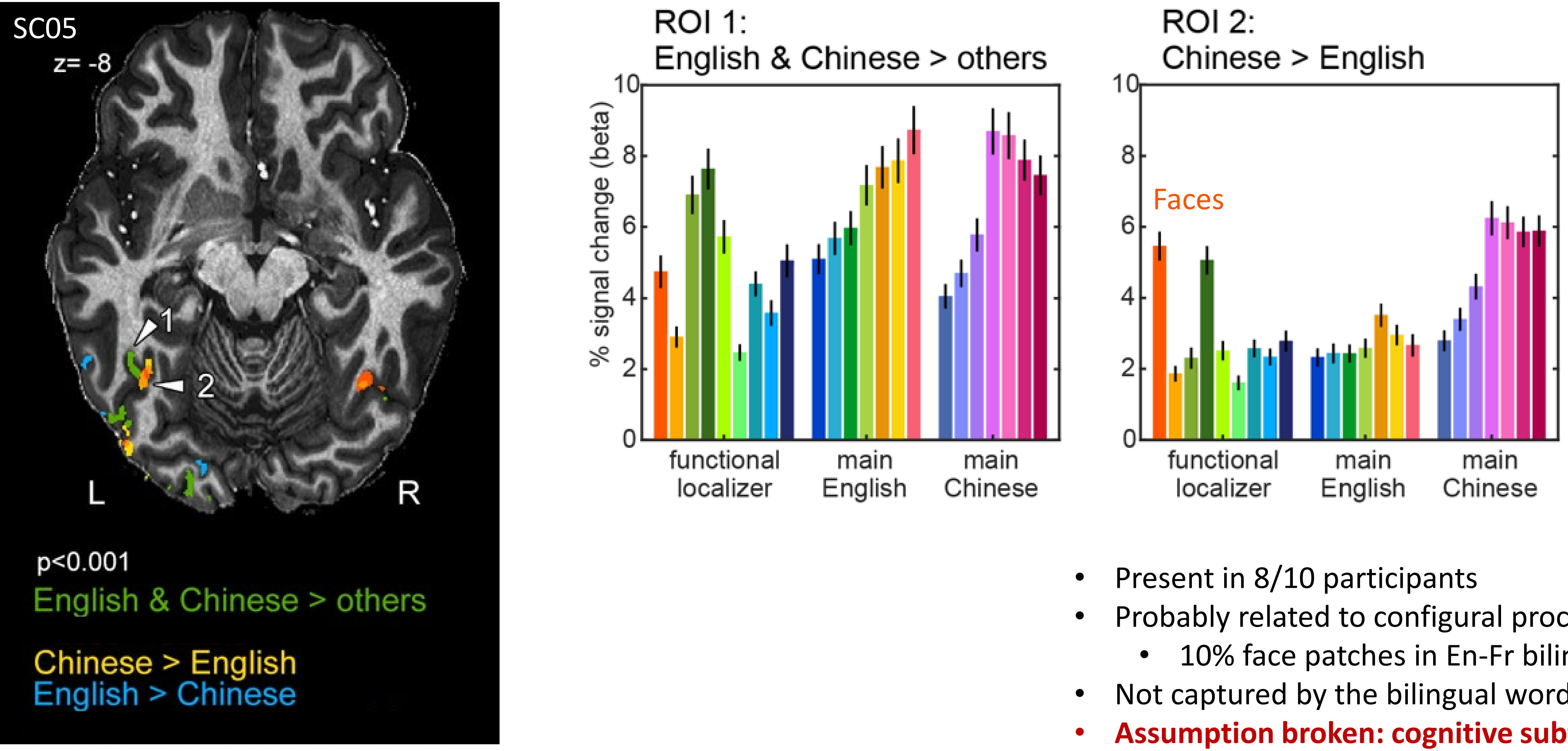


English & Chinese bilingual patches





Chinese-specific patches



- Present in 8/10 participants
- Probably related to configural processing
  - 10% face patches in En-Fr bilinguals
- Not captured by the bilingual word contrast
- **Assumption broken: cognitive subtraction**

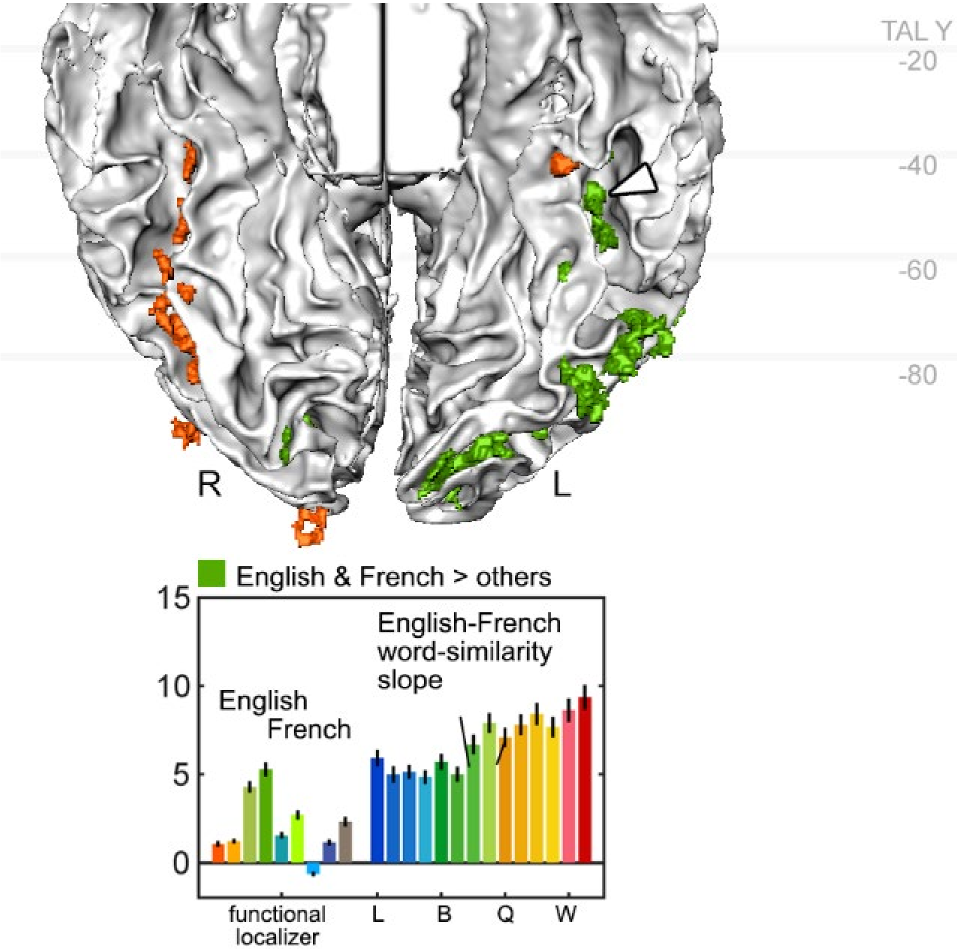
Summary and discussion

Summary

English-French bilinguals

Use the same VOTC areas to read English and French

- No separation of the two languages

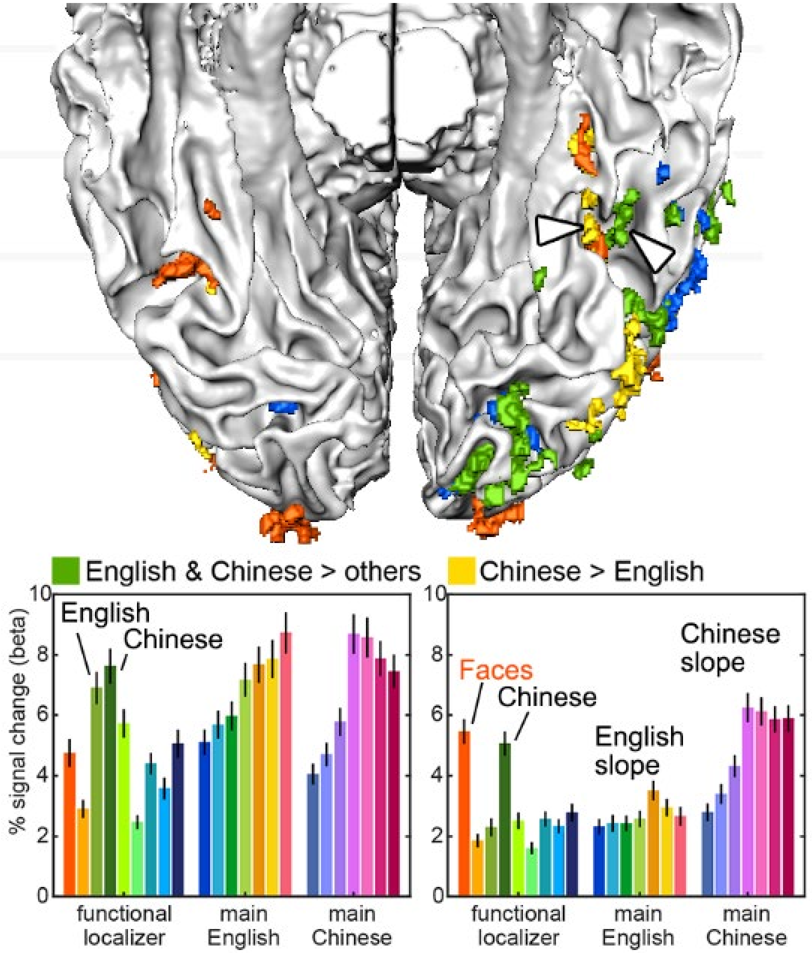


English-Chinese bilinguals

Some VOTC areas process both English and Chinese

Some areas are highly specialized for Chinese

- Surprisingly, also highly activated by faces



Discussion – 7T and beyond: how many 3T assumptions are broken?

3T analysis practice ← **Assumptions** ← **3T data property**

Whole-brain contrast and thresholding → Cognitive subtraction; Orthogonal/All-or-none activity

Multiple-comparison correction (FDR or cluster thresholding) — High false positive rate

Cluster thresholding should be contiguous and big — Activation clusters are big

Gaussian smoothing of 4 mm or more

Smoothing twice at first and second levels

Noise can be suppressed by smoothing

Effect shouldn't be noise, and needs to be generalizable across population

Whole-brain group-level analysis (averaging) — The same coordinate across different participants are performing the same function

Low SNR:

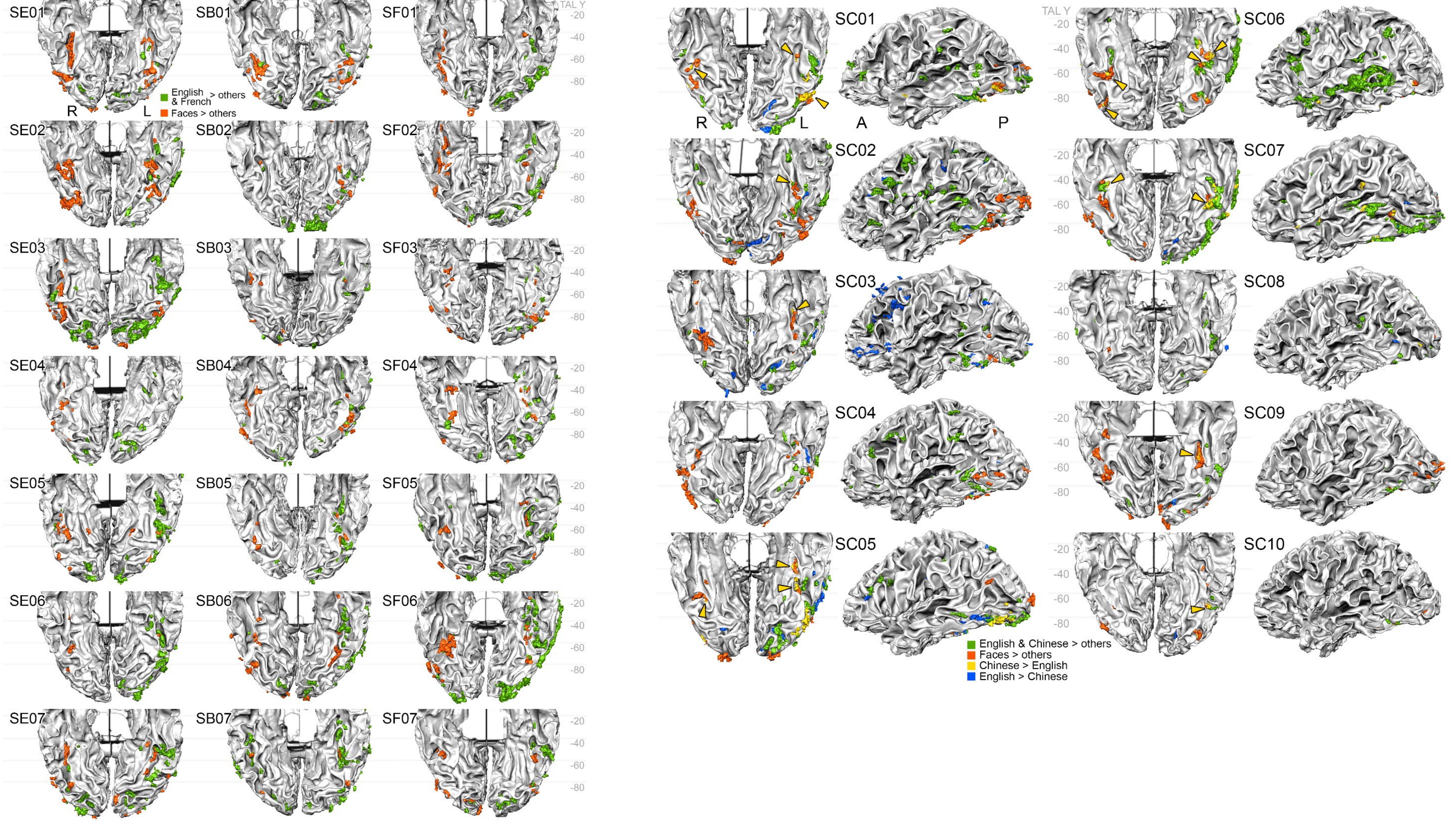
- **high noise**
- **low signal**

Low resolution:
big voxels

What should we do?

7T and beyond: need detailed individual analysis and alternative statistics

3T: precision fMRI


SE01 SB01 SF01
SE02 SB02 SF02
SE03 SB03 SF03
SE04 SB04 SF04
SE05 SB05 SF05
SE06 SB06 SF06
SE07 SB07 SF07
TAL Y
-20 -40 -60 -80
R L
English & French > others
Faces > others
SC01 SC02 SC03 SC04 SC05
SC06 SC07 SC08 SC09 SC10
A P
English & Chinese > others
Faces > others
Chinese > English
English > Chinese