Clinical fMRI as a quantitative imaging biomarker of brain function

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Collaborators

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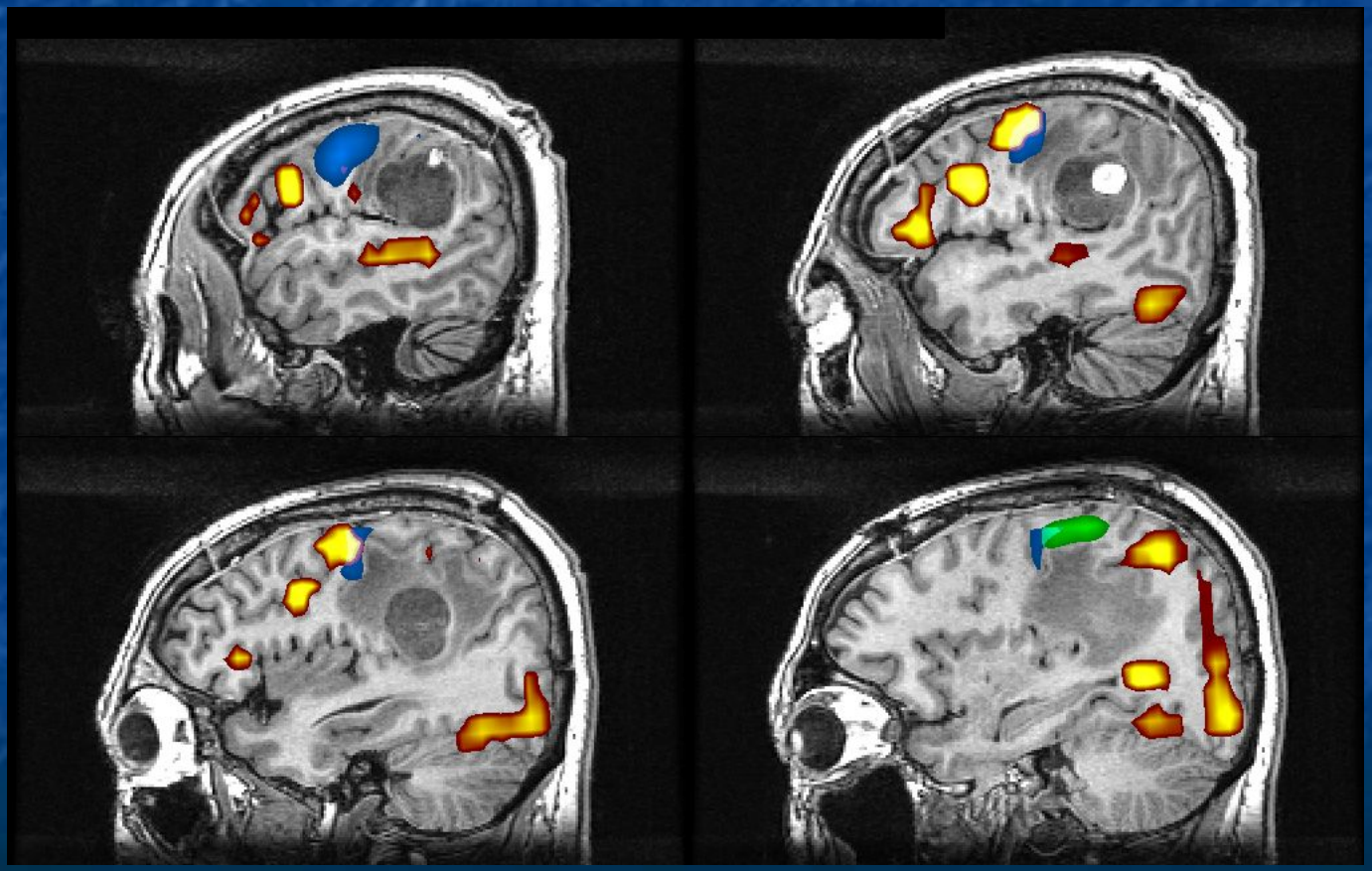
- James Carter, PA, Duke Neurosurgery

- QIBA fMRI Biomarker Committee

Functional MRI (fMRI) is primarily used clinically to map speech and motor function prior to brain surgery



fMRI – Patient performs tasks using simple visual cues and alternating block designs

Bilateral hand motion task

Silent sentence-completion task

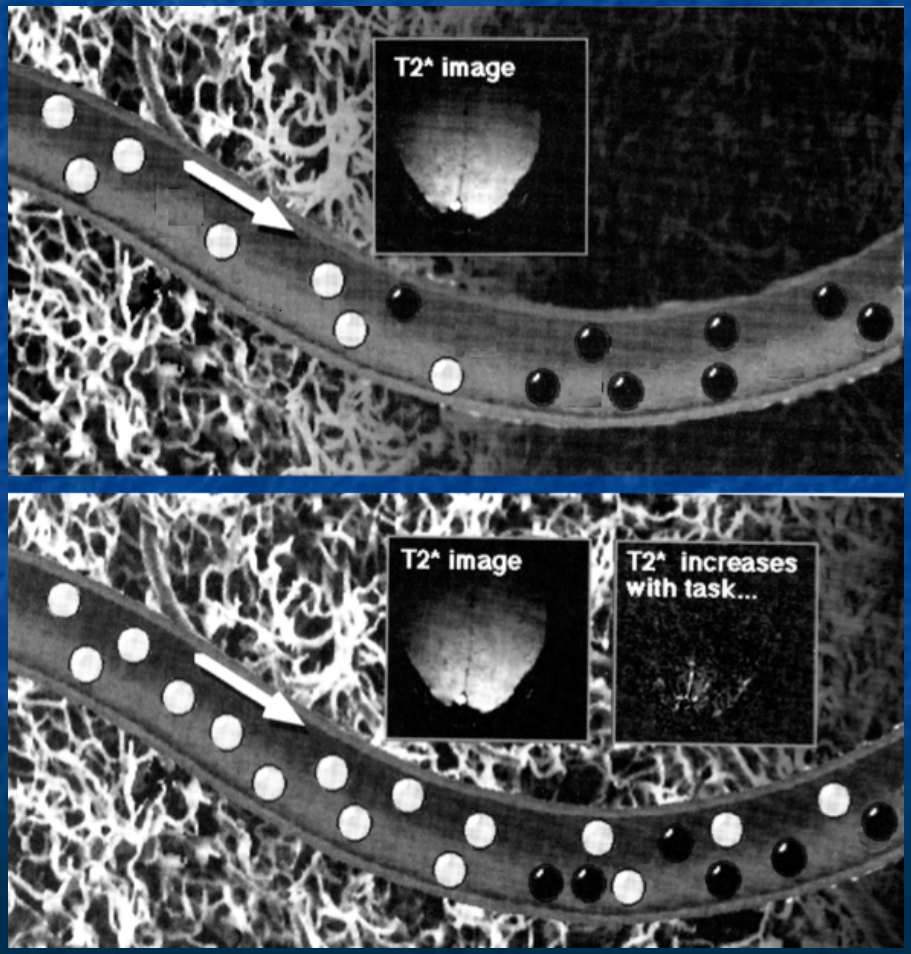
Old MacDonald had a _____ .	vs	Bnd MwjGhdchkj ckr n _____ .
15s		15s

How does fMRI work?

T2*-weighted imaging is sensitive to susceptibility changes caused by local blood oxygenation level dependent (BOLD) changes in cerebral blood flow

"Rest"

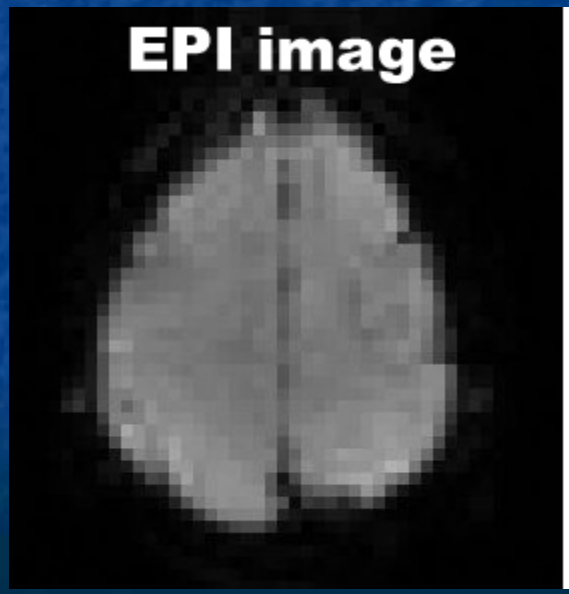
"Task"



from Mosley

Image acquisition

During a ~5-minute fMRI scan the patient performs many cycles of a simple task.
20-30 echo-planar images are acquired every TR (~1.5s),
This yields a time series of ~200 brain image volumes.
Image intensity varies with the task in some voxels.



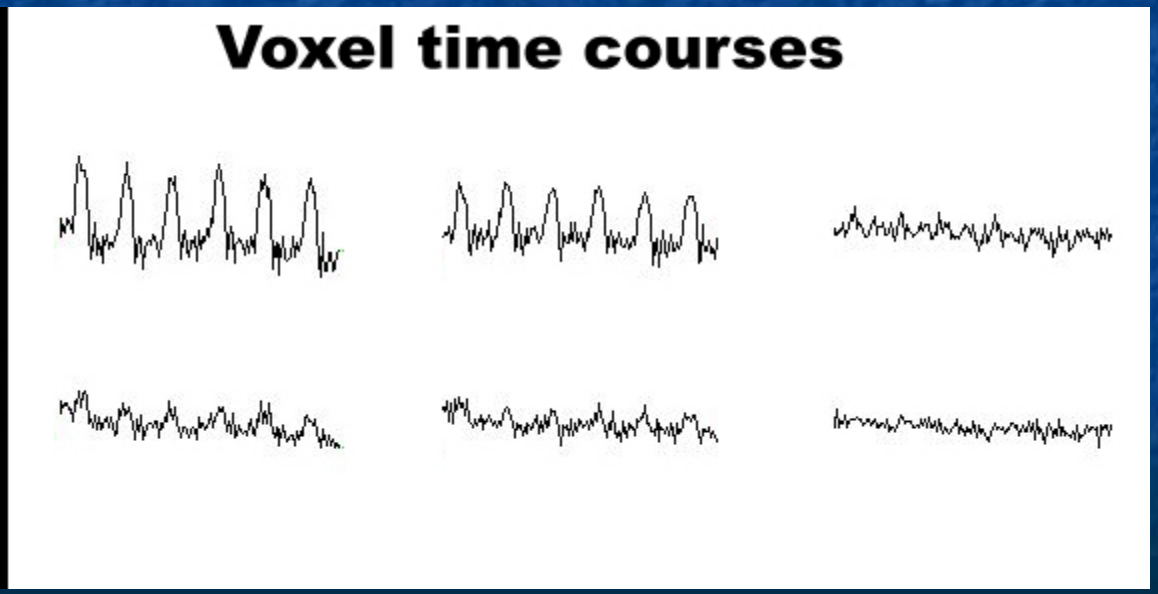


Image signal pre-processing

- Filter out known nuisance signals (usually)
  - Head motion (measure motion - realign images)
  - Regression filter (heartbeat, respiration, drift)
- Filter out high-frequency noise (always)
  - Spike filter
  - Spatial smoothing
  - Temporal smoothing

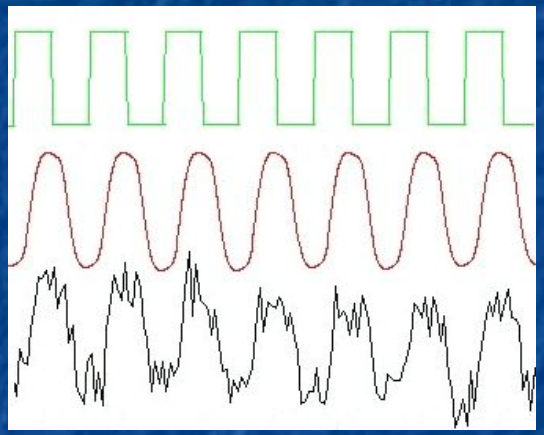
Statistical image processing

Compare the timing of the observed fluctuations in the fMRI images to the expected fluctuations of the BOLD response.

Task timing

Predicted response

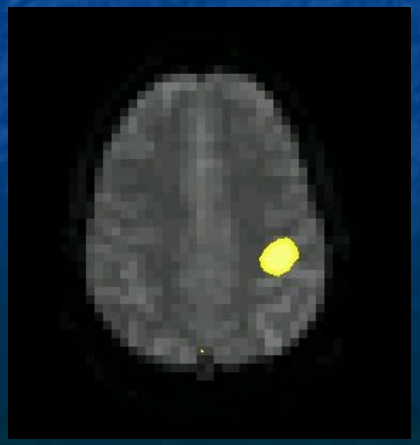
Actual response



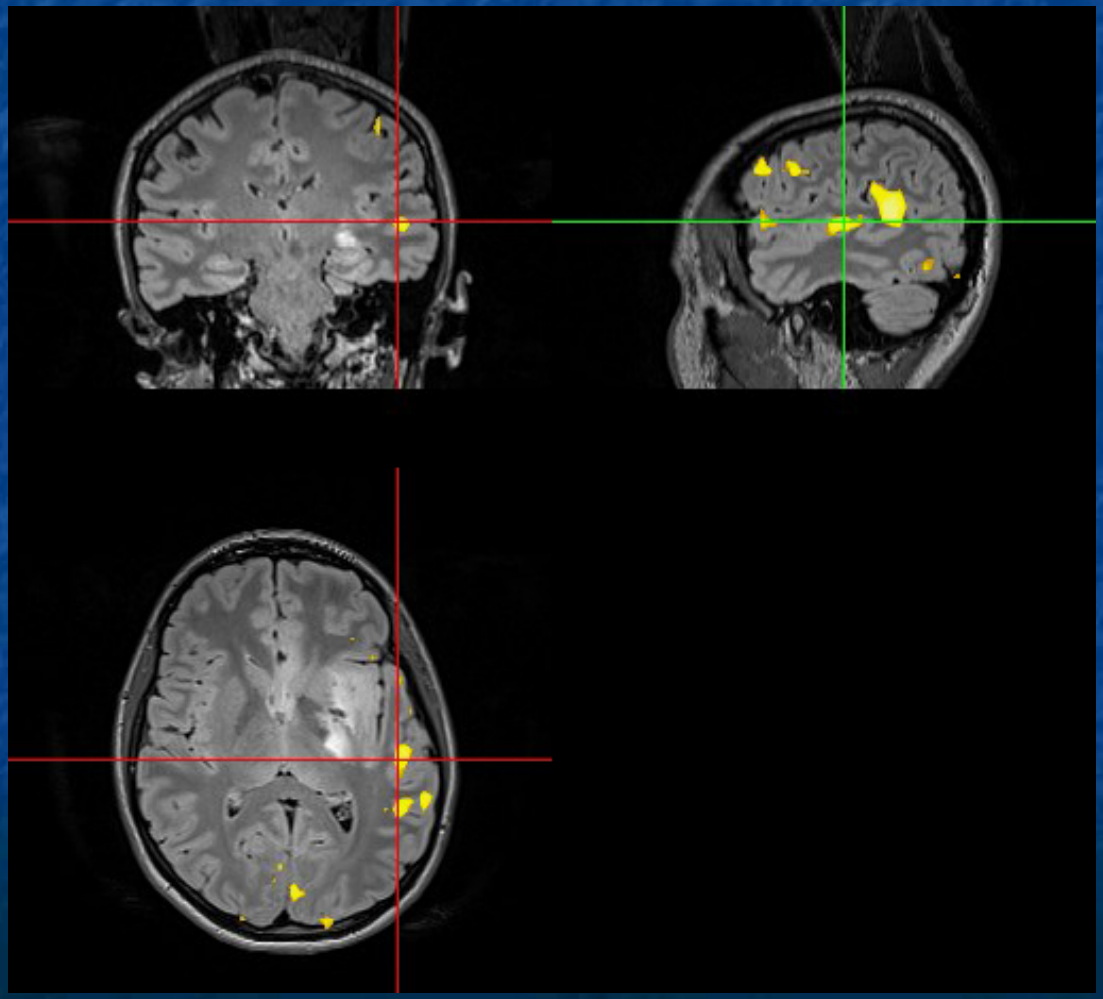
Comparison methods:
- image subtraction
- t-test differences
- frequency analysis (FFT)
- temporal correlation
- General Linear Model (analysis of variance)

Statistical significance identifies "active" voxels (statistical value above some minimum threshold)

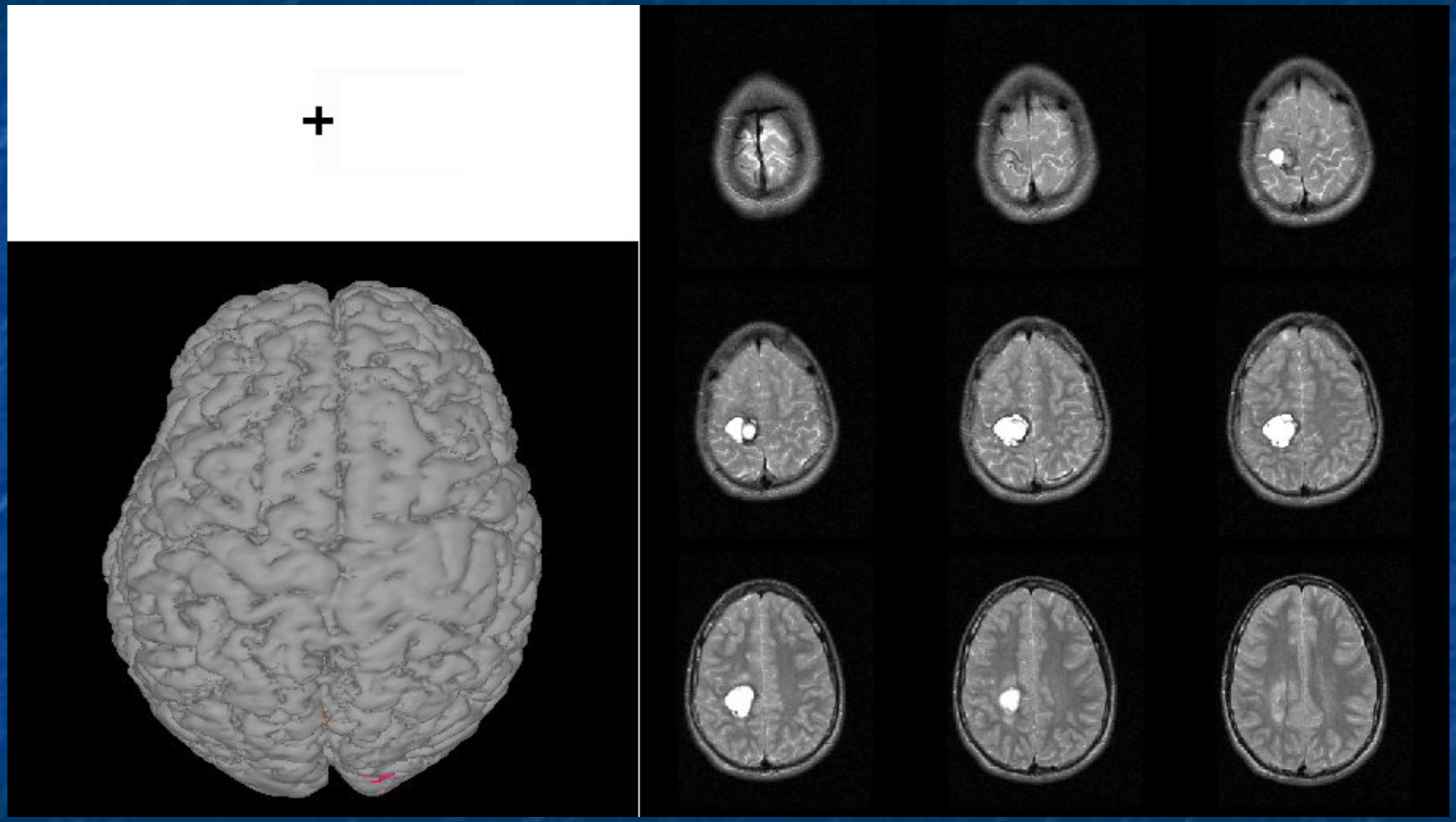
Thresholded "map" of active voxels is overlaid on MR images



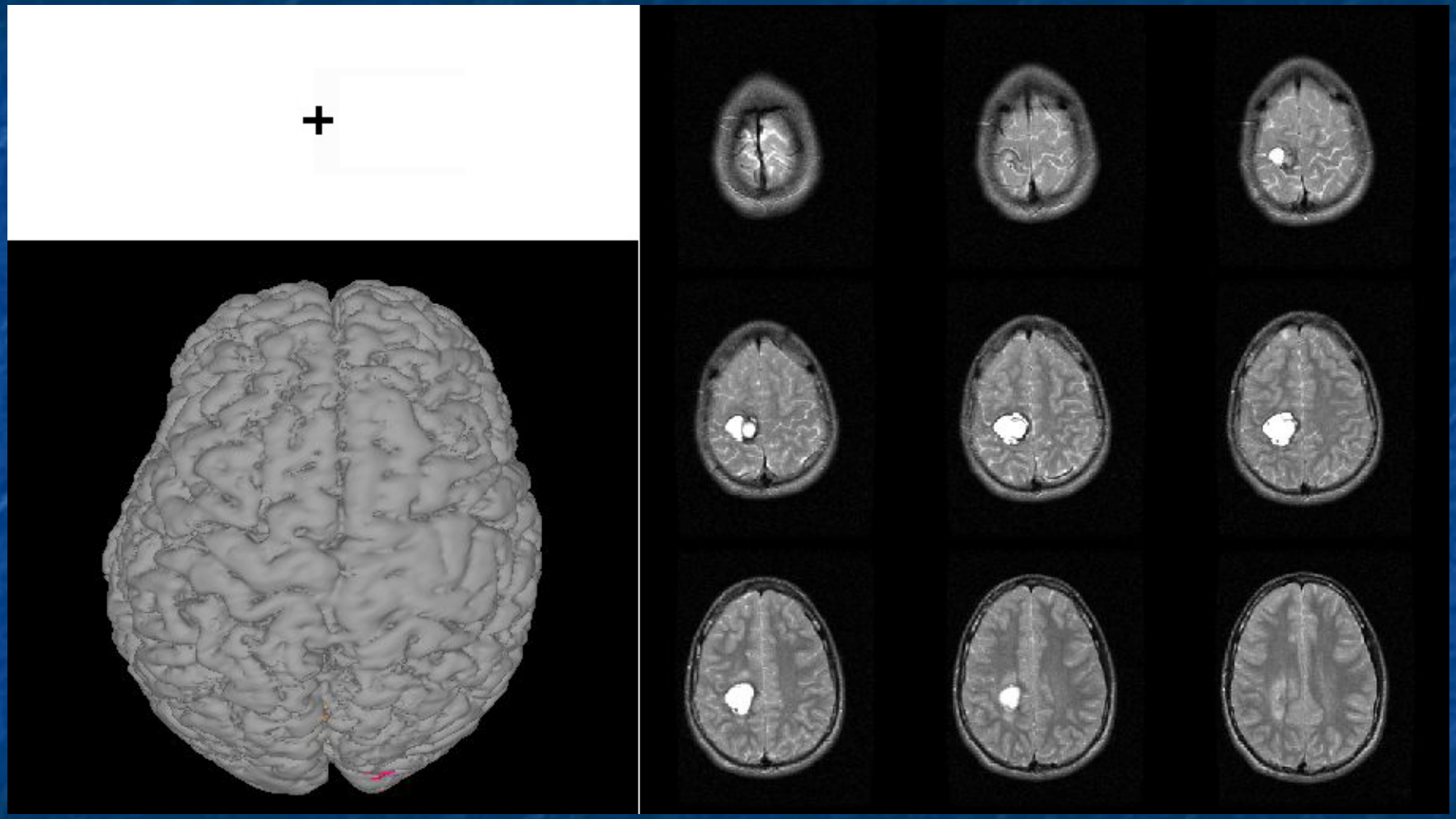
Functional maps can be overlaid on brain anatomical images, resampled, and viewed from any orientation



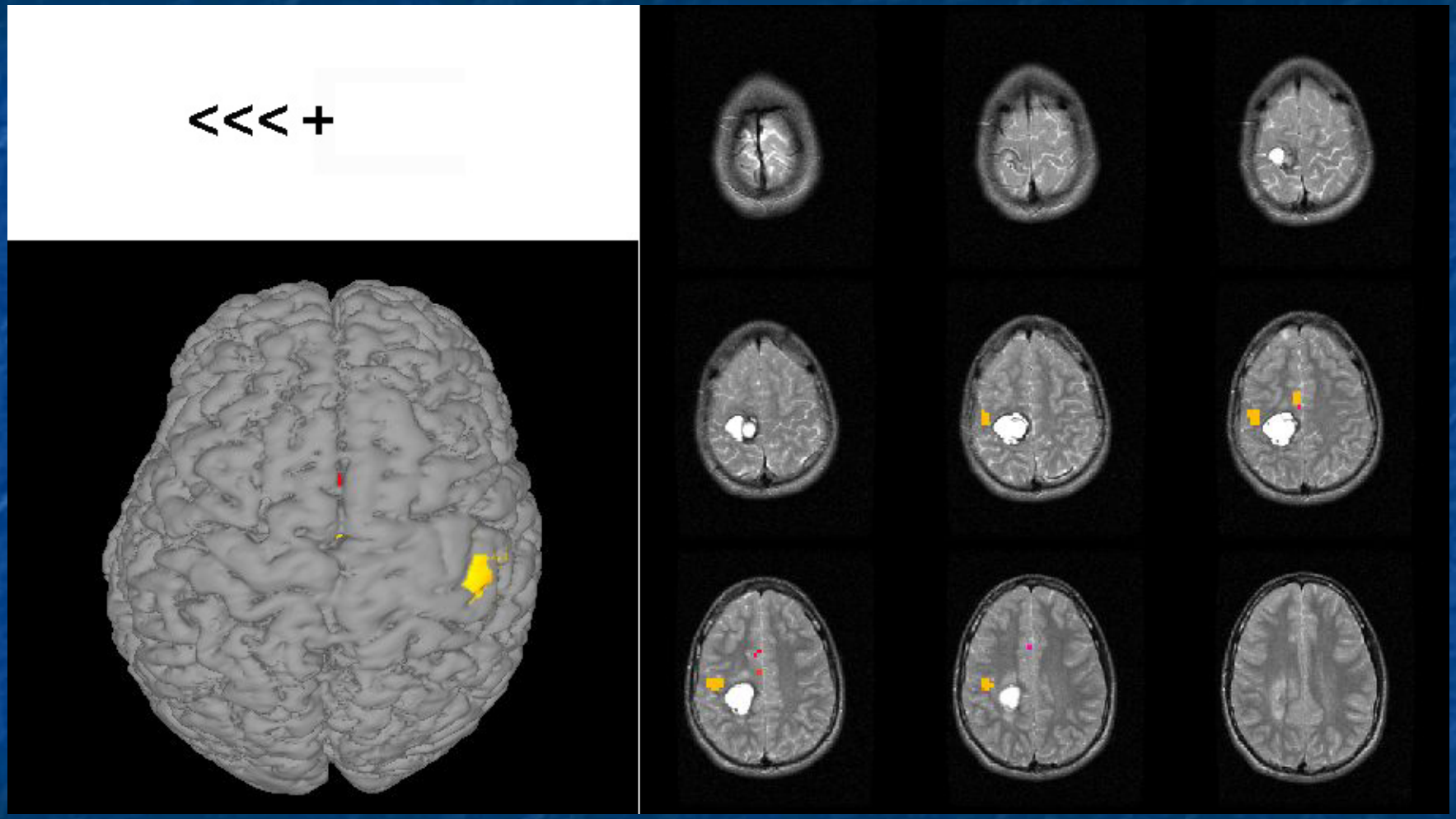
Motor cortex mapping prior to neurosurgery



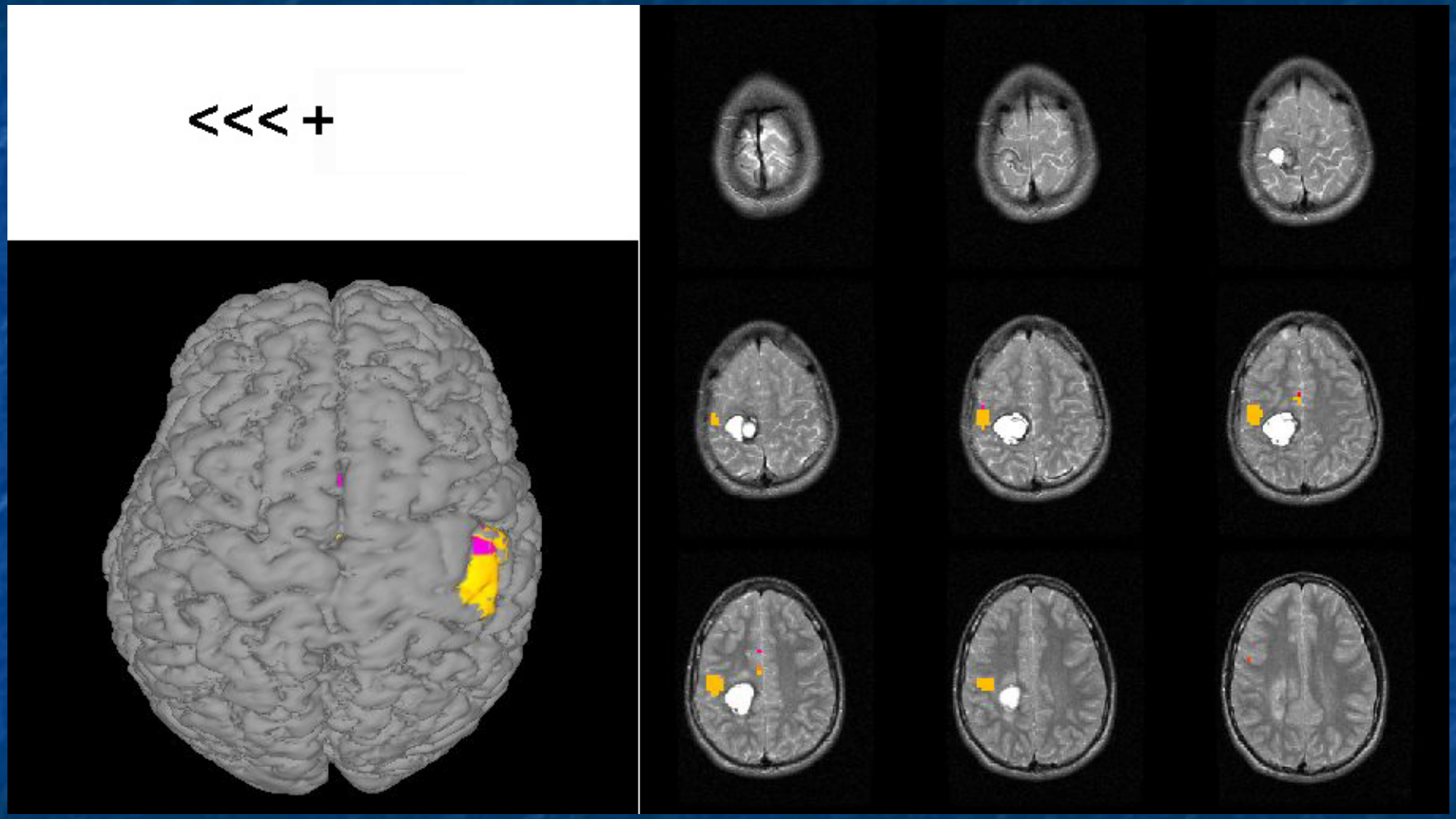
T = 0 s



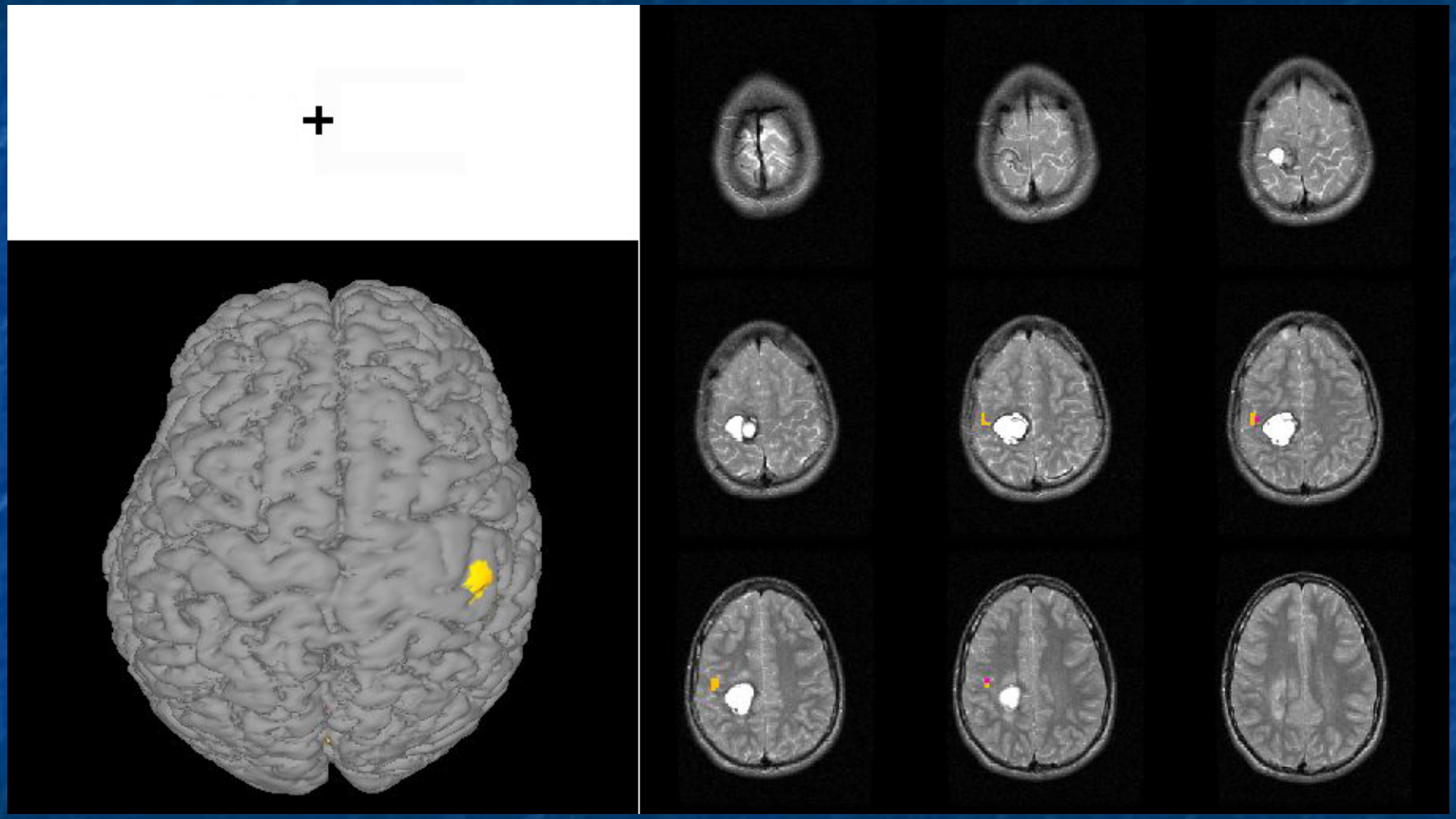
T = 4.5 s



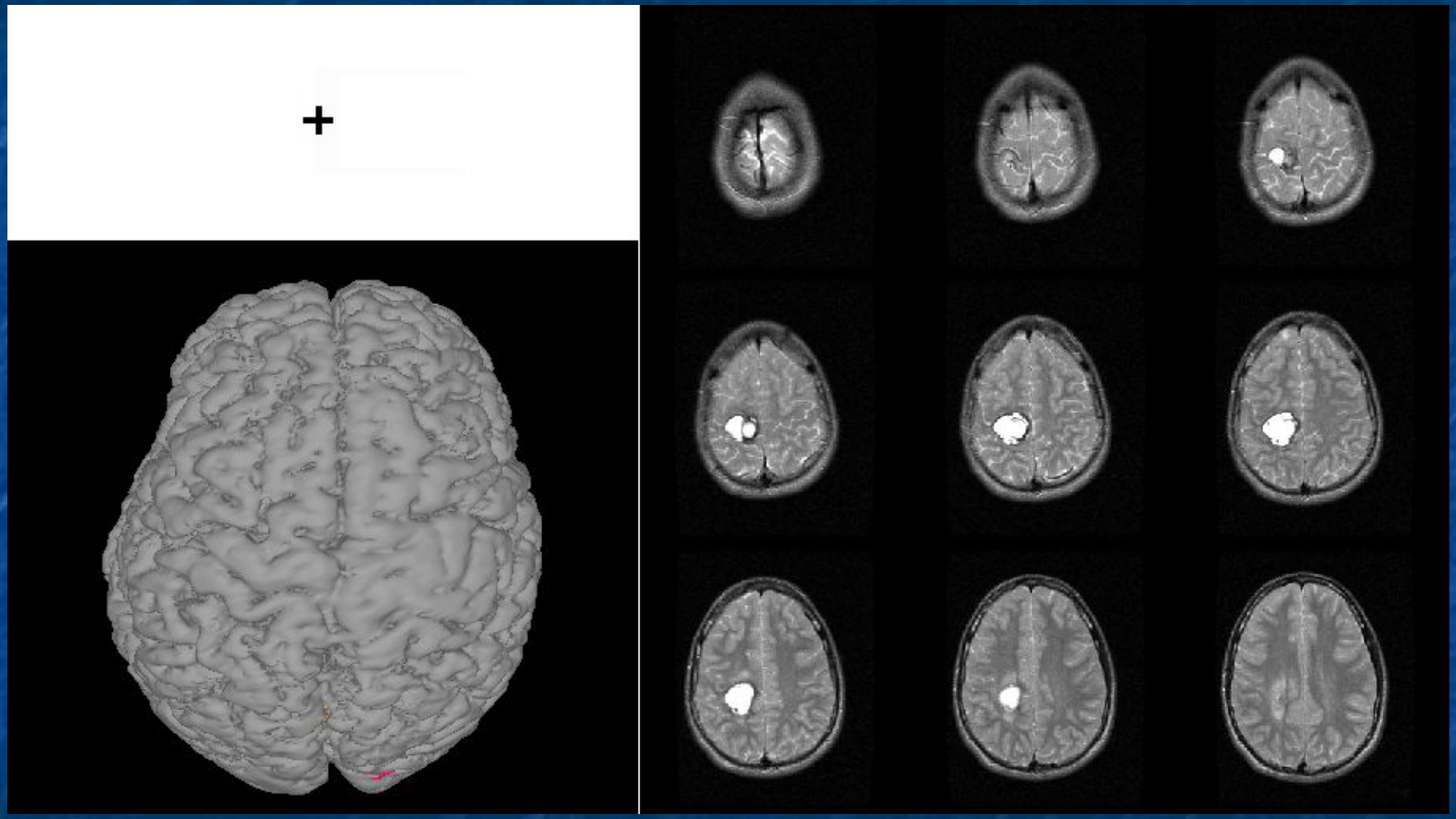
T = 9.0 s



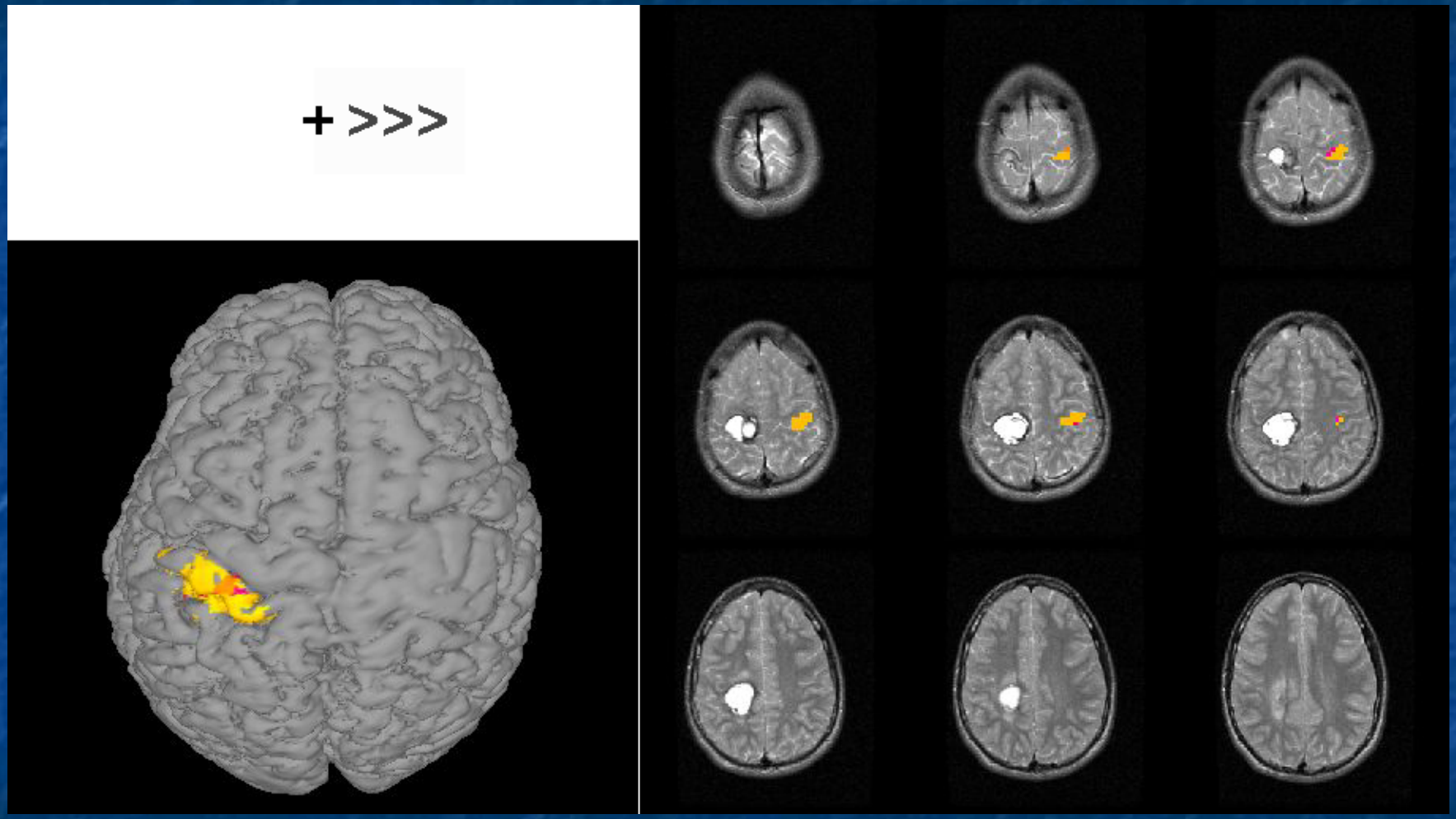
T = 13.5 s



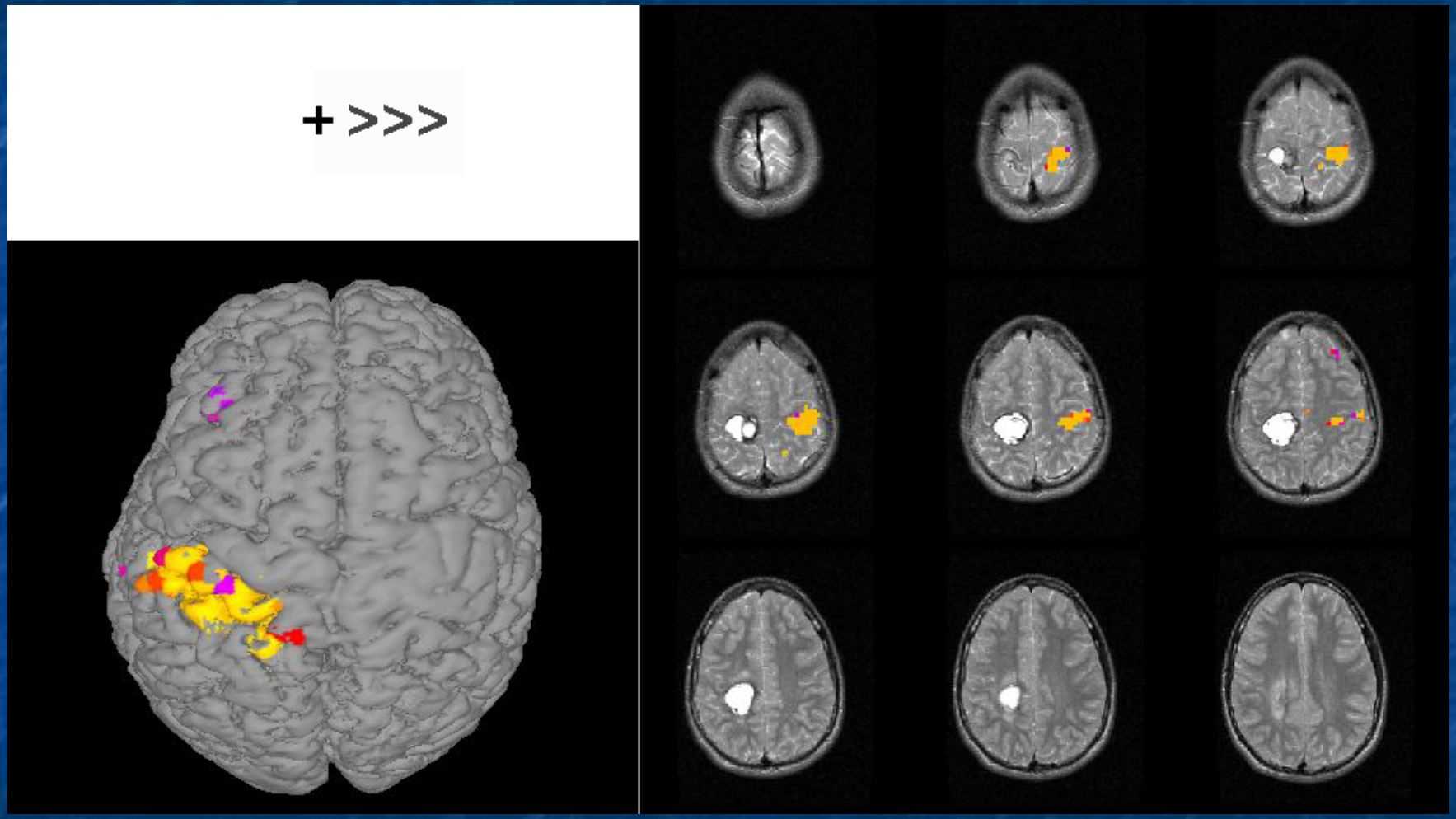
T = 18.0 s



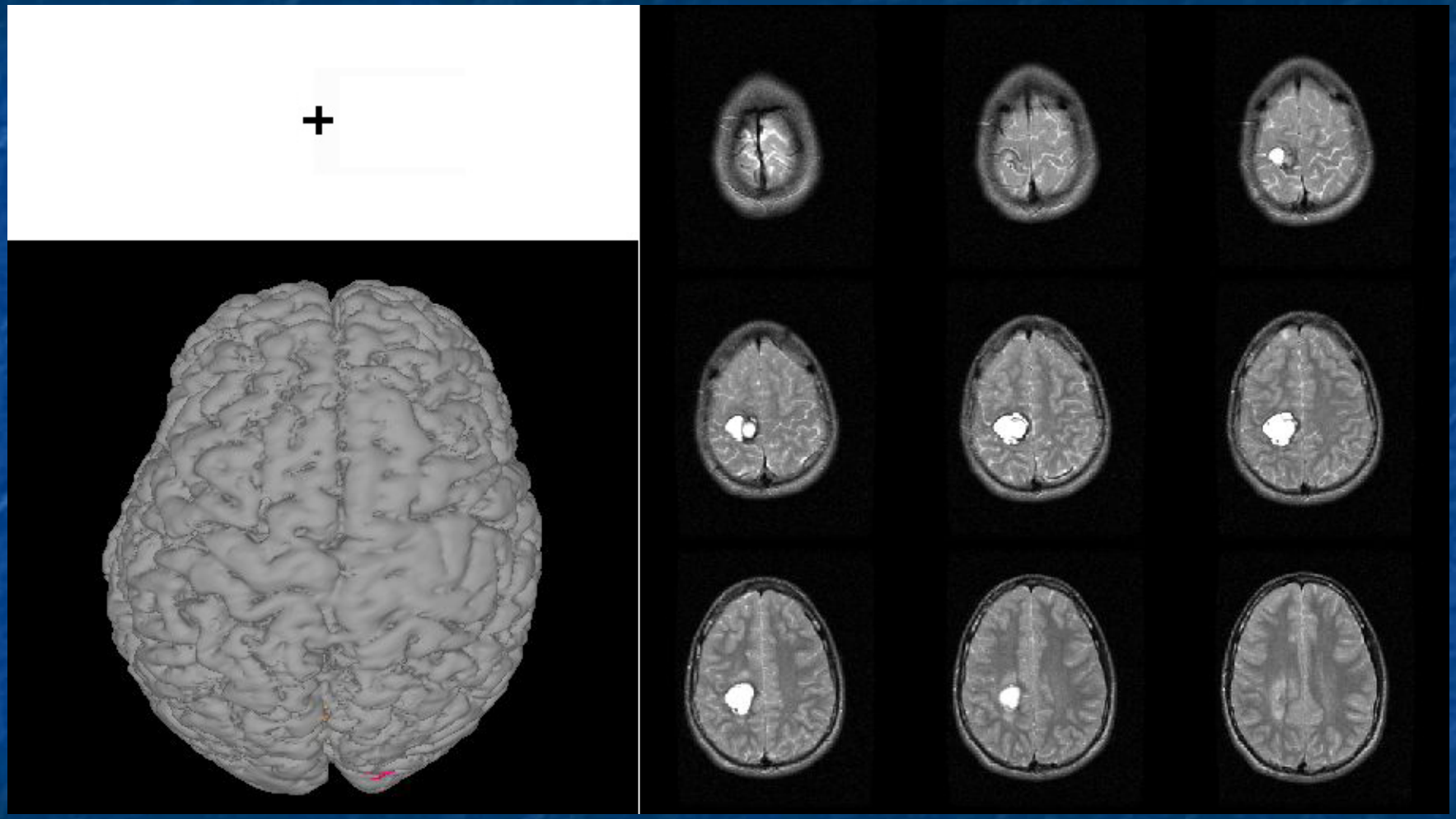
T = 22.5 s



T = 22.5 s



T = 31.5 s



T = 38.0 s

Clinical fMRI exam

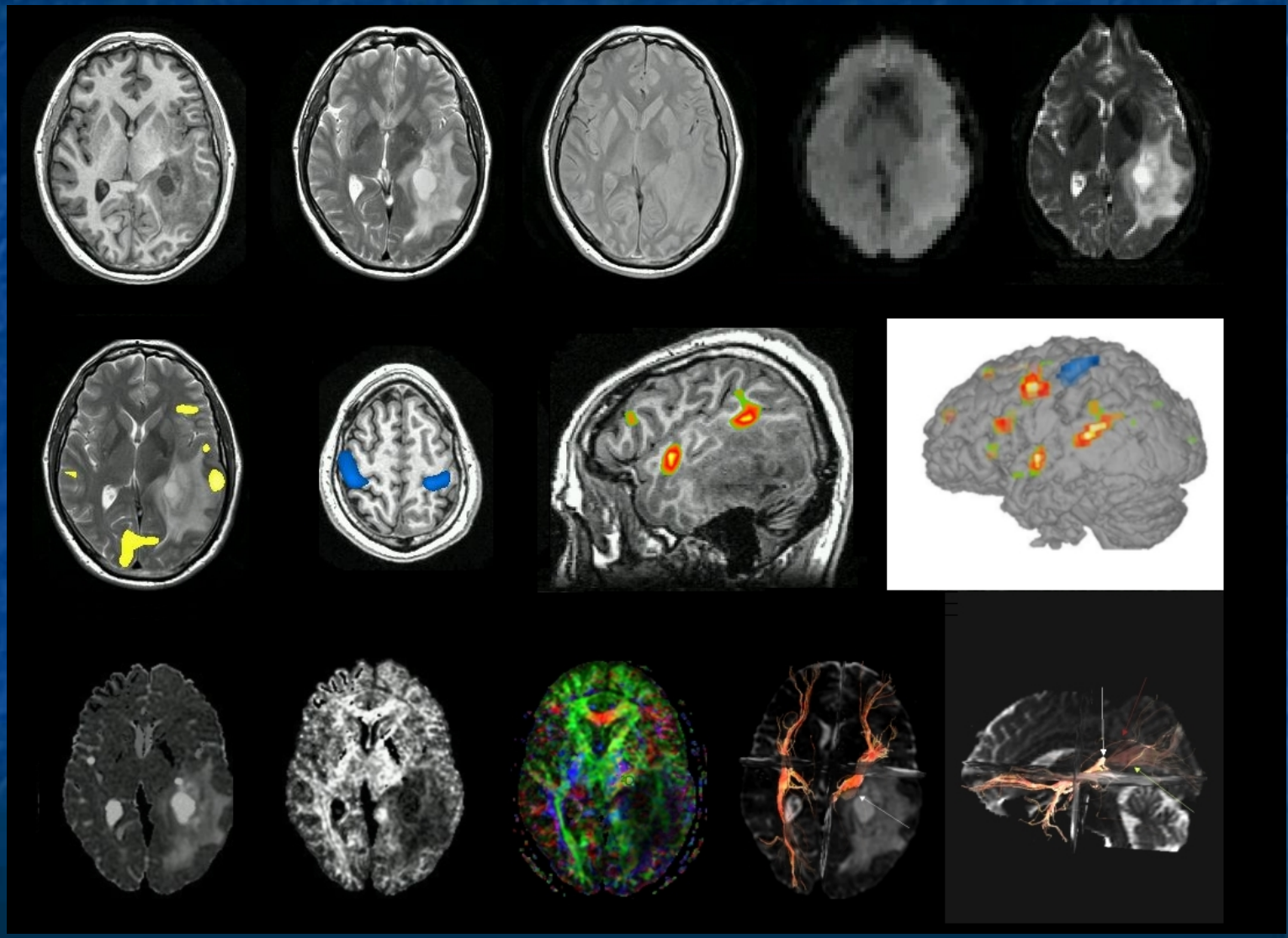
- 10 min pre-scan assessment and training
- 45 min MRI session
  - 10 min anatomical scans (T1 & FLAIR)
  - 15-20 min fMRI – 3-4 tasks (4 min each)
  - 5 min 30-direction DTI scan
- 30-60 min post-scan image analysis
  - Registration of fMRI and DTI with T1 images
  - Definition and statistical analysis of "active" voxels
  - Overlay of fMRI and DTI on anatomical images
- Neuroradiological interpretation

Clinical fMRI images

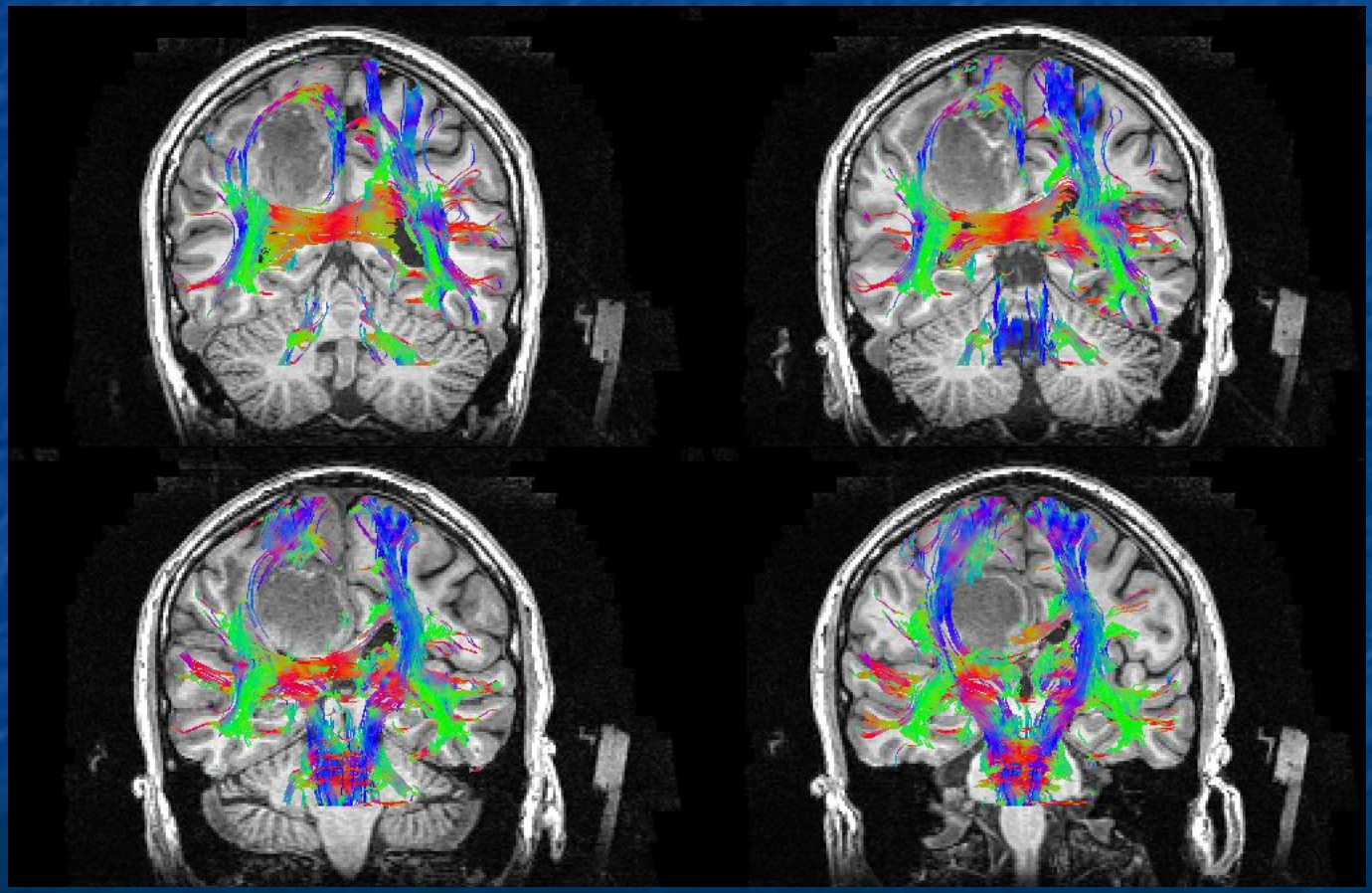
Anatomy & pathology

fMRI maps & 3D reconstructions

DTI Maps & Fiber tracks

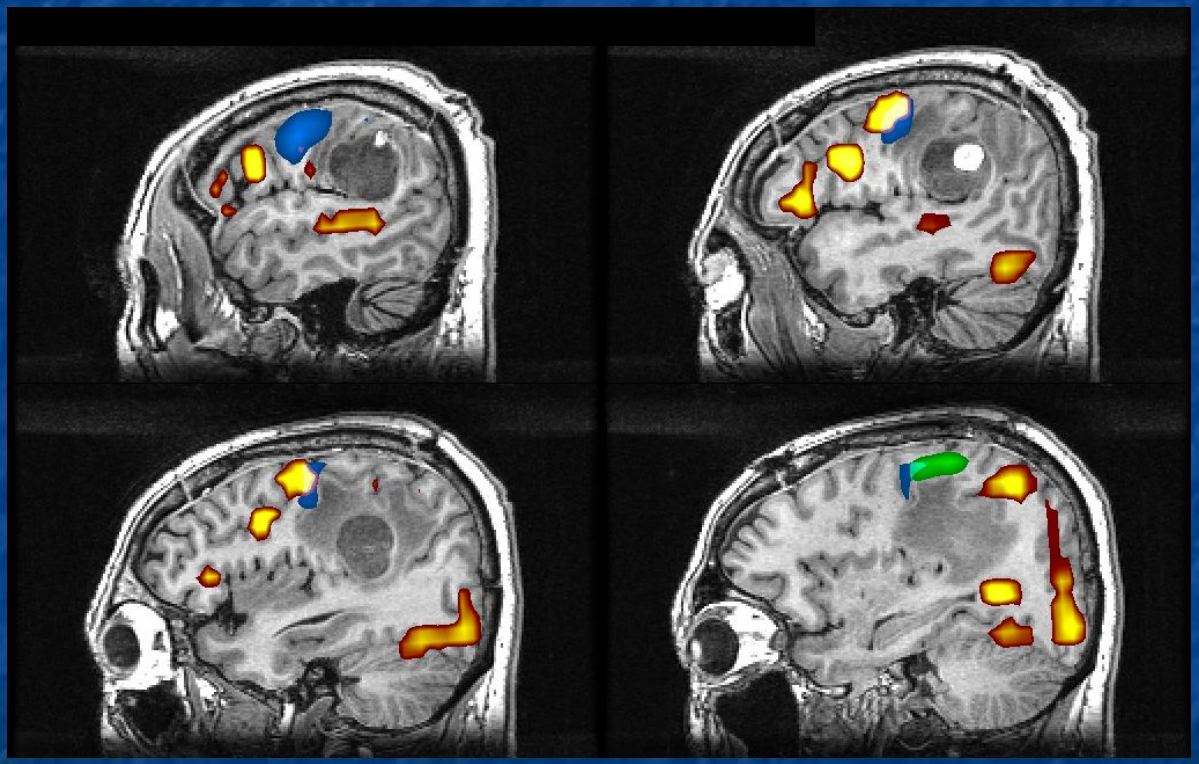


Diffusion tensor imaging (DTI) is used to map major white matter tracts



When all goes well fMRI is easy

Statistical significance provides map of brain activity



This fMRI map was computed from ~13,000 images.

Clinically, how do we assess whether all went well?

fMRI -- Clinical goals

- Determine location and borders of eloquent (essential) cortical areas relative to lesions
- Determine location of major white-matter tracts connecting eloquent areas
- Evaluate risk of post-surgical functional deficits
- Decide whether surgery is advisable
- Plan surgical approach and extent of resection
- Decide whether intraoperative mapping is necessary

fMRI -- Technical goals

- Tasks that selectively activate eloquent brain areas
  [appropriate and effective]
- Detect BOLD signals to identify eloquent brain areas
  [sensitivity & specificity]
- Map location relative to anatomy and pathology
  [image registration]
- Evaluate laterality of language dominance
  [relative activation]
- Map edges of areas and proximity to lesion
  [thresholding & quantitative reproducibility]
- Measure brain function (or change in function)

How to do quantitative fMRI?

- How best to acquire images?
- How best to analyze images?
- How to assess image quality?
  - What data quality metrics can distinguish good scan from bad?

Goal is to make fMRI a quantitative biomarker of brain function

Collaborative efforts to make fMRI quantitative & reproducible

Organizations:

- BIRN (Biomedical Informatics Research Network)
- ASFNR (American Soc. of Functional Neuroradiology)
- QIBA (Quantitative Imaging Biomarkers Alliance) of the RSNA (Radiol. Soc. of N. America)

Strategies:

- Standardize acquisition and analysis
- Improve quality assessment metrics (QA)
- Assess and reduce sources of signal variance
- Determine reproducibilty claims

Quantitative Imaging Biomarkers Alliance

RSNA

QIBA Profile Claims (tentative)

On a test-retest basis, BOLD fMRI can be performed reproducibly to a level such that:

- the center of mass of activation of a focus of interest can be determined within 5 mm with 95% confidence
- the spatial extent half-maximum border of activation clusters can be determined within ?? mm with 95% confidence
- the relative magnitude of activation in homologous regions across hemispheres can be determined within ?? % with 95% confidence

Biomarker quantitative properties

Precision – How similar are multiple measurements?
Assumes biological specimen is unchanged

Repeatability – Measured exactly the same way
i.e., Same scanner, same task, same procedures, etc

Reproducibility – Measured in similar ways
e.g. Different scanners, different tasks, etc

Bias – How close is measured value to true value?
Assumes there is a true measurable value
(thermometer example)

Obstacles to fMRI reproducibility

- BOLD is an indirect measure of neural activity
  - Many factors intervene between activity and BOLD
- Brain function is complex and variable
  - Task design affects activity pattern
  - Task performance affects BOLD signal
- Traditional analysis methods emphasize statistical significance over signal amplitude
  - Significance is used to define active areas
  - Significance is very sensitive to noise components

Sources of variance affecting fMRI

- Scanner*
- Task design*
- Training procedures*
- Stimulus presentation system*
- Physiology
- Pathology
- Patient movement
- Task performance
- Analysis procedures

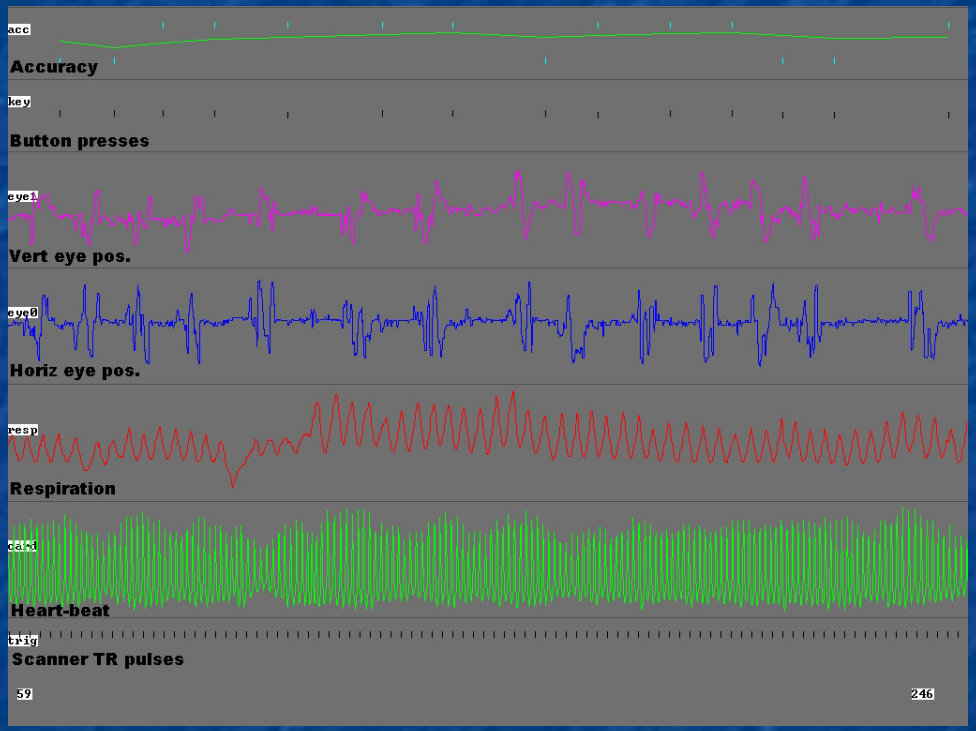
* Controlled by standardization

Patient compliance is a bigger issue for fMRI than other scan procedures

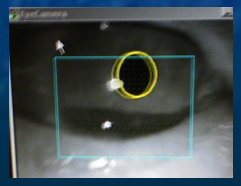
- Training
  - Patients must actively participate in fMRI
  - Tasks must be appropriate and understood
  - Task fMRI is done on patients 5yo to >80yo
- Task performance
  - Anxiety affects fMRI results
    - Getting patients relaxed is important
  - Head motion is most common problem
  - Important to assess performance in real-time

Real-time monitoring is critical for successful clinical fMRI

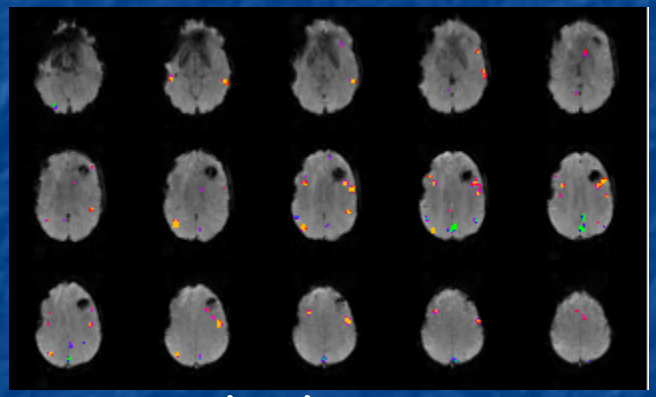
Dual screen real-time behavioral display



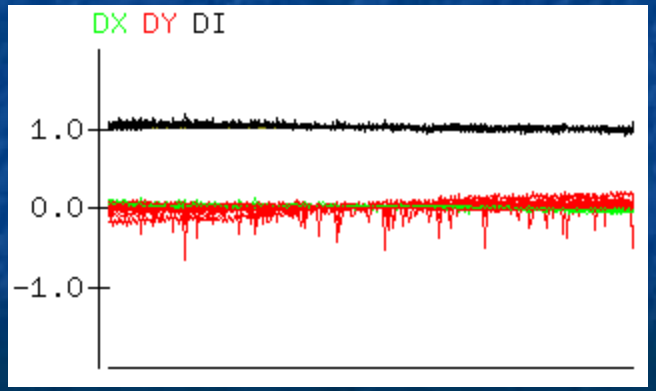
Direct observation of eye and hand movements



Real-time MRI analysis



Activation maps

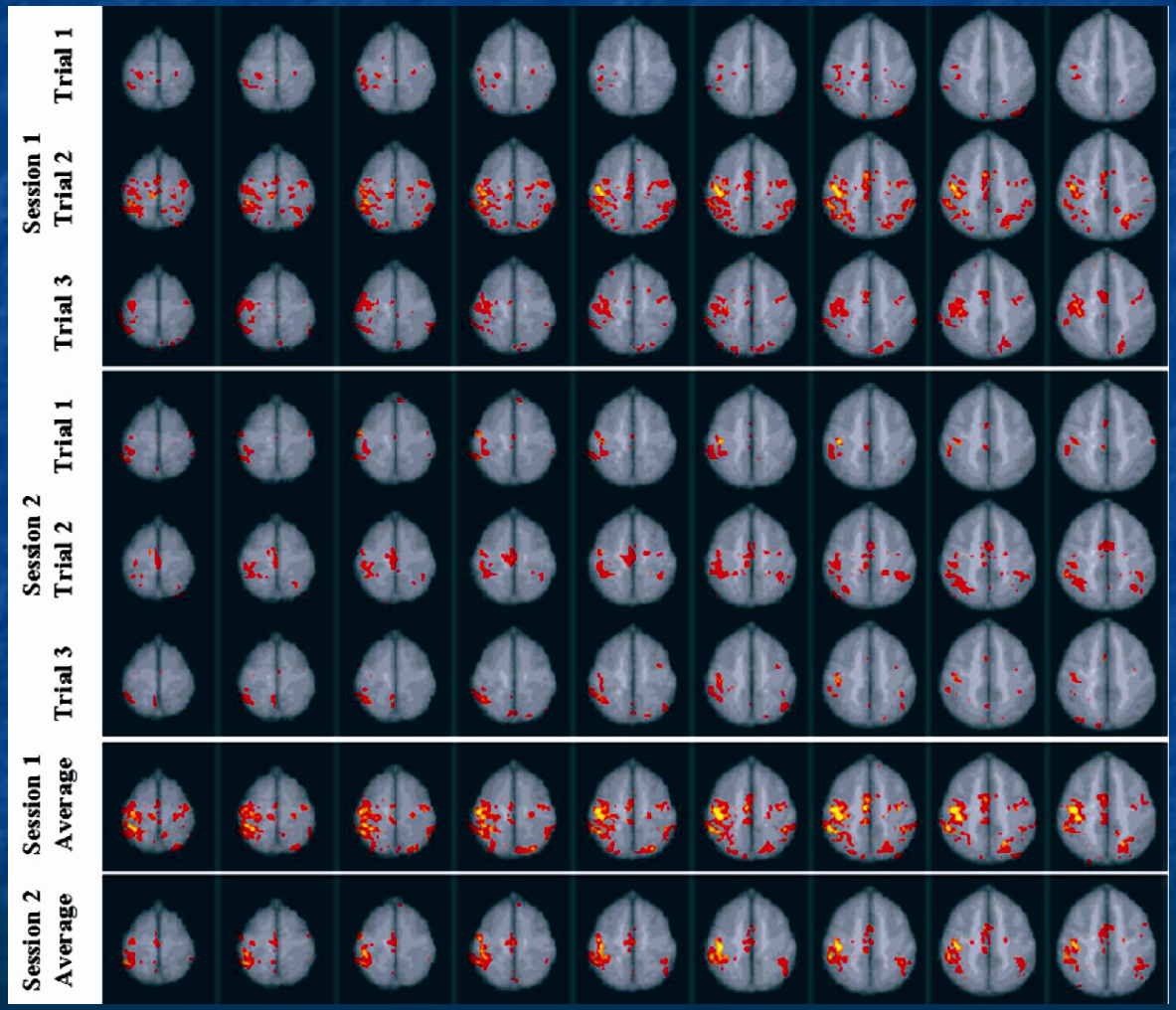


Head motion & mean intensity

Voyvodic et al., Frontiers Neuroinfo. (2011)

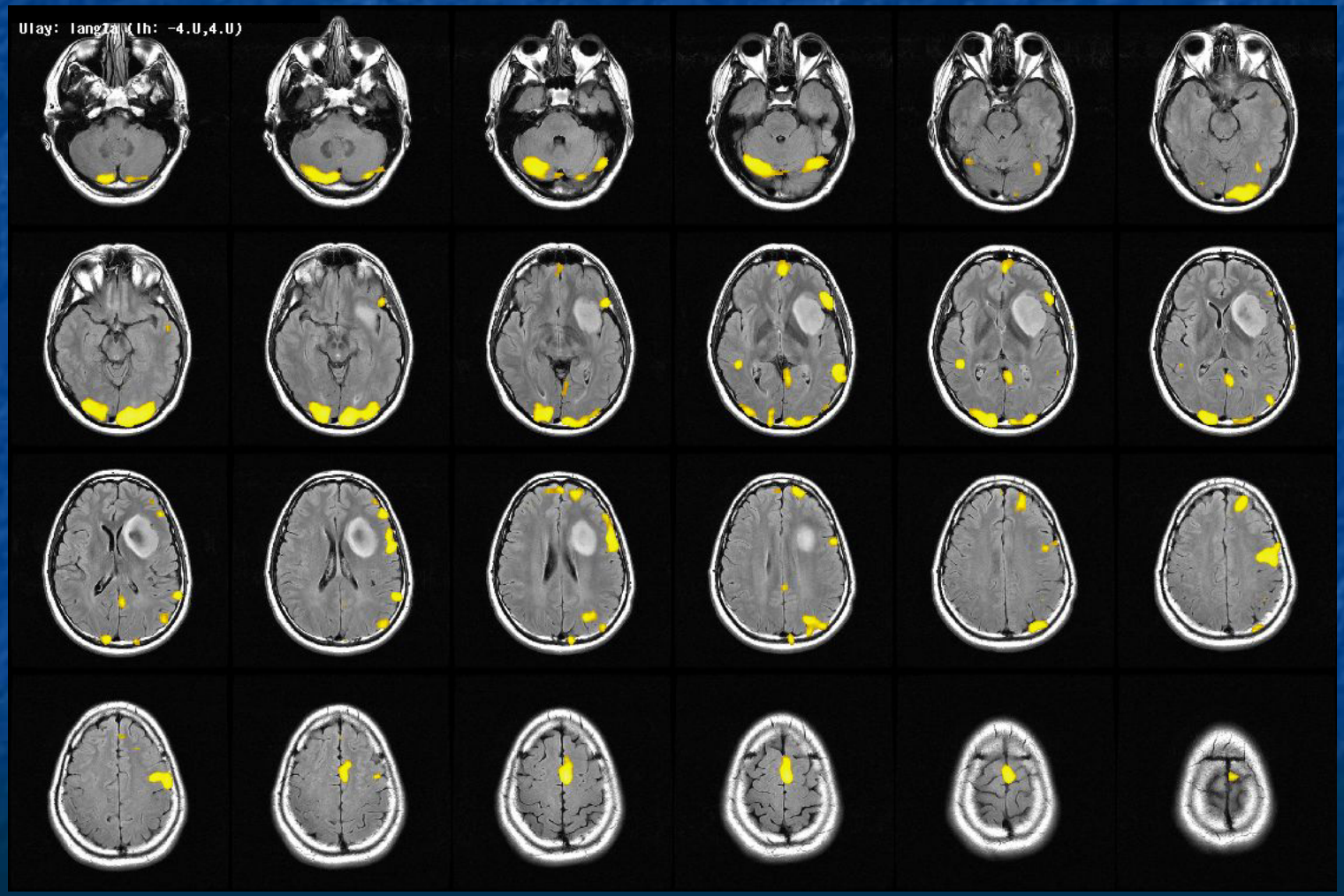
Voyvodic, NeuroImage (1999)

Traditionally, fMRI is quantitatively not reproducible

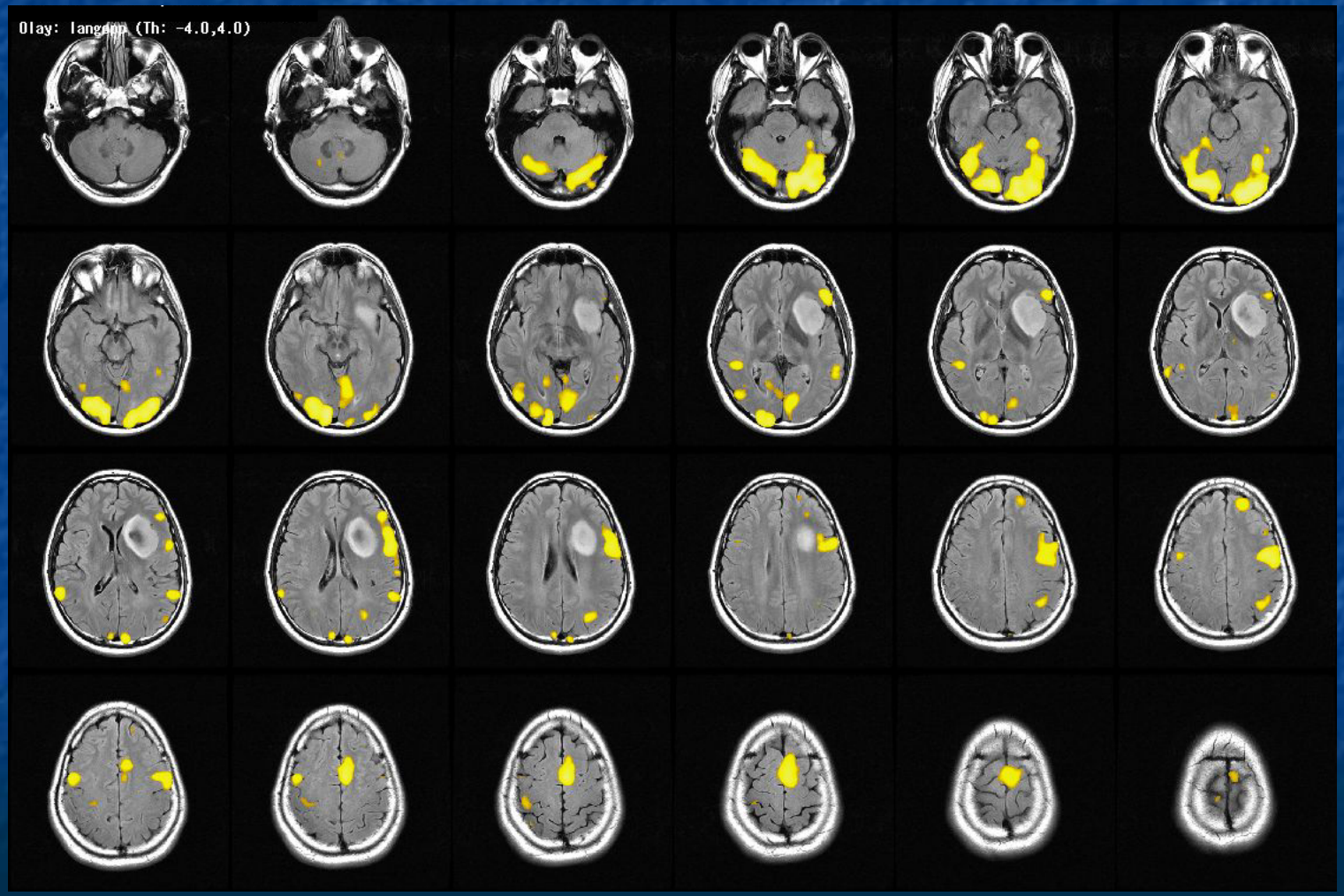


Liu et al., “Reproducibility of fMRI at 1.5T in a Strictly Controlled Motor Task”, MRM 2004

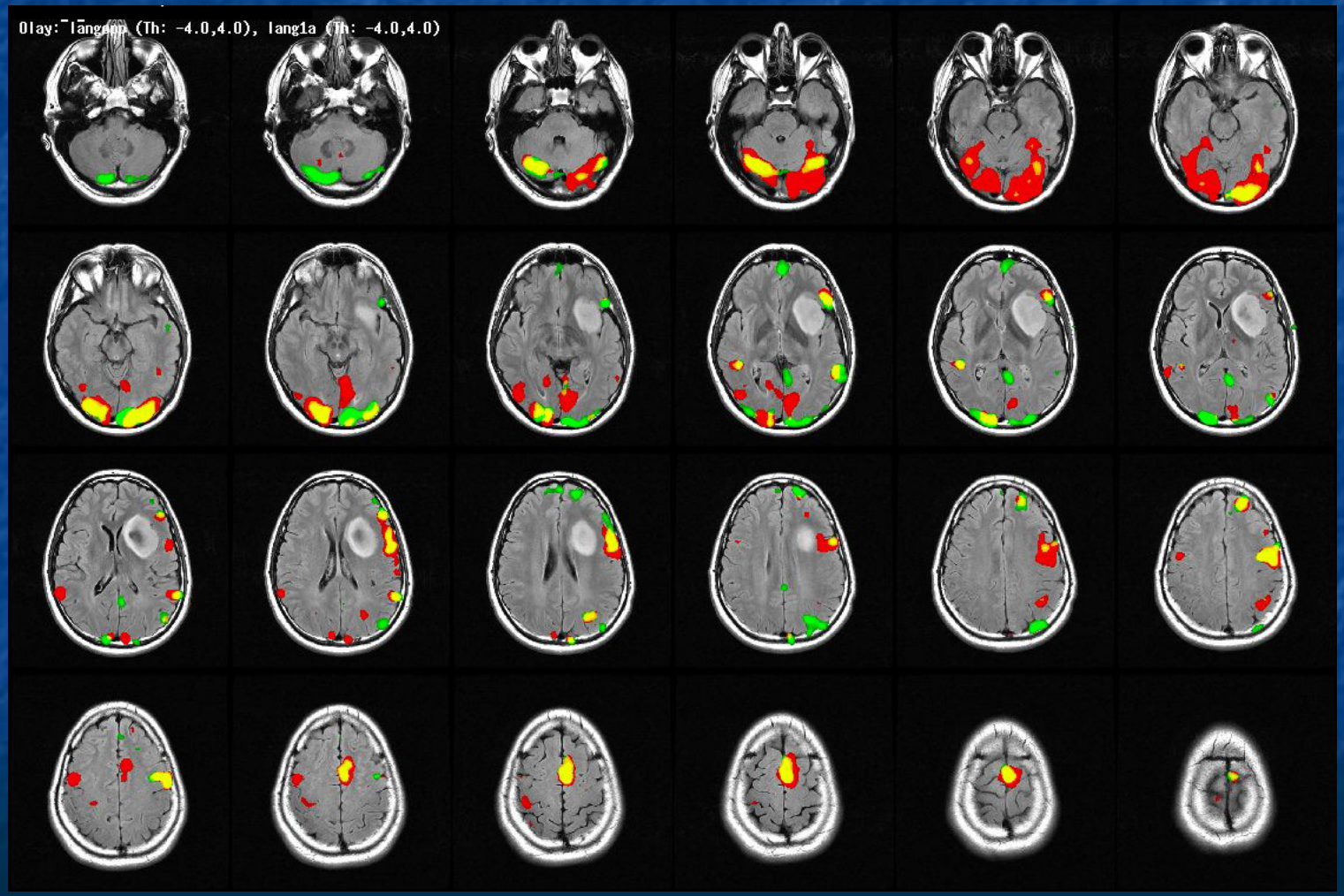
Language – first scan



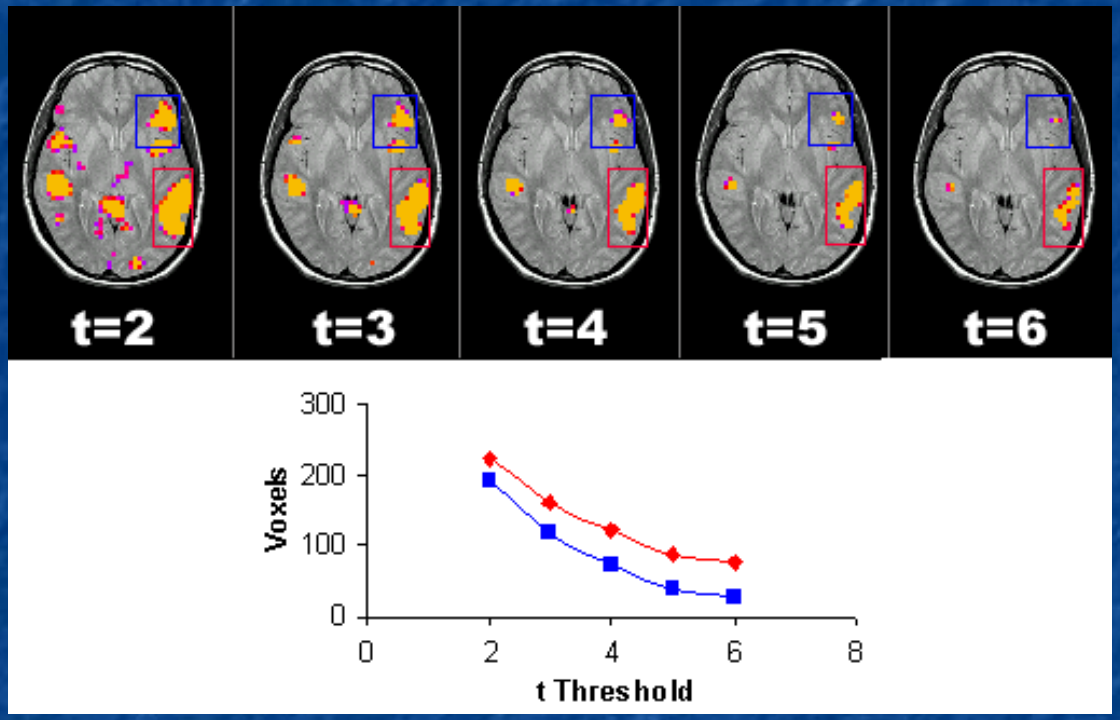
Language -- rescan



Overlap of 2 Language t-maps



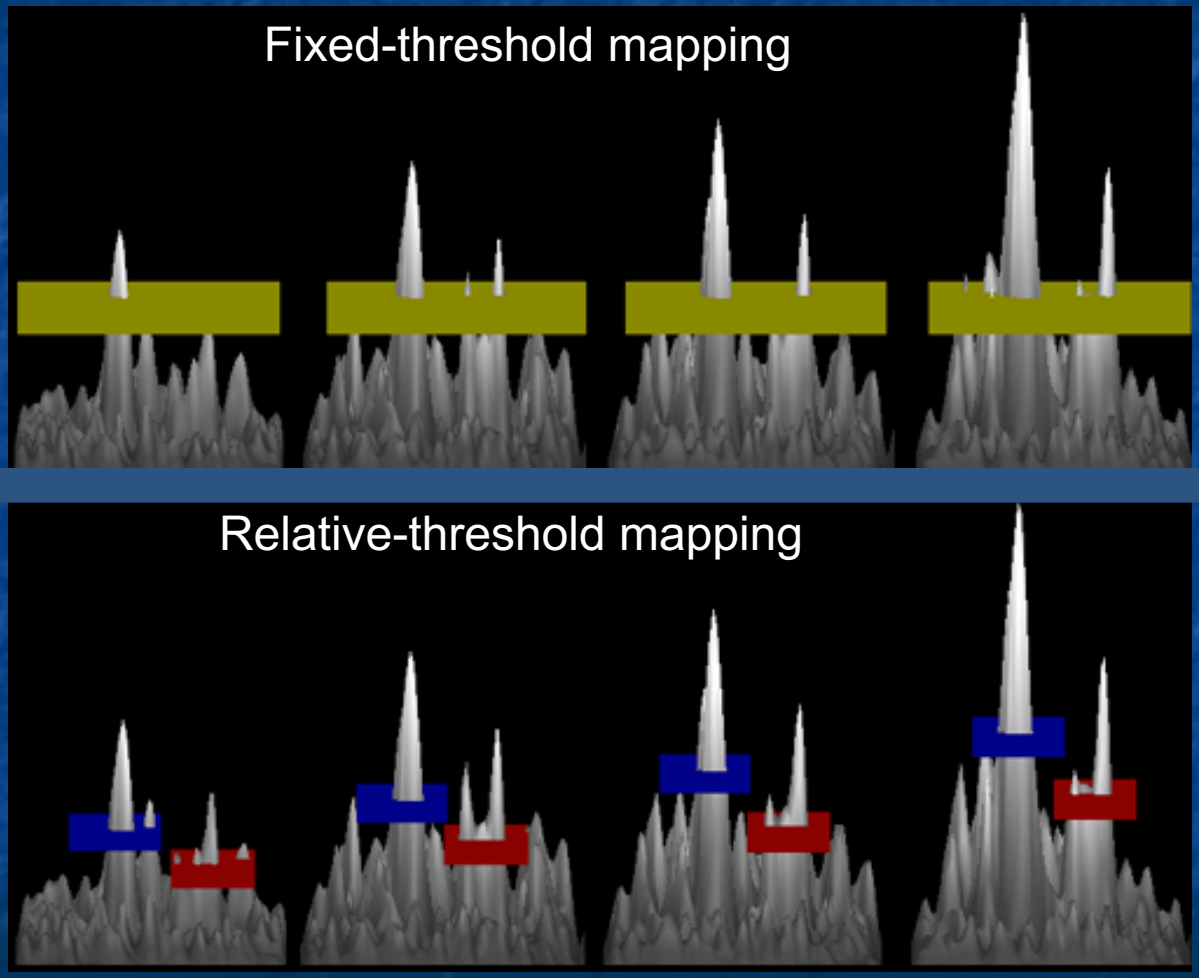
Statistical thresholding is a major source of variability



Even a constant pattern of brain activity can result in very different activation maps, depending on statistical threshold

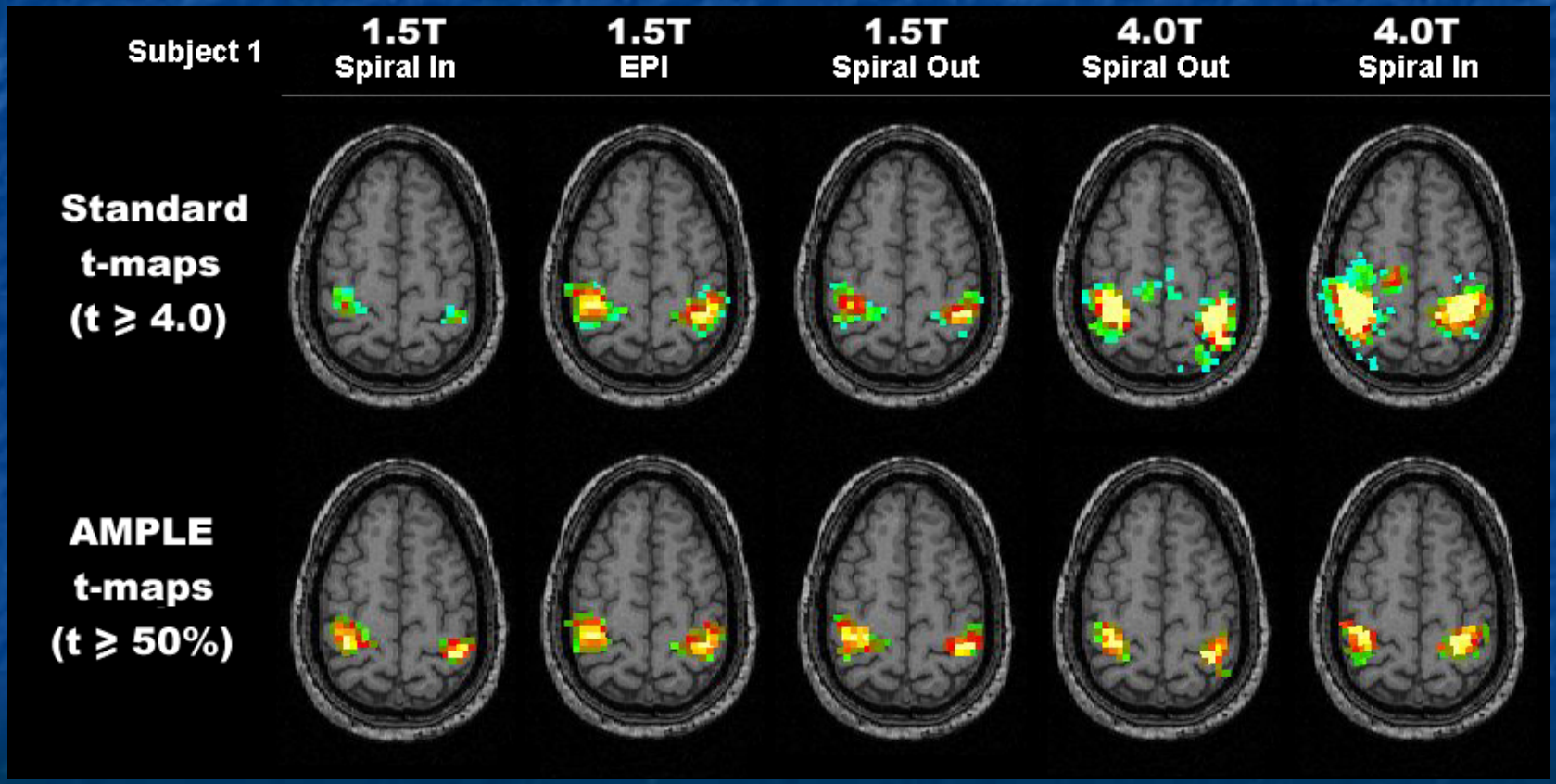
Voyvodic, MRI, 2006

Statistical significance of activation changes as a function of scan time



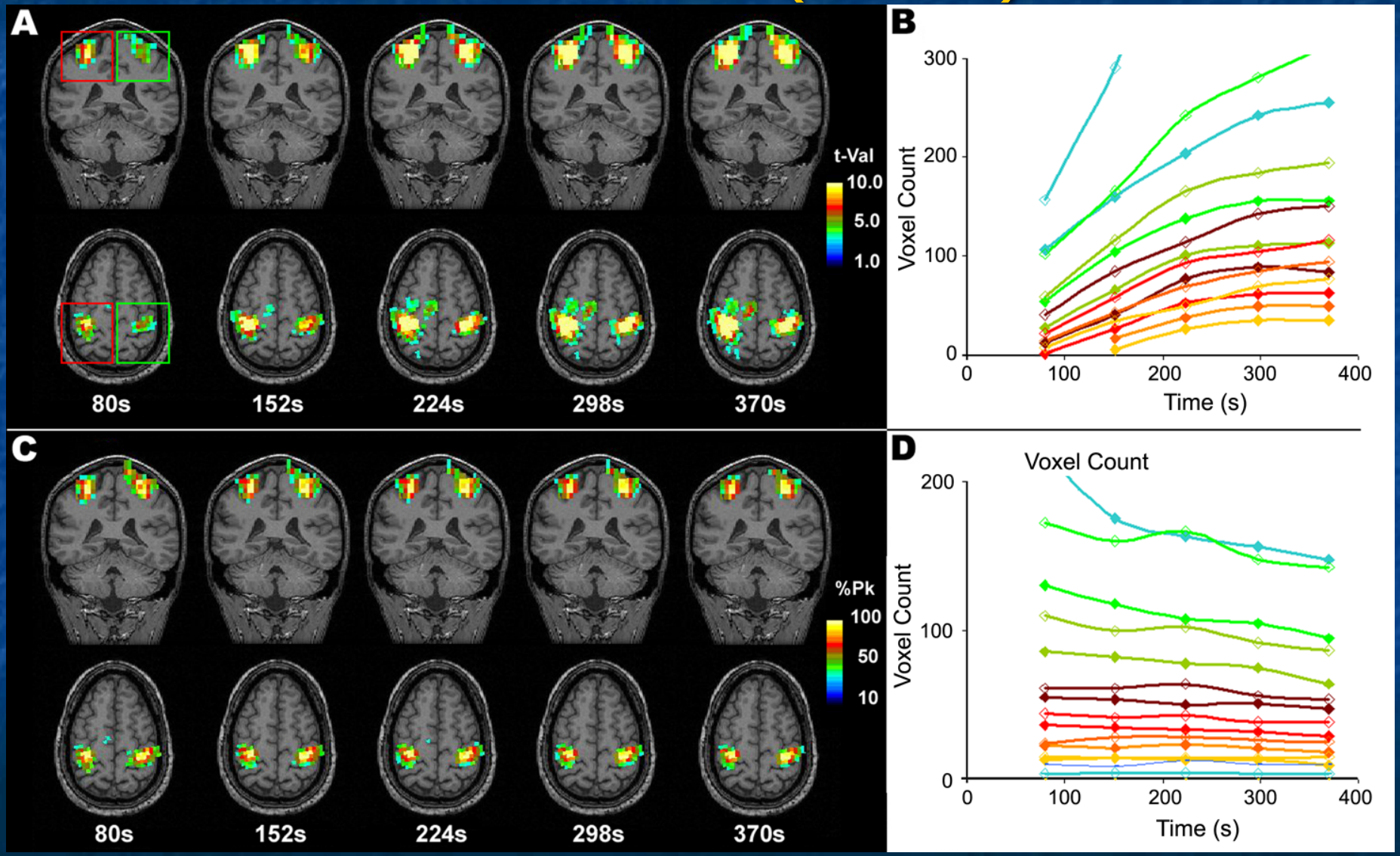
Activation mapping as percentage of local excitation (AMPLE)

AMPLE maps are consistent across scans or scanners



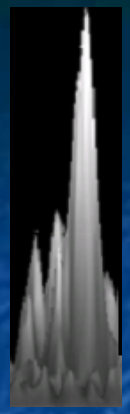
Voyvodic, MRI, 2006

Activation mapping as percentage of local excitation (AMPLE)

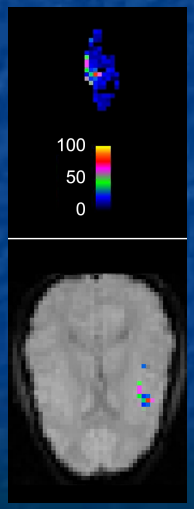


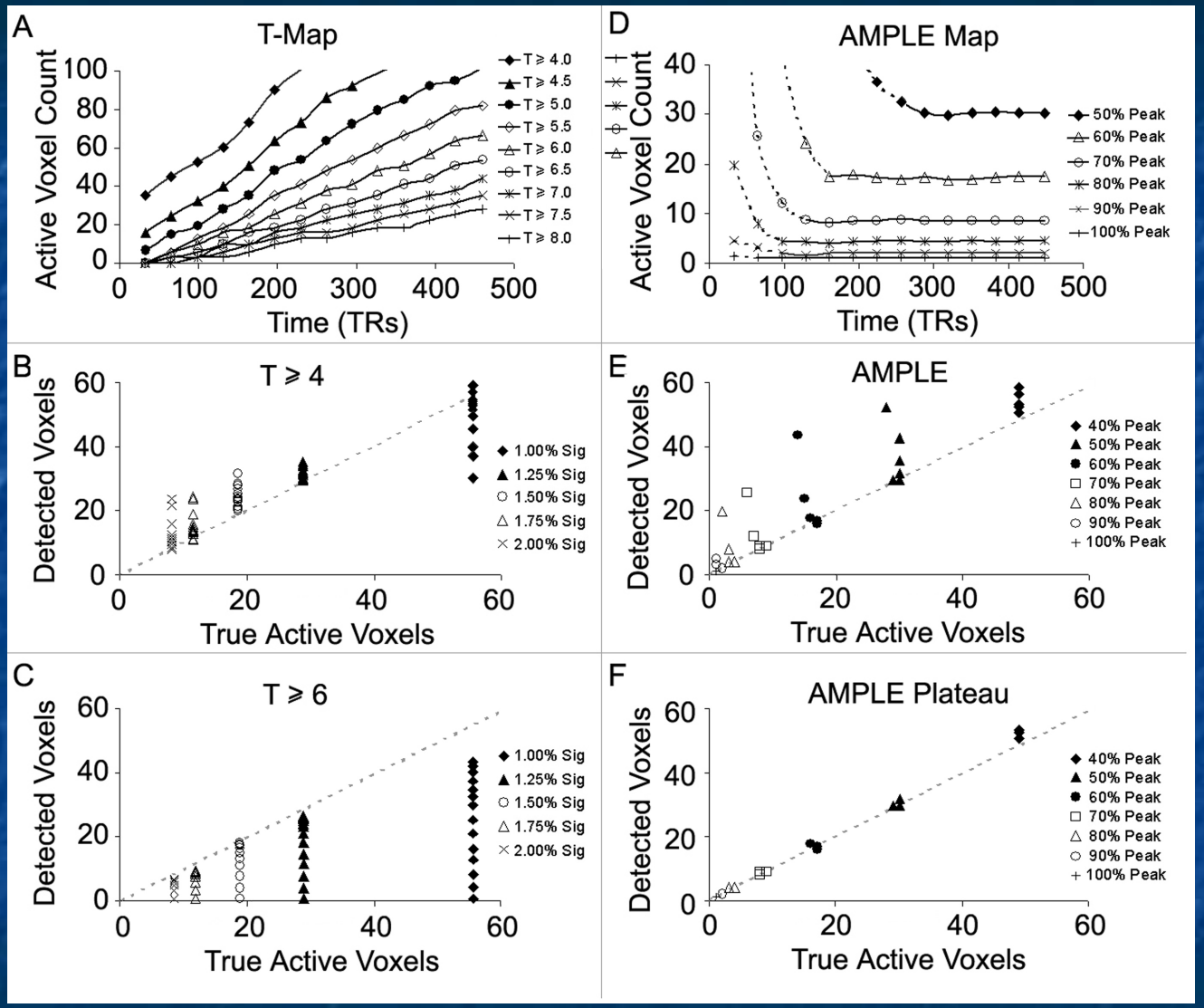
Voyvodic, MRI, 2006

Threshold Reproducibility DROs



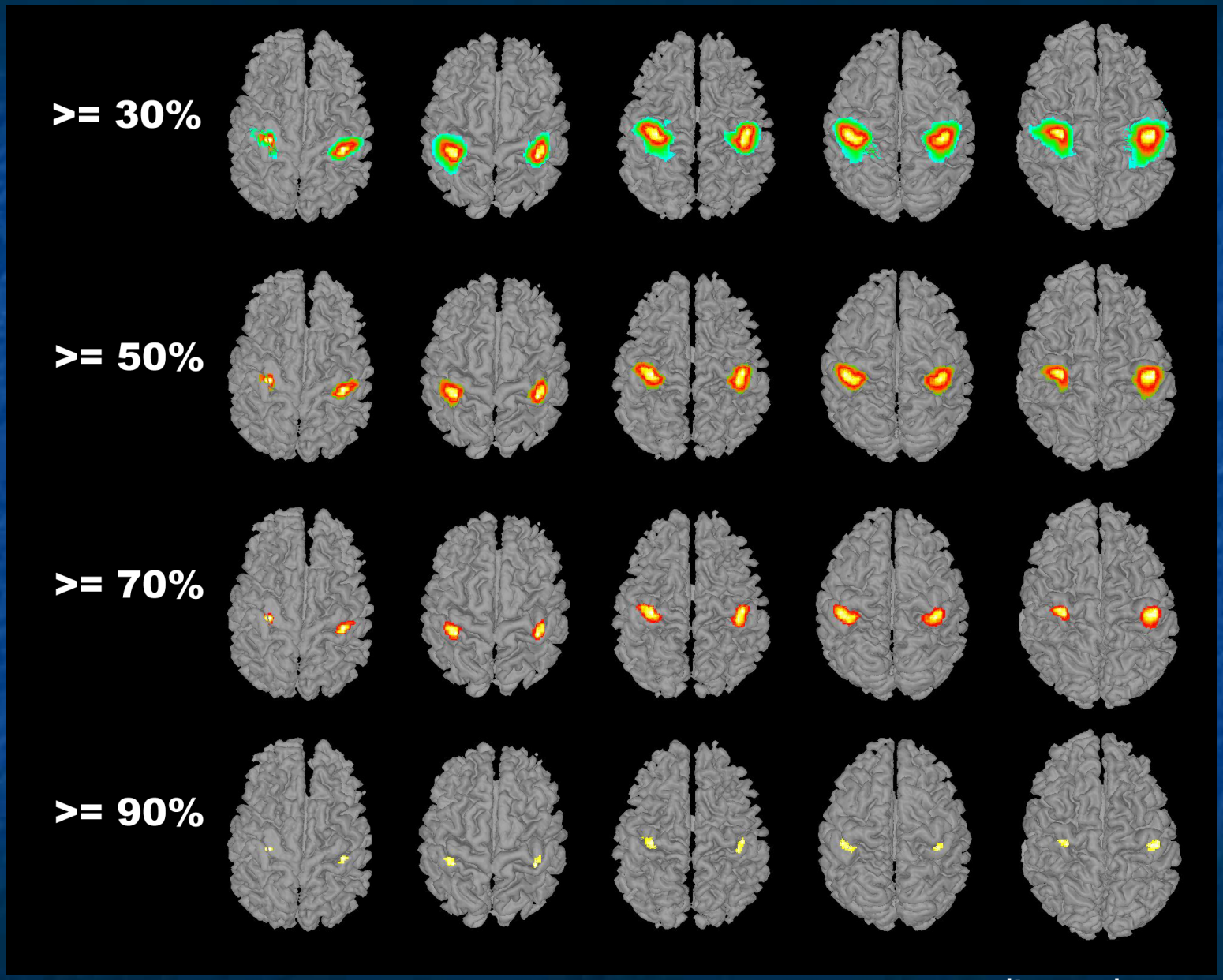
Generate simulated fMRI data with known activity levels



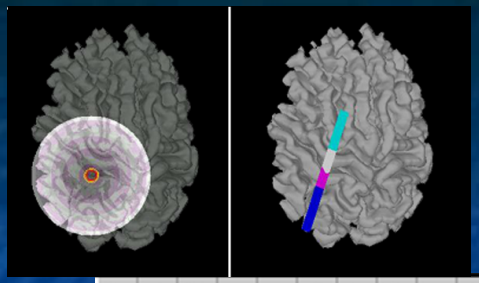


Conclusion: Once AMPLE time plots stabilize activation is reliable.

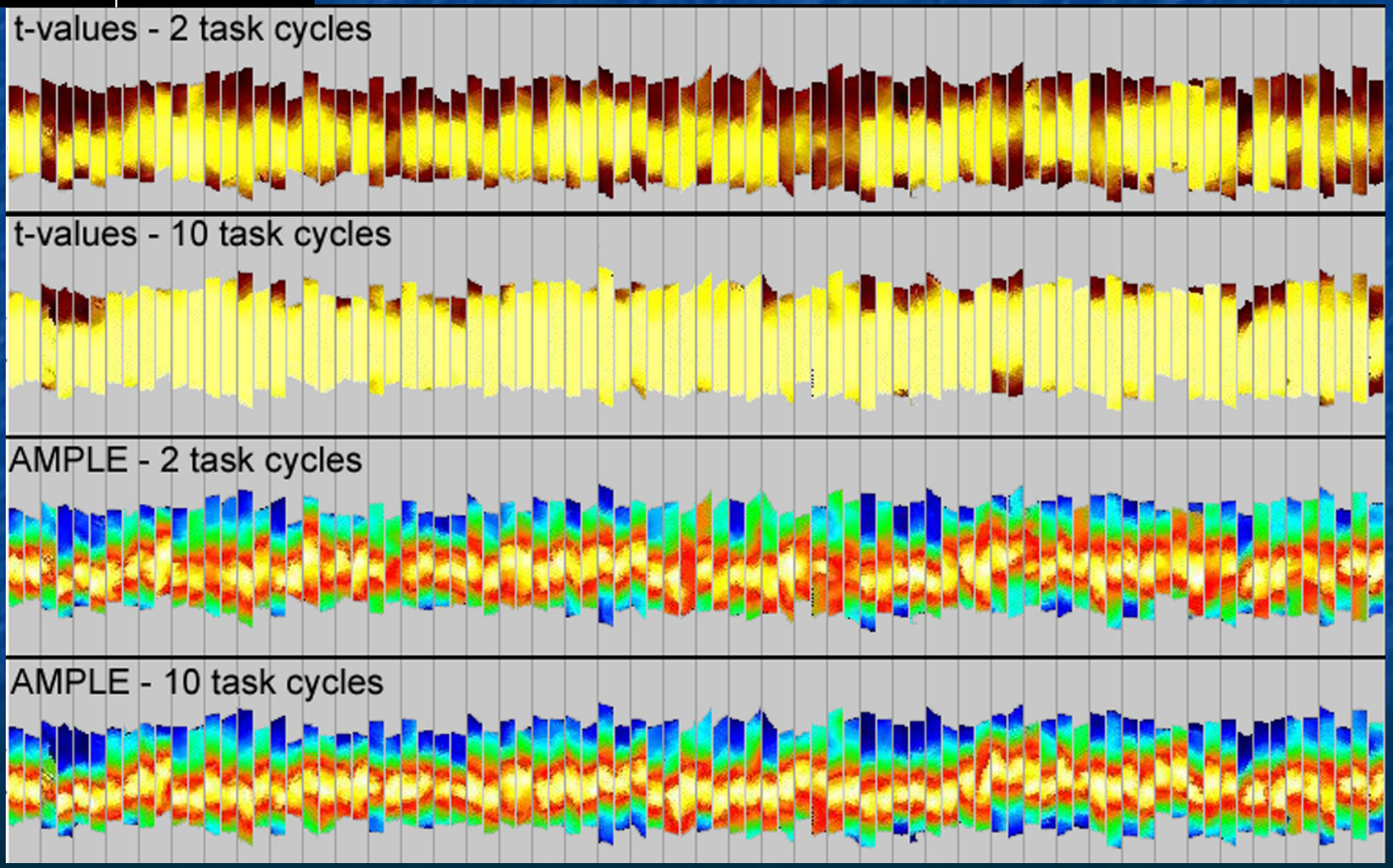
Anatomical spread of active voxels



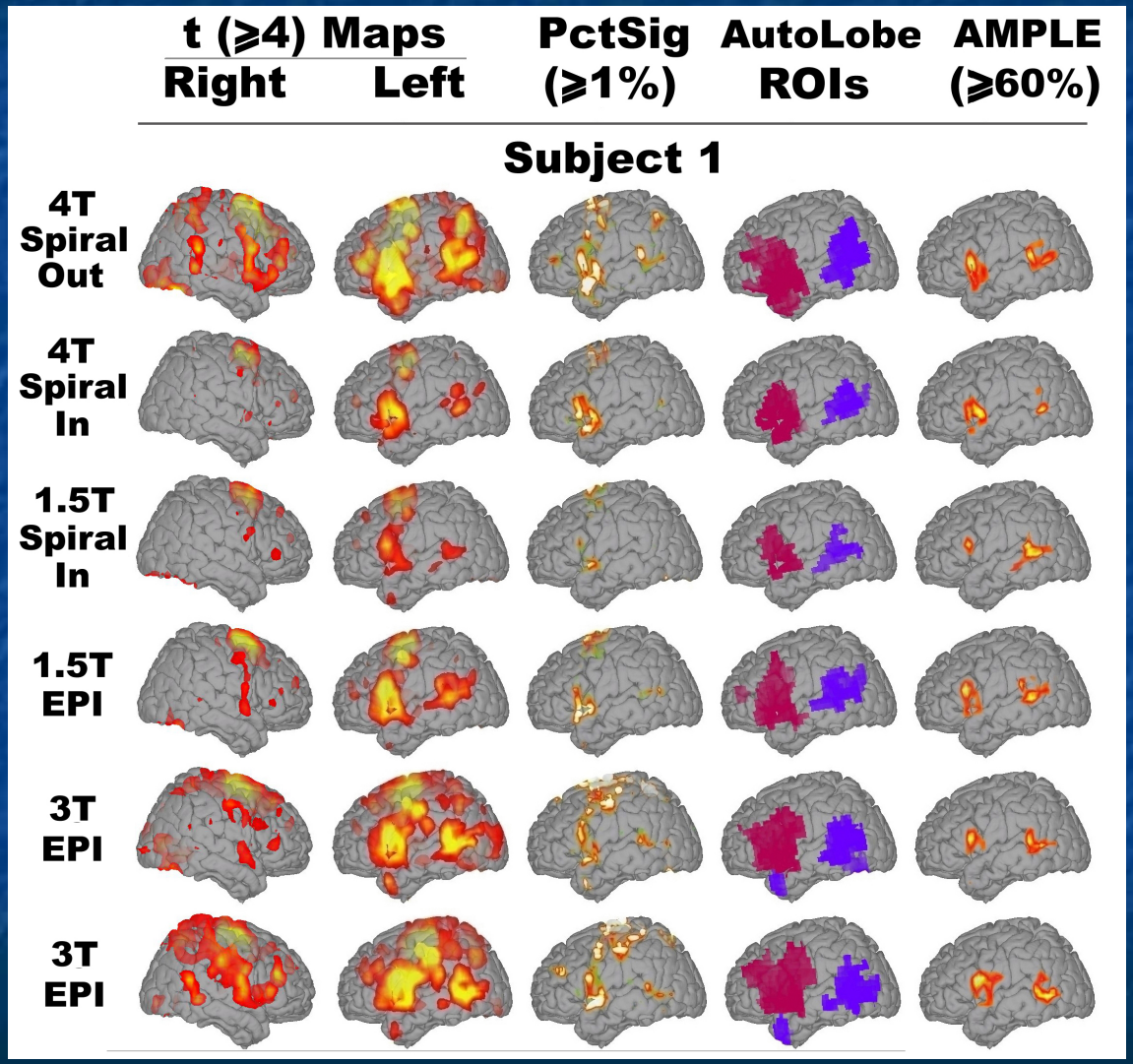
Voyvodic et al, JMRI, 2009



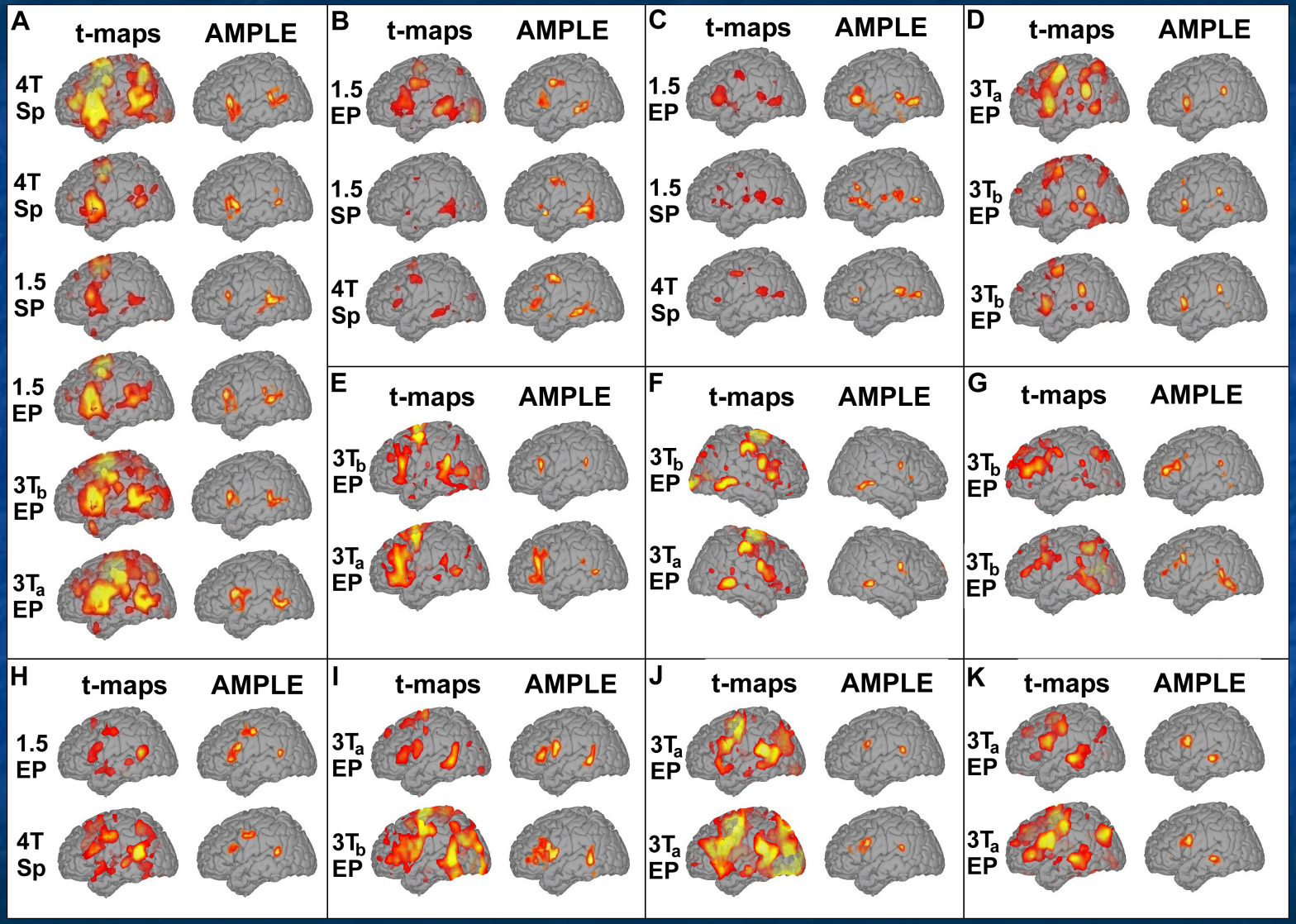
Central sulcus profiles



AMPLE maps improve language reproducibility



Language AMPLE maps improve reproducibility

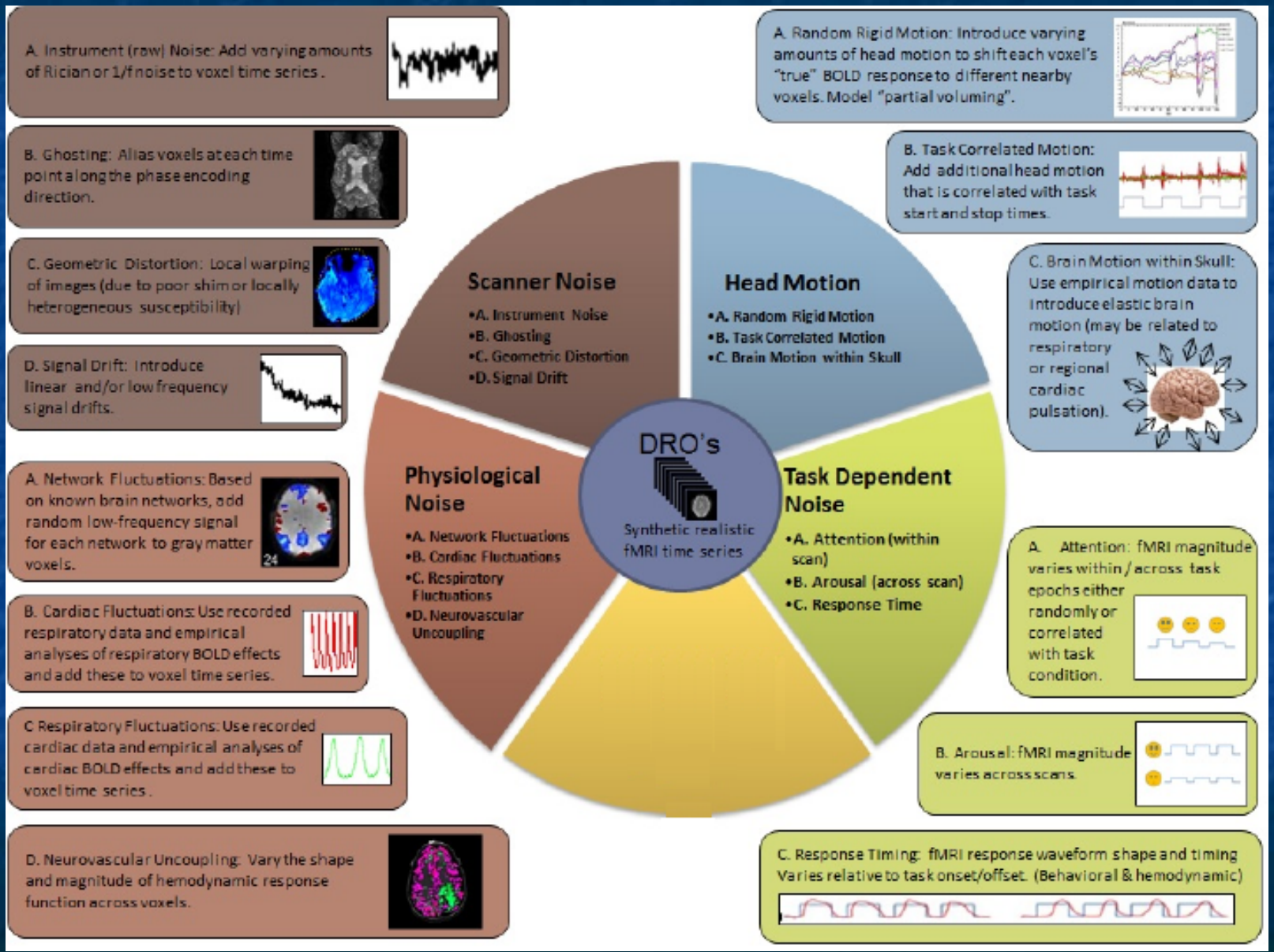


Upper 40% of AMPLE peaks are most reproducible

Assessing fMRI results: QA metrics

- Identifying useful metrics
  - Stability of activation signal
  - Head motion
    - Average or Maximum displacement and rotation
    - Fraction of images with motion greater than X
  - Task performance
  - Image SNR
  - BOLD signal contrast (between vs within blocks)
  - Pathology – neurovascular uncoupling
- Determining threshold values
  - E.g. How much motion is too much?

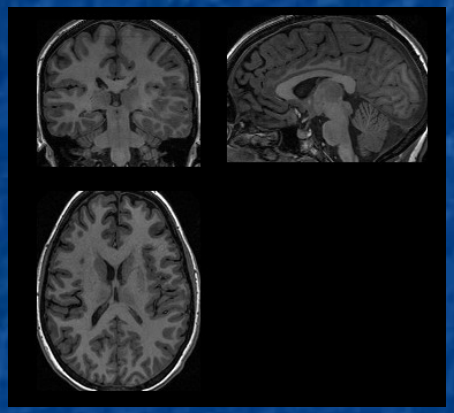
Determine sources of signal variance



Digital reference objects (DROs)

Synthetic realistic imaging data

Brain anatomy



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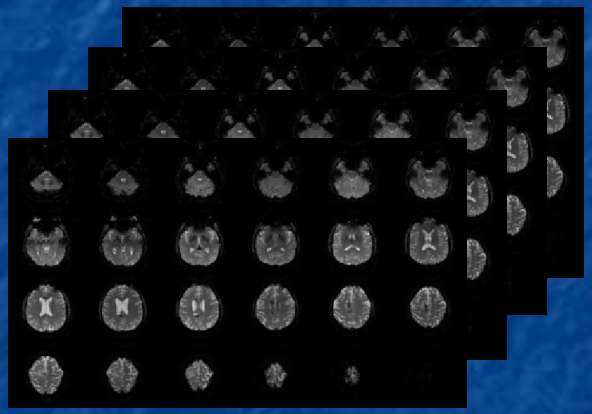
Static EPI images



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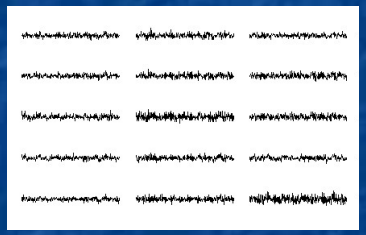
Physiological noise



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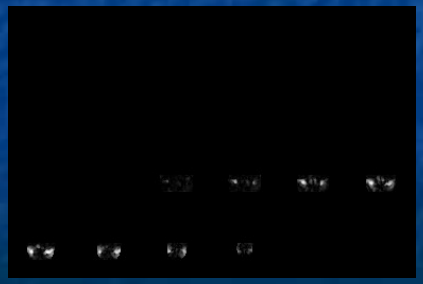
Map of active areas



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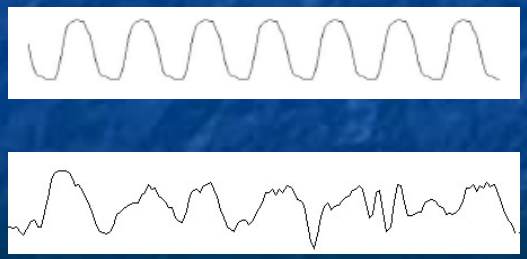
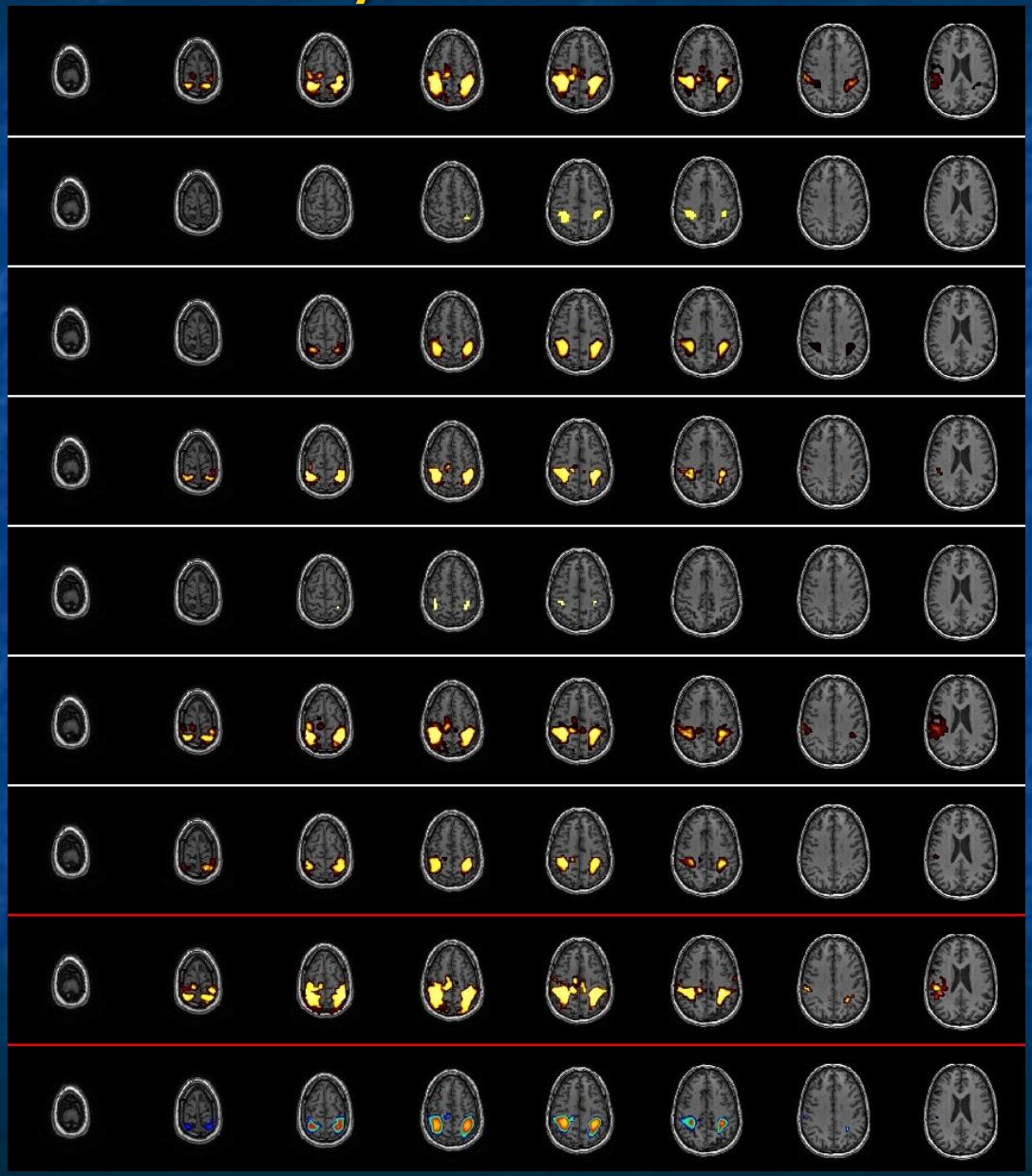
Task-dependent signals



Analysis

fMRI maps

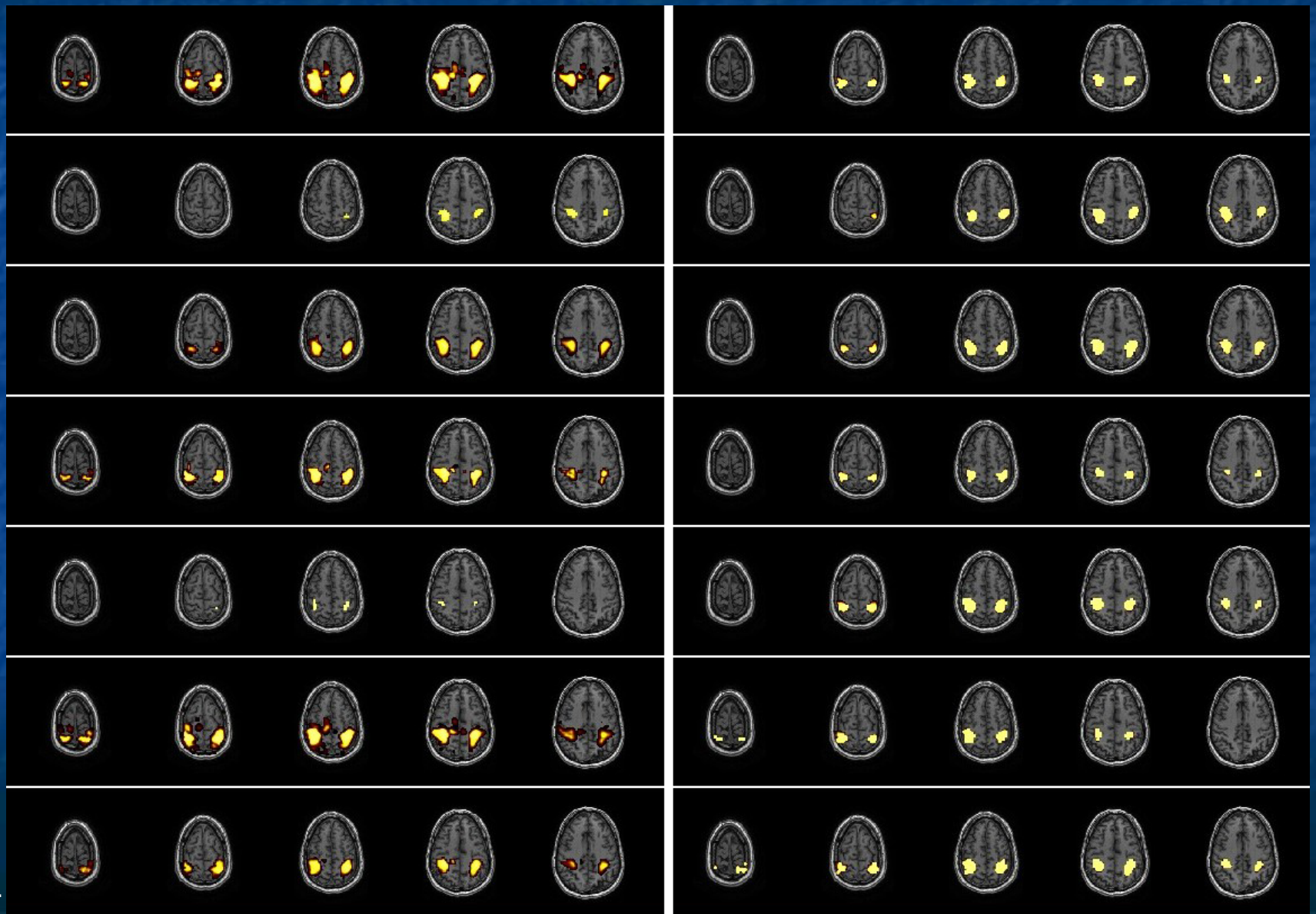
Same data analyzed at 8 clinical fMRI sites



Hand-movement task

"Standard" threshold

AMPLE 50% threshold



DRO1

Sentence language task

"Standard" threshold

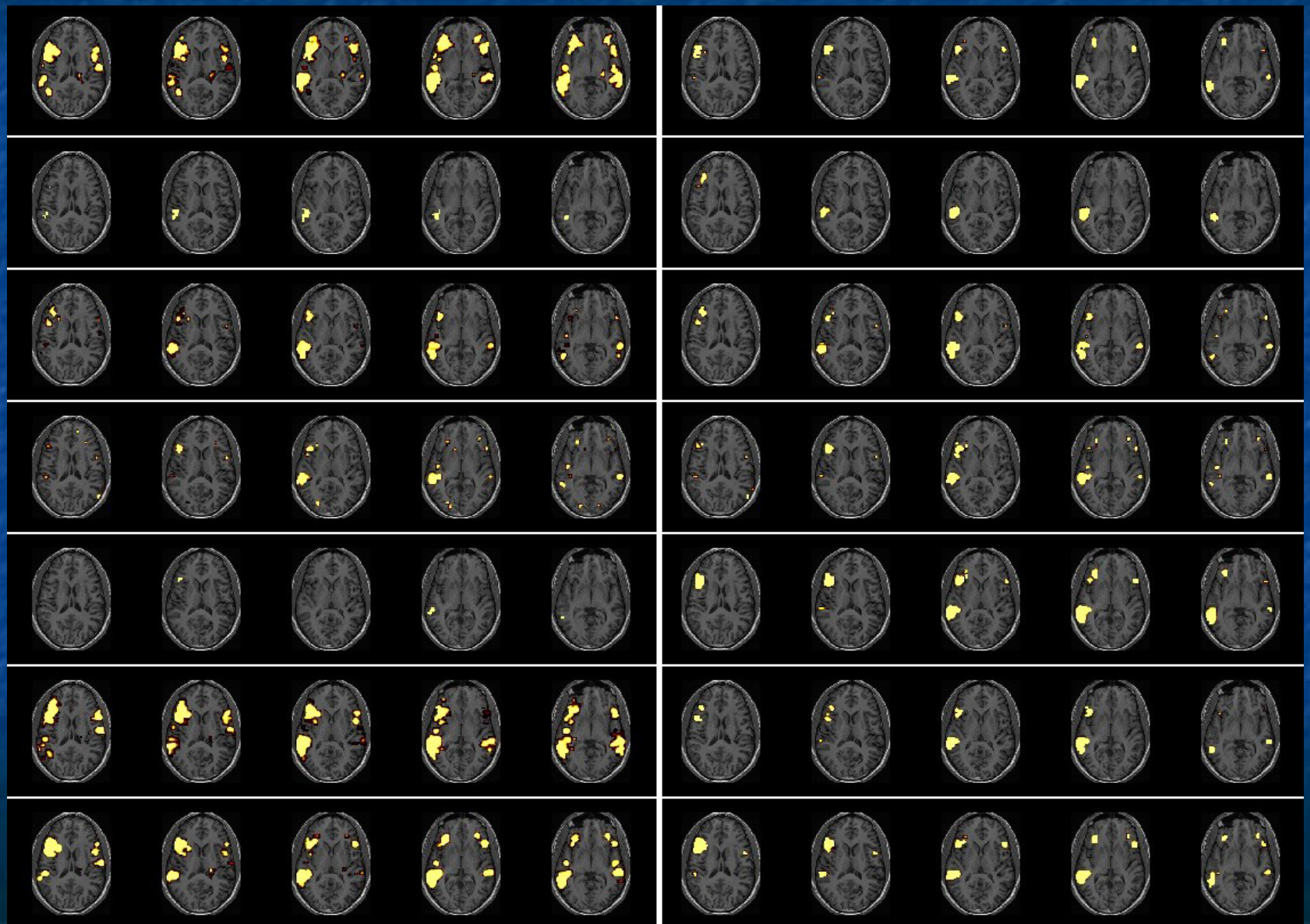
AMPLE 50% threshold

DRO1

Sentence language task

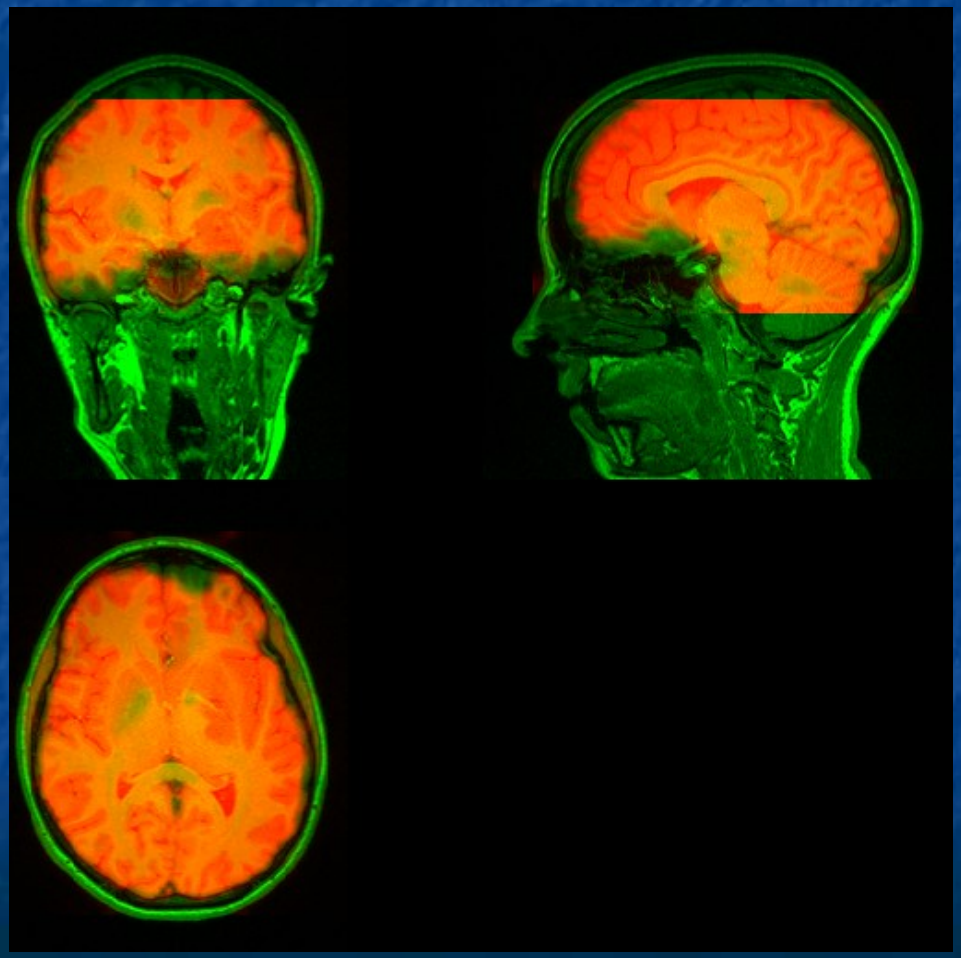
"Standard" threshold

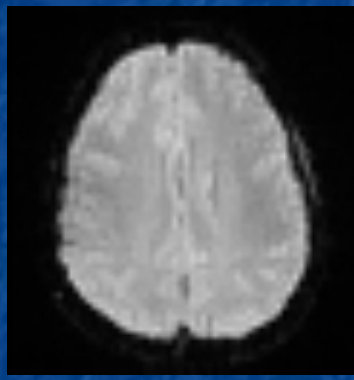
AMPLE 50% threshold

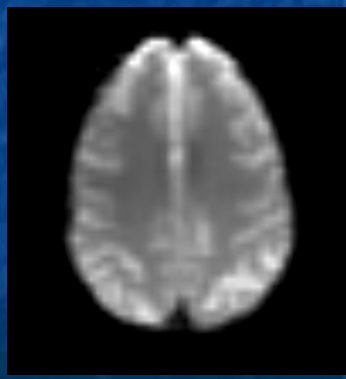


DRO3

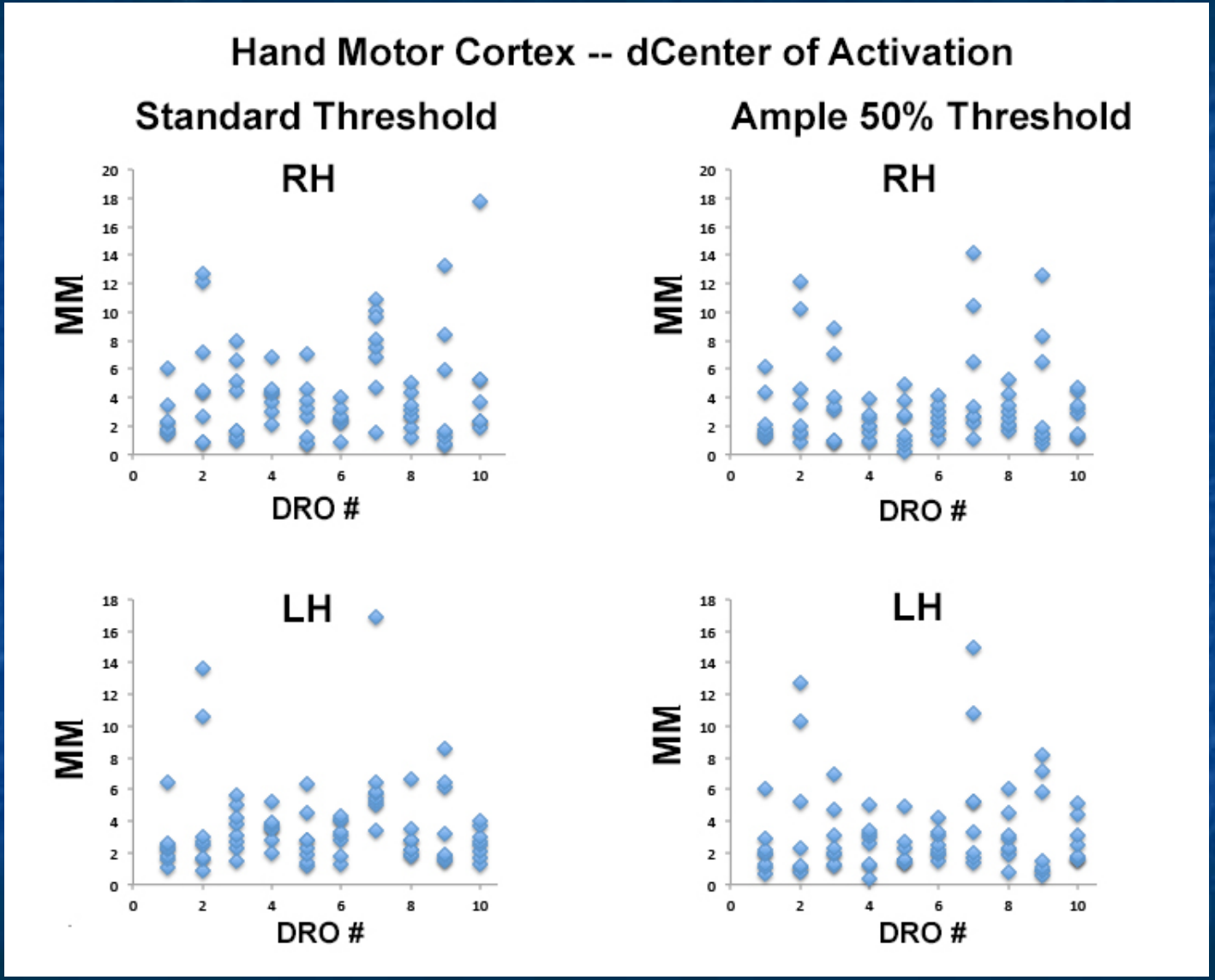
Registering functional and anatomical images





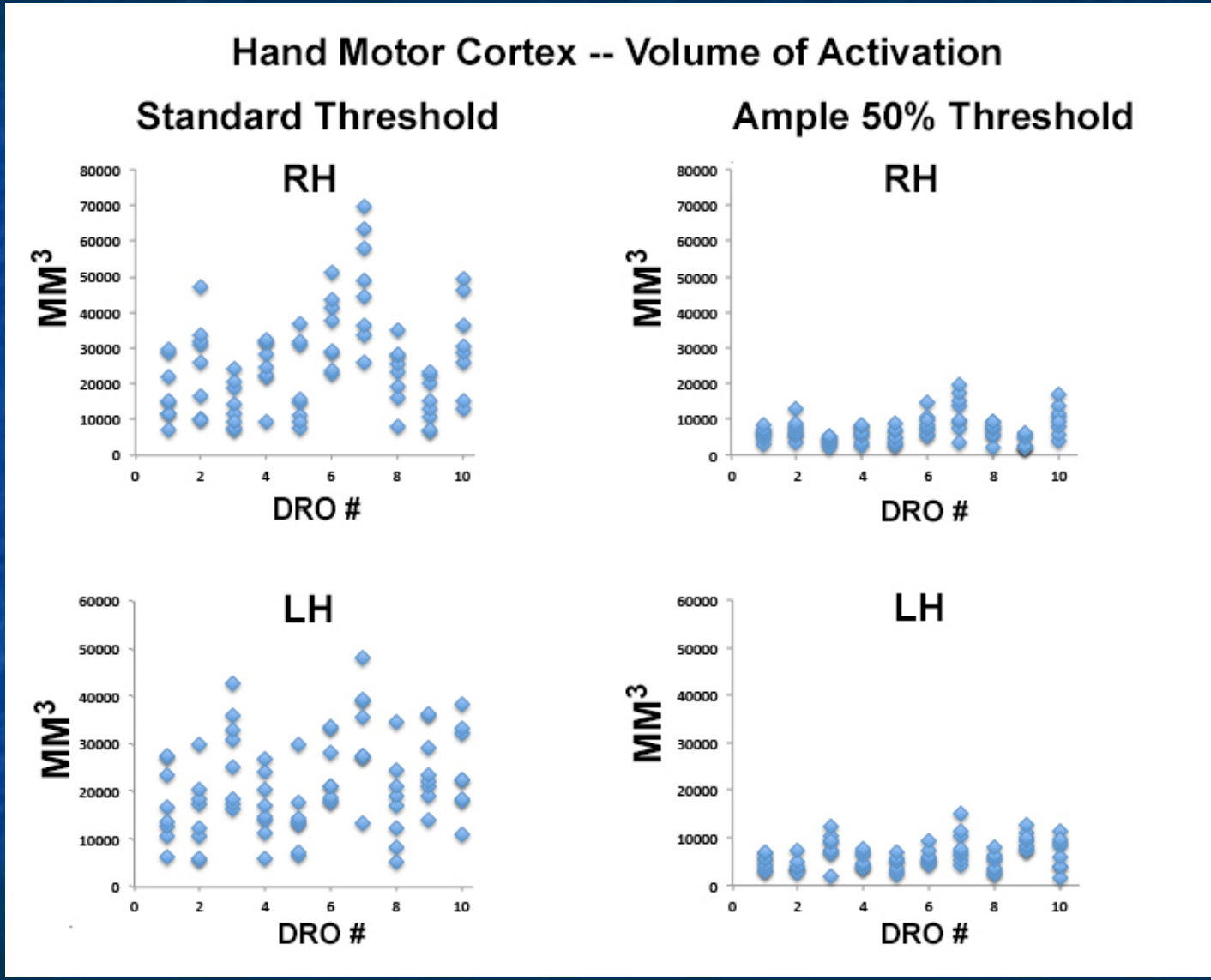


Quantifing center of mass of activation (CMA)



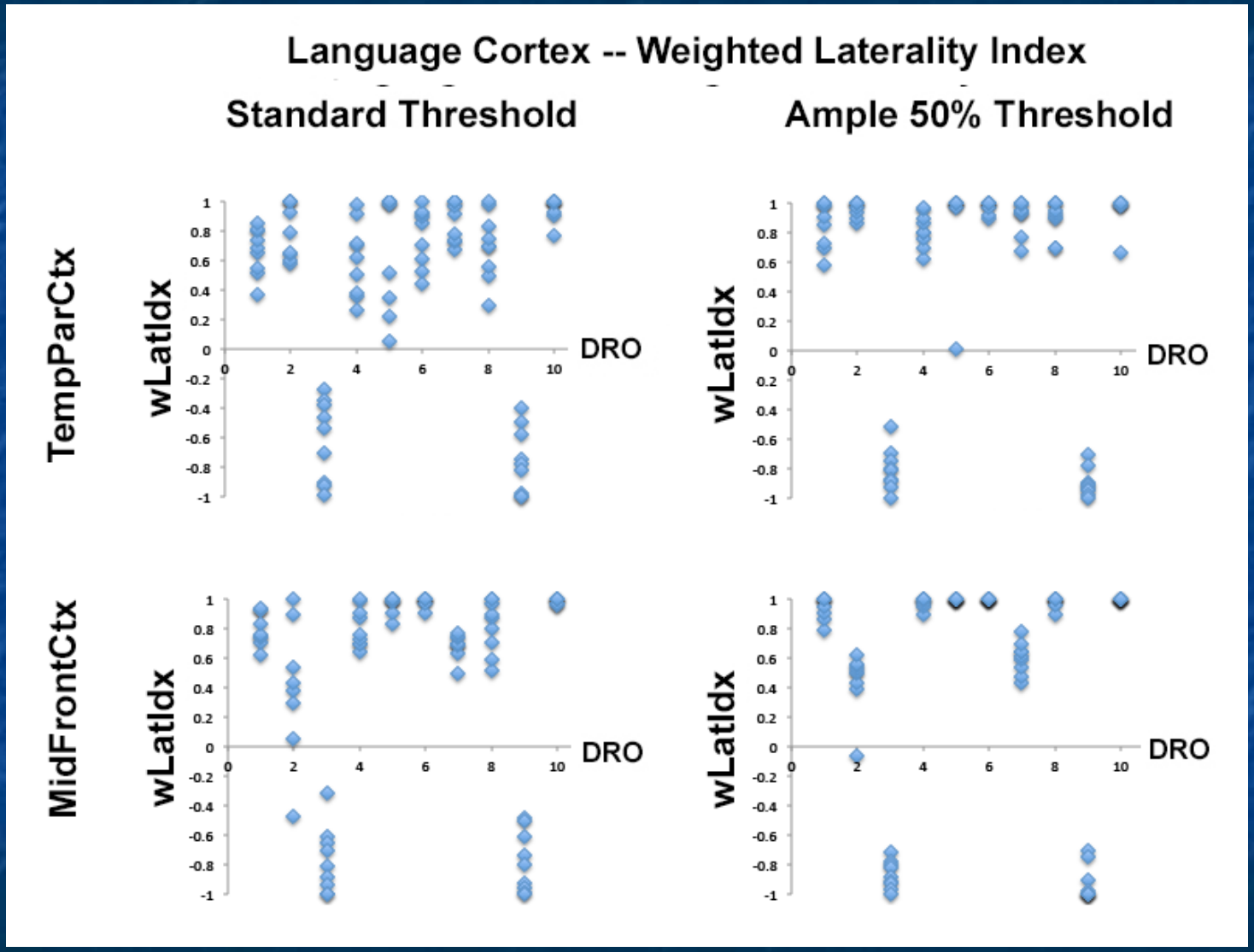
Single activation cluster CMA displacement for 8 sites for each DRO

Quantifing spatial extent of activation



Single activation cluster volumes for 8 sites for each DRO

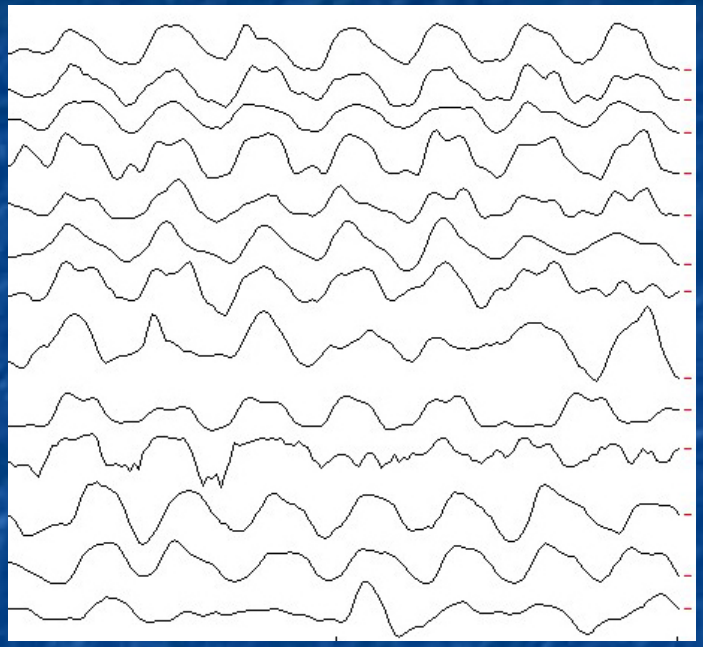
Quantifing language hemispheric dominance



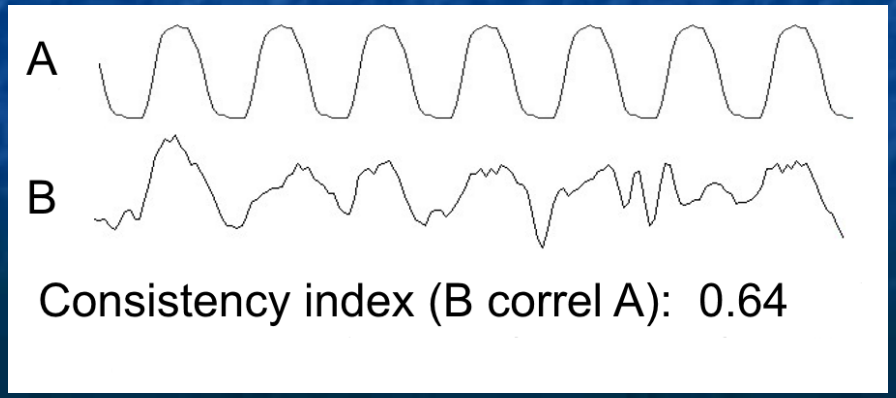
Receptive and expressive laterality for 9 site maps for each DRO

Task performance DROs: Signal consistency

Activation-weighted average time course signal for different patients

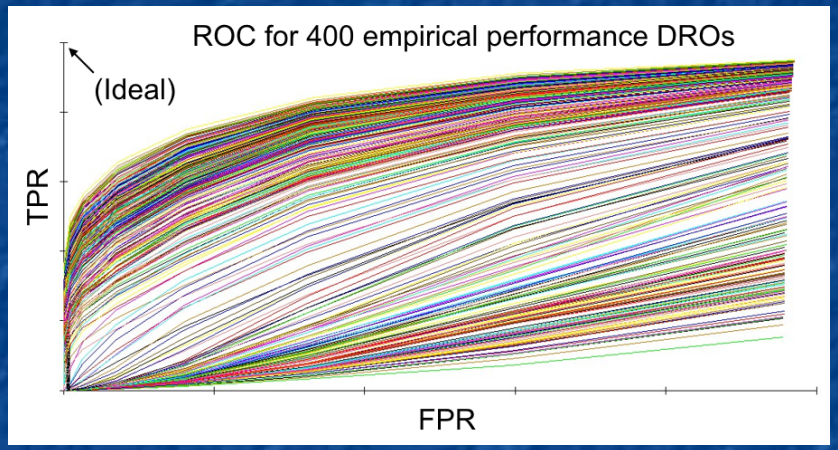


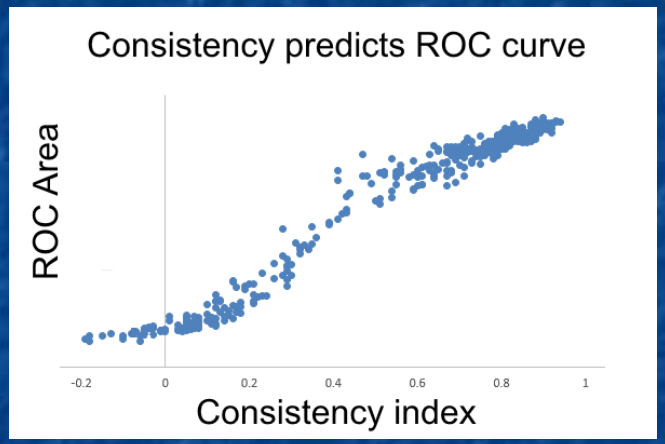
Consistency index:



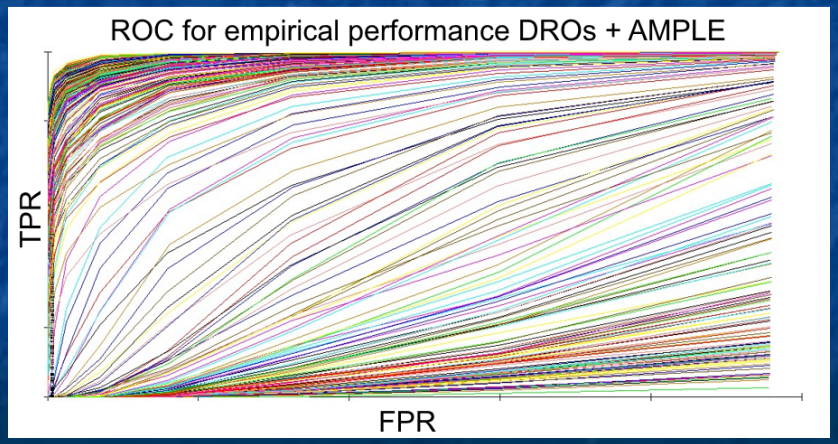
Simulations using average time course signals from 400 different patients

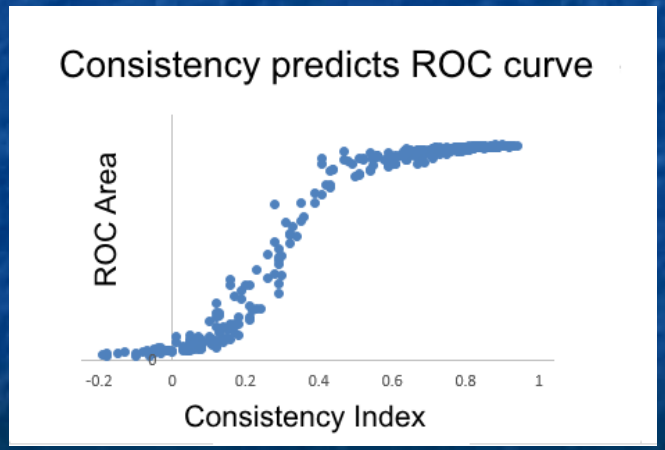
Standard t-maps





AMPLE t-maps





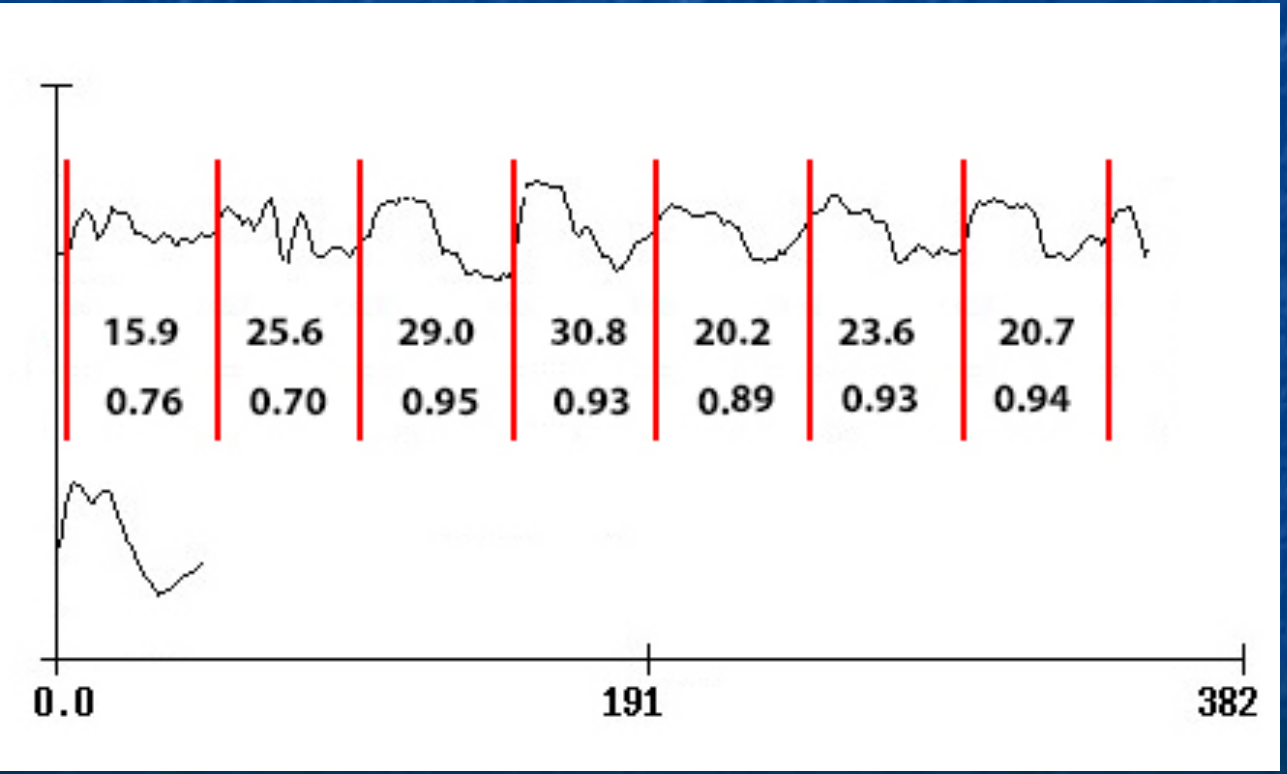
Conclusion: Consistency index > 0.5 is good task perfomance

Consistency of performance across multiple task cycles

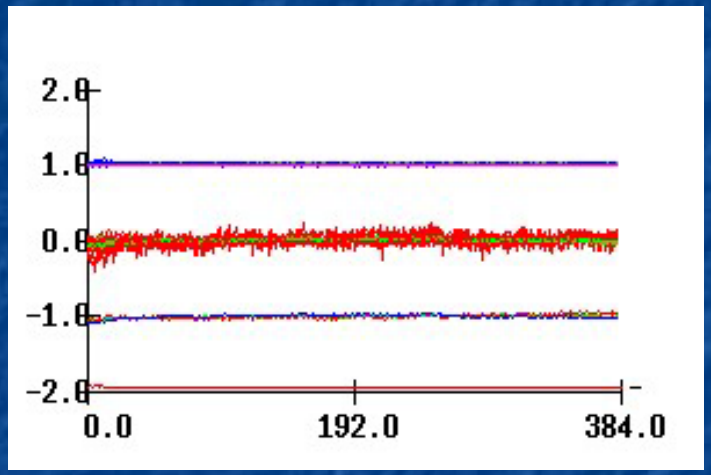
Mean active signal

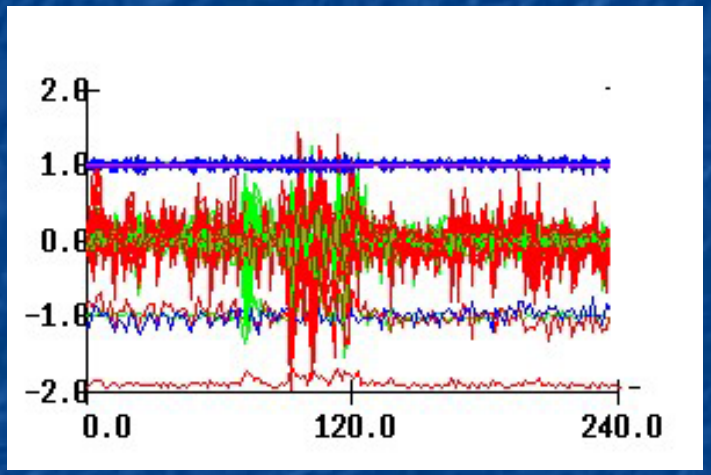
Cycle amplitude
Cycle correlation

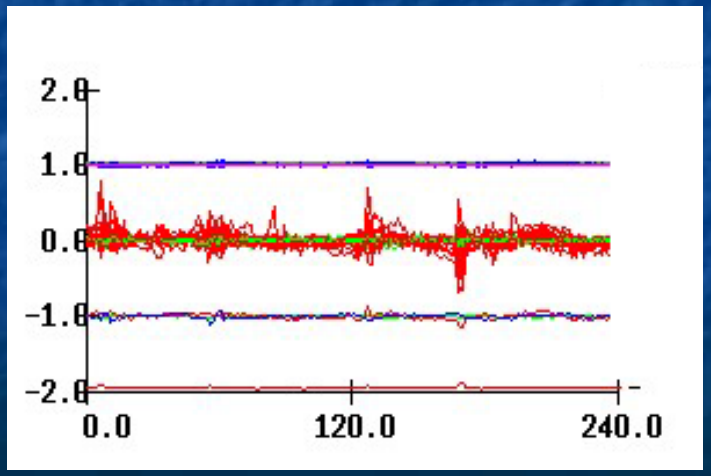
Mean single cycle



Head motion is a pervasive problem in fMRI







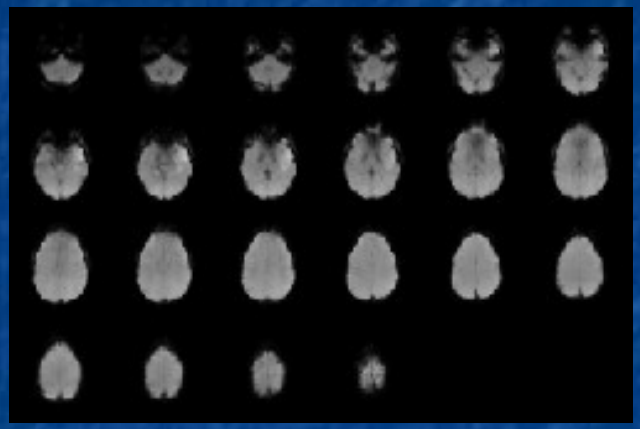
Examples of different Patterns of head motion.

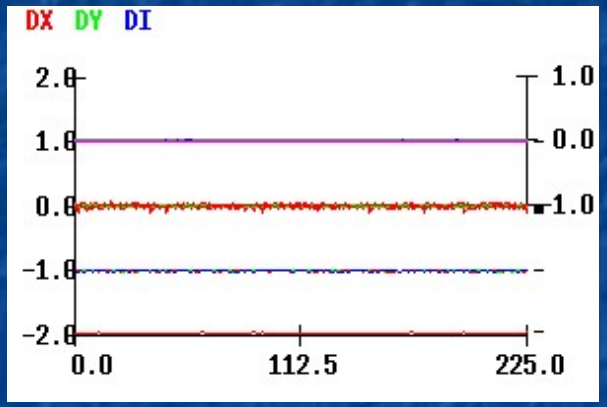
Motion Issues

- How to avoid motion
- Head motion complexity
- How to measure (estimate) motion
- How to compensate for motion
- Effectiveness of "motion correction”
- How much motion is too much?

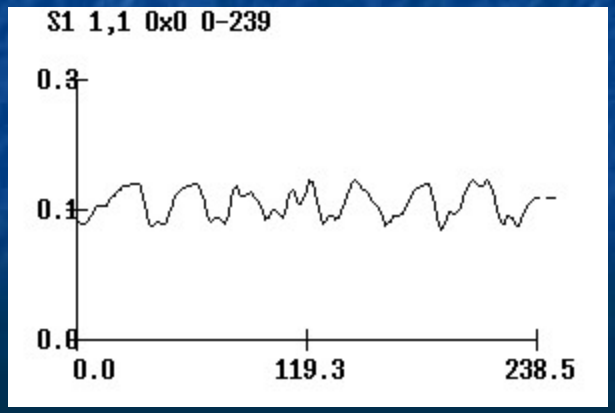
Creating motion phantoms (DROs)

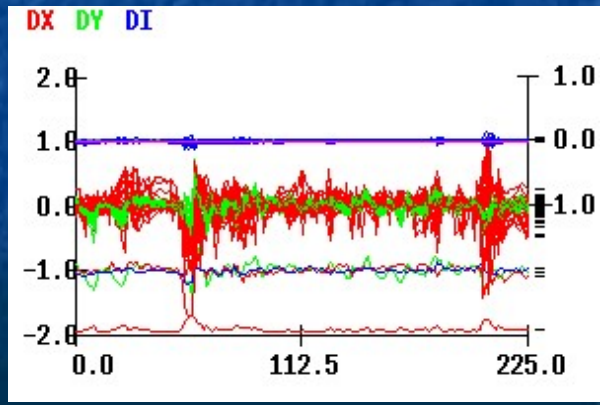
Base images with no activity and no motion



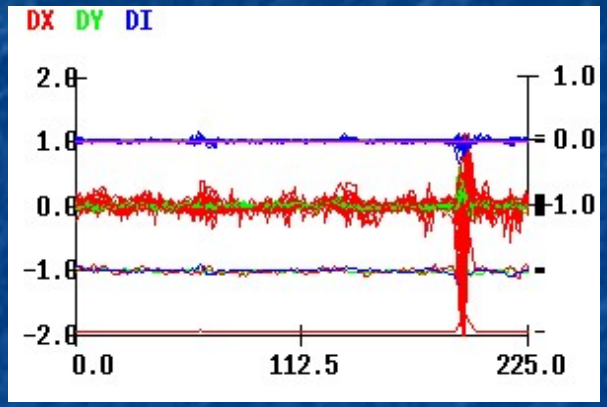


Add activation pattern, activation time course, and motion



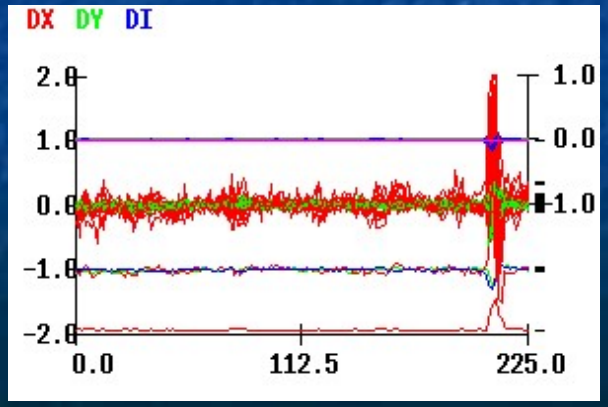


Digital motion phantoms – added motion is very similar to original actual

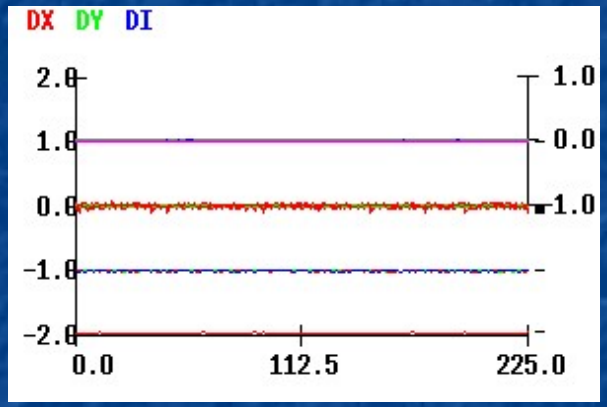


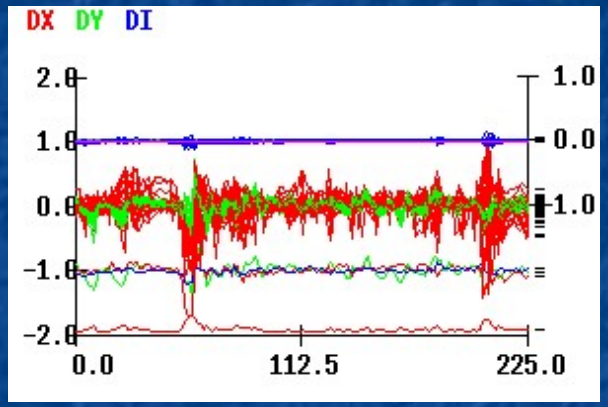
Human

Phantom



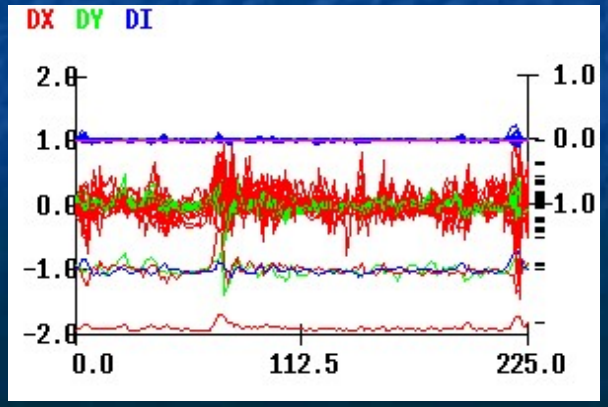
Base



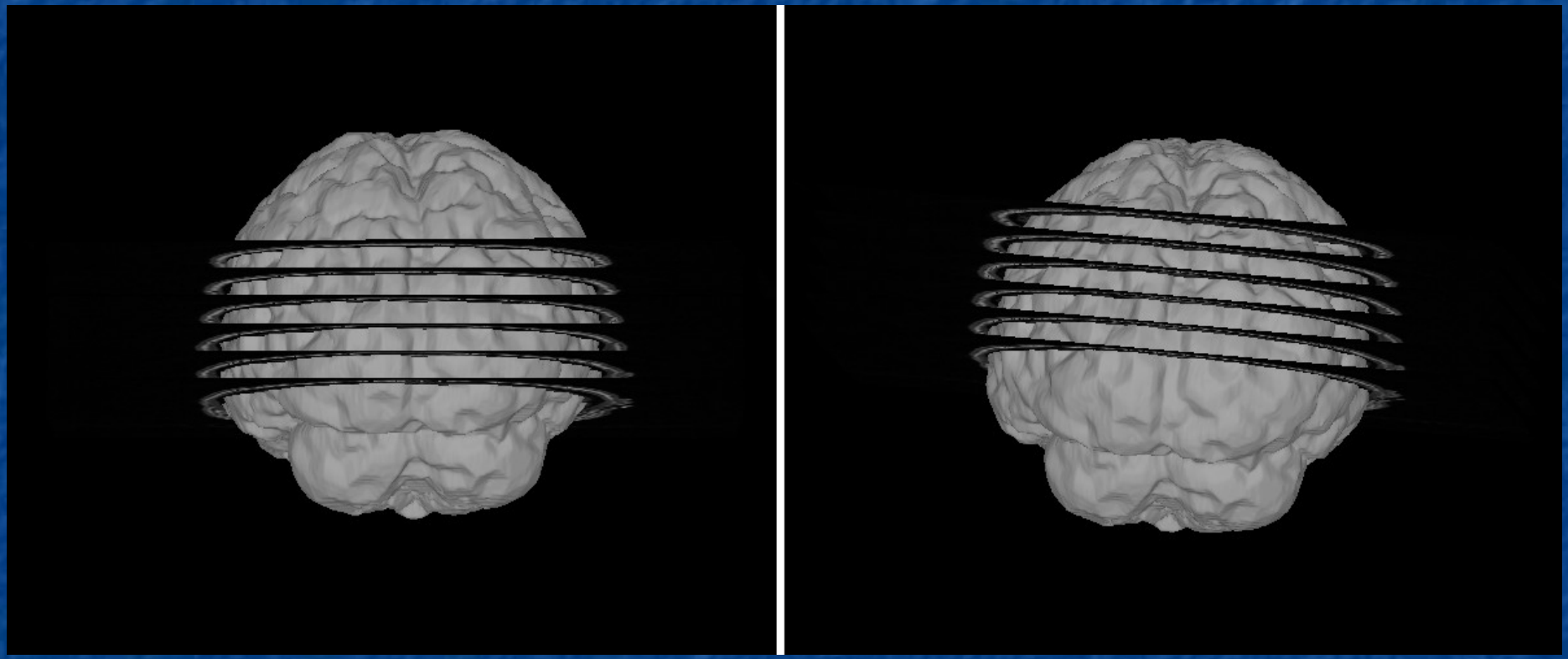


Human

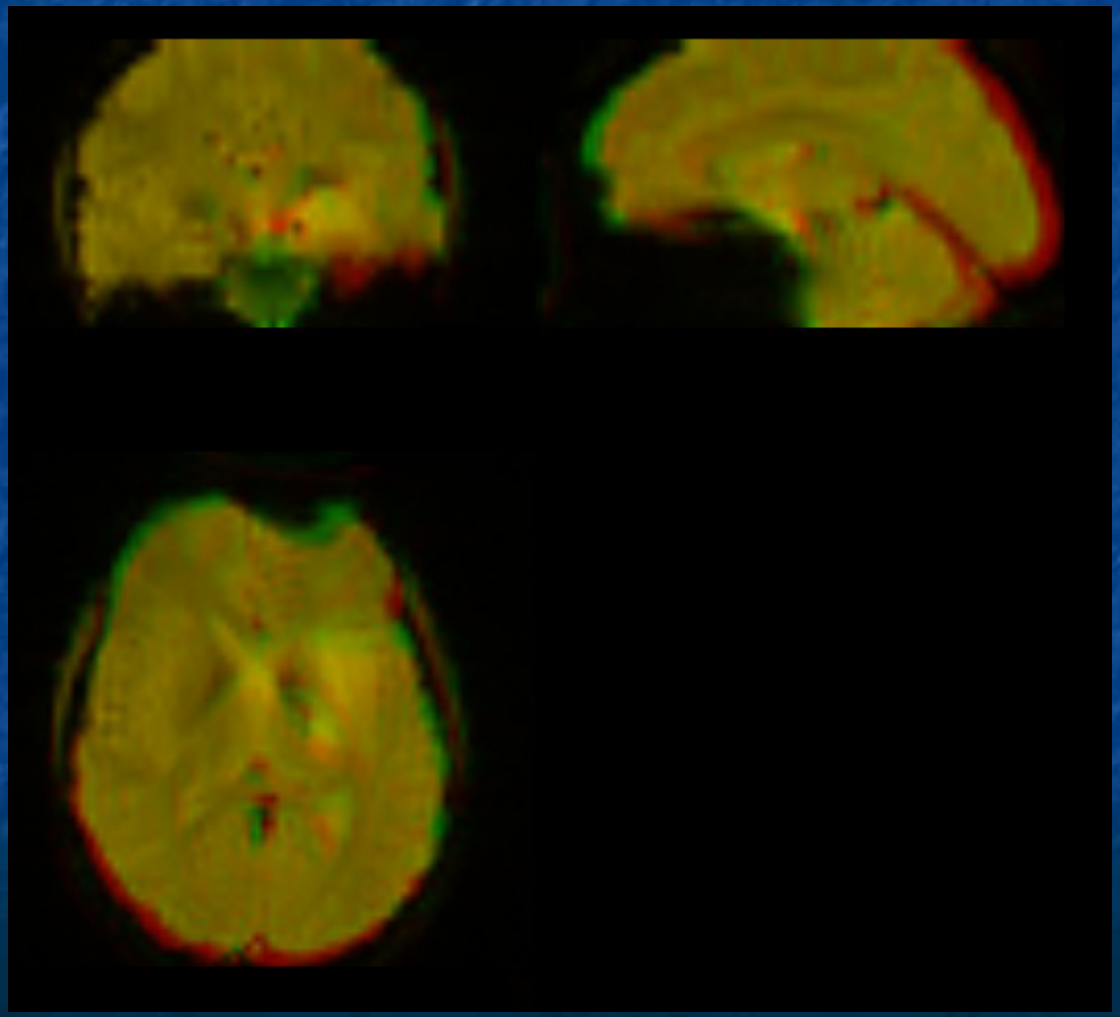
Phantom



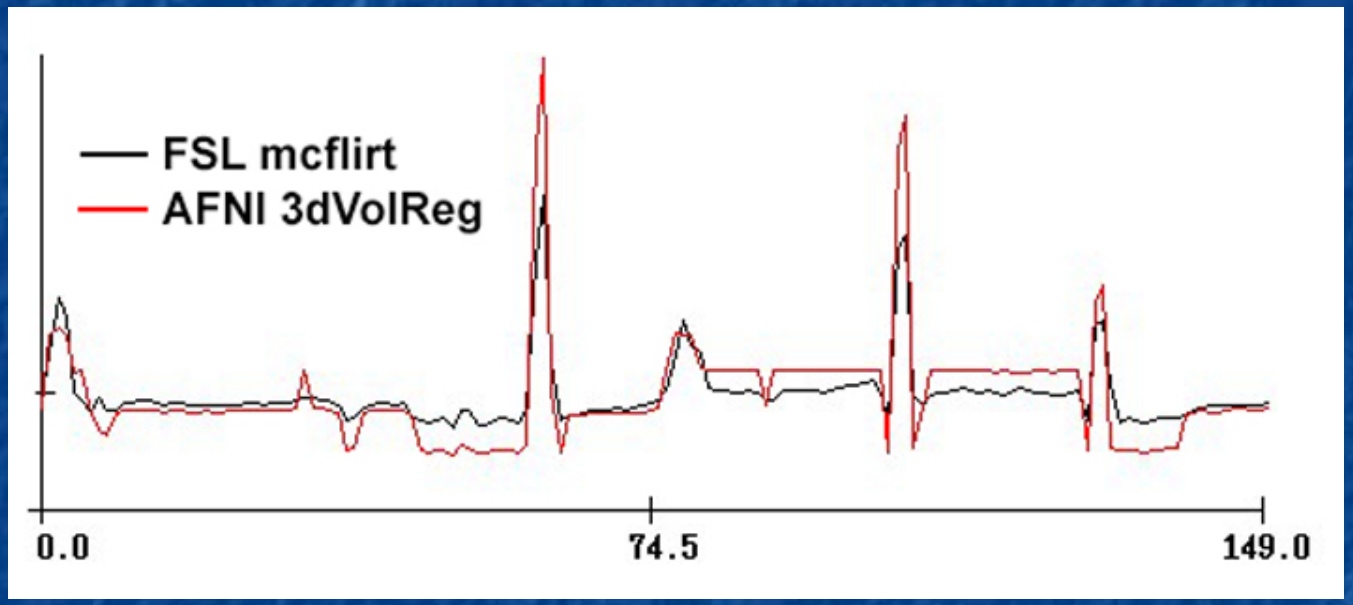
Motion correction:
Motion between volumes is correctable



Realign image volumes to "correct" motion



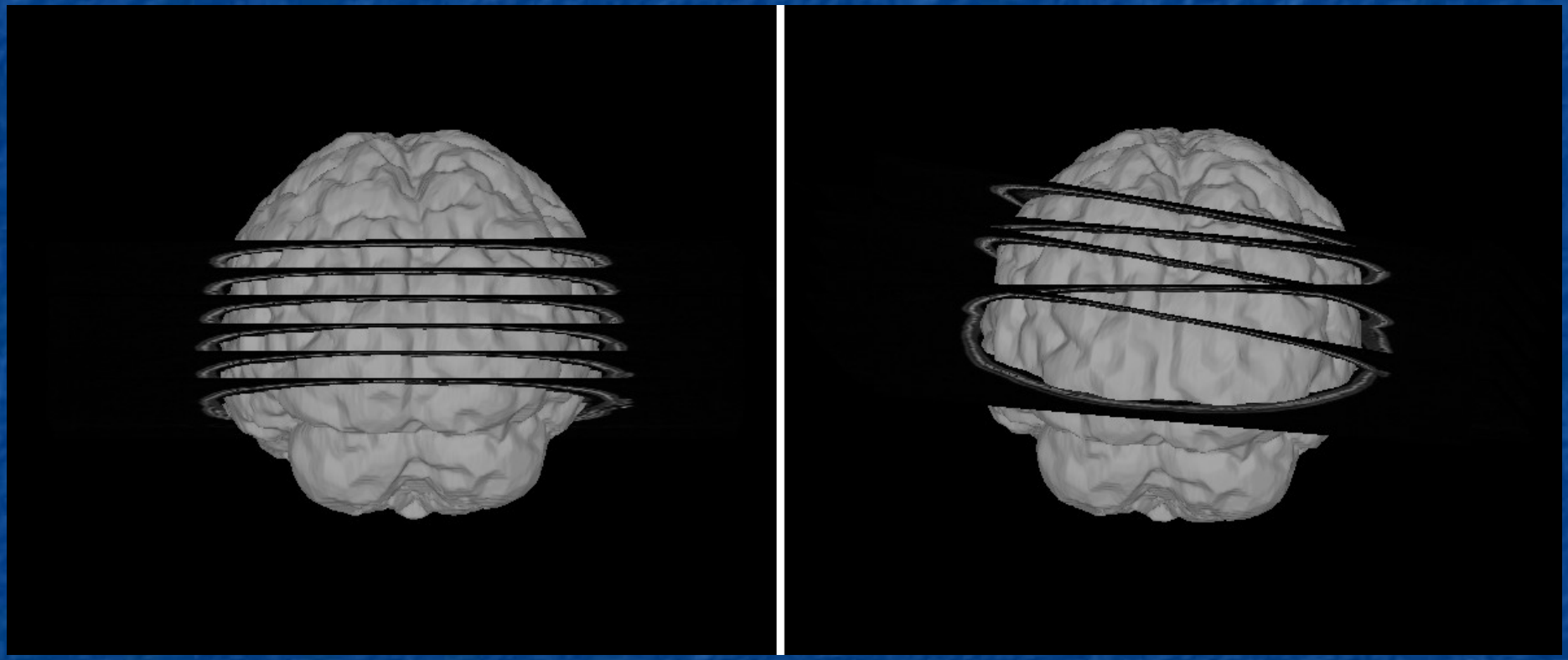
Choice of reference volume can affect motion correction



Measure "residual motion" by recalculating motion metrics after realignment.

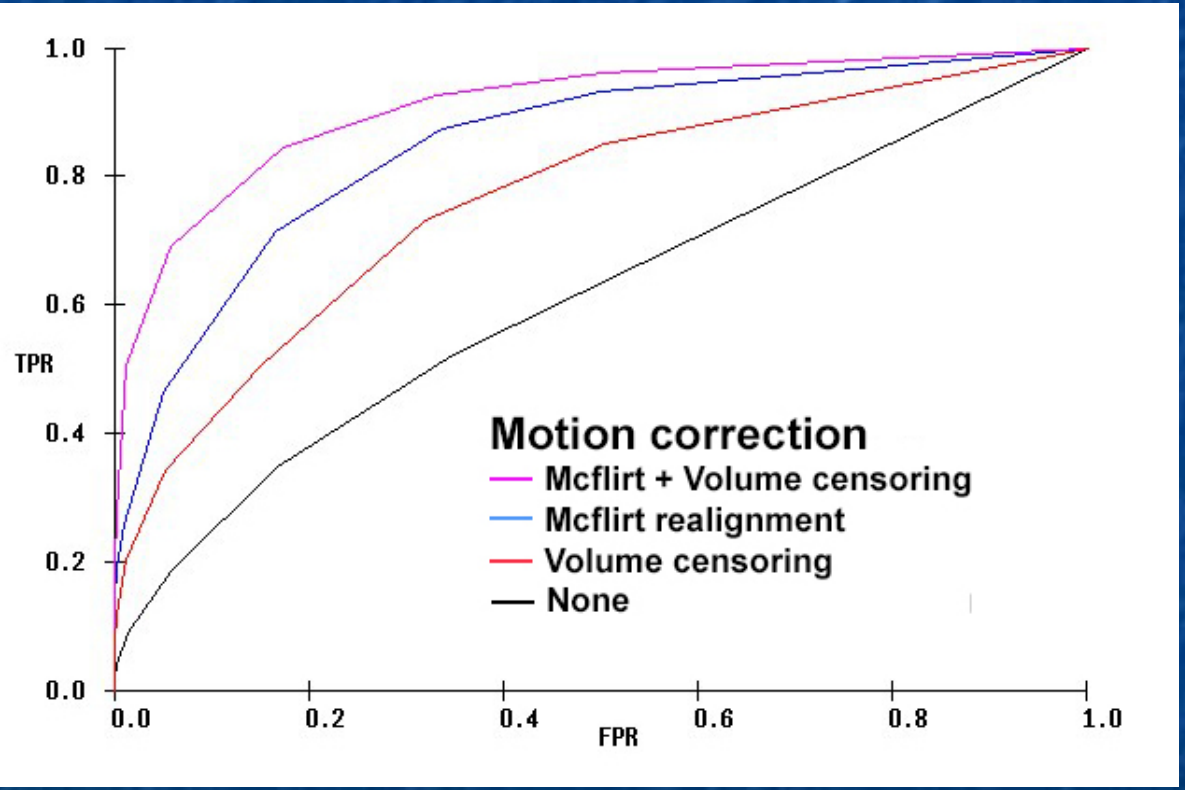
Residual motion varies as a function of realignment reference volume.

Motion within volume is not correctable by realignment



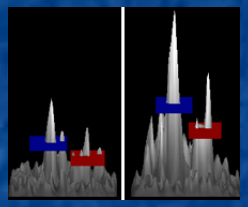
Conclusion: Use image registration to reposition volumes between movements, and omit volumes when head is actively moving. Problem scan if more than ~10% of volumes actually moving.

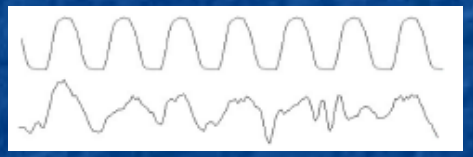
Combining realignment and censoring can enhance signal detection

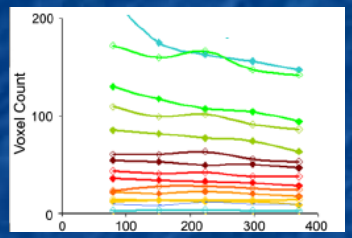


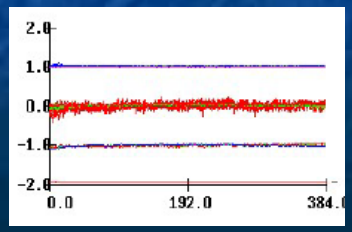
Conclusions

- To be reproducible and quantitative, clinical fMRI should satisfy specific QA metrics:
  - BOLD signal amplitude is significantly above noise (AMPLE 50%: $p < .05$), and
  - Task performance is reasonably consistent (CI > 0.5), and
  - The spatial pattern stablizes over time, (AMPLE 50% reaches plateau), and
  - Residual head motion after correction is minimal (no motion > 1mm?)









Future

- Once it is quantitative and reproducible fMRI will be able to actually measure brain activity (not just locate activity)
- Then fMRI could be used clinically to assess neurological or psychiatric disorders, disease progression, and patient response to therapies