Pattern Recognition of Functional Neuroimage Data of the Human Sensorimotor System after Stroke

Camille Gómez-Laberge, M.A.Sc., B.Eng., B.Sc.

Ph.D. Candidate
Faculty of Engineering, Carleton University
Neuroscience Program, Ottawa Hospital Research Institute

May 13, 2010

Outline

1. Cerebral microcirculation
2. Experimental protocol
3. Pattern recognition of neuroimage data
4. Space-time structure of BOLD response signals
5. Bayesian hierarchical correlation model
6. Results from normal and stroke participants
7. Conclusion

The cerebral microcirculation

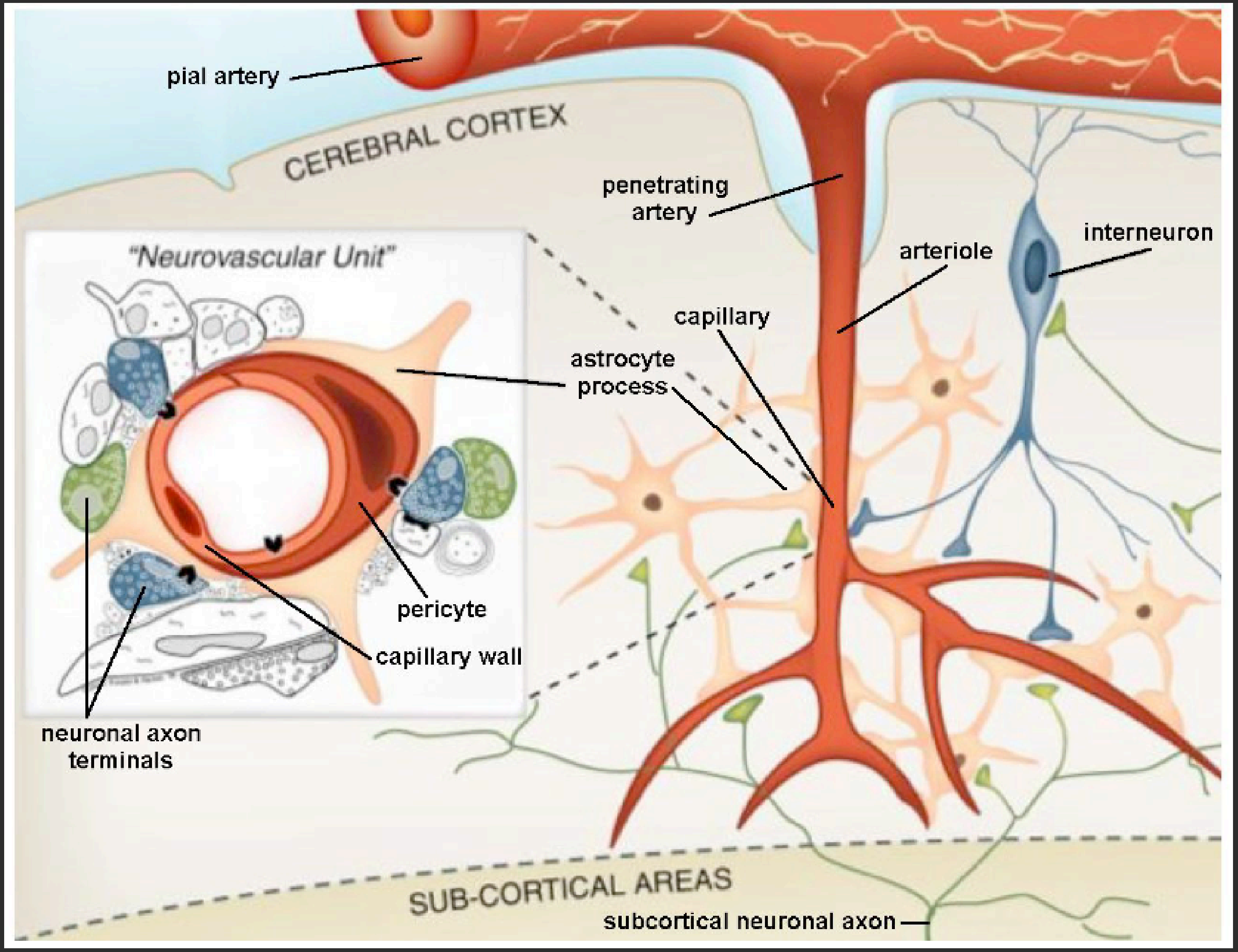
Cerebral microcirculation

<u>Microcirculation plays a critical role in brain function</u>

- neurons need a continuous blood supply of oxygen and glucose
- the human brain is a highly perfused organ being 2% of body mass and getting 15% of cardiac output
- the microcirculation is endowed with cellular mechanisms that control cerebral blood flow
  - *cerebrovascular autoregulation*
  - *functional hyperemia*

Cerebral microcirculation

The neurovascular unit



[adapted from Hamel, *J Appl Physiol*, 2006]

<u>Unit members in the cerebral cortex are</u>

- neurons
- astrocytes
- vascular pericytes

Neurons & glia release vasoactive chemicals to influence vessel tone *via* pericytes

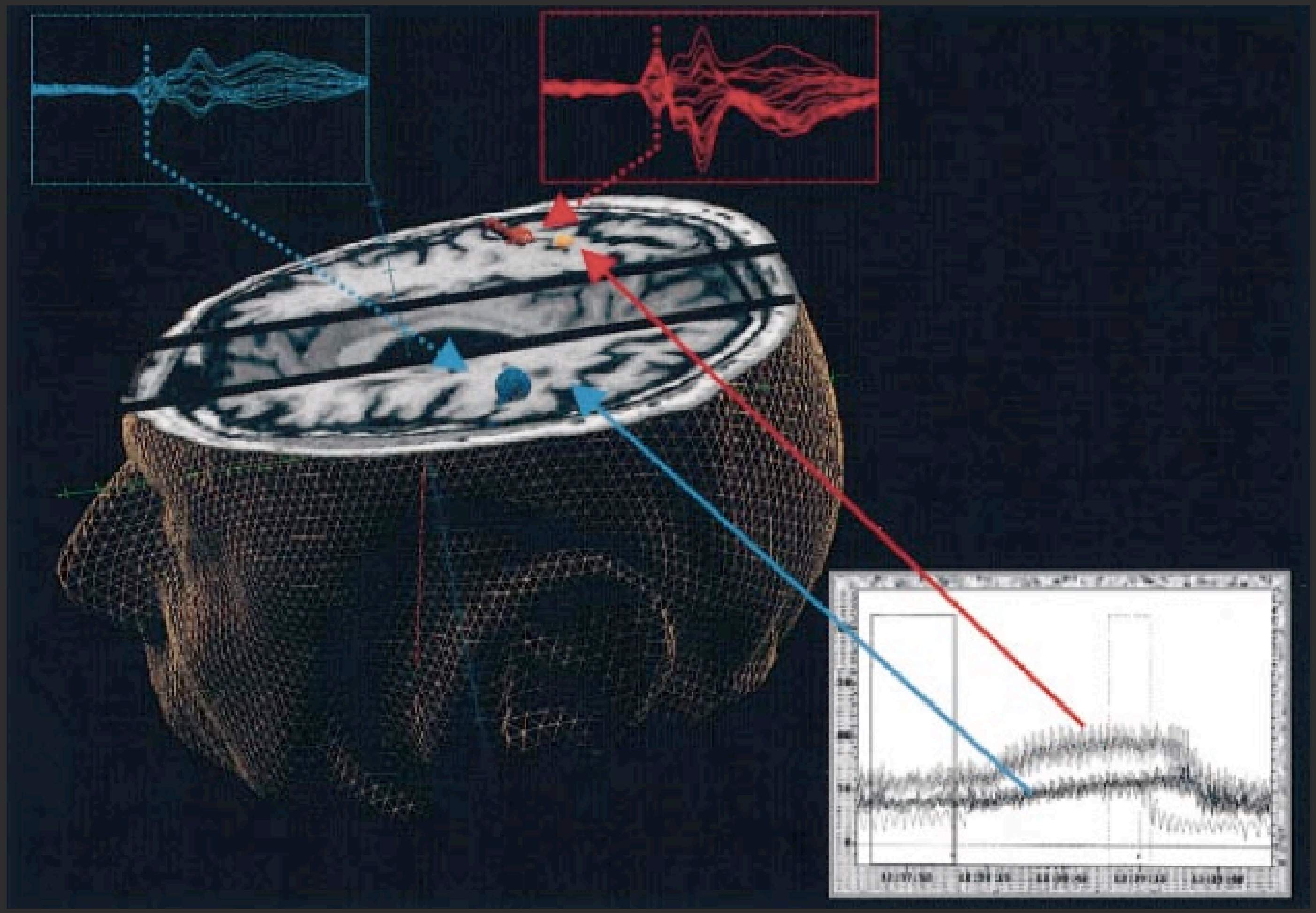
Cerebral microcirculation

Functional hyperemia is a complex phenomenon

- regional microvessels do not possess sufficient vascular resistance to account for flow changes
- a retrograde vasodilation propagates upstream to relax the feeding pial artery the smooth muscle
- neurovascular units at all levels release signalling chemicals that act in concert to produce a timely and focused hemodynamic response

Ischemic stroke

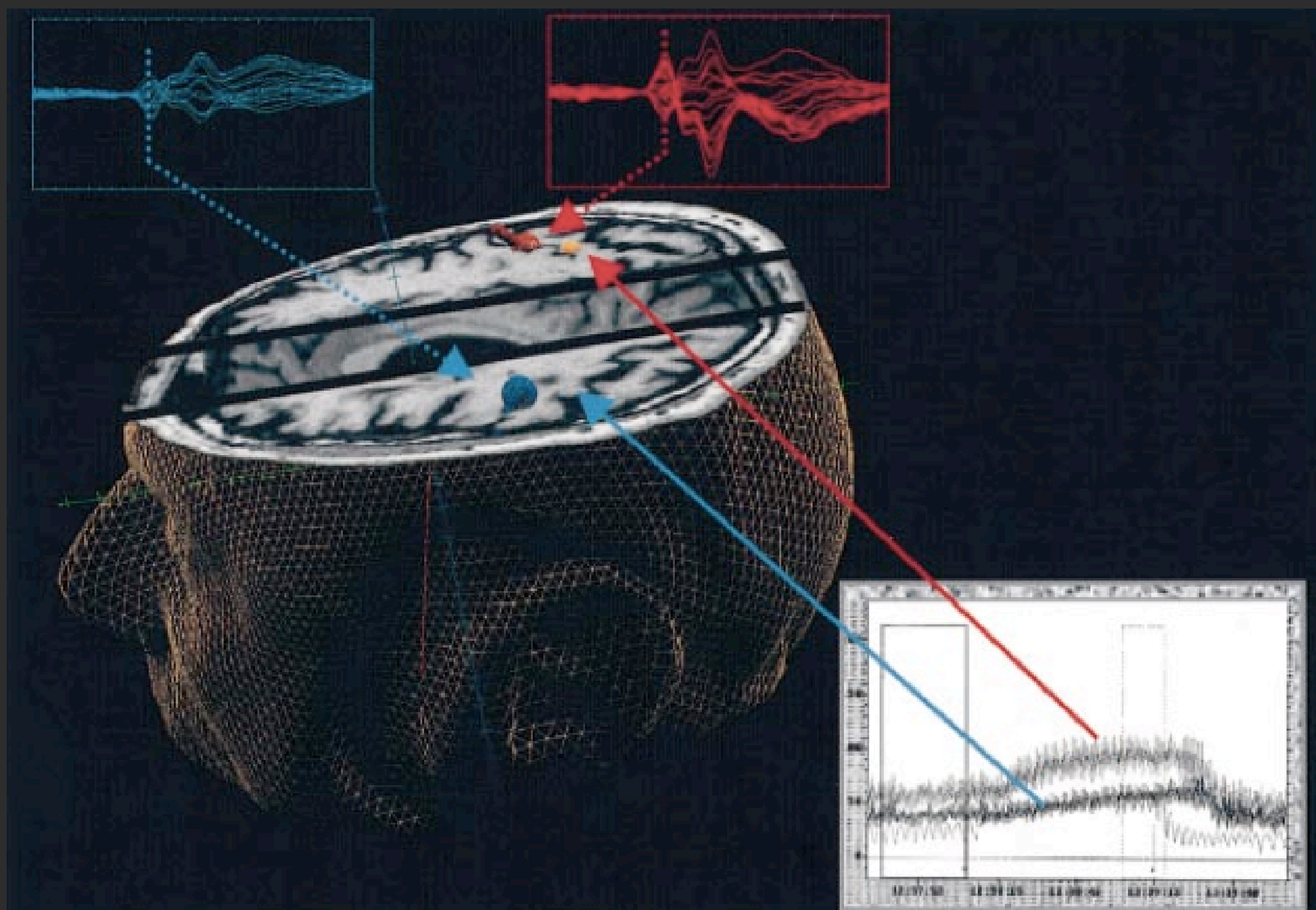
Impairment of functional hyperemia takes place after stroke

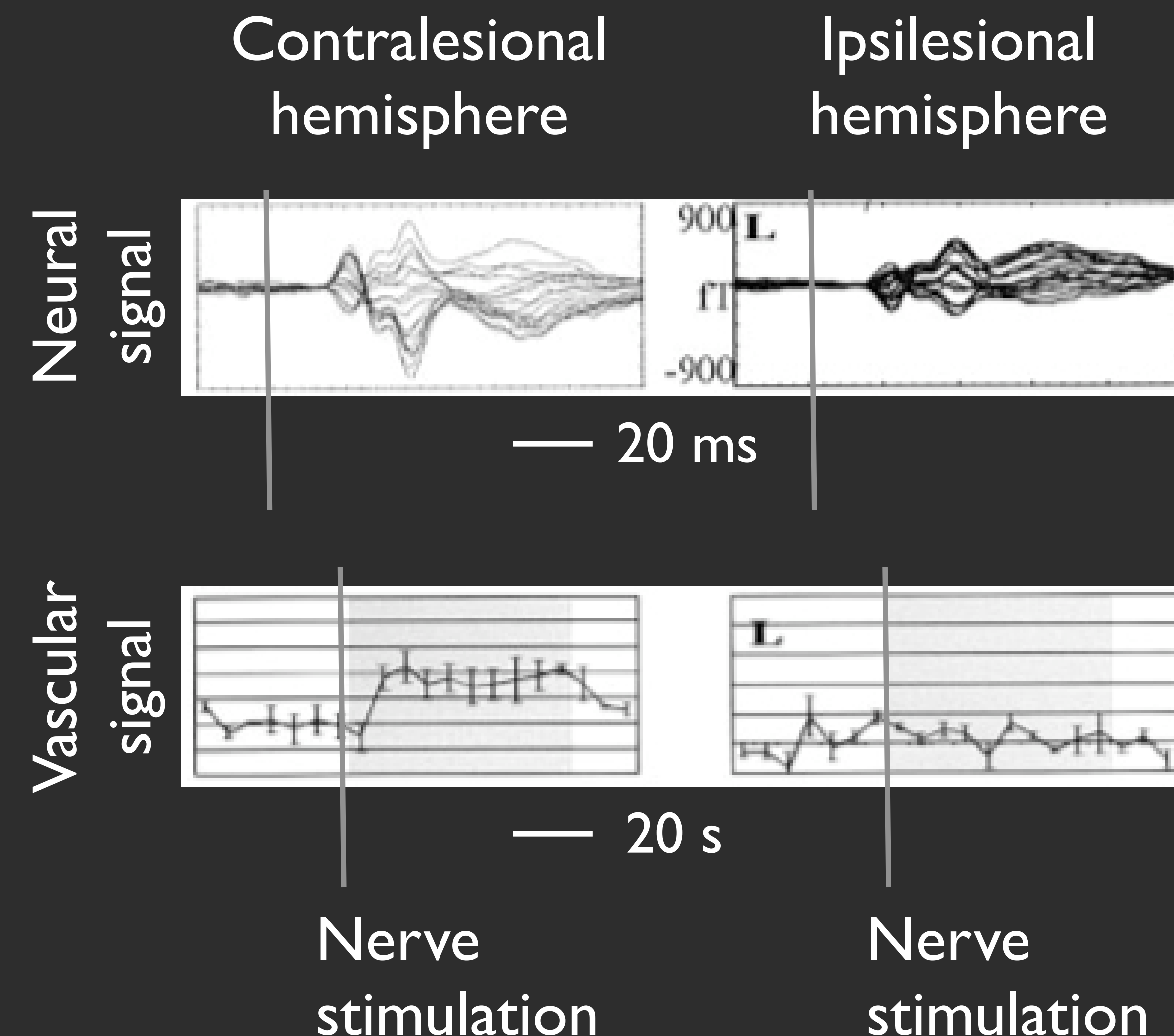


[adapted from Rossini *et al*, *Brain*, 2003]

Ischemic stroke

<u>Impairment of functional hyperemia takes place after stroke</u>





[adapted from Rossini *et al*, *Brain*, 2003]

- others report functional hyperemic alterations including attenuation, time delays, and absence in either hemisphere

Ischemic stroke

Motivating question for my research:

Since the cerebral microcirculation is altered in cerebrovascular disease, then is it possible to locally characterise the state of the disease by monitoring functional hyperemia?

Ischemic stroke

<u>Motivating question for my research:</u>

Since the cerebral microcirculation is altered in cerebrovascular disease, then is it possible to locally characterise the state of the disease by monitoring functional hyperemia?

- require a method that can simulatneously monitor neuronal and vascular signals
- the method must be non-invasive to enrol subjects in normal and patient populations
- the analysis must be flexible to identify a signal whose shape is unknown *a priori*

Experimental protocol

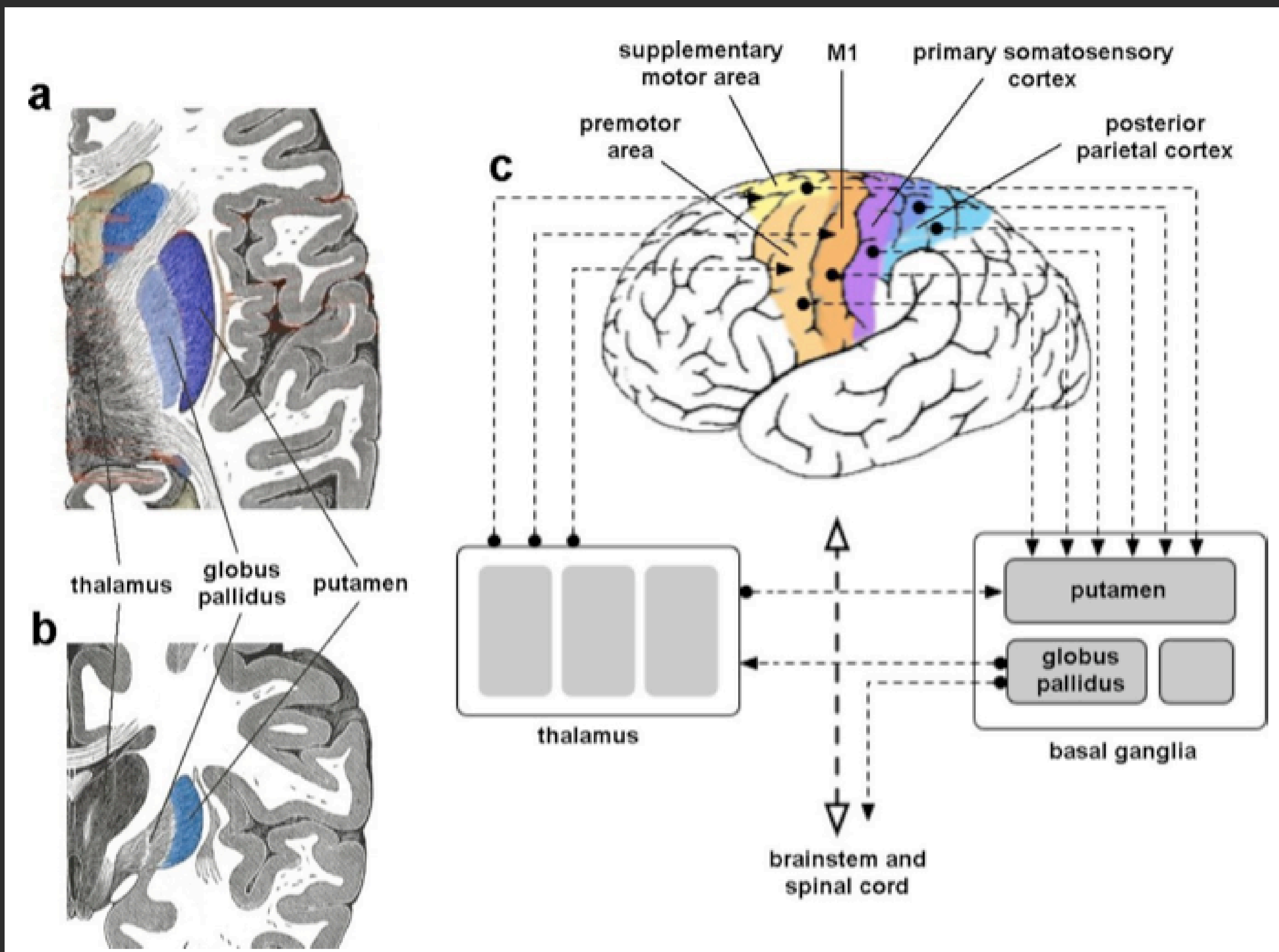
Experimental protocol

<u>Experimental objectives:</u>

1. to reproducibly induce functional hyperemia
2. to simultaneously observe the nervous system response and the cerebrovascular response

Experimental protocol

The sensorimotor system



[adapted from Gray, *Anatomy*, 1977 and Kandel et al, *Prinicples of Neural Science*, 2000]

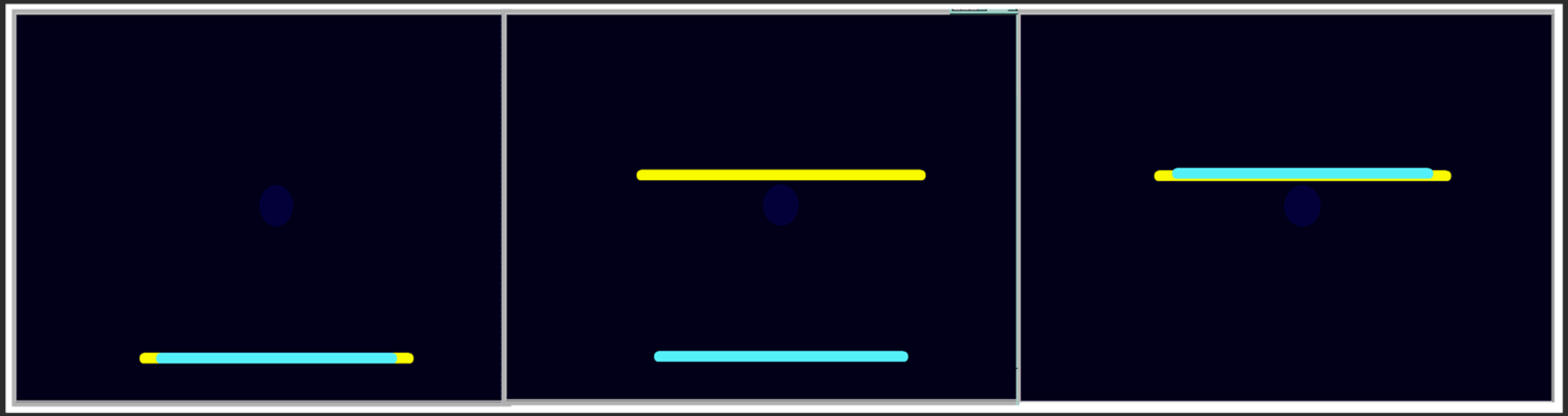
Why this system?

- evoked *via* basic sensorial and motor stimuli
- motor responses can be monitored
- has been previously studied

Experimental protocol

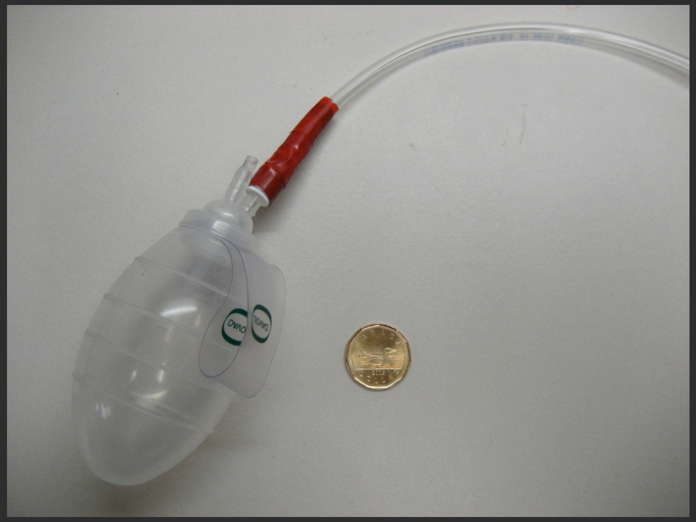
Event-related visual feedback controlled motor task

Display



Rest Event Response

Hand grip device

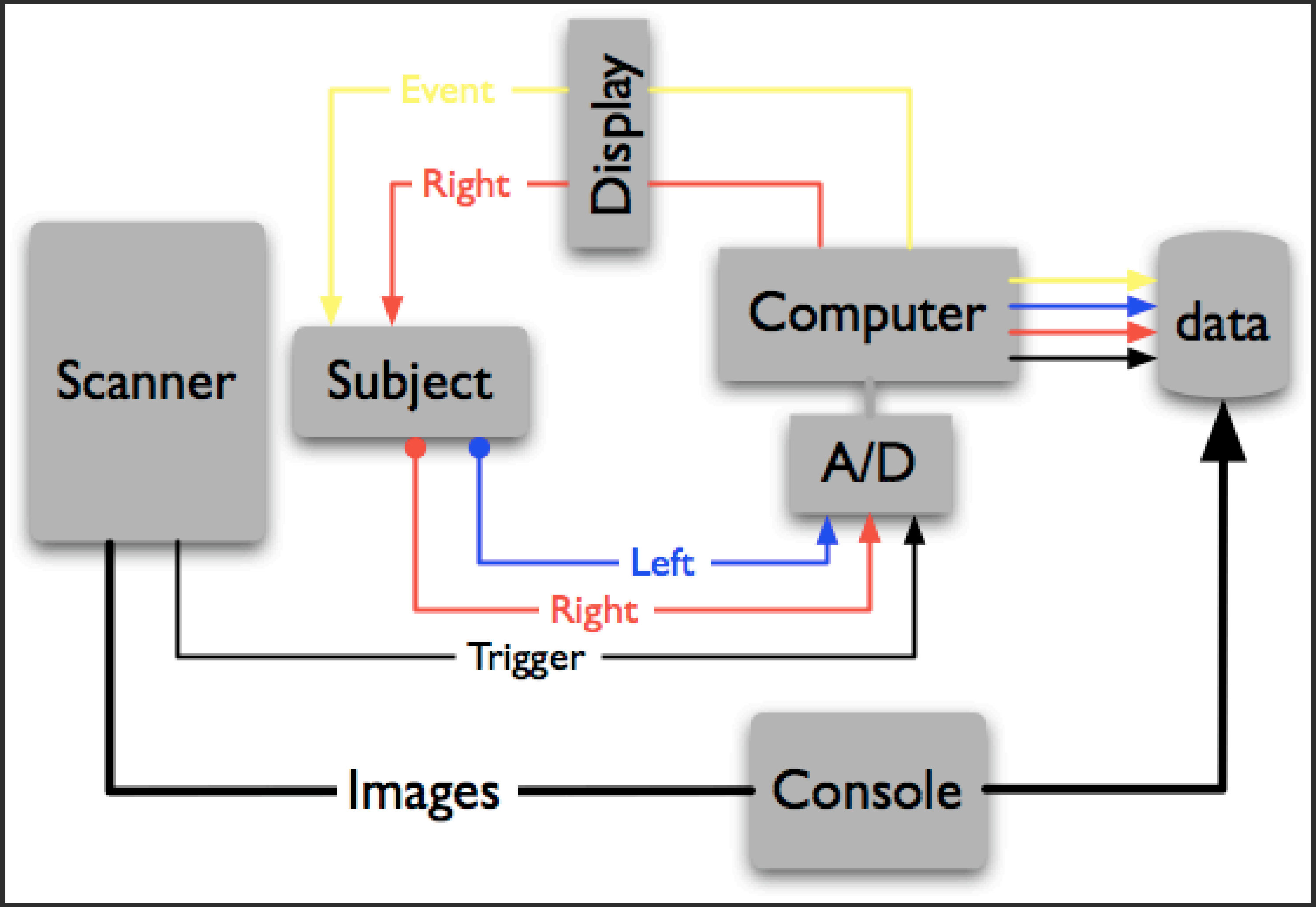


Training:
- MVC calibration
- motor task training

MRI:
- 1.5 Tesla
- 5 minute scan
- both hands monitored
- single-handed response
- target force: 25% MVC

Experimental protocol

Event-related visual feedback controlled motor task



Data sources:

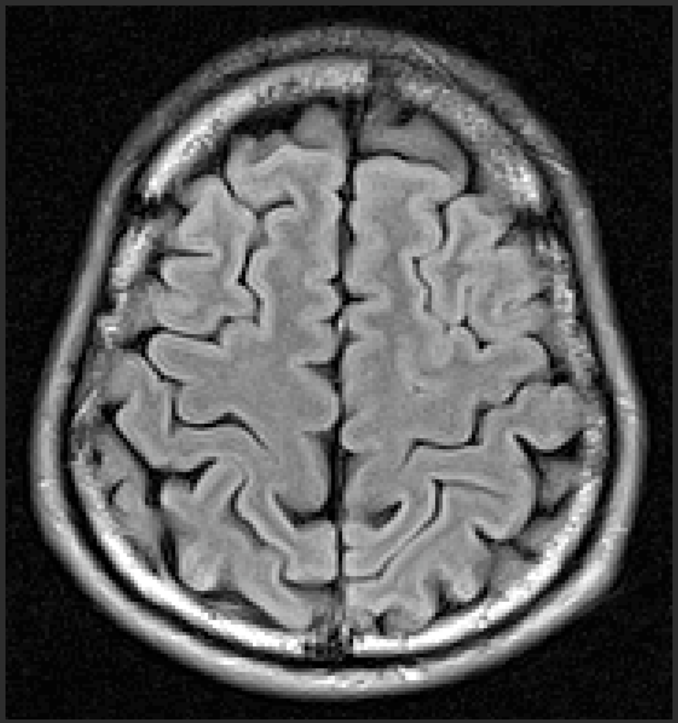
- Images: 160 GE-EPI
  1 T2 FLAIR

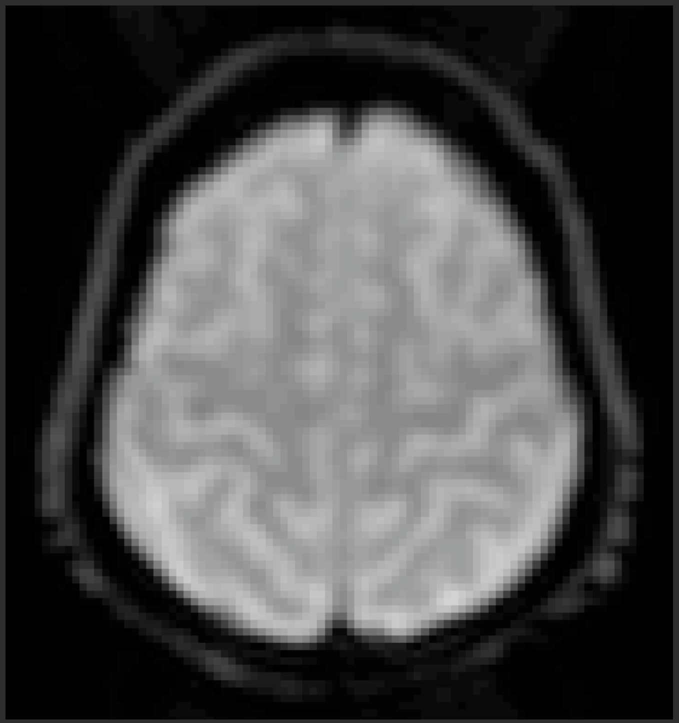
- Timing: Scanning trigger
  Event schedule

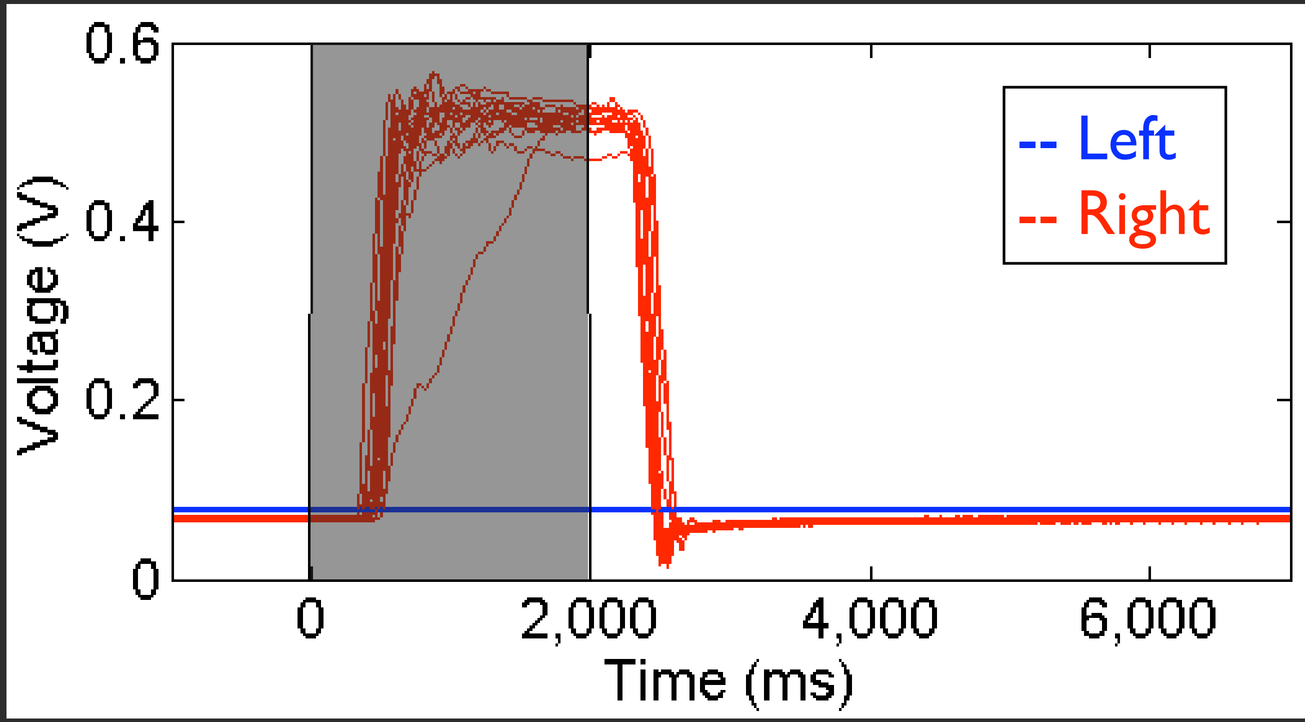
- Motor: Left hand
  Right hand

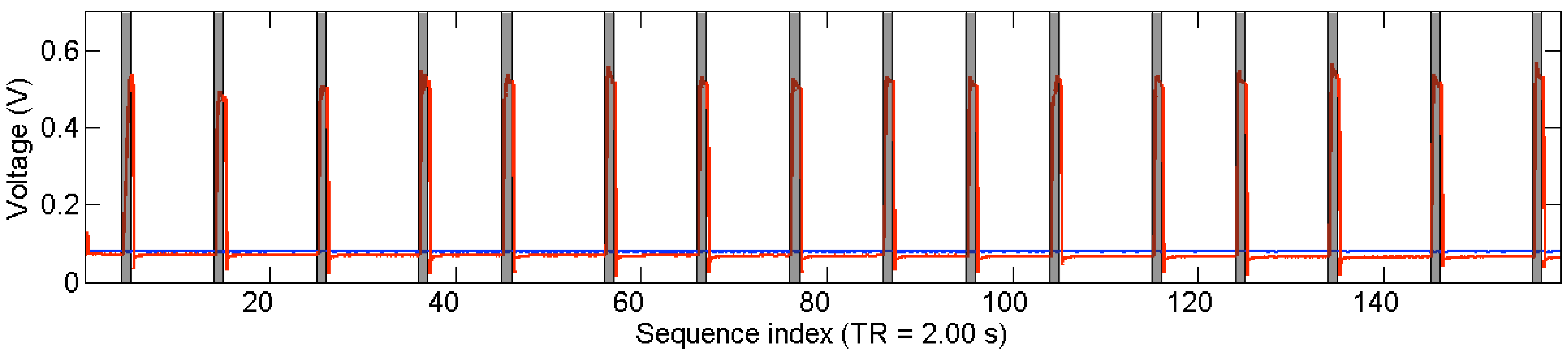
Experimental protocol

Event-related visual feedback controlled motor task









Pattern recognition of neuroimaging data

Pattern Recognition

Pattern recognition is “a <u>search</u> for <u>structure</u> in the data”

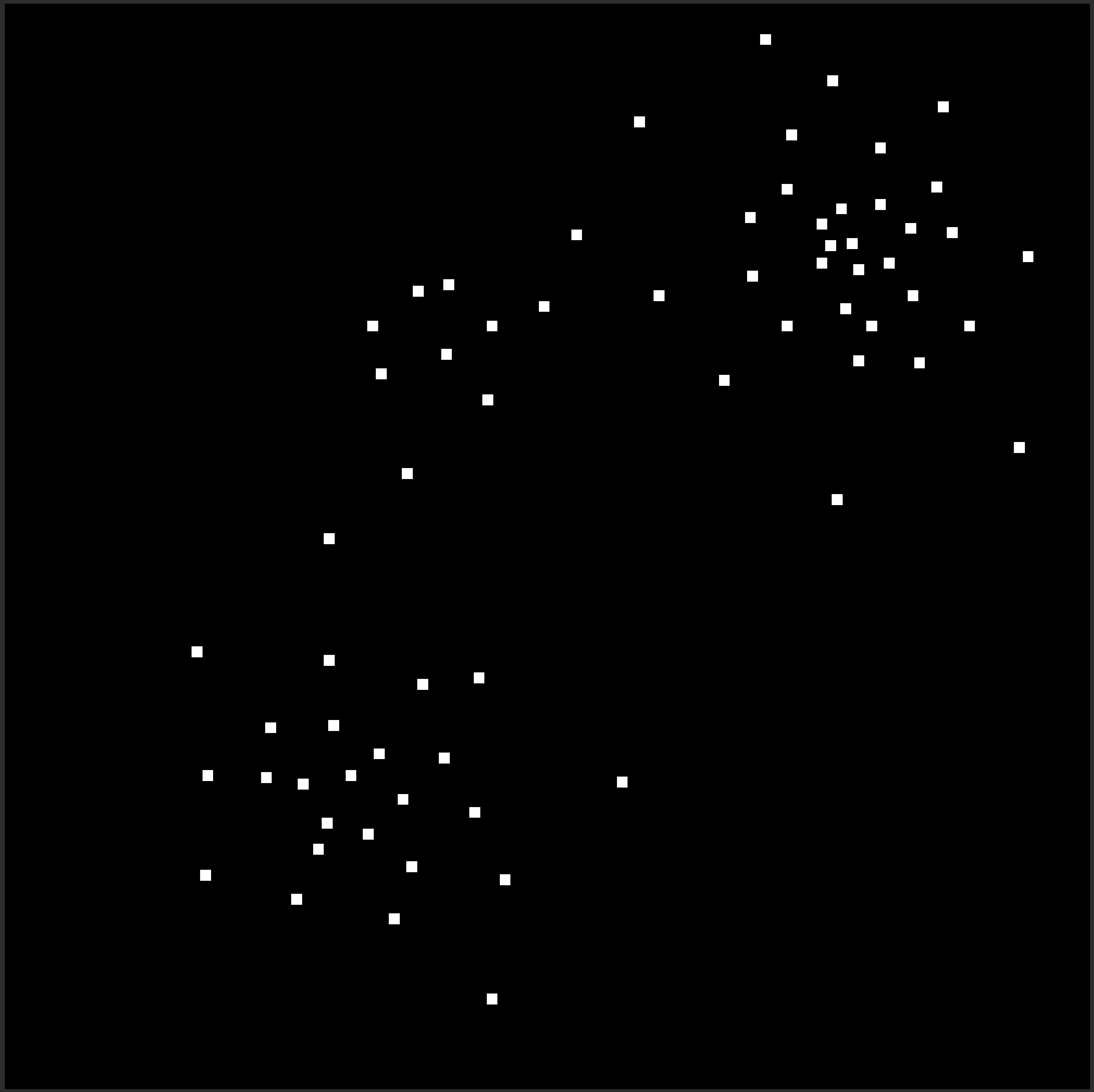
<u>The search</u>:

- subjective assessment (eg human intuition)
- statistical modelling (eg estimation of the data generating process)
- component analysis (eg representation of the whole by its parts)

<u>The structure</u>:

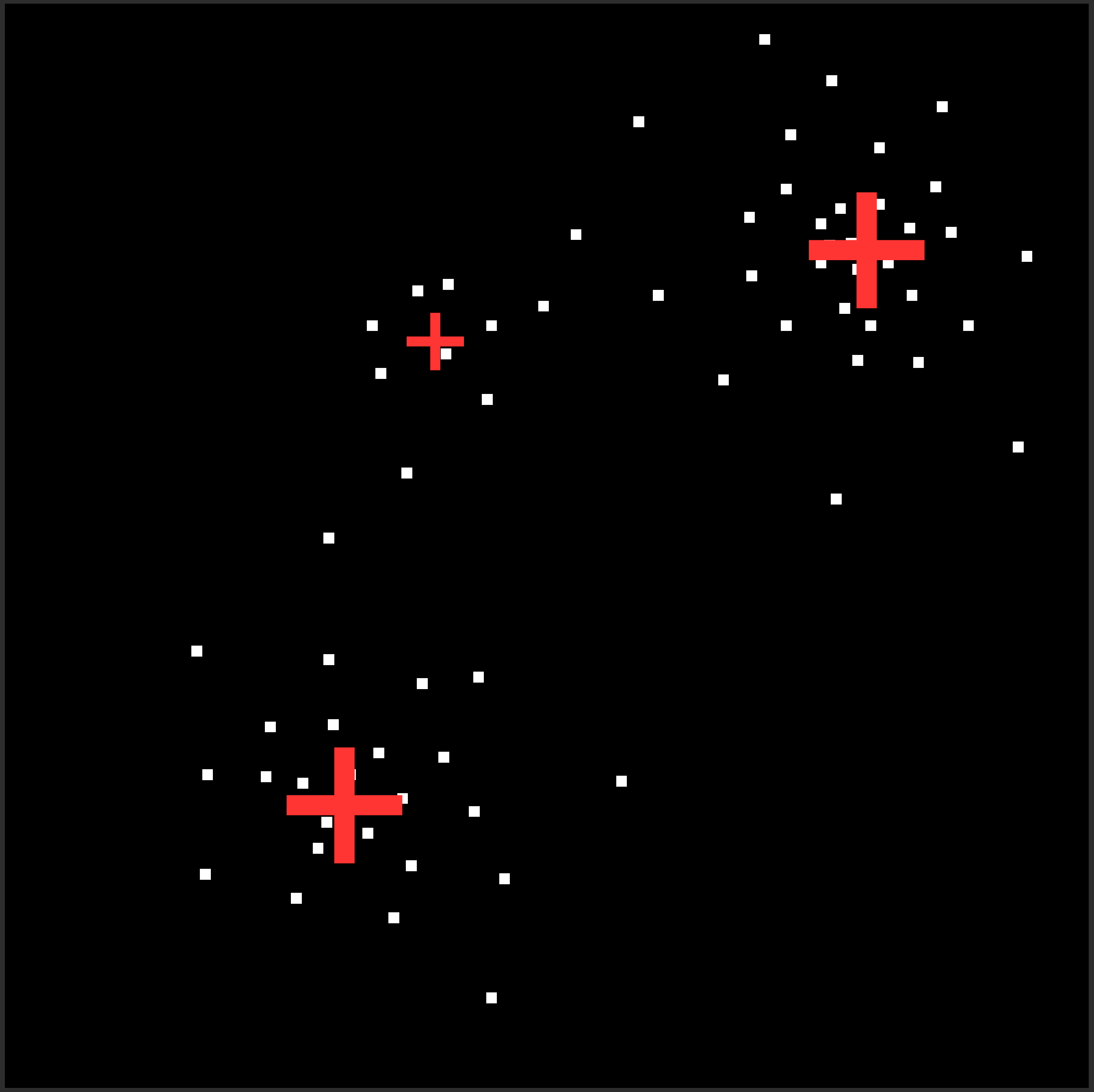
- how information is organised within a data set

Pattern Recognition



data X

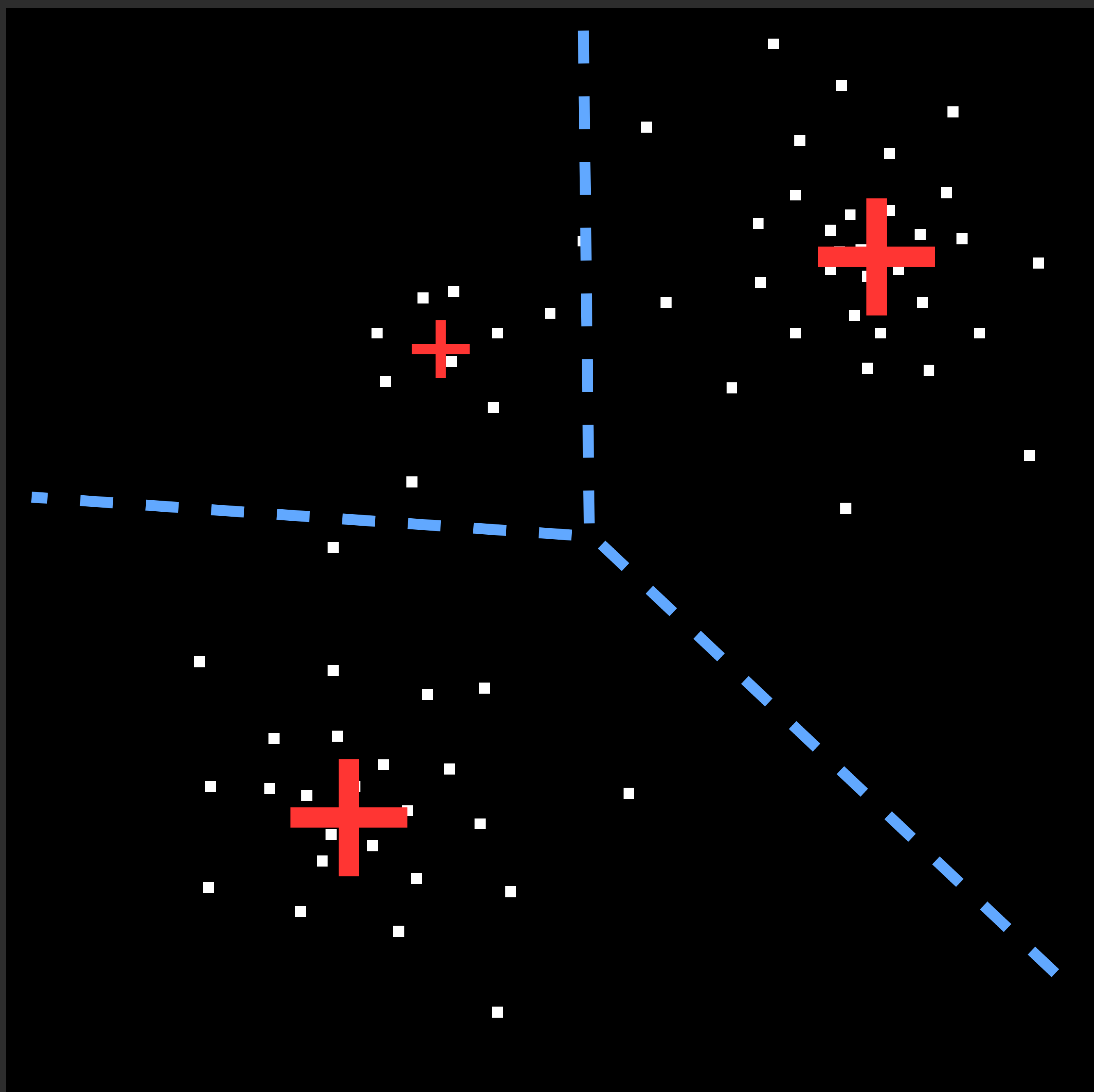
Pattern Recognition



data X

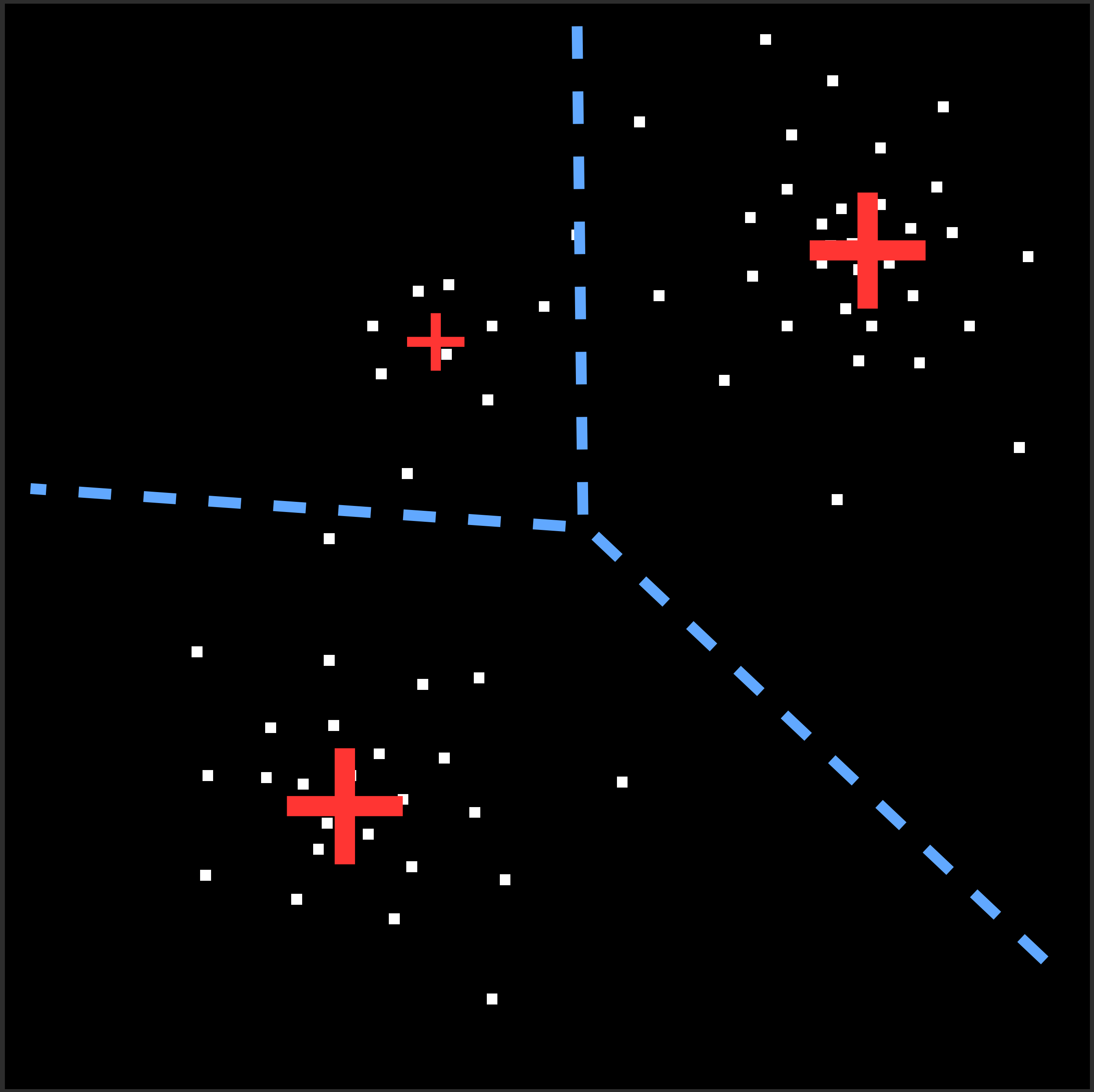
assume k=3

Pattern Recognition



data X
assume k=3
form a 3-partition by NN

Pattern Recognition



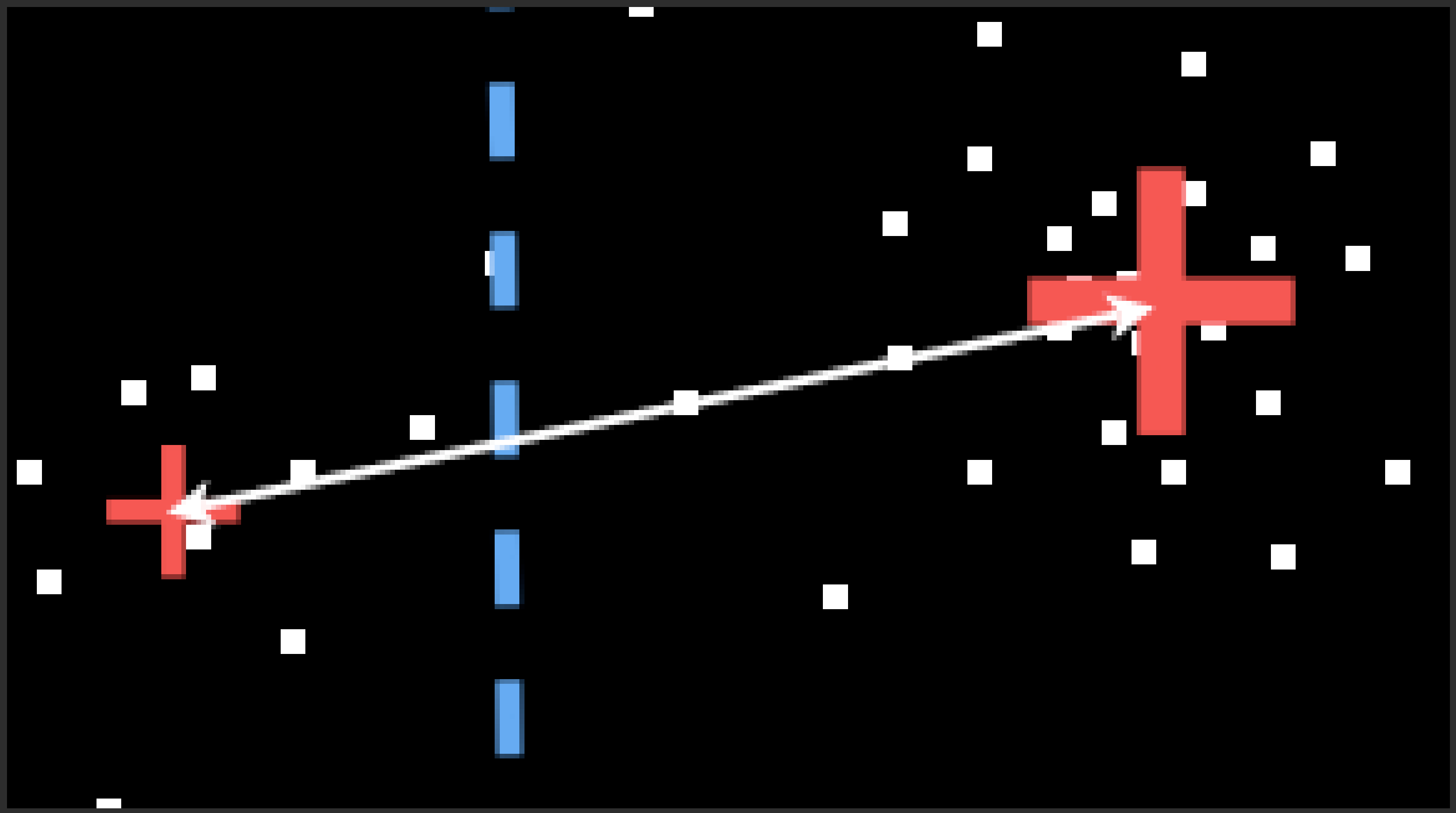
data X

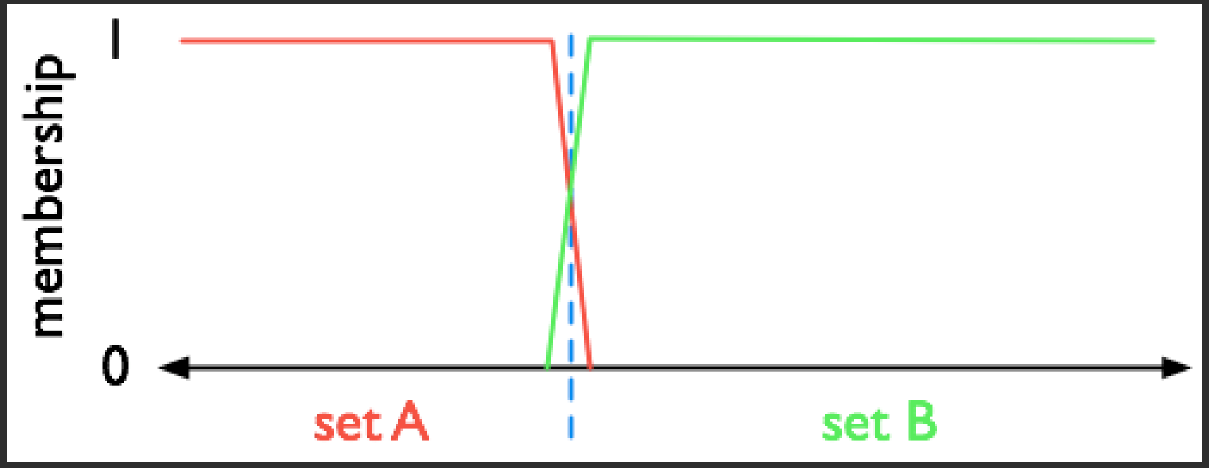
assume k=3

form a 3-partition by NN

Question: how to validate our choice of k=3? is this the optimal k-partition?

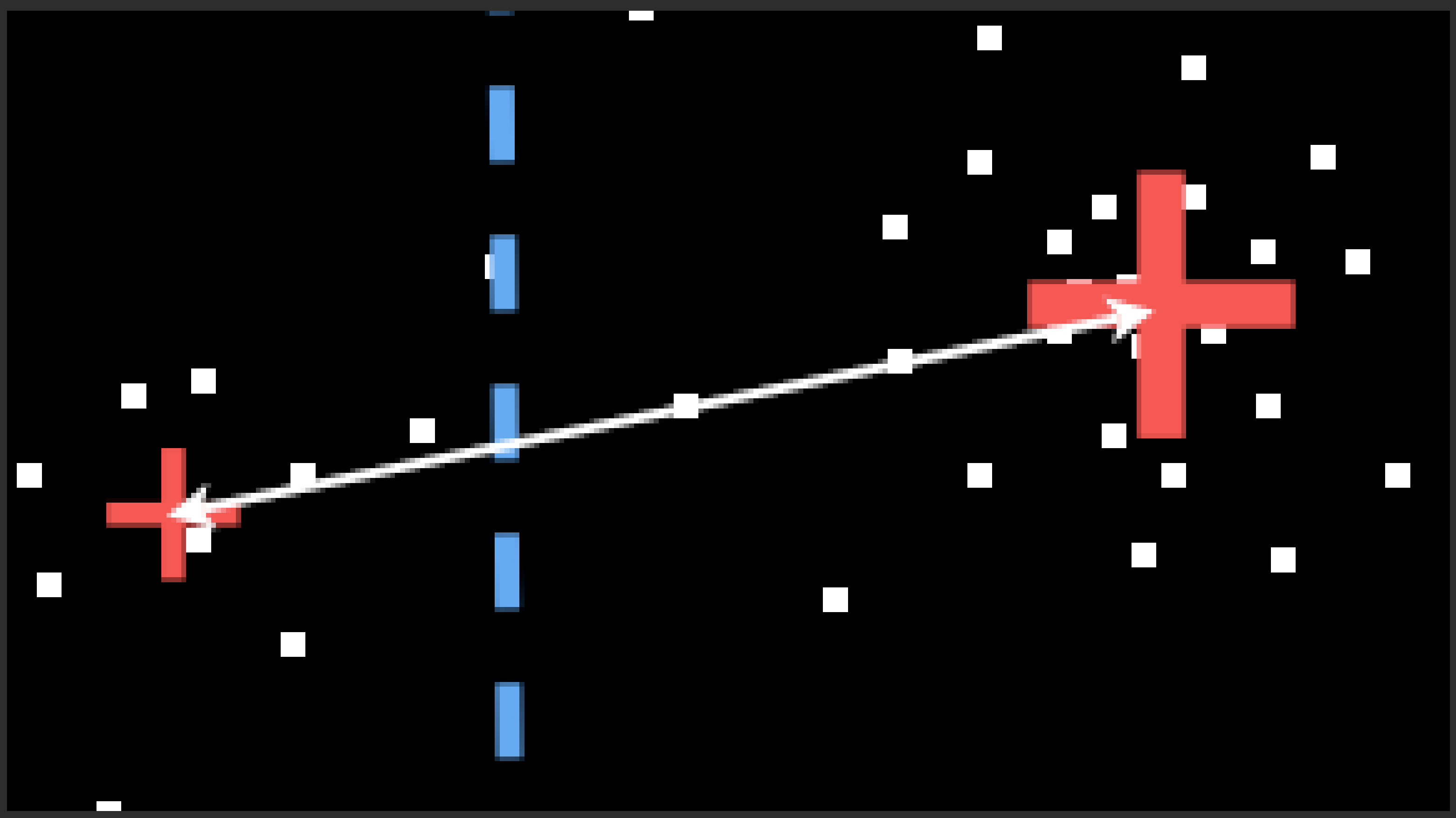
Pattern Recognition

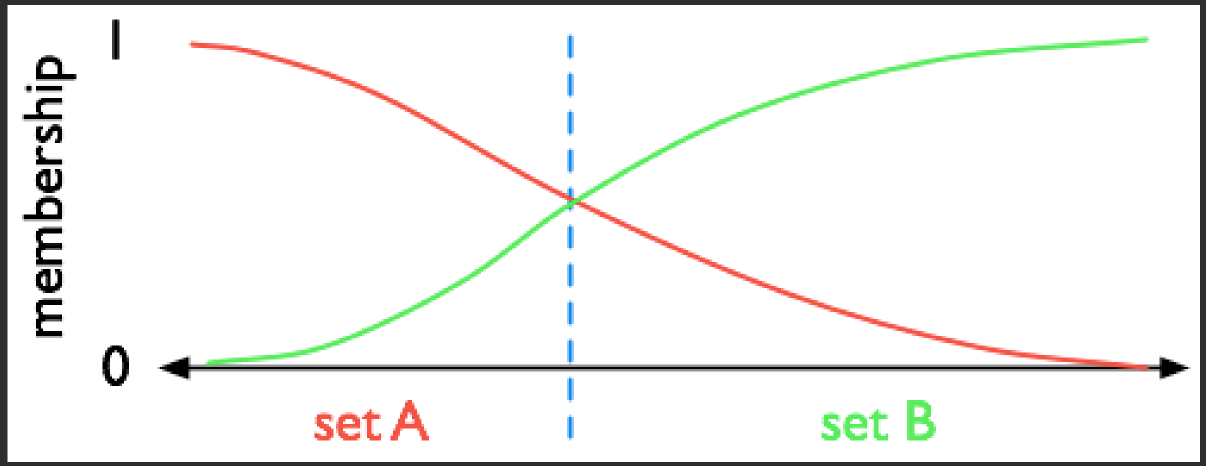




- a data point either belongs to A or B but not both
- points in A are considered equivalent
- thus set membership is uninformative of partition validity

Pattern Recognition



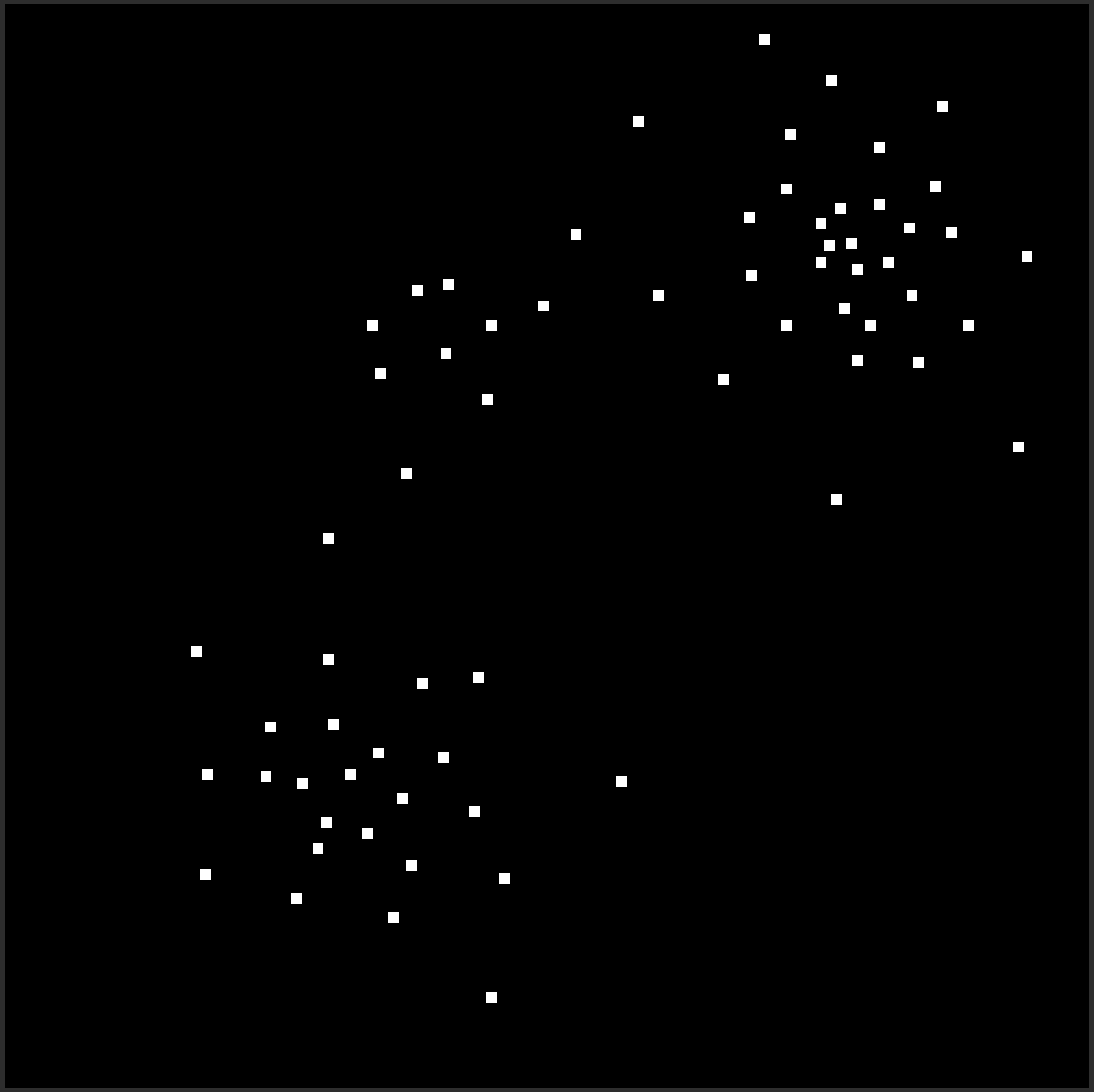


- data points have "fuzzy" membership-- belong to some extent to both sets

- the points are now distinguishable

- set membership is now informative of partition validity

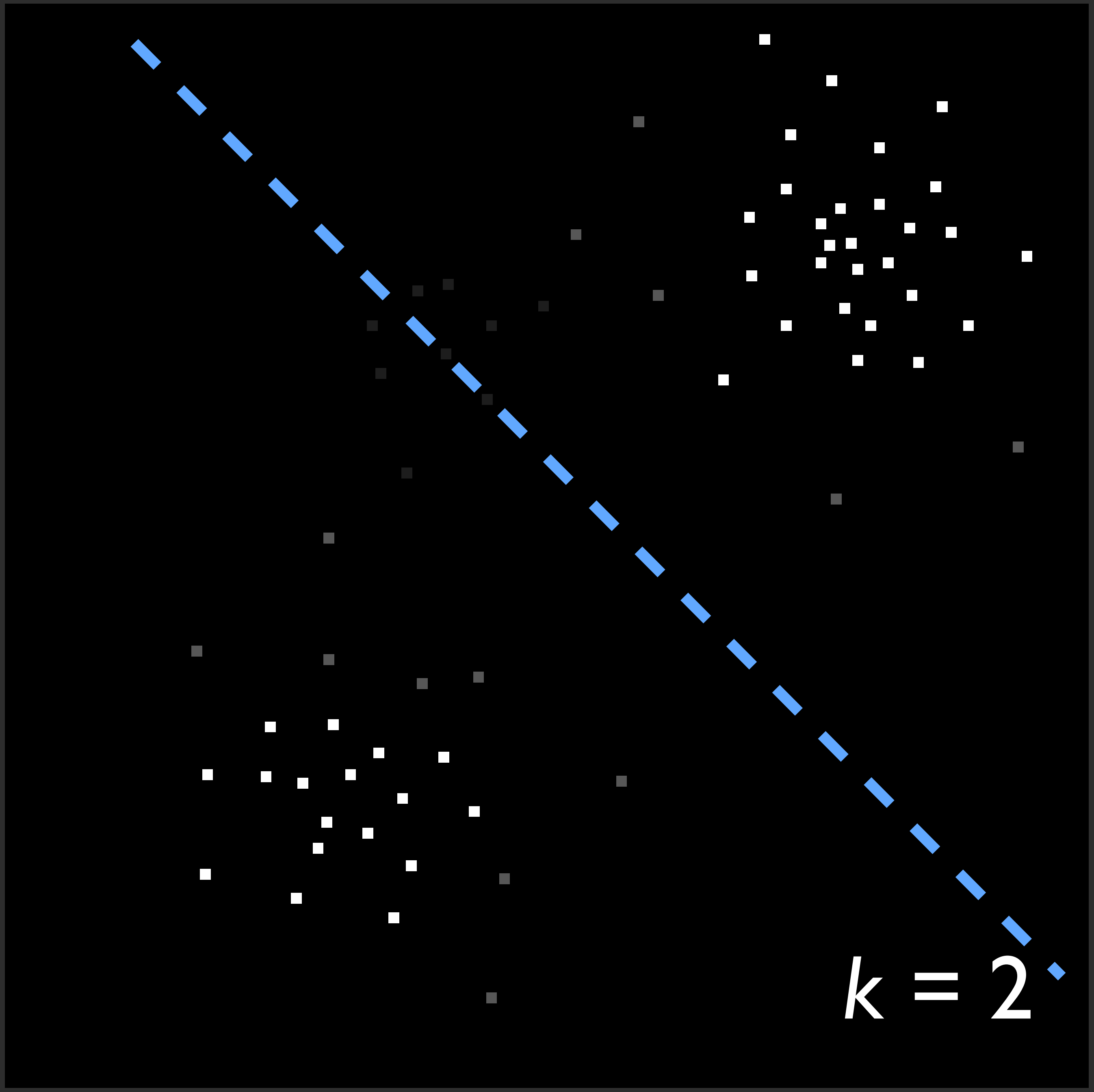
Pattern Recognition



- form a *k*-partition and represent membership by pixel intensity

- then different *k* lead to distributions of membership values

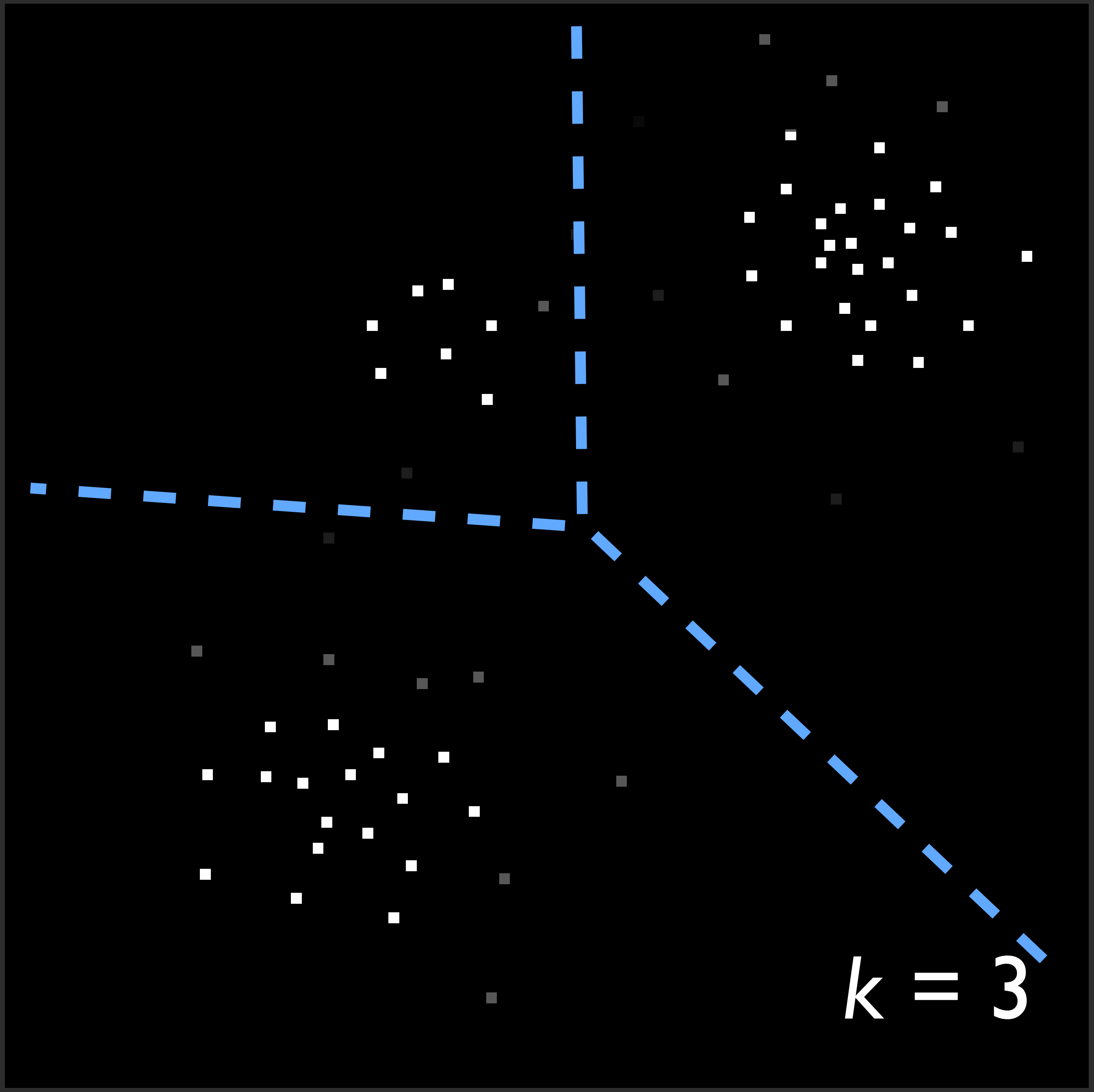
Pattern Recognition



- form a k-partition and represent membership by pixel intensity

- then different k lead to distributions of membership values

Pattern Recognition



- form a k-partition and represent membership by pixel intensity

- then different k lead to distributions of membership values

Pattern Recognition

Dunn (1973) derived fuzzy k-means clustering algorithm based on a least-squares minimisation problem

$$J(X,U,V) = \sum_{i=1}^{k} \sum_{\mathbf{x} \in X} u_i^2(\mathbf{x})\, d^2(\mathbf{x}, \mathbf{v}_i)$$

- input: data *X*, metric *d*, and partition number *k*
- output: cluster memberships *U* and centroids *V*

$$\mathbf{v}_i = \frac{\sum_{\mathbf{x} \in X} u_i^2(\mathbf{x})\, \mathbf{x}}{\sum_{\mathbf{x} \in X} u_i^2(\mathbf{x})} \quad \text{for } 1 \le i \le k$$

$$u_i(\mathbf{x}) = \frac{1/d^2(\mathbf{x}, \mathbf{v}_i)}{\sum_{j=1}^{k} 1/d^2(\mathbf{x}, \mathbf{v}_j)} \quad \text{for } 1 \le i \le k$$

Dunn, (1973), *J. Cybern.*, 3, 32-57.

Pattern Recognition

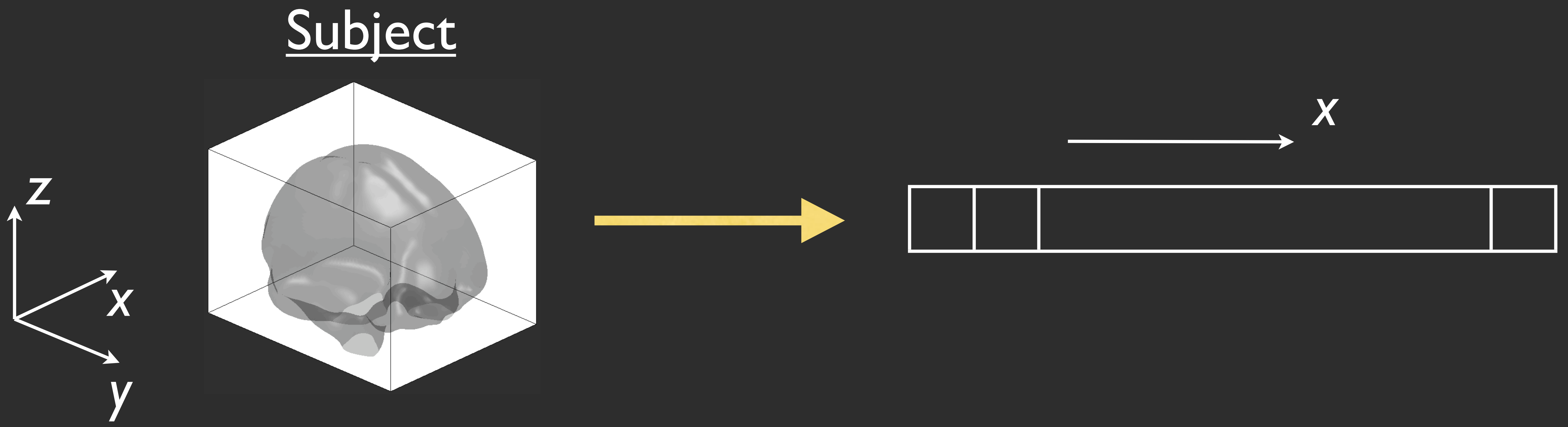
The major caveat of fuzzy sets is the missing link between <u>cluster validity</u> and <u>probability theory</u>

- cannot say "given X, we reject the null hypothesis that $k = 1$ if $p < 0.05$"

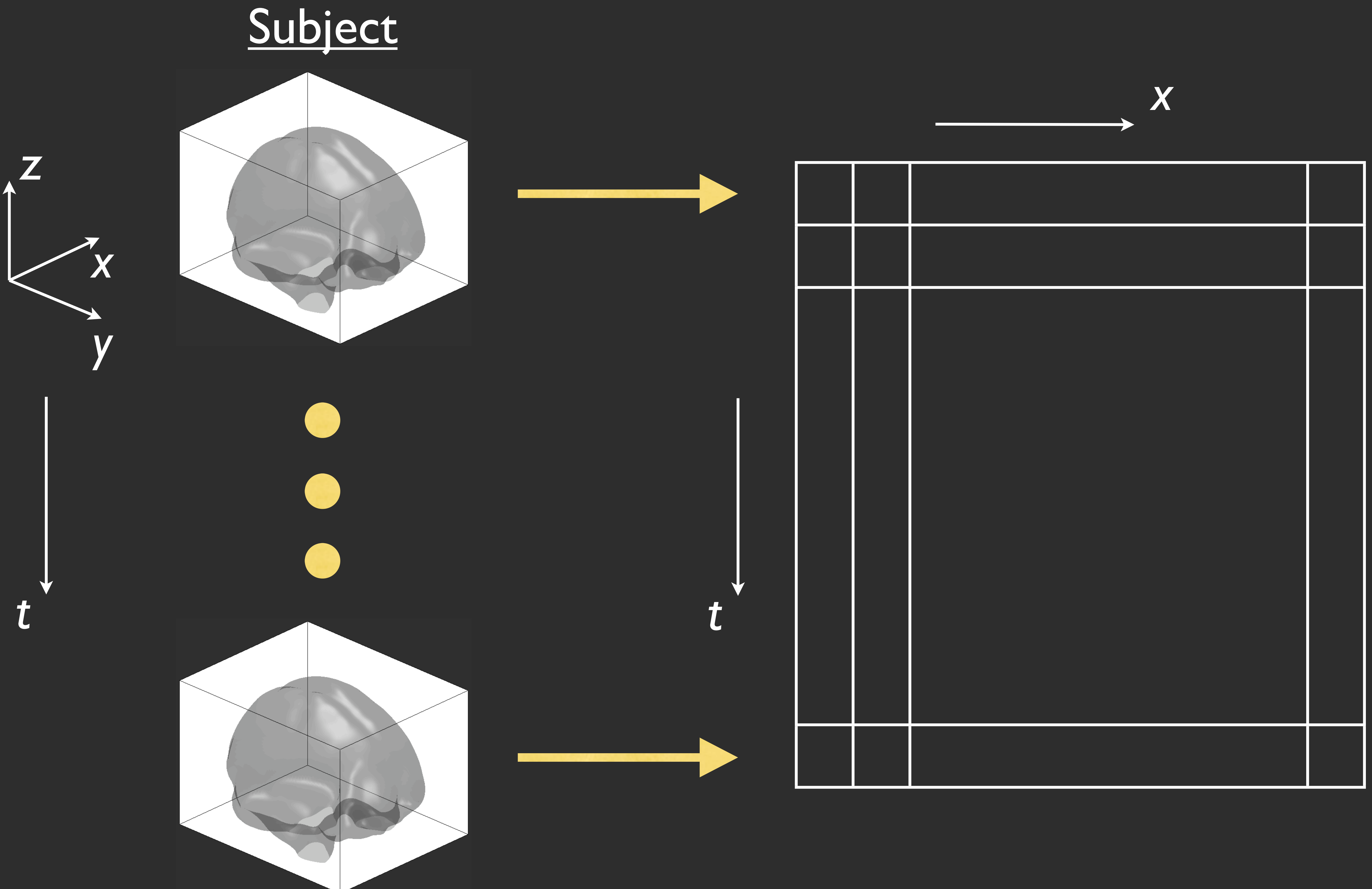
Unique advantages:

- systematically analyses complex data yielding results in a human-readable form
- does not require model pattern *a priori*
- quantitatively determines optimal k value

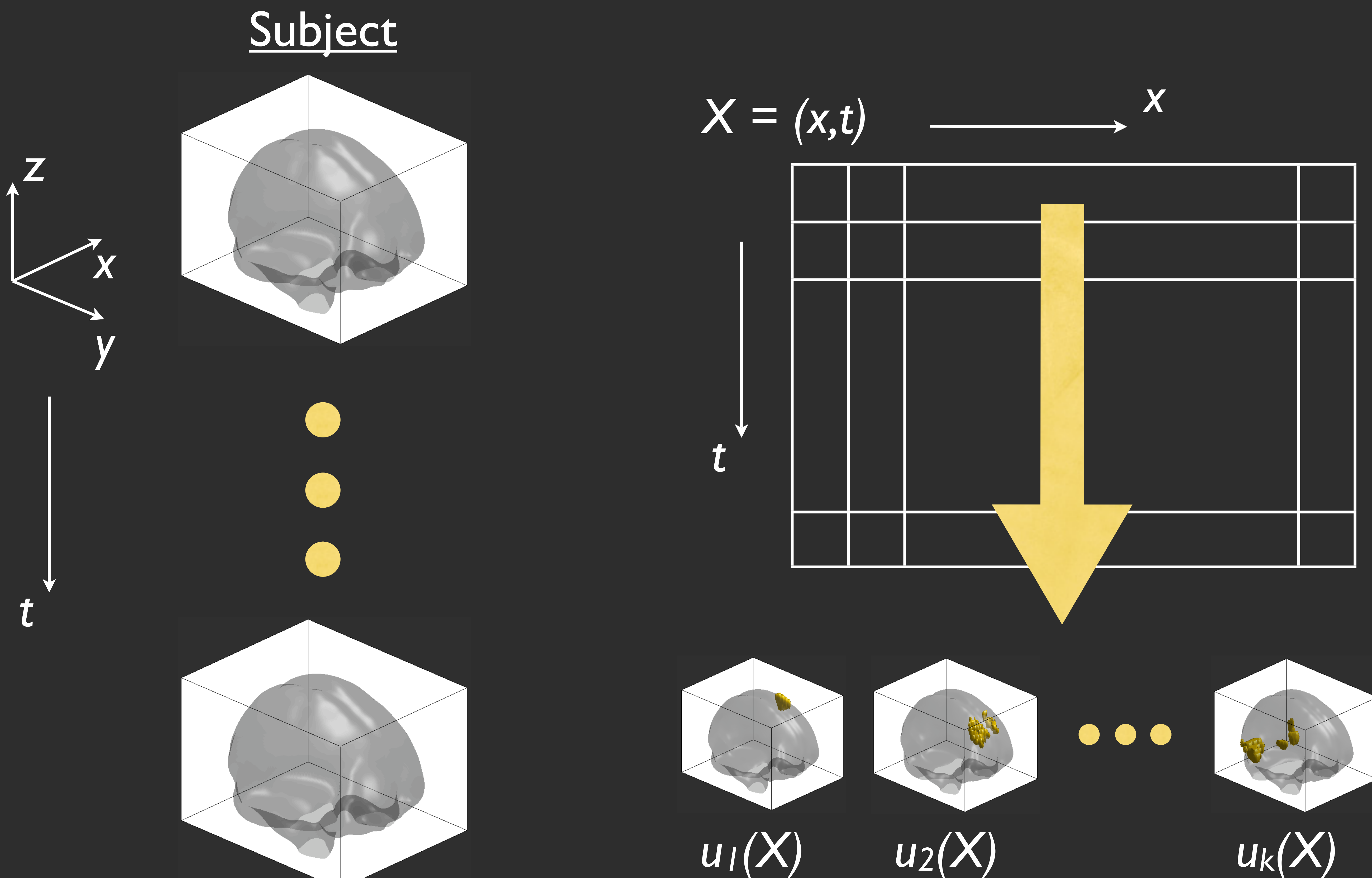
Neuroimage Analysis



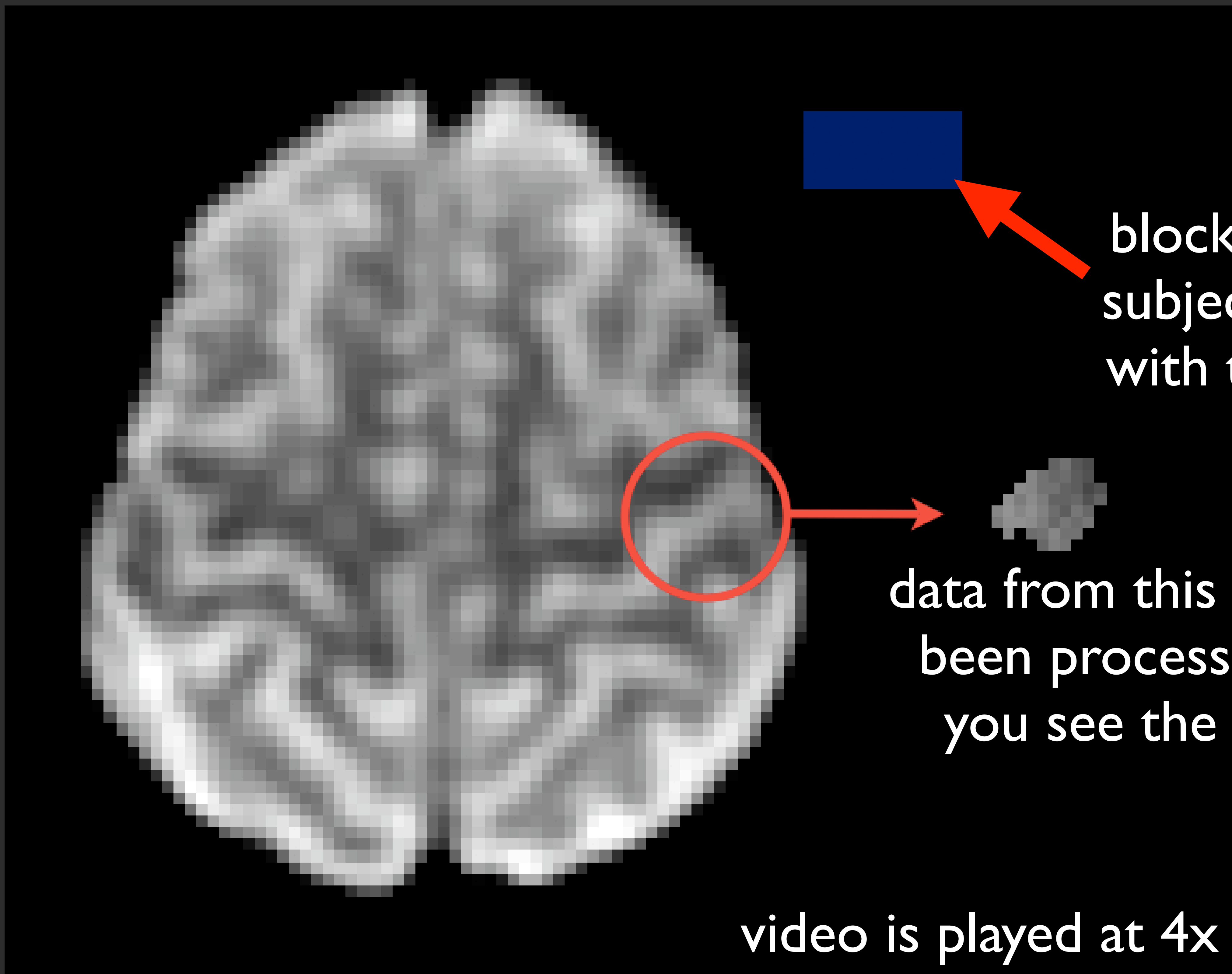
Neuroimage Analysis



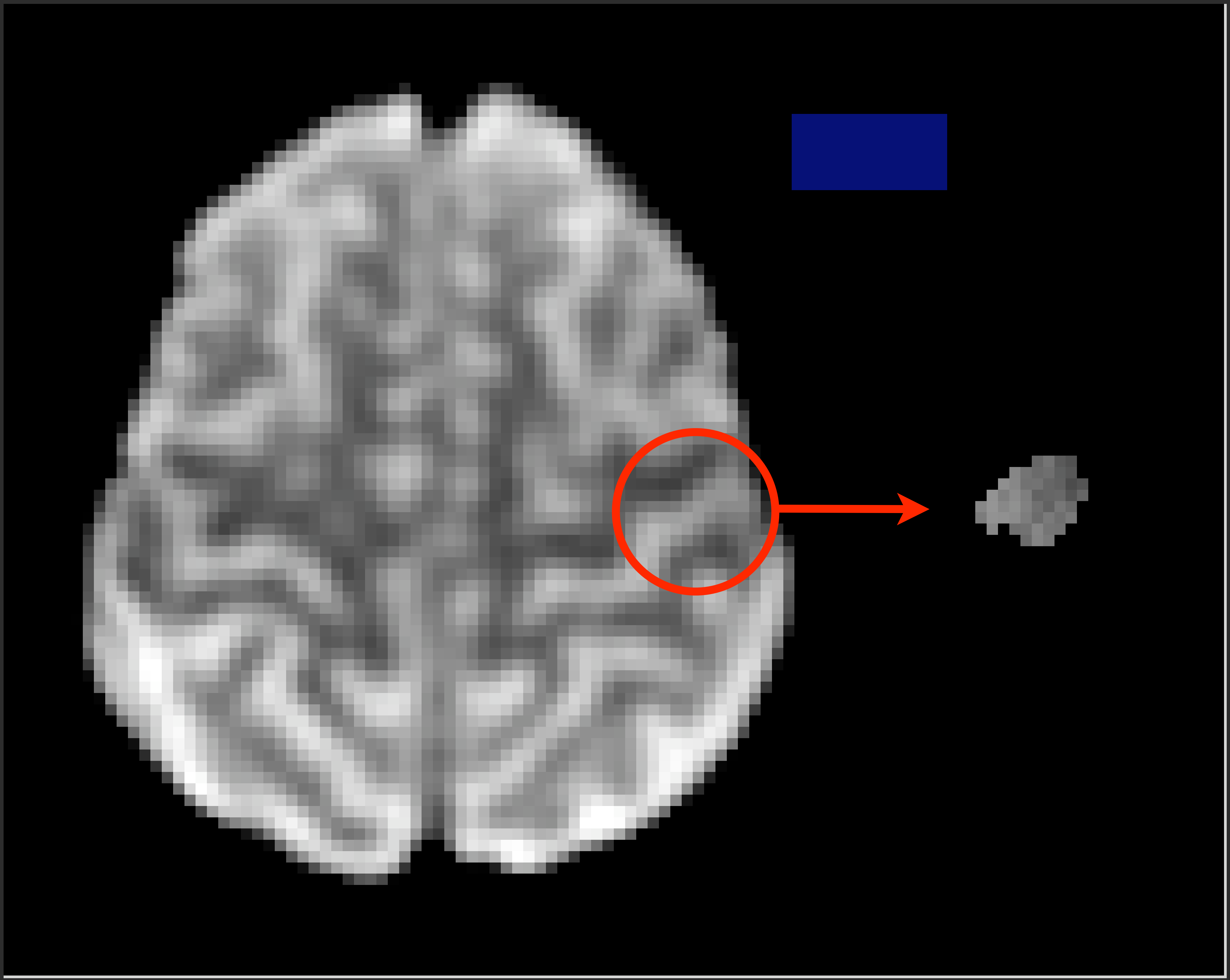
Neuroimage Analysis



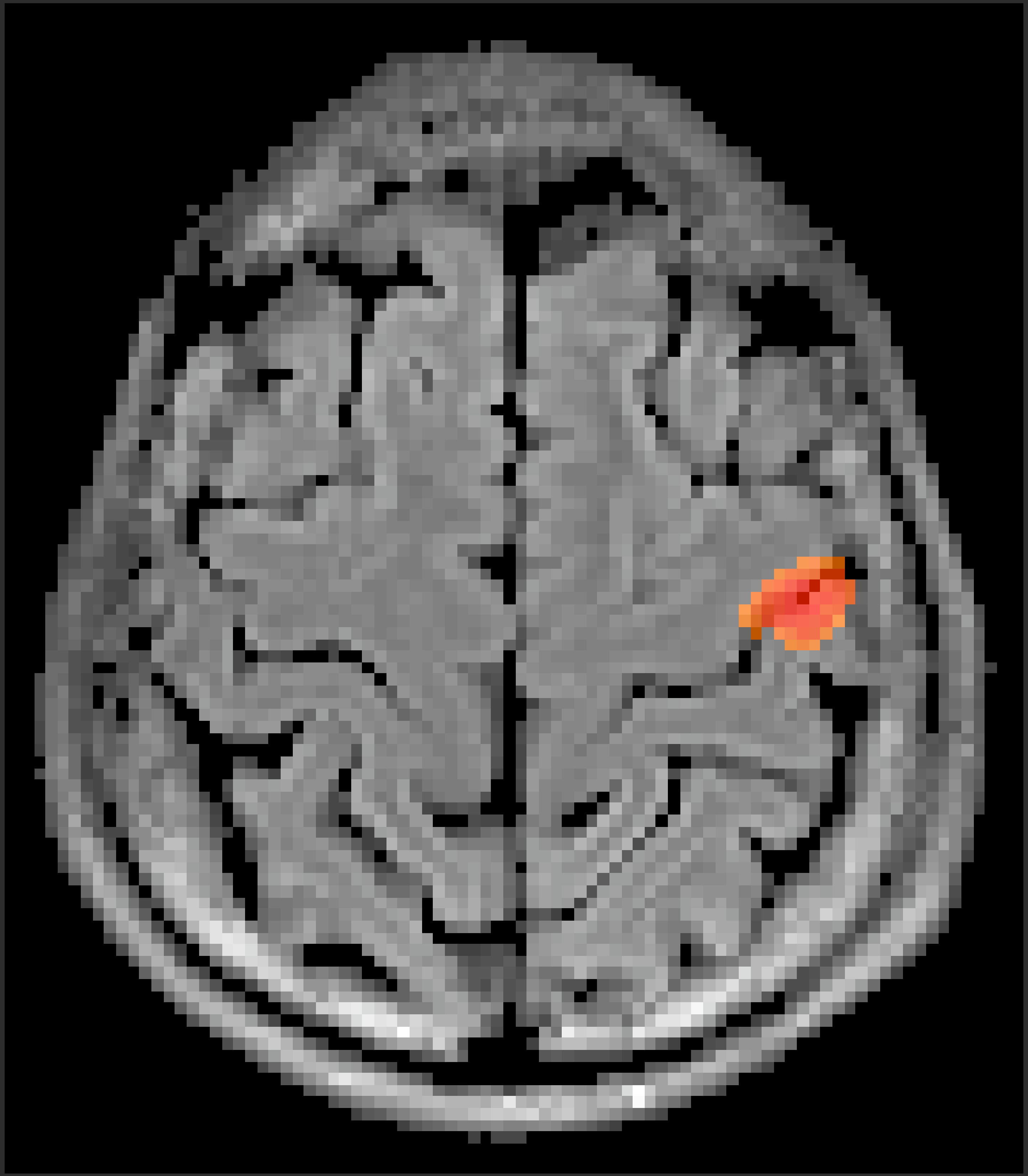
Neuroimage Analysis

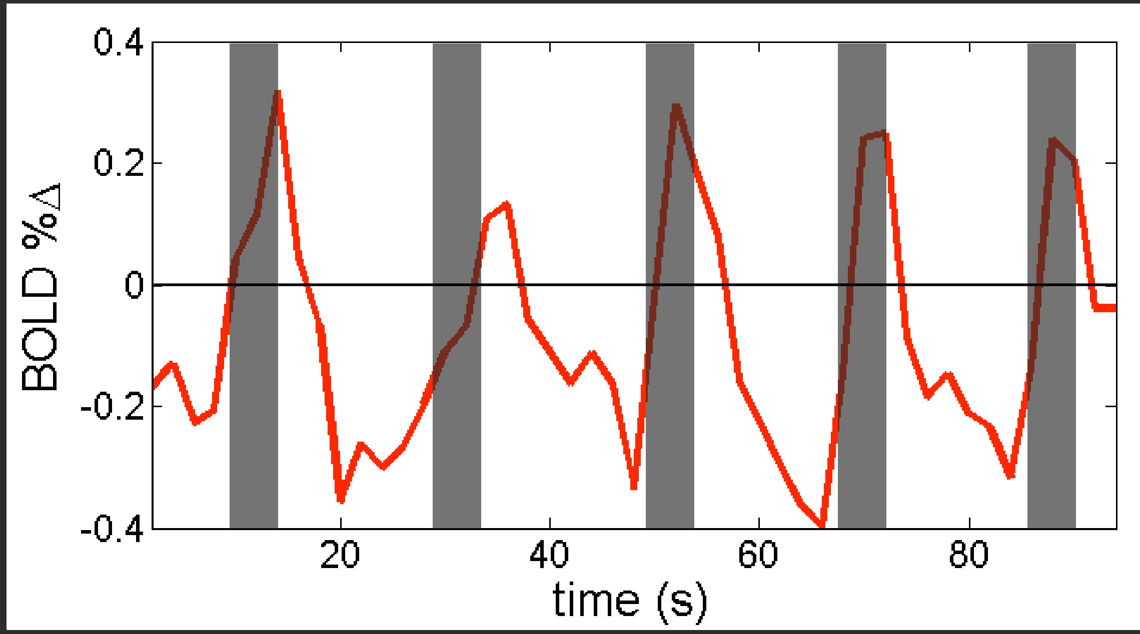


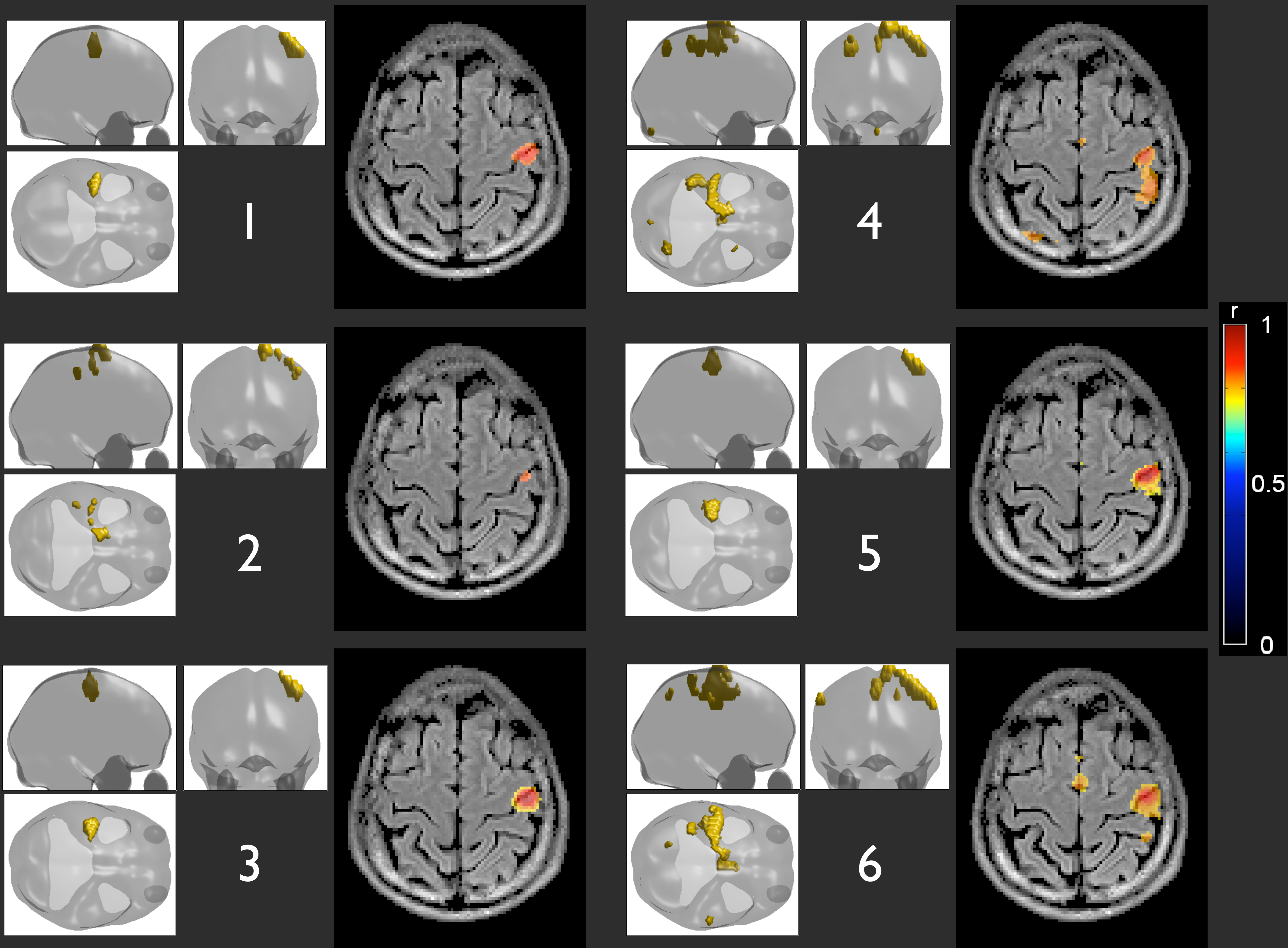
Neuroimage Analysis

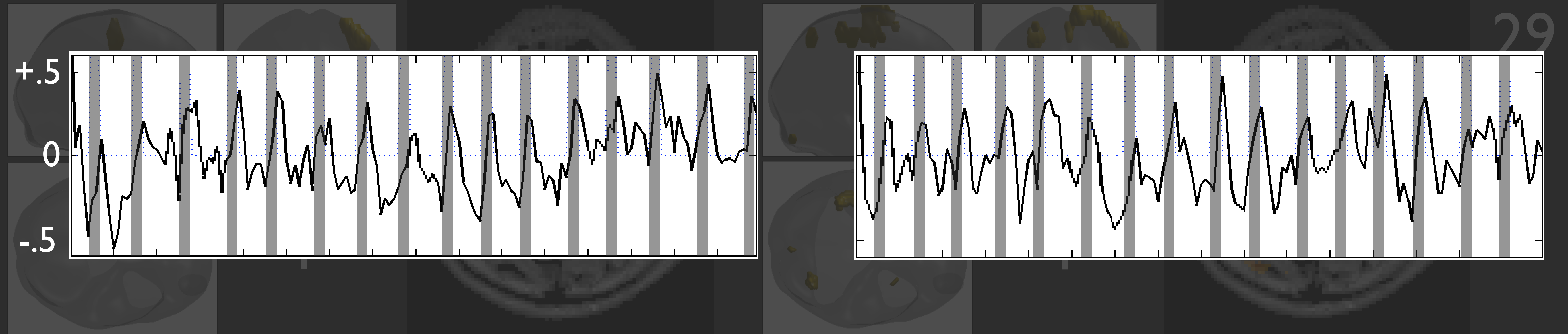


Neuroimage Analysis

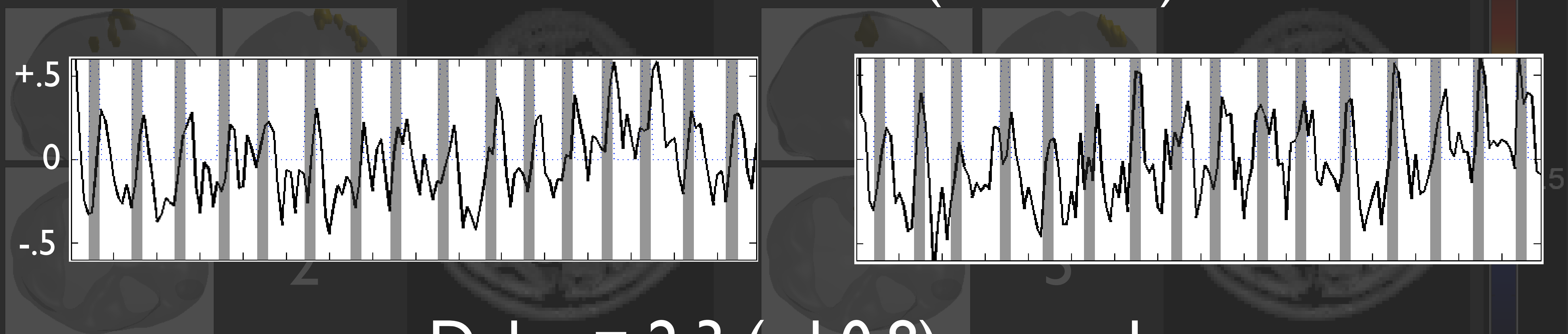




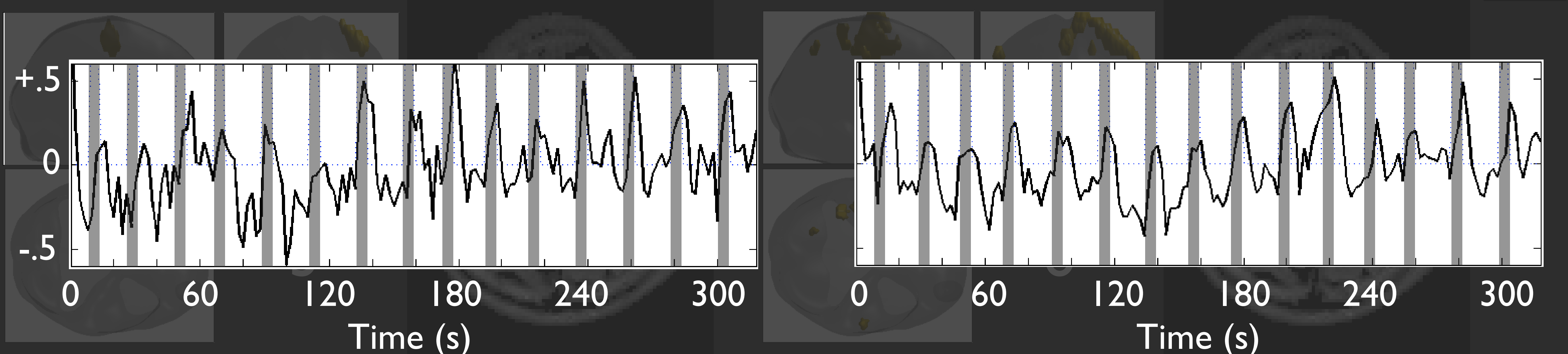

1
2
3
4
5
6
r
1
0.5
0



Correlation = 0.48 (sd 0.035)



Delay = 2.3 (sd 0.8) seconds

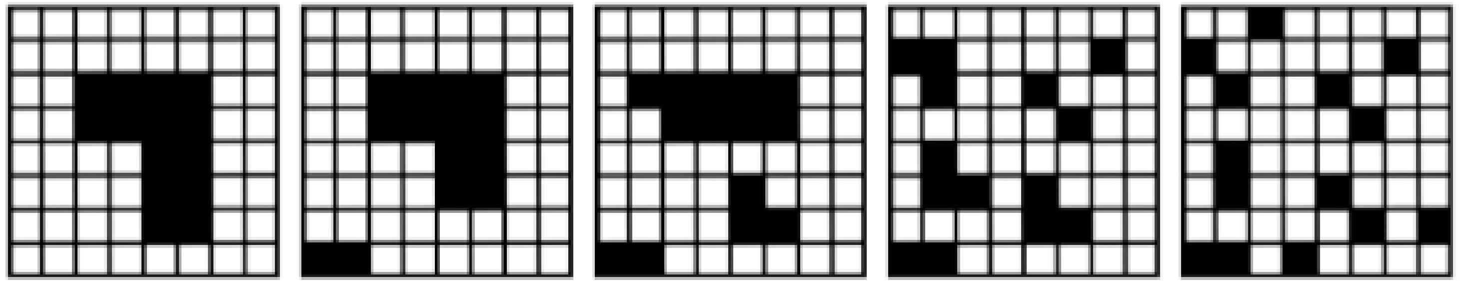


Space-time structure of BOLD response signals

Space-time structure

Space: cluster contiguity function

- measures the spatial contiguity of a cluster based on the position of its member voxels



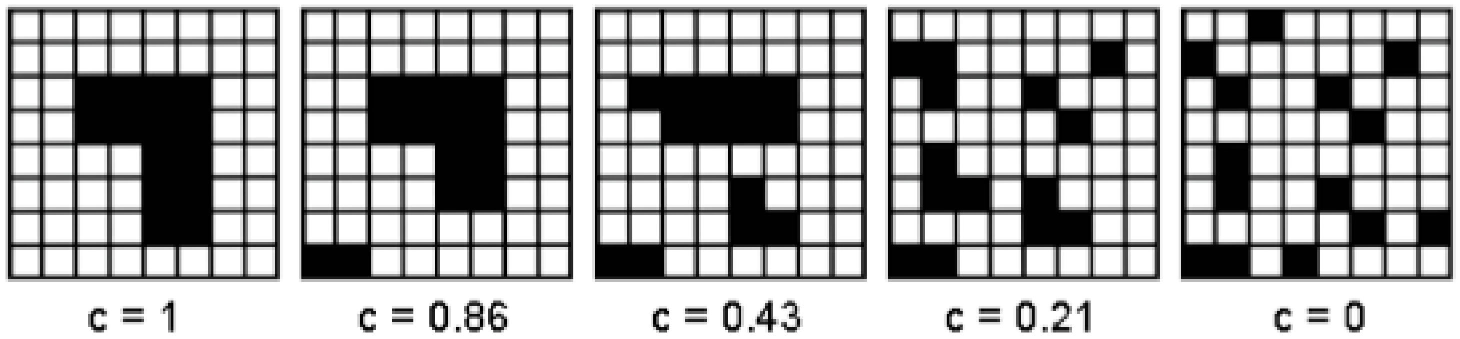
c = 1 | c = 0.86 | c = 0.43 | c = 0.21 | c = 0

$$c = \frac{1}{G_i |X_i|} \sum_{j=m}^{M} j g_j$$

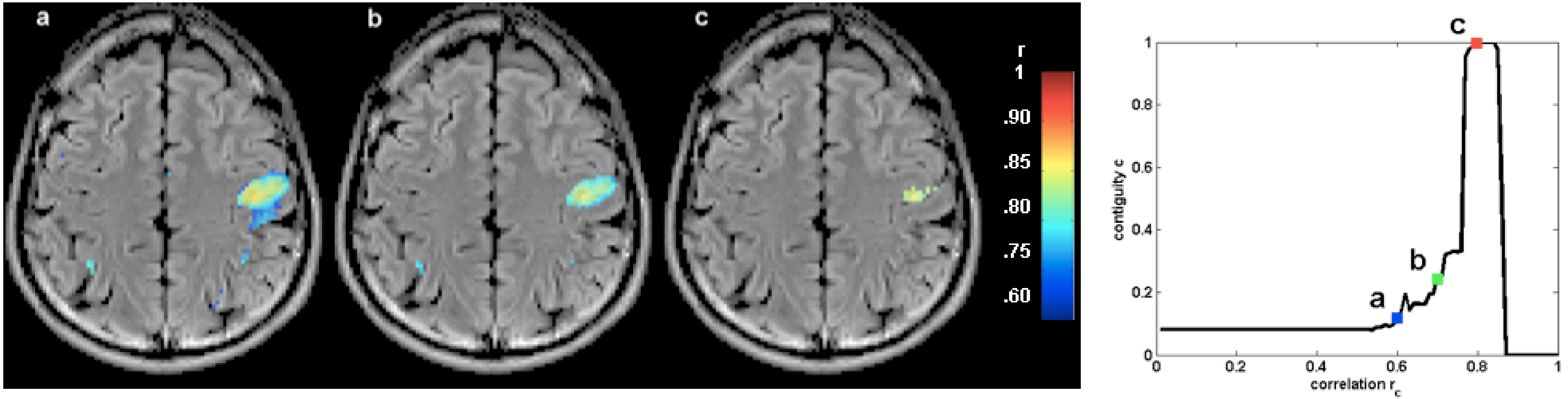
Space-time structure

Space: cluster contiguity function

- measures the spatial contiguity of a cluster based on the position of its member voxels



$$c = \frac{1}{G_i|X_i|}\sum_{j=m}^{M} j g_j$$



Space-time structure

Time: causal cross-correlation function

- stimulus response measured by correlation between *delayed voxel* and *motor* time series

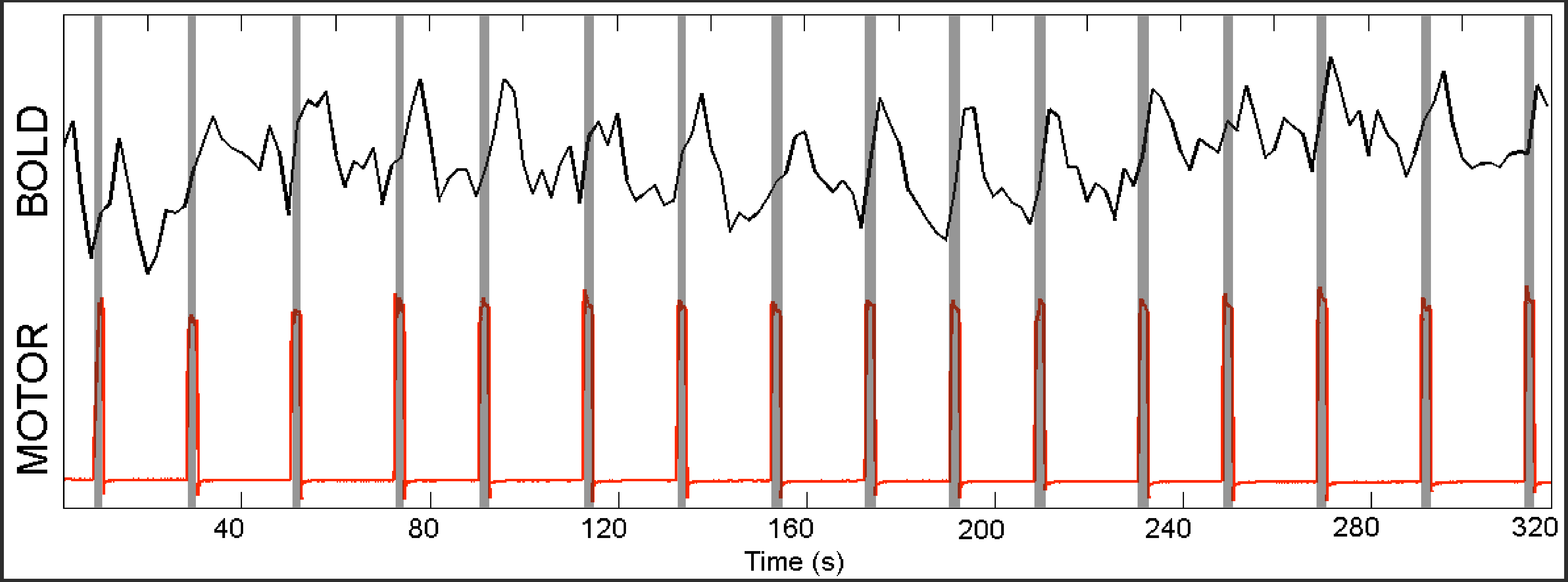
$$x[n] \star p[n] = \sum_{n=0}^{N-1} x[n+d-N]p[n], \quad d = N, \cdots, N + \Delta t,$$

Space-time structure

Time: causal cross-correlation function

- stimulus response measured by correlation between *delayed voxel* and *motor* time series

$$x[n] \star p[n] = \sum_{n=0}^{N-1} x[n+d-N]p[n], \quad d = N, \cdots, N+\Delta t,$$



Space-time structure

Comments on the proposed features

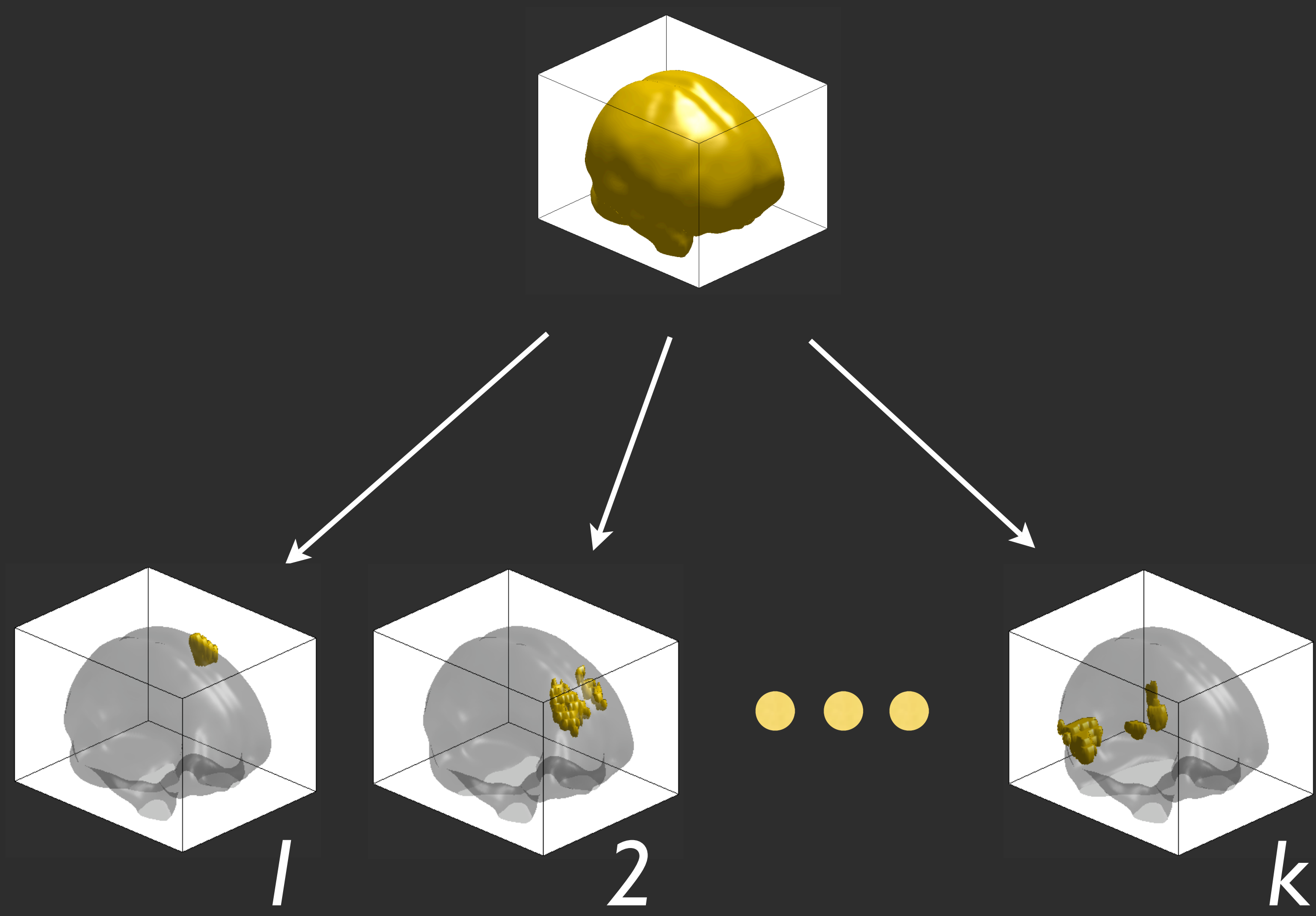
- spatial contiguity function:
  + indicates presence of focused responses
  + responses can be of any shape
  - requires input for minimum group & clique size
- causal cross-correlation function:
  + indicated presence of delayed responses
  + responses can be positive or negative
  - is not suitable if delay varies during session

Bayesian hierarchical model for cluster analysis

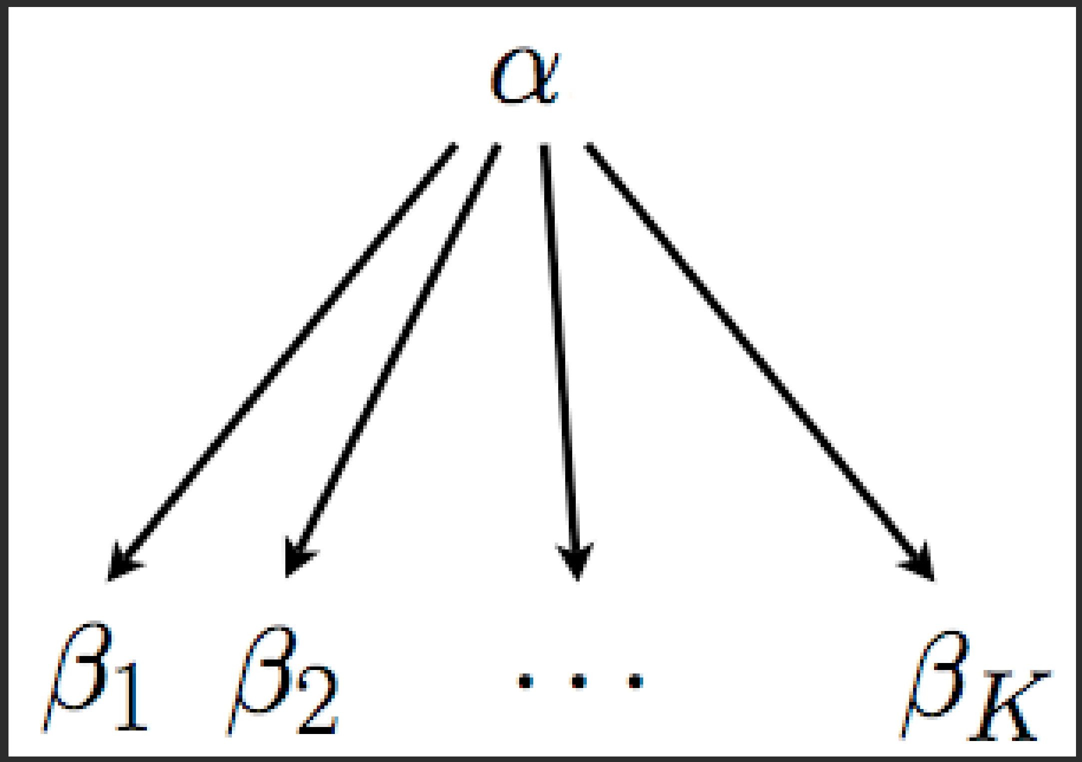
Bayesian hierarchical model

Bayesian hierarchical correlation model w.r.t. the motor signal

Model



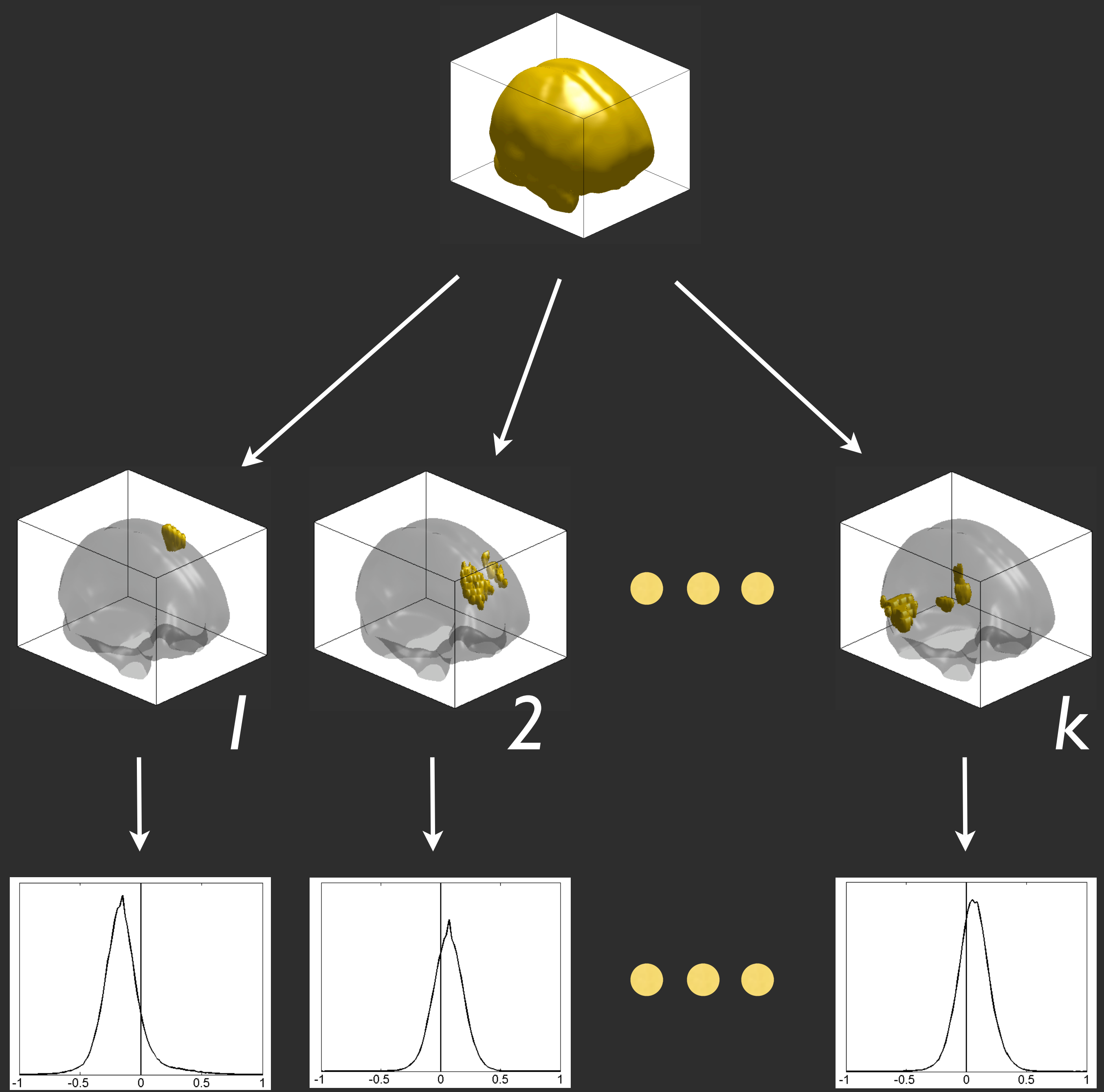
Parameters



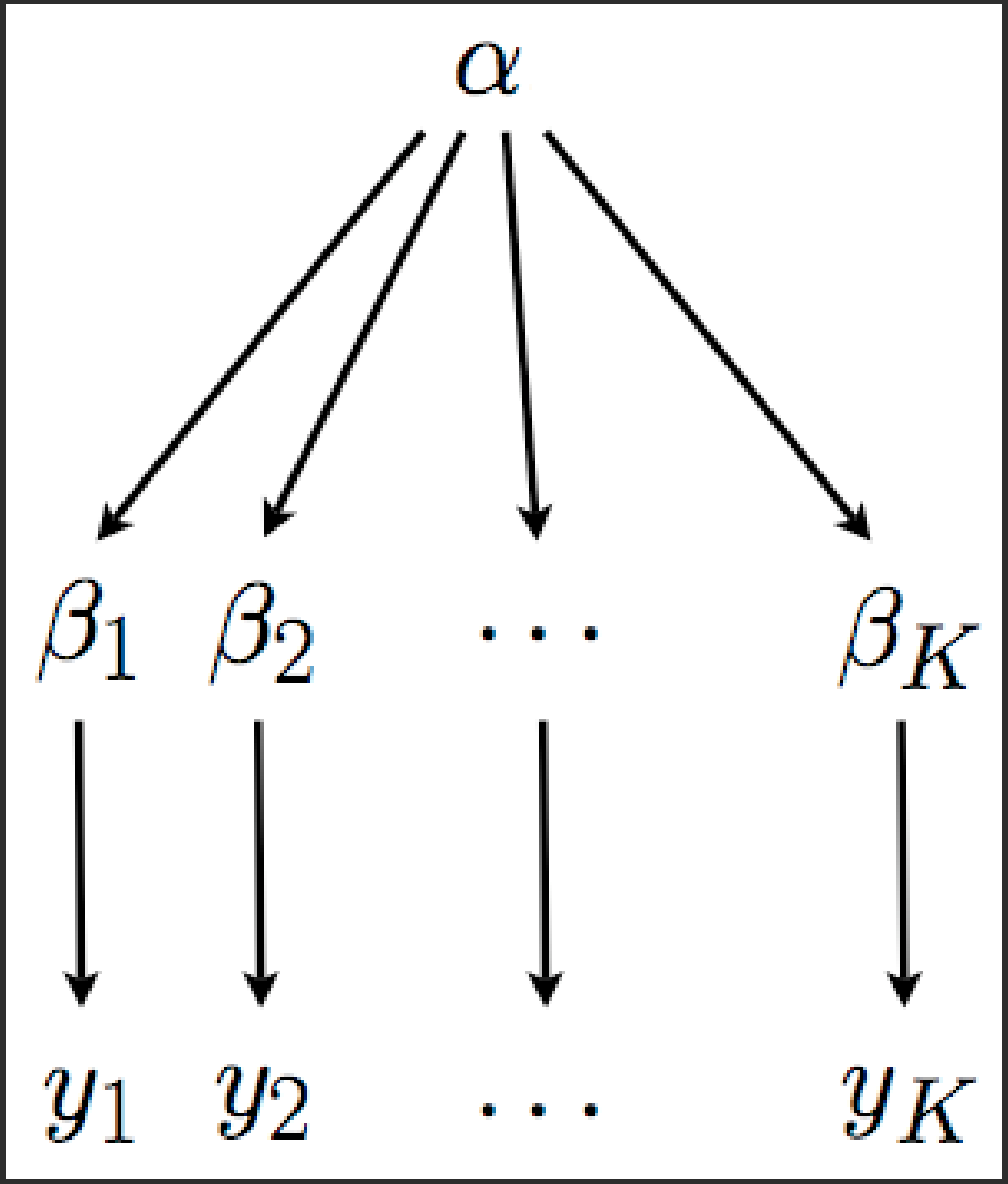
Bayesian hierarchical model

Bayesian hierarchical correlation model w.r.t. the motor signal

Model



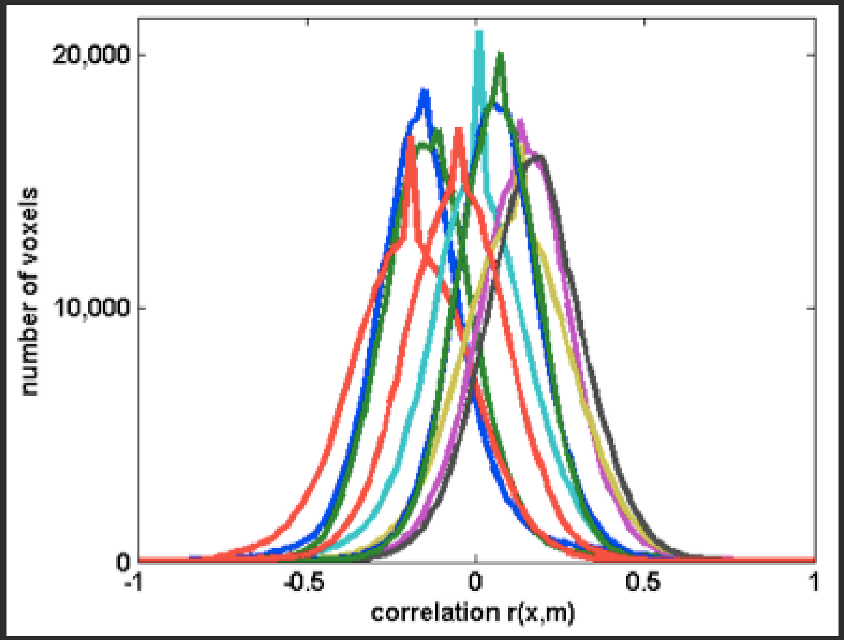
Parameters



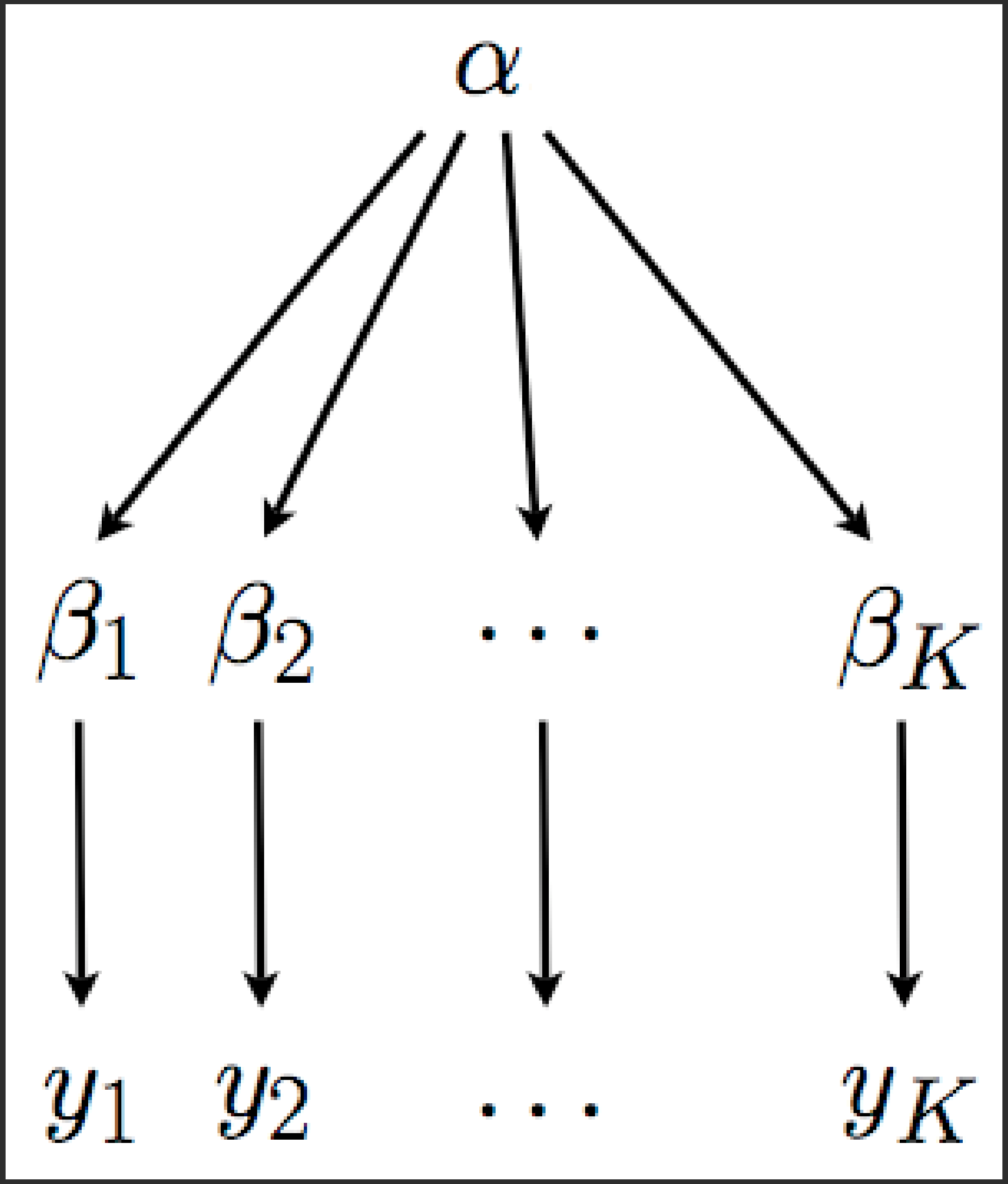
Bayesian hierarchical model

Bayesian hierarchical correlation model w.r.t. the motor signal

Global signal



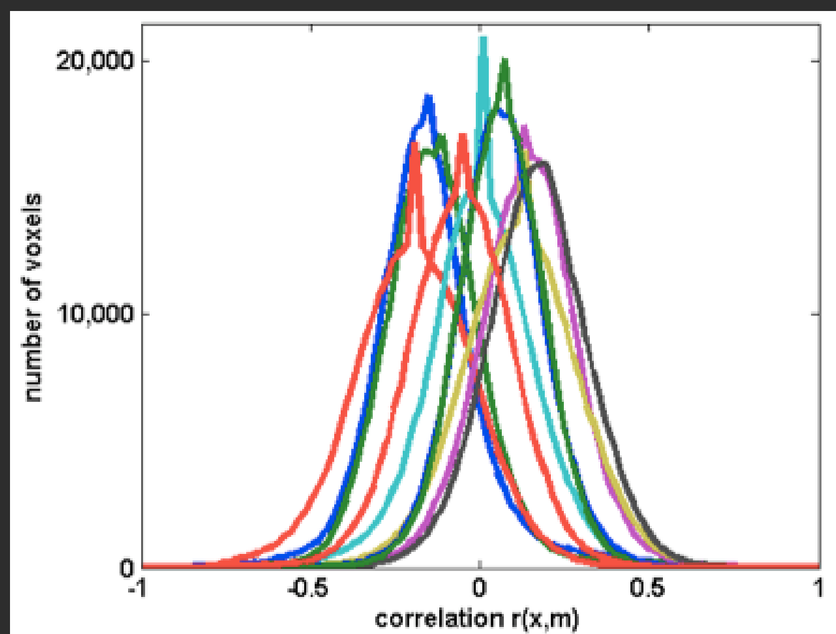
Parameters



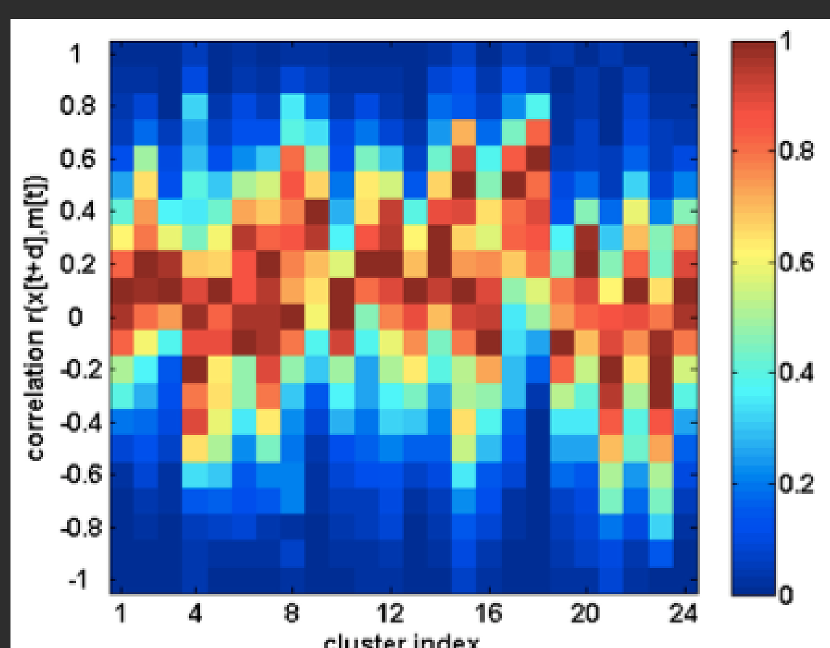
Bayesian hierarchical model

Bayesian hierarchical correlation model w.r.t. the motor signal

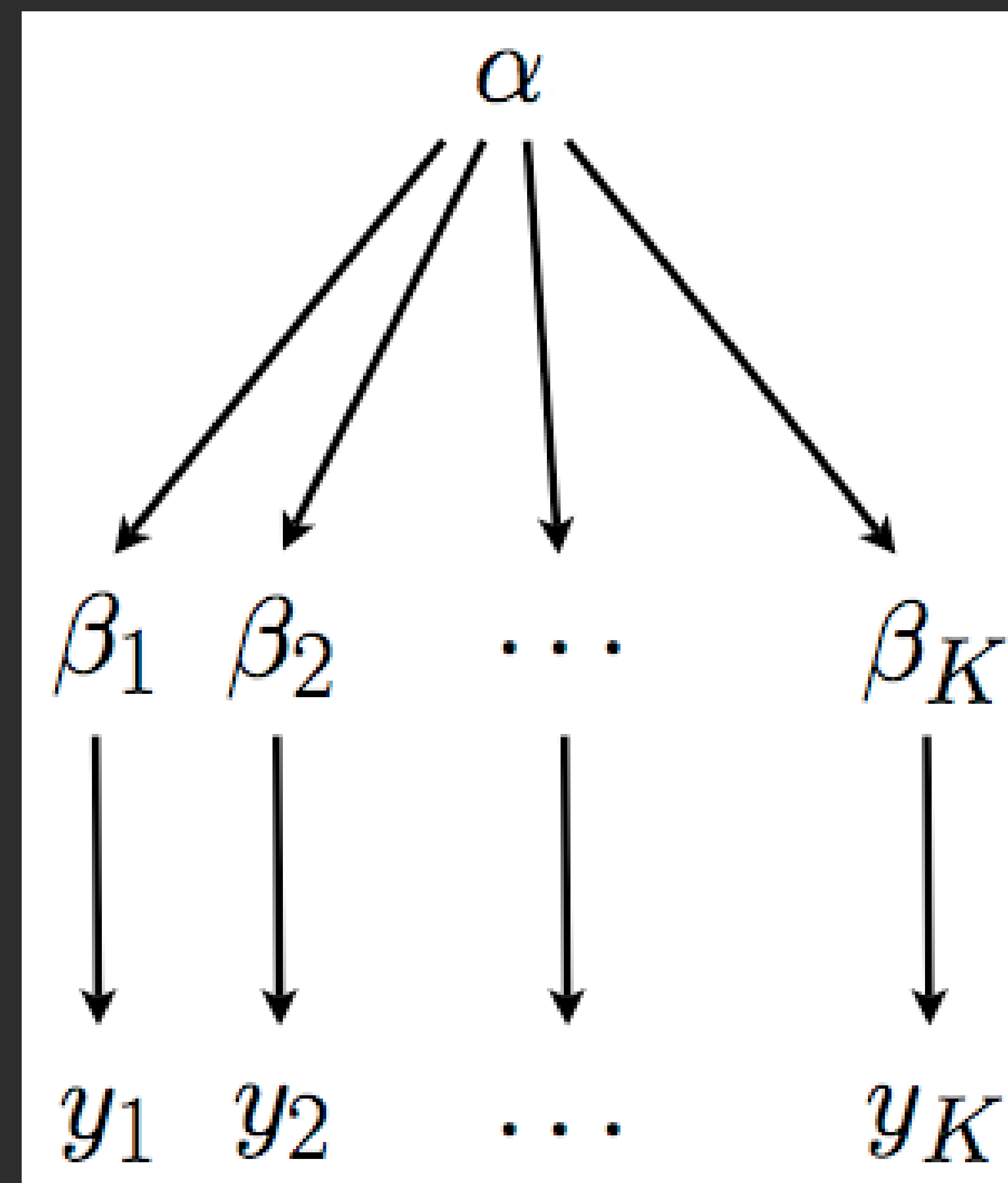
Global signal



Cluster signals



Parameters



Bayesian hierarchical model

Model implementation

- we seek the *joint posterior probability density* for the parameters modelling *global signal* and *each cluster*

$$p(\alpha, \beta \,|\, y) \propto p(\alpha)\, p(\beta \,|\, \alpha)\, p(y \,|\, \alpha, \beta)$$

Bayesian hierarchical model

Model implementation

- we seek the *joint posterior probability density* for the parameters modelling *global signal* and *each cluster*

$$p(\alpha, \beta \mid y) \propto p(\alpha)\, p(\beta \mid \alpha)\, p(y \mid \alpha, \beta)$$

  - the model (alpha, beta) is fit to the data (y) by Bayesian methods
  - used Markov chain Monte Carlo simulation to sample the posterior density

Bayesian hierarchical model

Model implementation

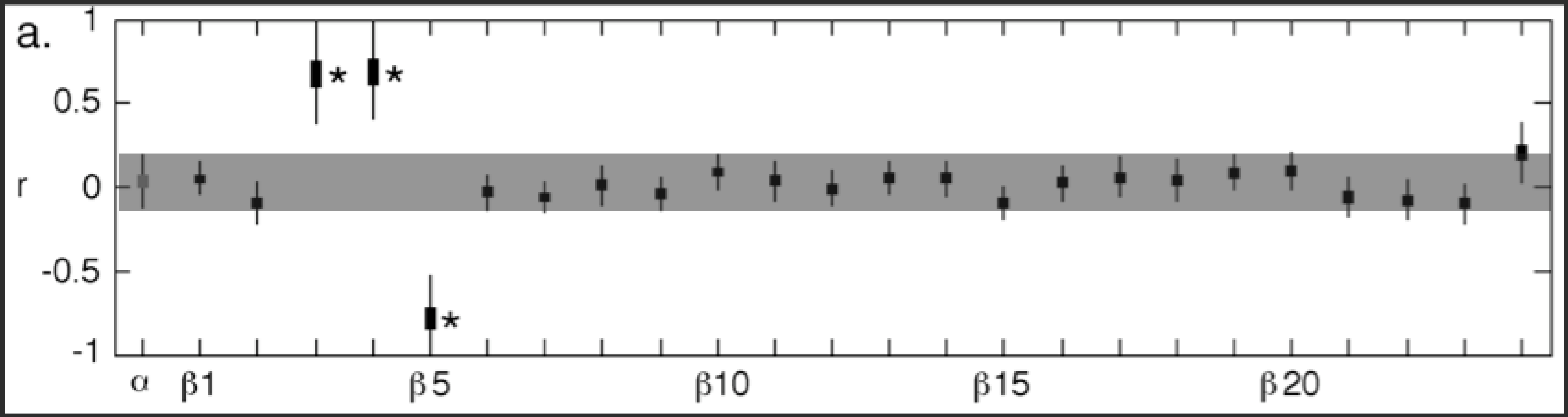
- we seek the *joint posterior probability density* for the parameters modelling *global signal* and *each cluster*

$$p(\alpha, \beta \,|\, y) \propto p(\alpha)\, p(\beta \,|\, \alpha)\, p(y \,|\, \alpha, \beta)$$

  - the model (alpha, beta) is fit to the data (y) by Bayesian methods
  - used Markov chain Monte Carlo simulation to sample the posterior density
- we consider a cluster significantly different from the global signal when $\Pr(\beta_i = \alpha \,|\, y) < 0.05$

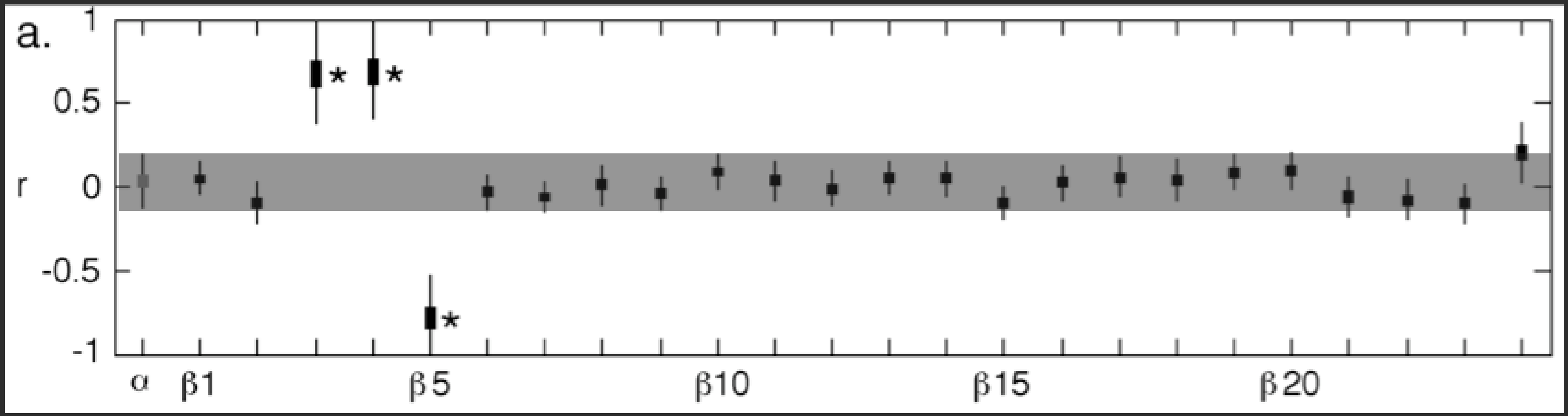
Bayesian hierarchical model

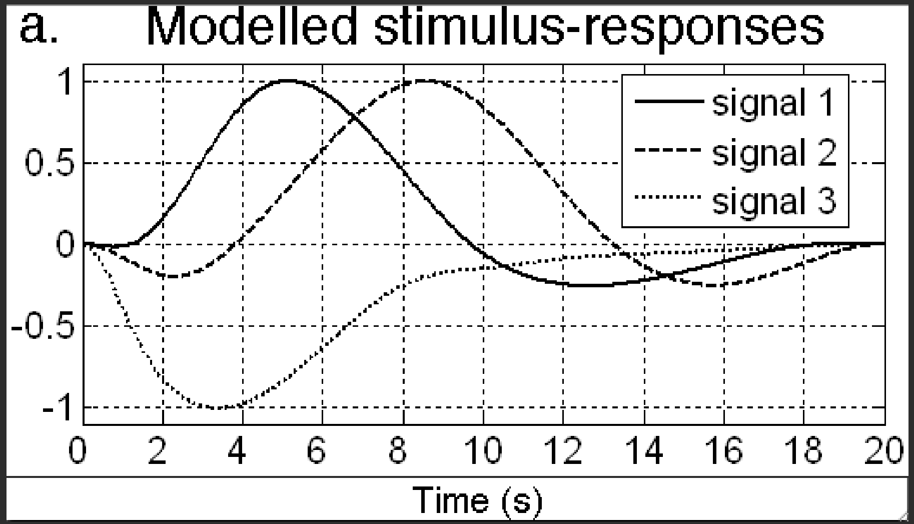
Demonstration using simulated data



Bayesian hierarchical model

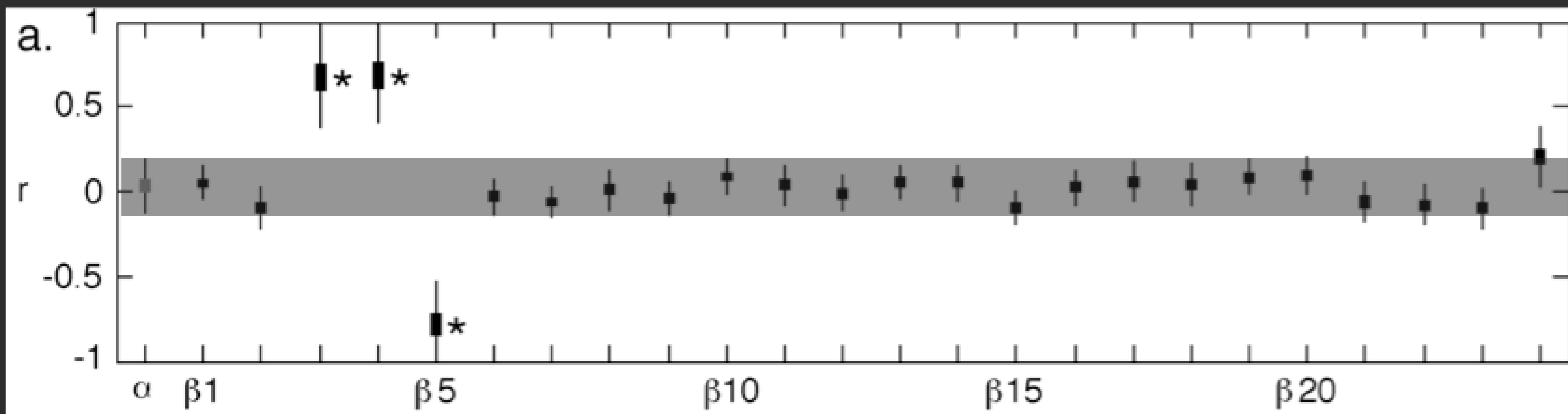
<u>Demonstration using simulated data</u>

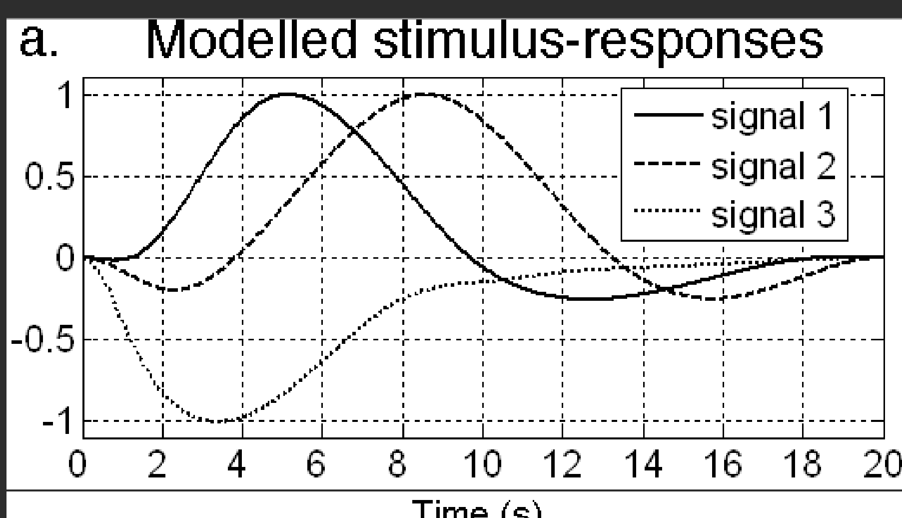


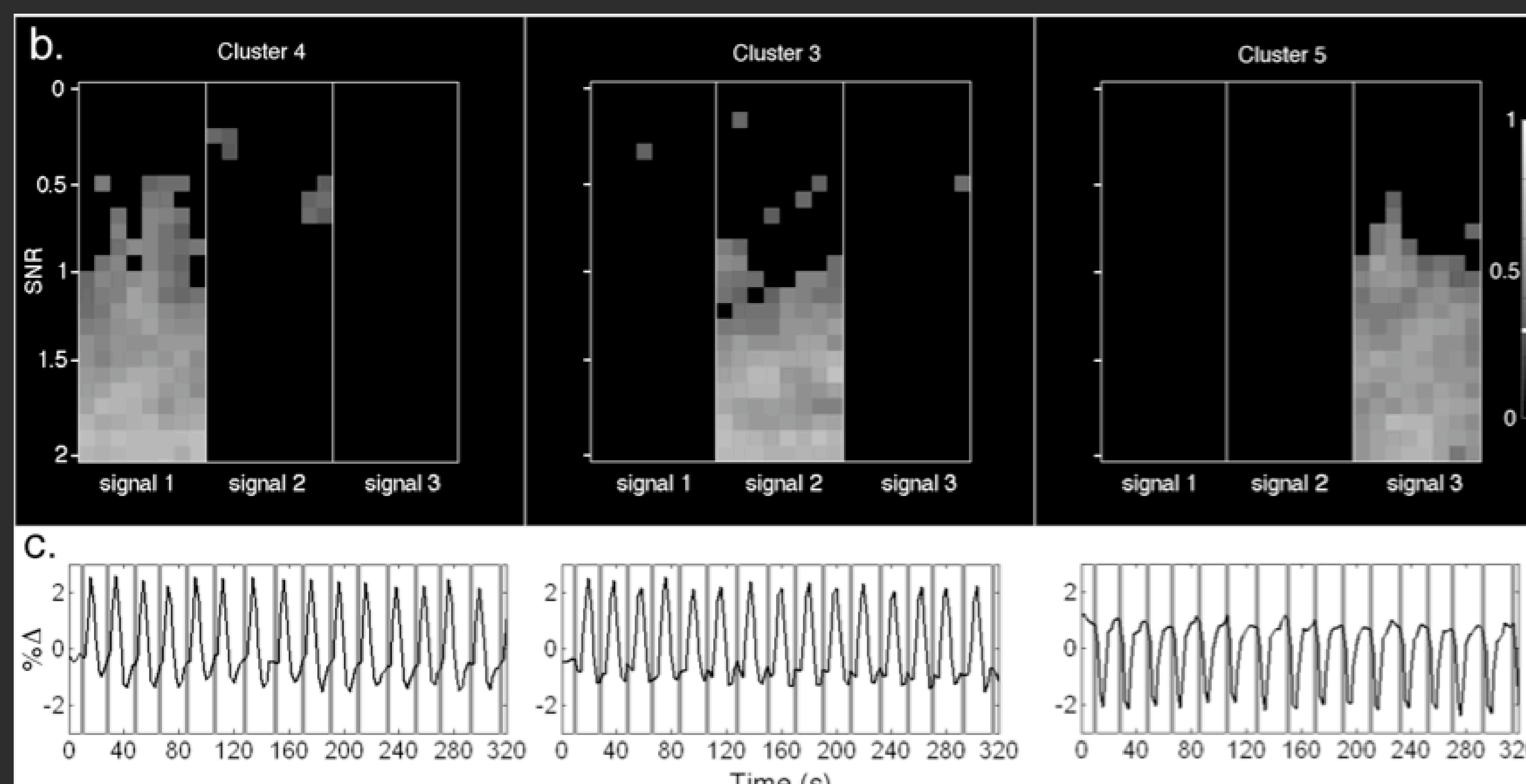


Bayesian hierarchical model

Demonstration using simulated data







Results

Results

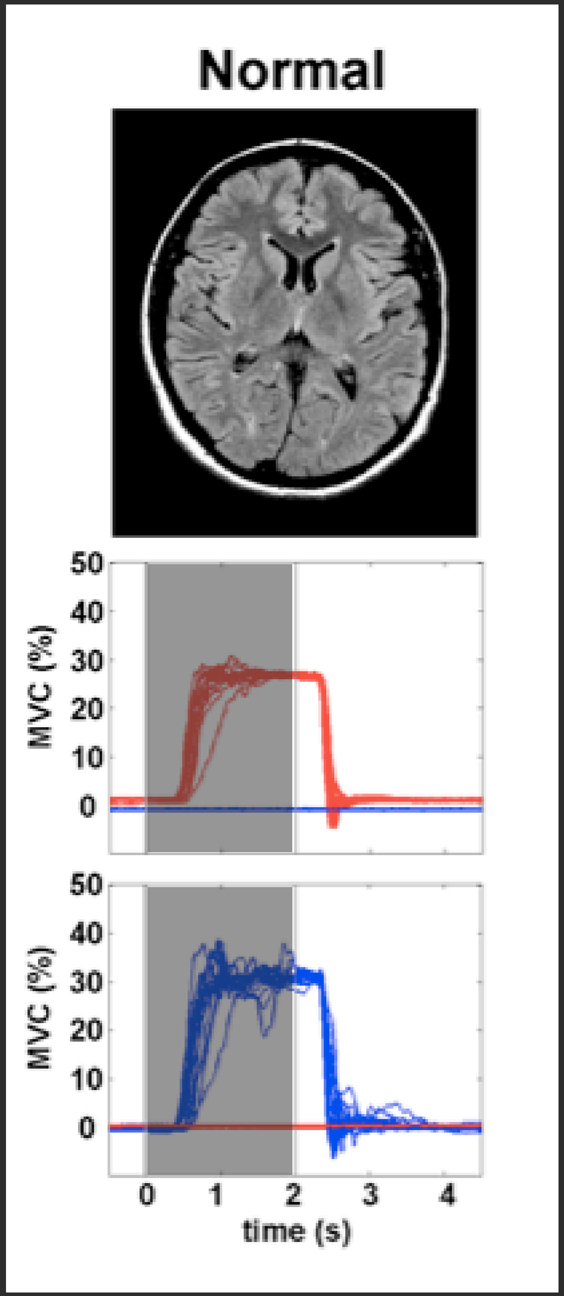
Motor task performance

Results

Motor task performance

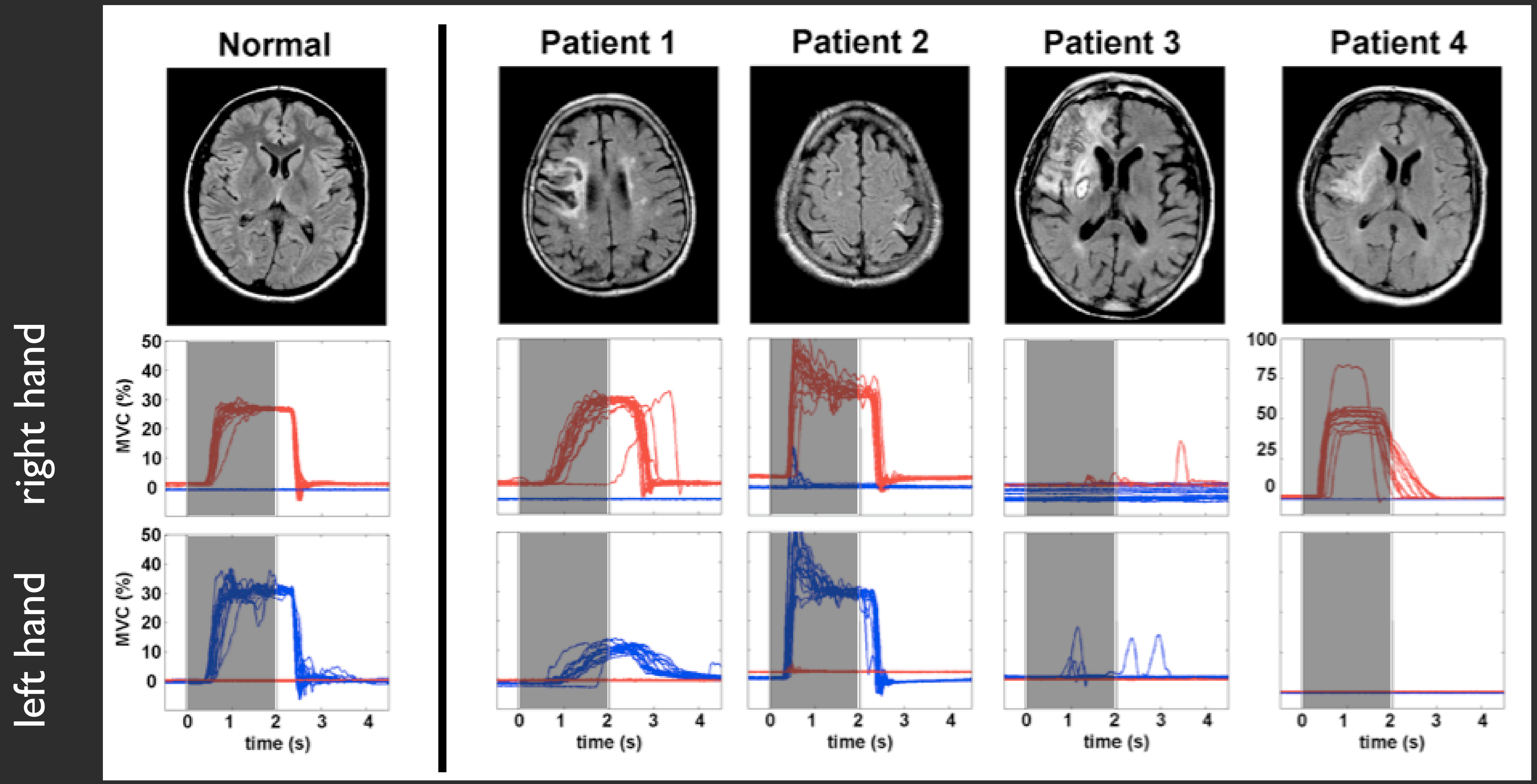
right hand

left hand



Results

Motor task performance



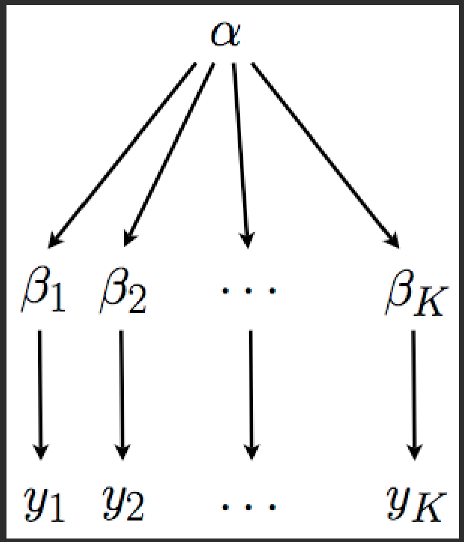
Results

<u>Motor task performance</u>

- Normal group responded to all events without extra responses
- Performance from stroke patients varied widely:
  - event responses 92-98% across group
  - patients 2 & 3 often performed extra responses
  - patient 2 often performed mirror responses
  - patient 3 exhibited cognitive deficit during task
  - patient 4 has a plegic left hand

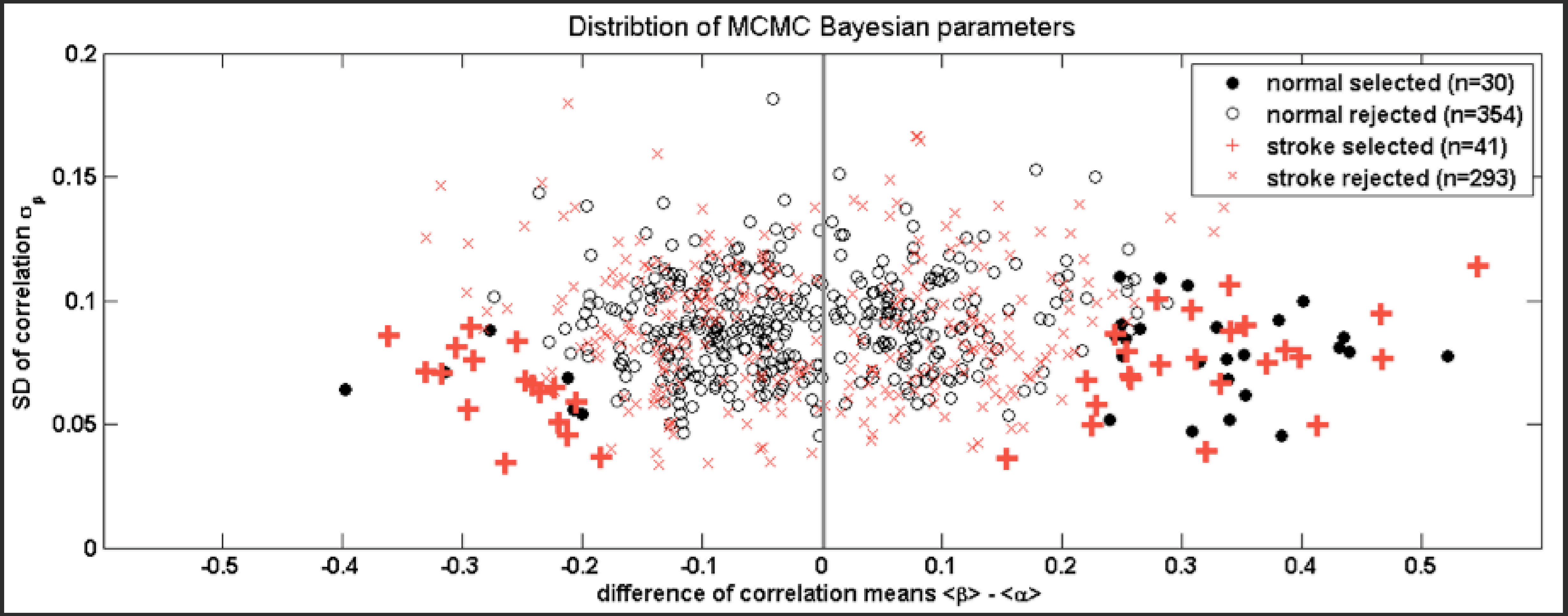
Results

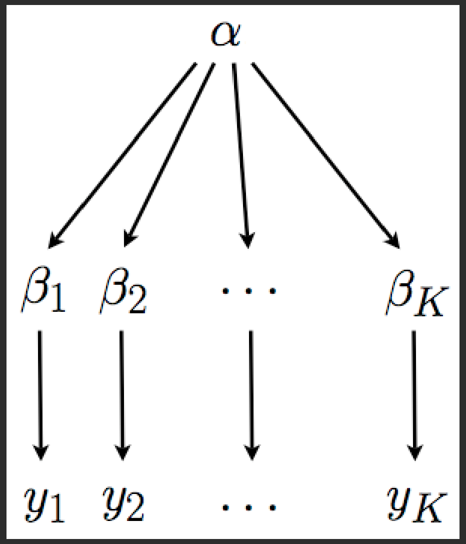
Bayesian hierarchical cluster analysis



Results

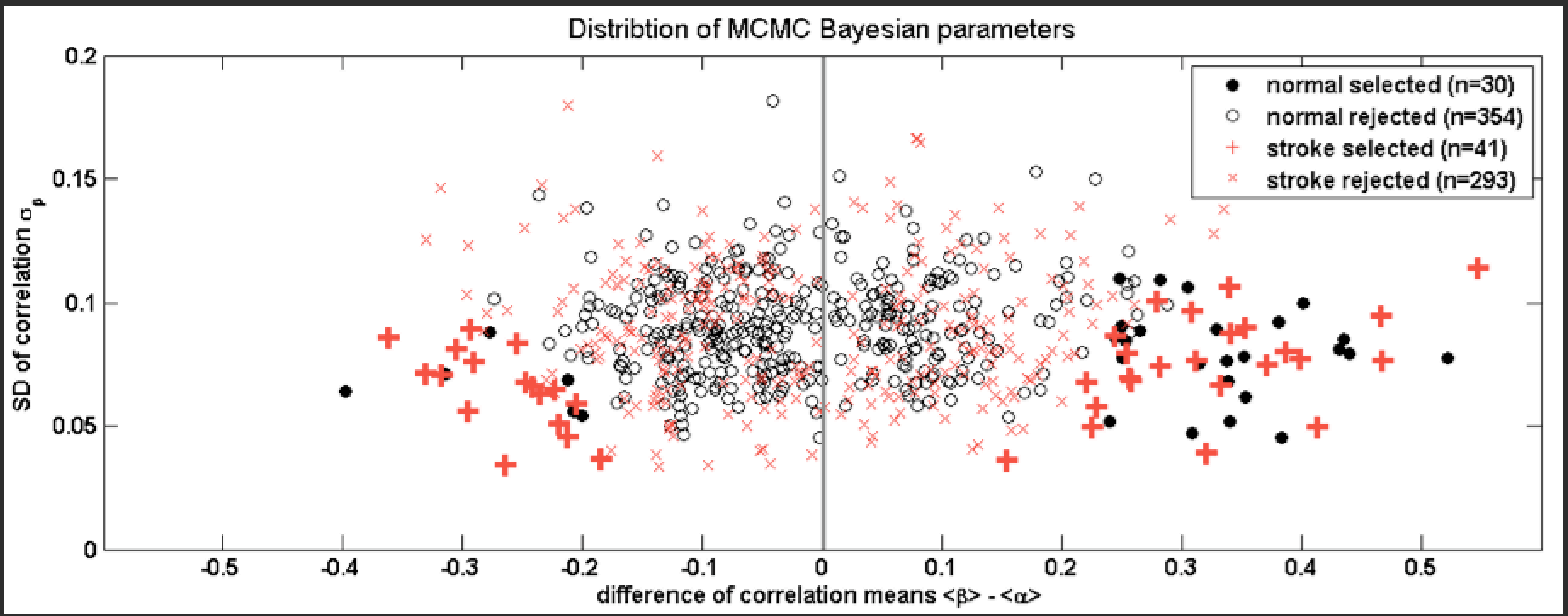
Bayesian hierarchical cluster analysis

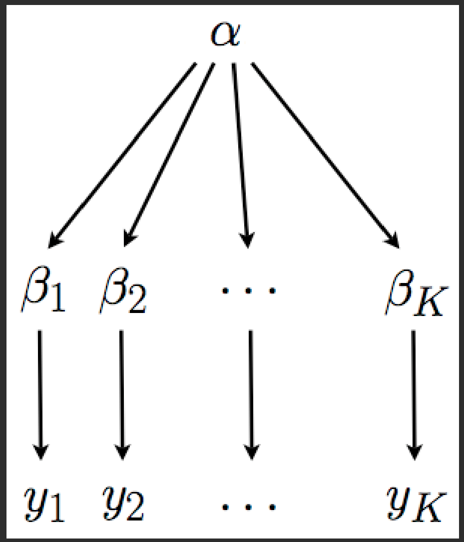




Results

Bayesian hierarchical cluster analysis





- the factors for cluster selection: *difference & certainty*
- rejected clusters fall evenly around **alpha**
- most normal selected clusters are positively correlated
- 58% more selected clusters from stroke group than normal
- many stroke group selected clusters are negative correlated

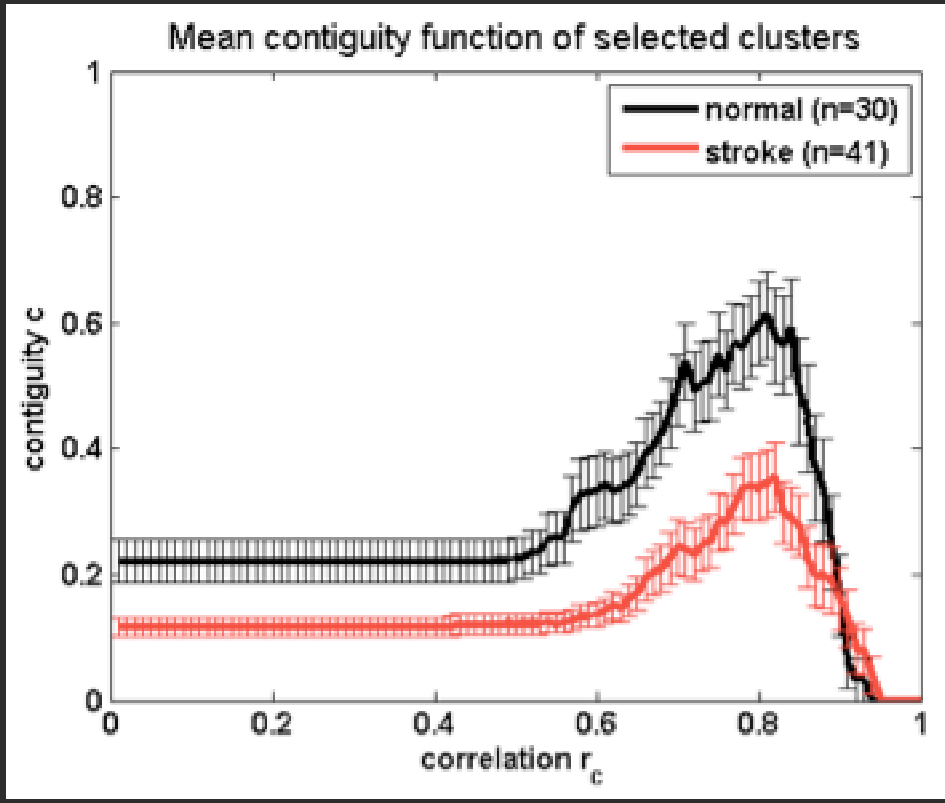
Results

Space-time structure of BOLD response signals

Results

Space-time structure of BOLD response signals

Space

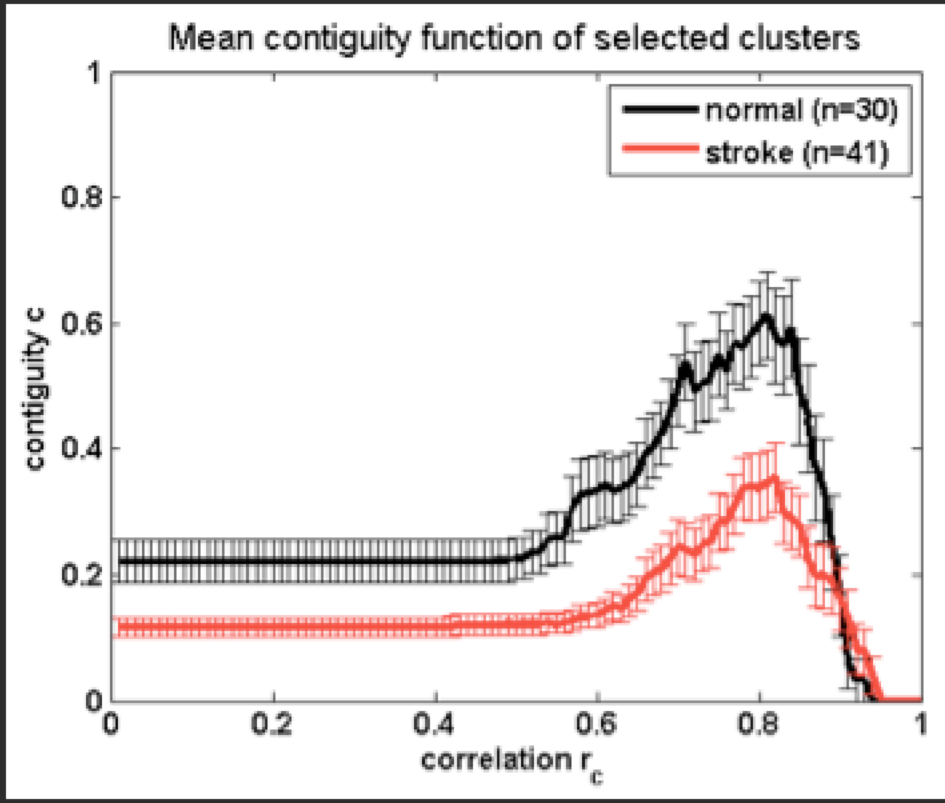


- stroke clutsers are significantly less contiguous than normal
- both groups have comparable signal-to-noise ratio

Results

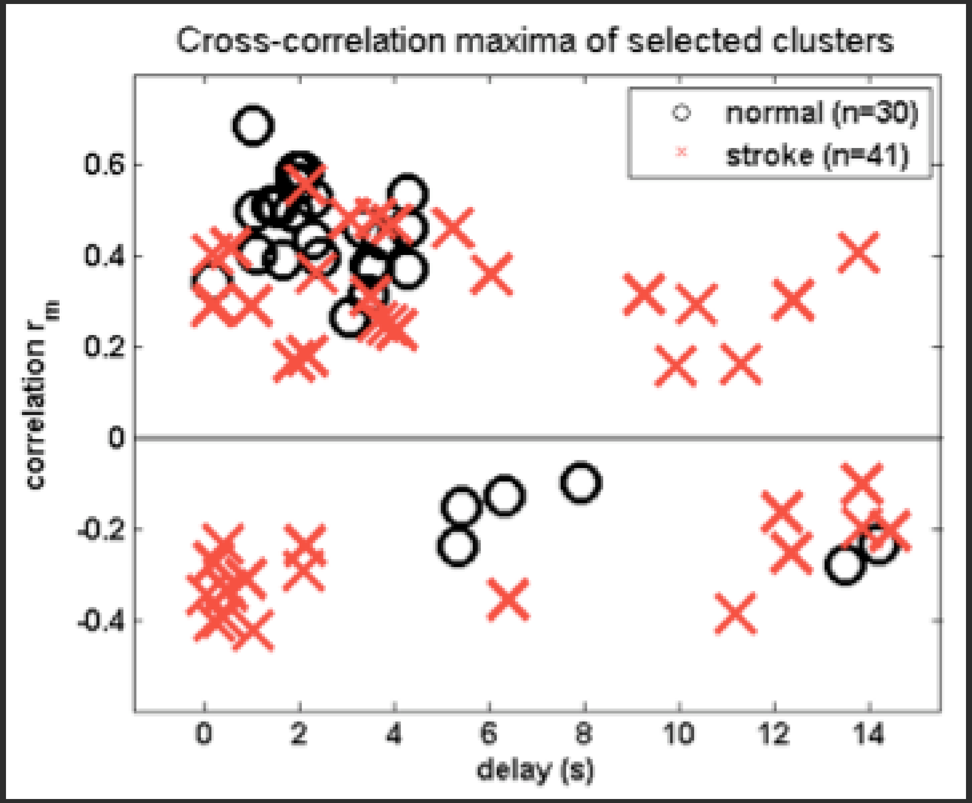
Space-time structure of BOLD response signals

Space



- stroke clutsers are significantly less contiguous than normal
- both groups have comparable signal-to-noise ratio

Time



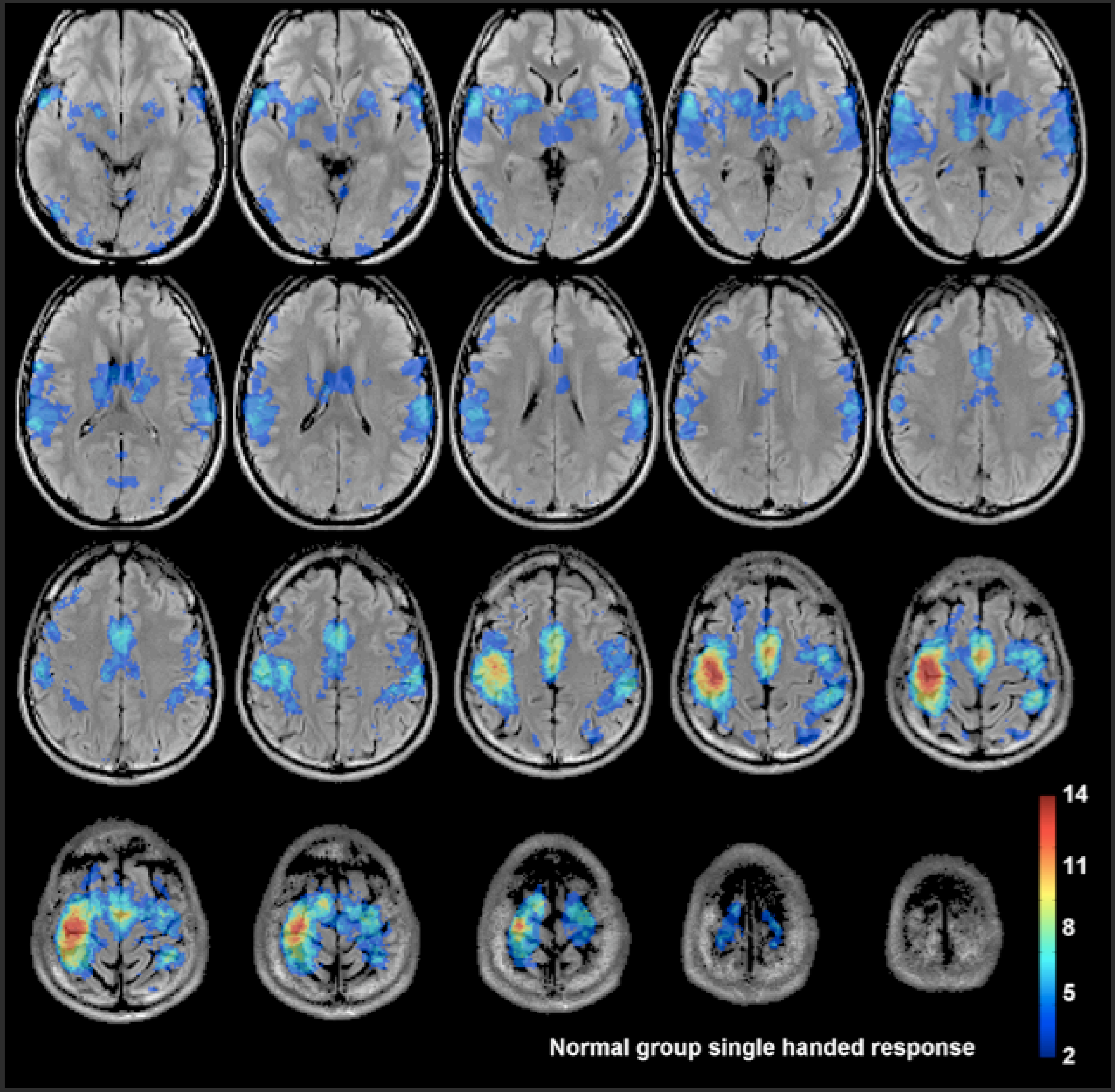
- 80% normal clusters are positive correlated (2-4 s delay)
- 44% stroke clusters are negative correlated (0-2 s delay)

Results

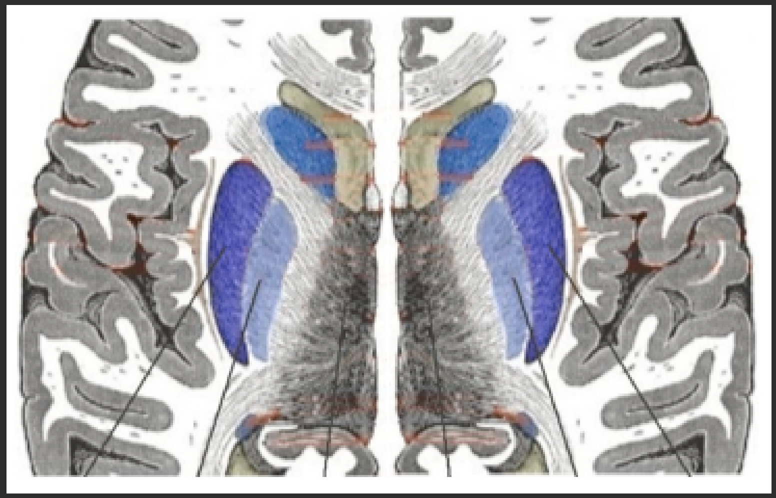
Identified brain regions: NORMAL GROUP

Results

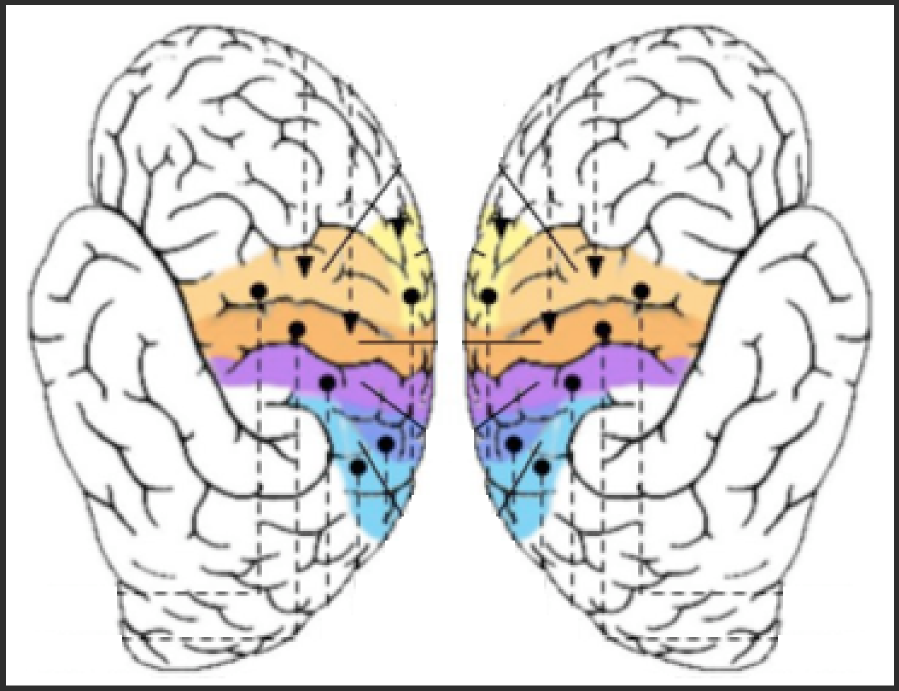
Identified brain regions: NORMAL GROUP



Basal ganglia

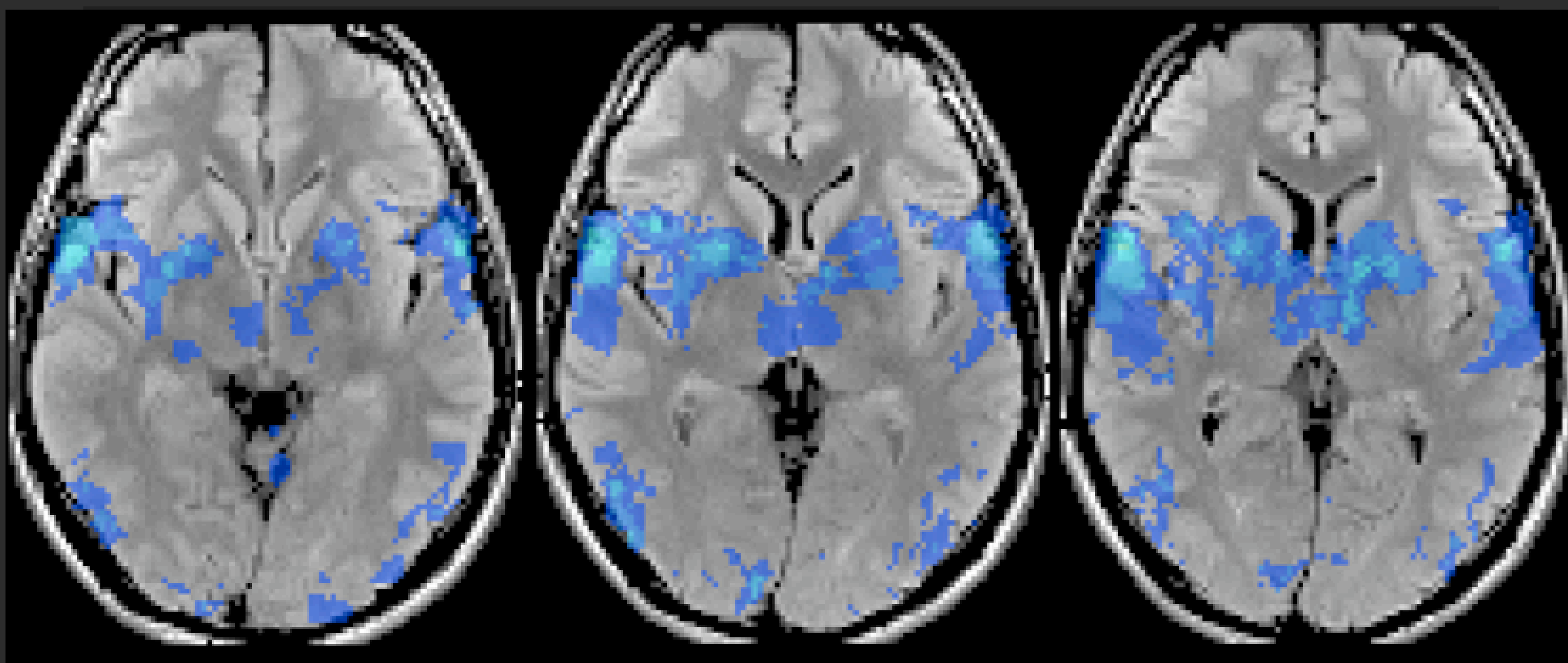


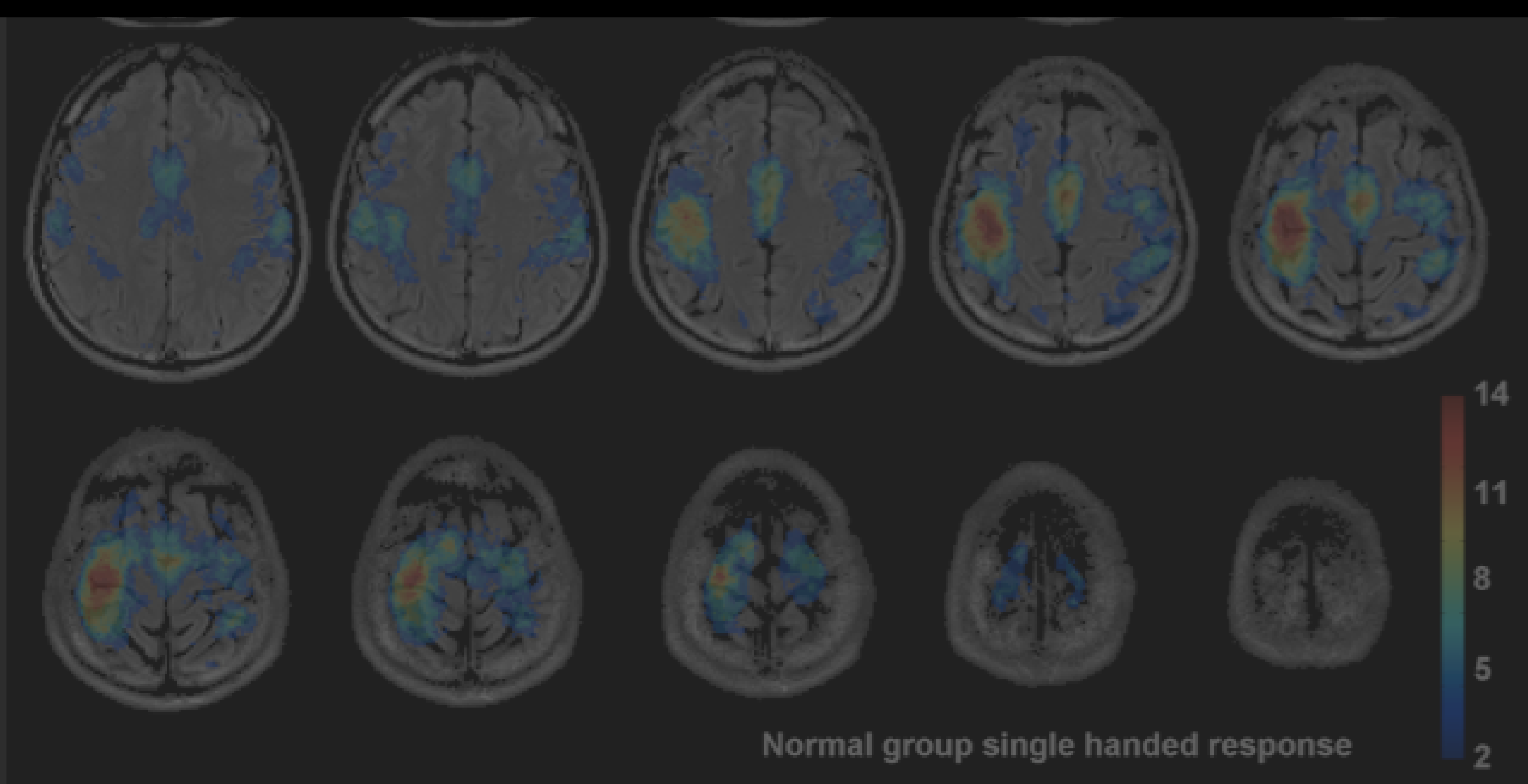
Sensorimotor cortex



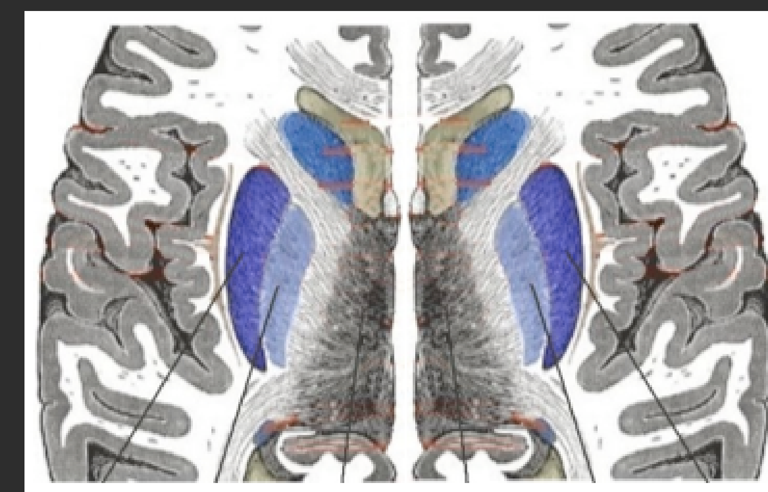
Results

Identified brain regions: NORMAL GROUP

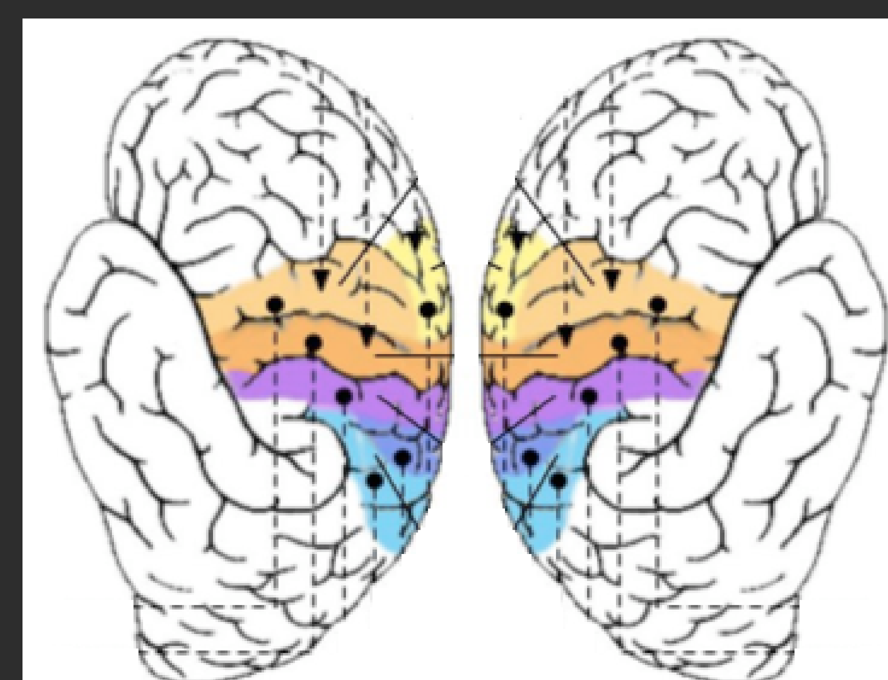




Basal ganglia

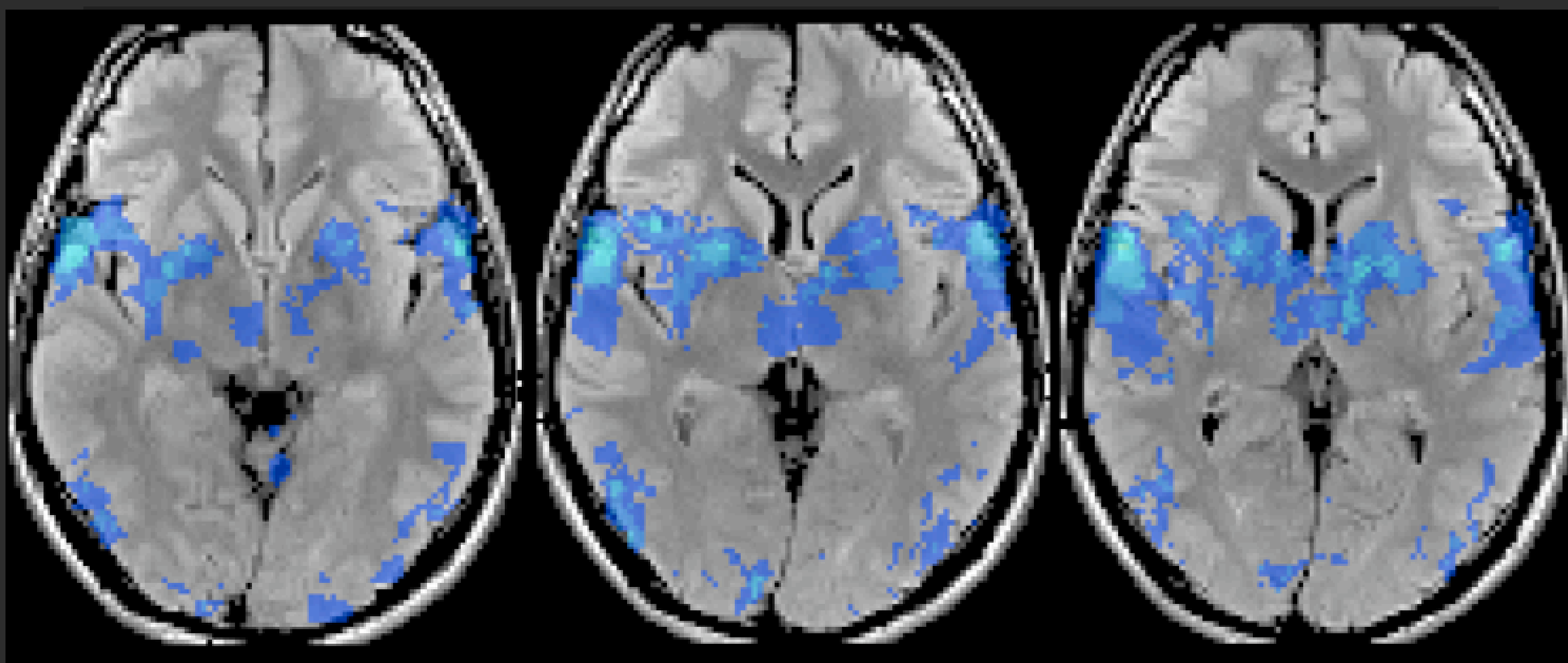


Sensorimotor cortex

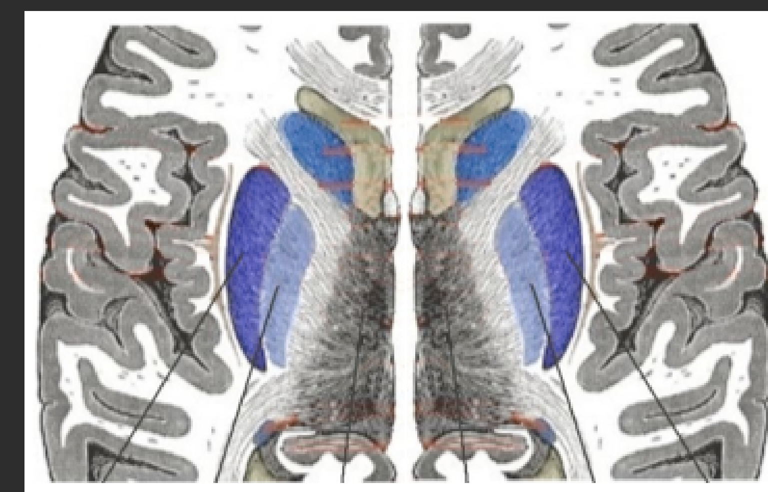


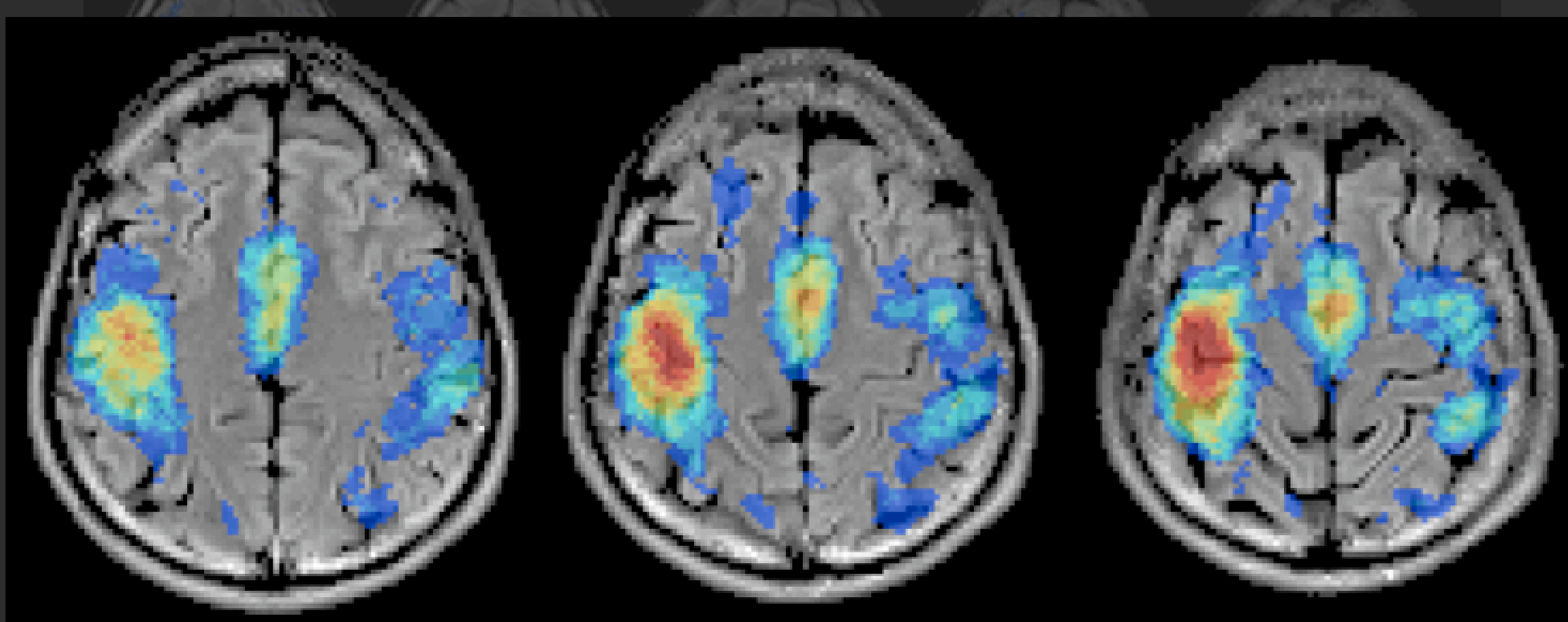
Results

Identified brain regions: NORMAL GROUP

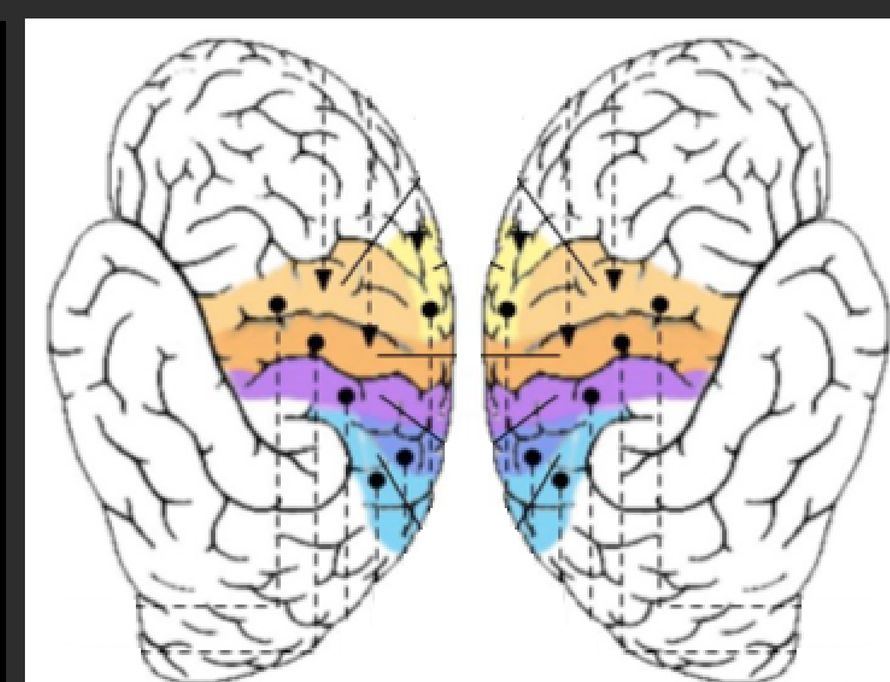


Basal ganglia



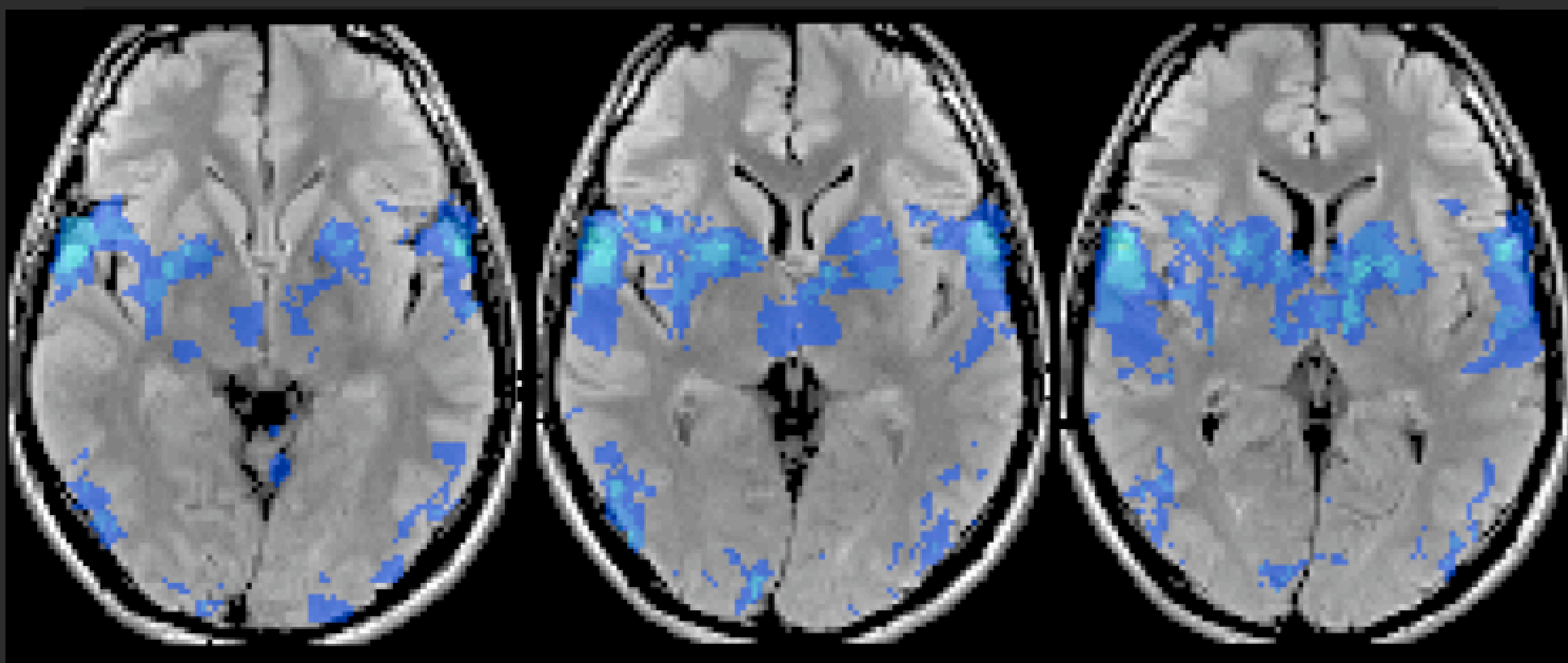


Sensorimotor cortex



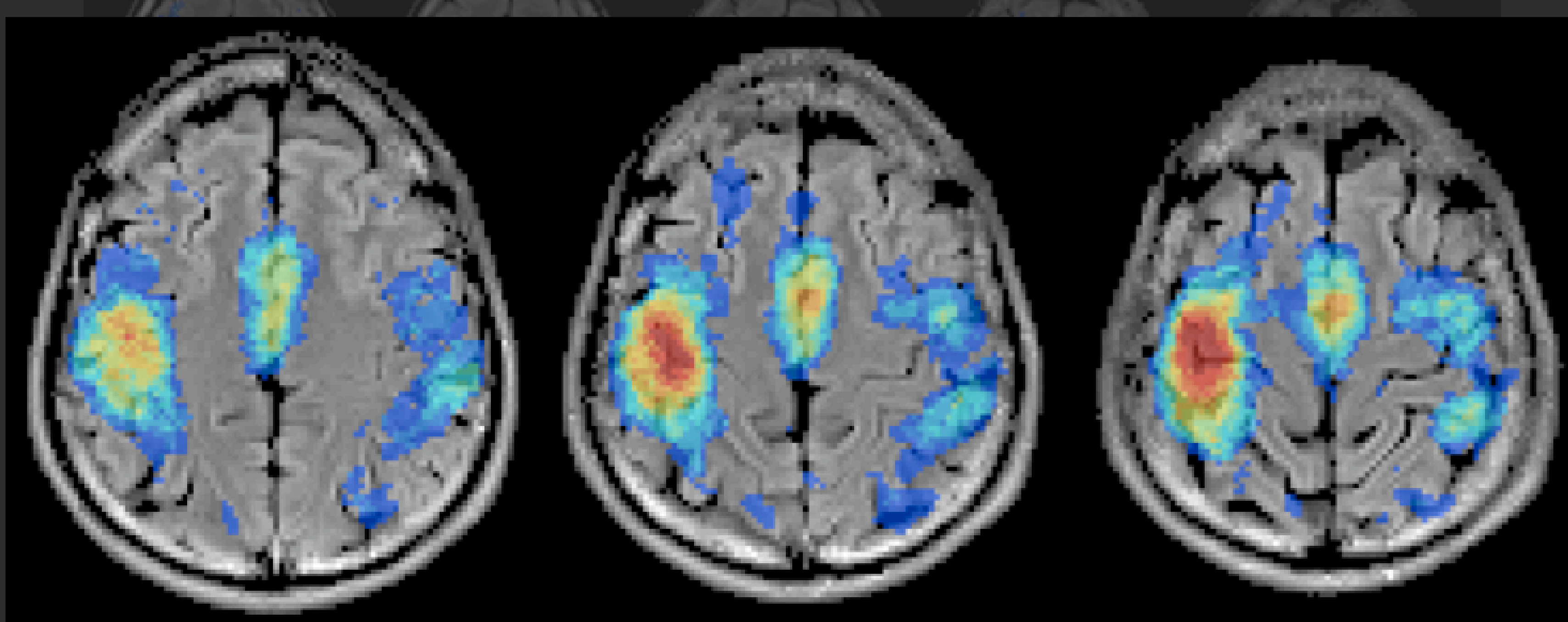
Results

Identified brain regions: NORMAL GROUP



Basal ganglia

Putamen & globus pallidus:
- Turner et al. (2003), *J Neurophysiol*



Cerebral cortex

Contralateral SMC:
- Kandel et al. (2000) *Princ Neur Sci*

SMA:
- Nachev et al. (2008), *Nat Neurosci*

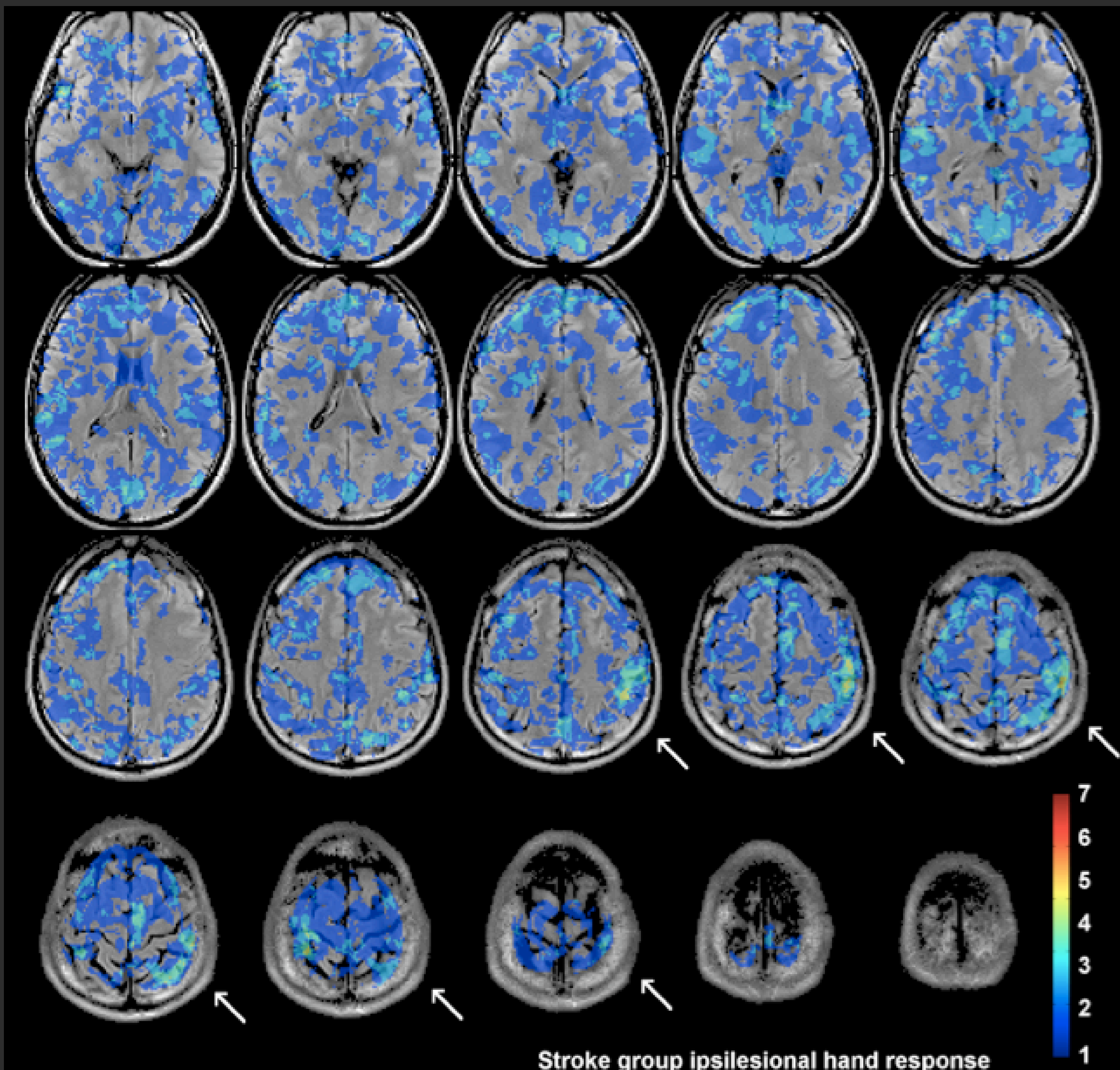
Ipsilateral premotor & parietal:
- Reis et al. (2008), *J Neurophysiol*

Results

Identified brain regions: STROKE GROUP

Results

Identified brain regions: STROKE GROUP



- as expected, responses are sparse and inconsistent

- Rossini et al (2003), *Brain* provide compelling evidence of neurovascular dysfunction in both hemispheres

- Ward et al (2003), *Brain,* also describe sparse activation patterns in longitudinal stroke cohorts where best motor recovery correlated with SMC focused BOLD responses

Results

Identified brain regions: STROKE GROUP

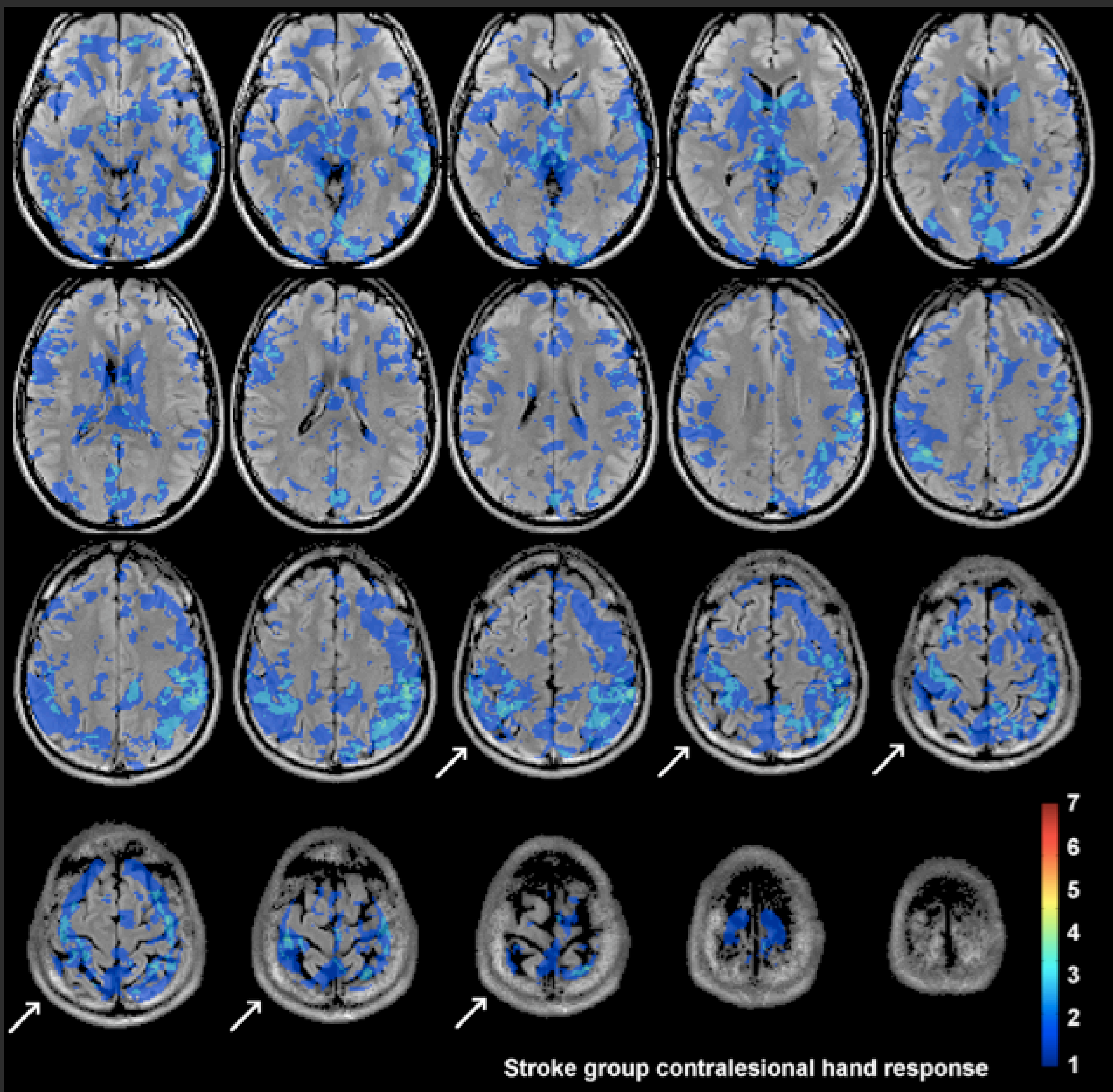
- as expected, responses are sparse and inconsistent

- Rossini et al (2003), *Brain* provide compelling evidence of neurovascular dysfunction in both hemispheres

- Ward et al (2003), *Brain,* also describe sparse activation patterns in longitudinal stroke cohorts where best motor recovery correlated with SMC focused BOLD responses

Results

Identified brain regions: STROKE GROUP



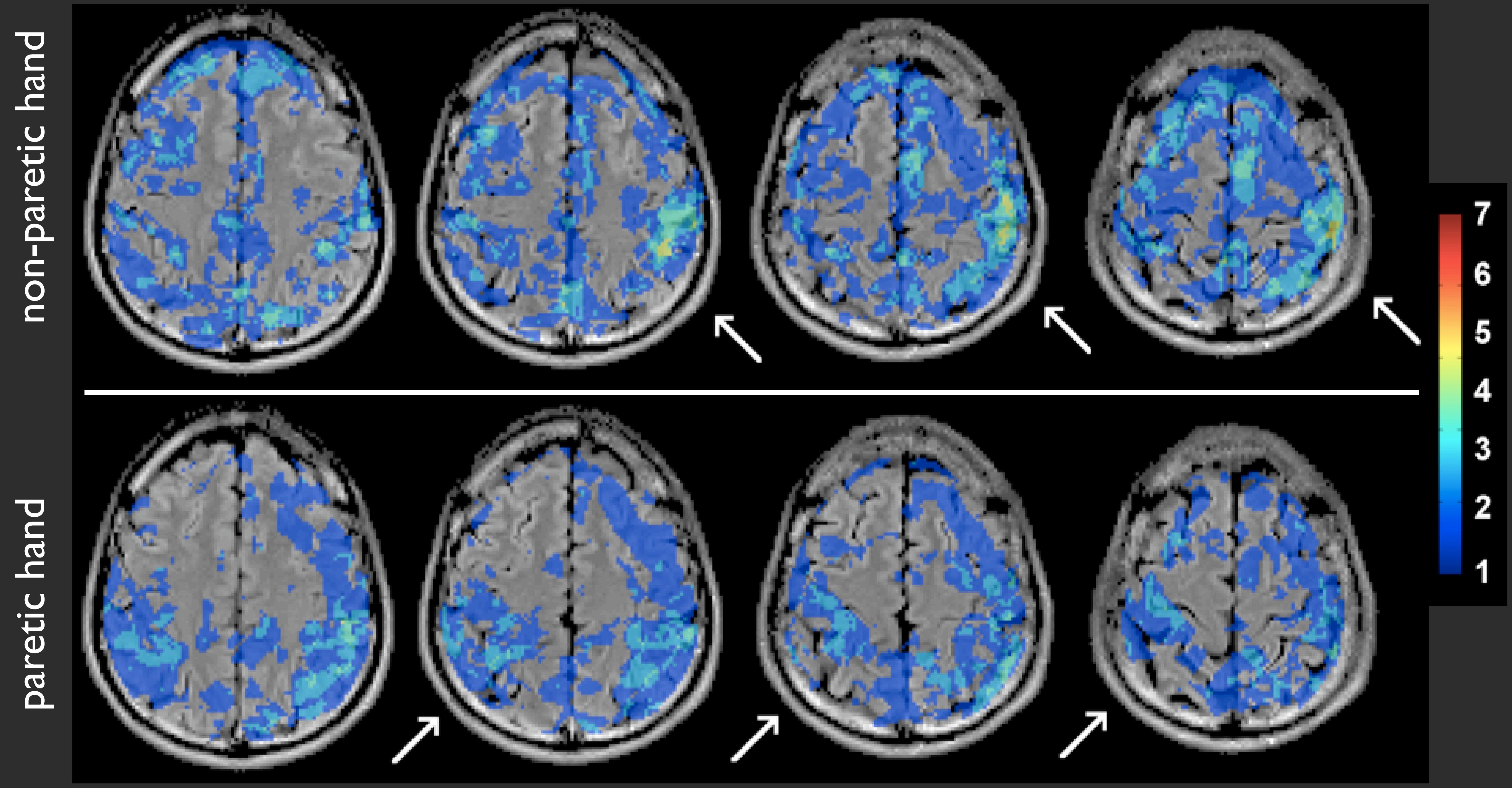
- as expected, responses are sparse and inconsistent

- Rossini et al (2003), *Brain* provide compelling evidence of neurovascular dysfunction in both hemispheres

- Ward et al (2003), *Brain,* also describe sparse activation patterns in longitudinal stroke cohorts where best motor recovery correlated with SMC focused BOLD responses

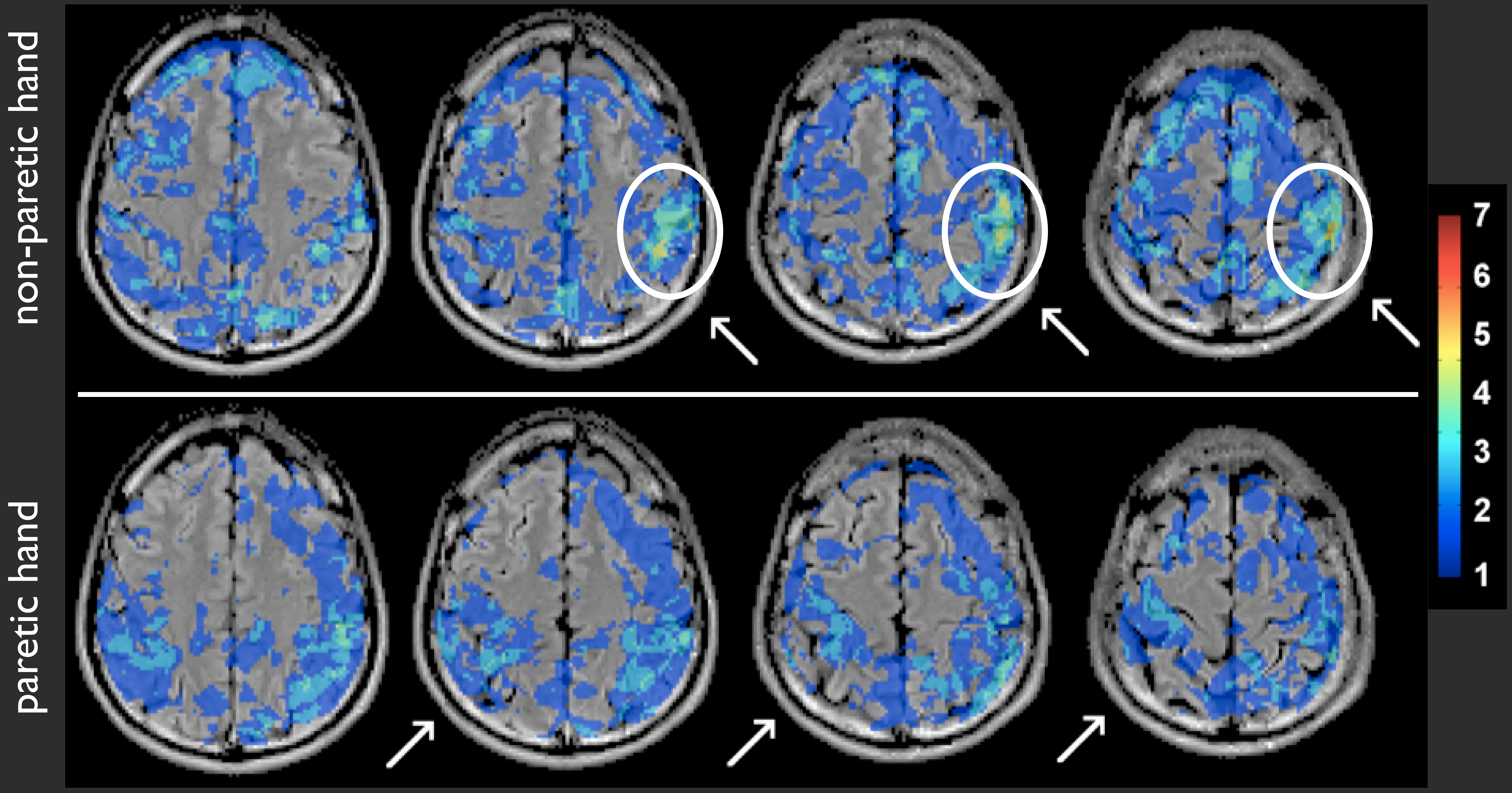
Results

Identified brain regions: STROKE GROUP



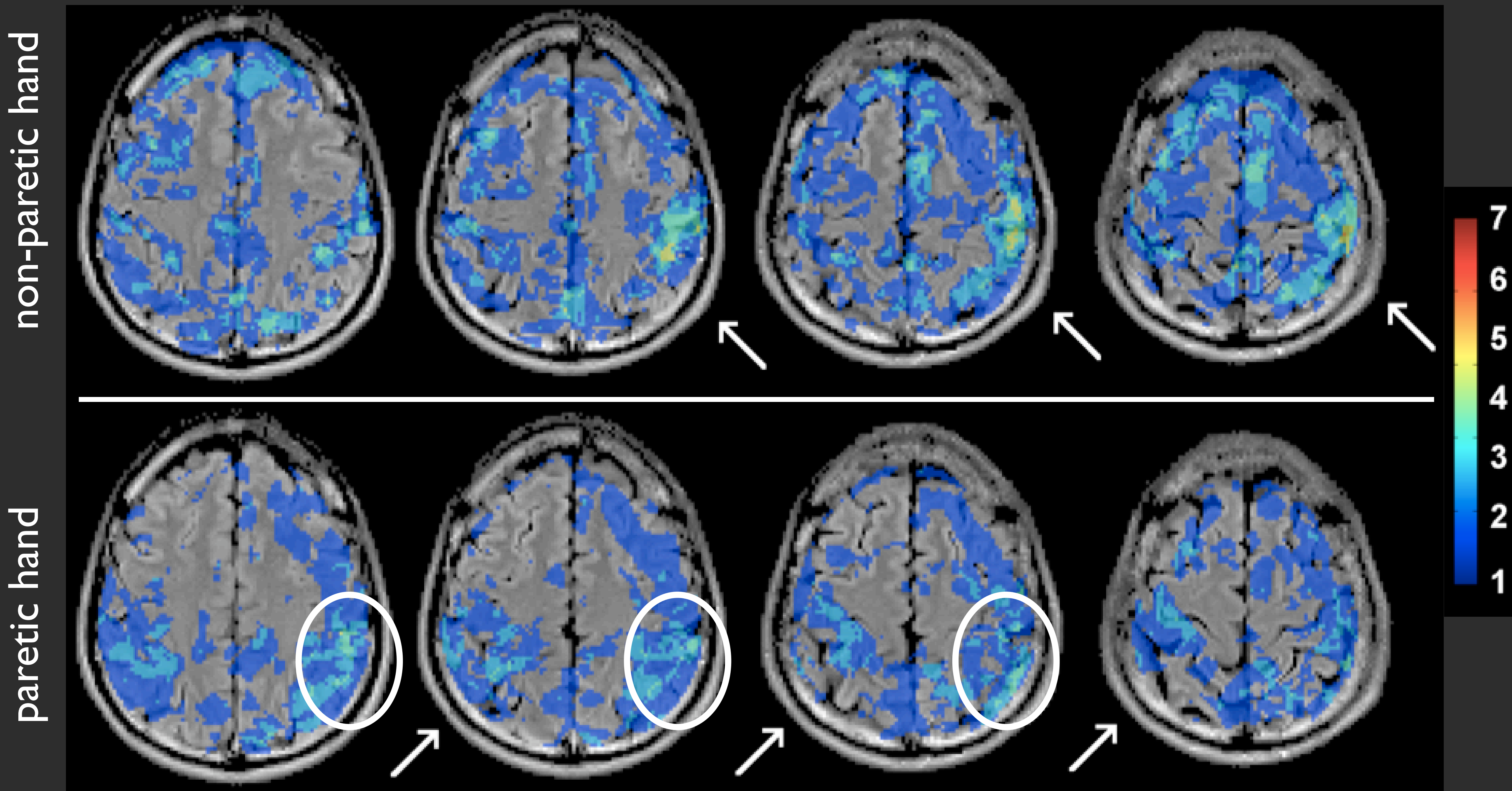
Results

Identified brain regions: STROKE GROUP



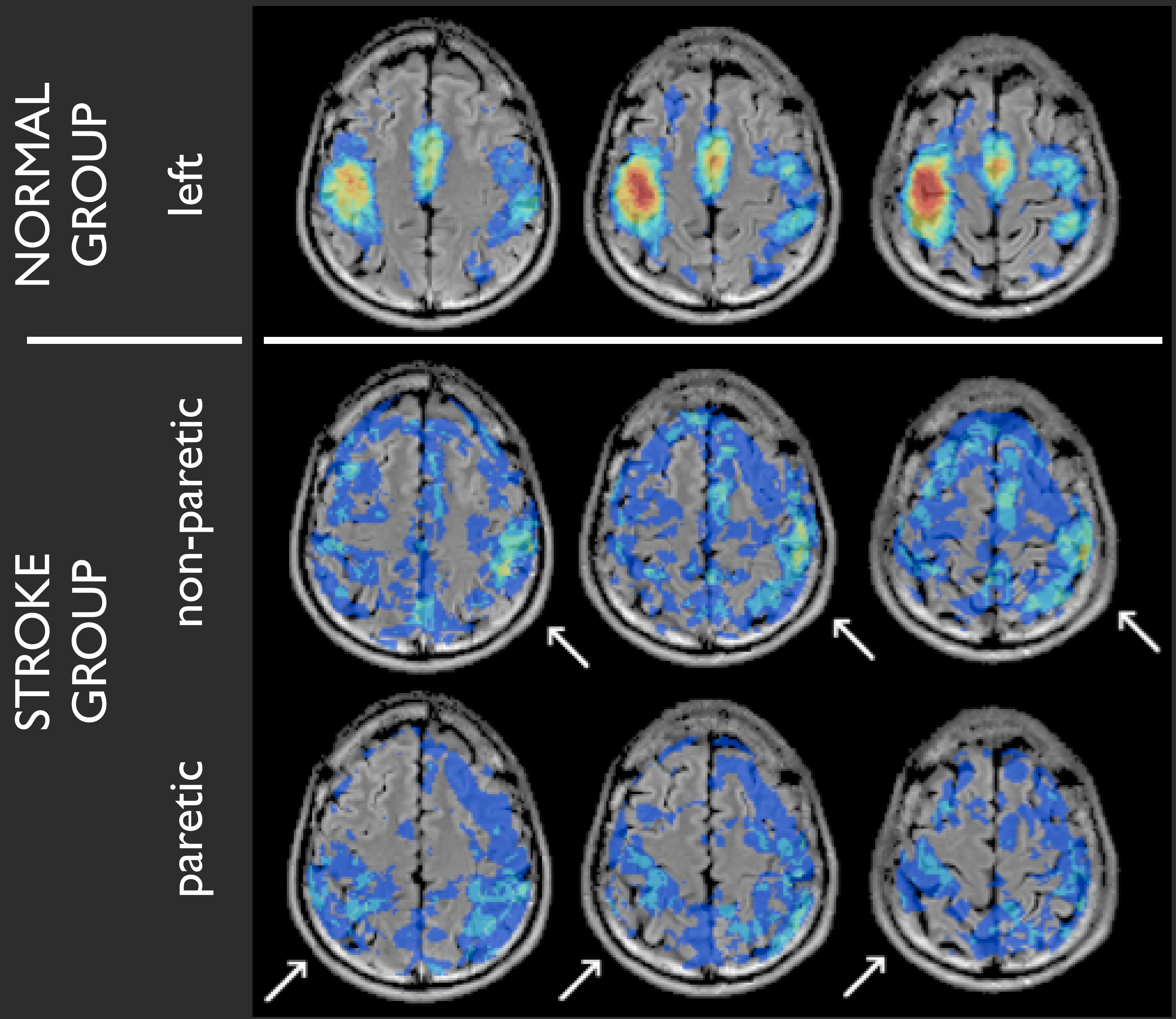
Results

Identified brain regions: STROKE GROUP



Results

Identified brain regions



References:

Contralateral SMC:
- Kandel et al. (2000)

SMA:
- Nachev et al. (2008)

Ipsilateral premotor & parietal:
- Reis et al. (2008)

Contralateral SMC after stroke:
- Cramer et al. (1999)

SMA after stroke:
- Carusone et al. (2002)

Ipsilateral premotor & parietal:
- Ward et al. (2003)

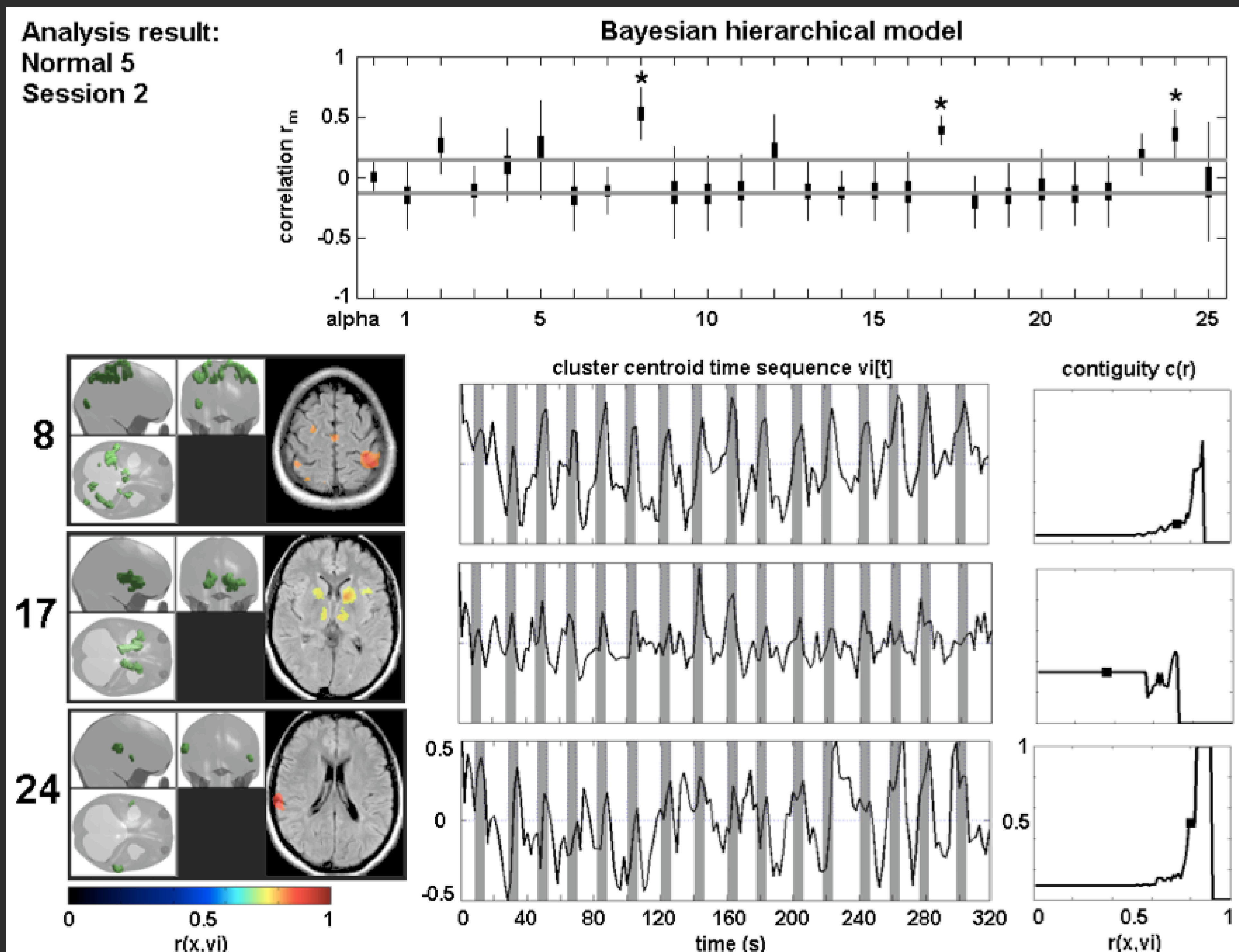
Ipsilateral SMC after stroke:
- Cramer et al. (1999)
- Carusone et al. (2002)
- Ward et al. (2003)

Results

Proposed method is useful for case study

Results

Proposed method is useful for case study



Conclusion

Conclusion

Experimental protocol & data acquisition

- Event-related visual feedback motor task:
  + reproducible BOLD signal in normal group
  + identify sensorimotor network
  + potential for wide range of stroke population
  - results limited to sensorimotor network only
  - no simulataneous neural activity images

Conclusion

<u>Proposed analysis method</u>

- Fuzzy cluster analysis:
  + to identify and distinguish different BOLD signals
  + membership informative of optimal k-value
  - link to probabilistic framework is still missing
  - lacking accountability for temporal dependence

Conclusion

Proposed analysis method

- Fuzzy cluster analysis:
  + to identify and distinguish different BOLD signals
  + membership informative of optimal k-value
  - link to probabilistic framework remains elusive
  - lacking accountability for temporal dependence
- Space-time structure:
  + features can separate normal and stroke groups
  - insensitive to signal magnitude and delay change

Conclusion

<u>Proposed analysis method</u>

- Fuzzy cluster analysis:
  + to identify and distinguish different BOLD signals
  + membership informative of optimal k-value
  - link to probabilistic framework remains elusive
  - lacking accountability for temporal dependence

- Space-time structure:
  + features can separate normal and stroke groups
  - insensitive to signal magnitude and delay change

- Bayesian hierarchical model:
  + multilevel approach to data analysis
  + no multiple comparisions corrections necessary
  - first application: will improve with further development

Conclusion

Interpretation of results

- A pilot study with small sample size
  - hence, our clinical interpretation is very limited
- Changes in BOLD responses in stroke group
  - our results corroborate the changes observed in previous research
- Are these changes directly caused by stroke?
  - we cannot provide a definite answer due to uncontrolled factors e.g., *age, co-morbidity, drugs, etc...*
- Neurovascular dysfunction or neural plasticity?
  - literature & our normal group results suggest that neurovascular dysfunction is likely to persist after stroke

Conclusion

Future work should take place in a larger stroke trial: longitudinal stroke rehab with age-matched normals

- are there distinct BOLD indicators of CVD?
- can BOLD be related to degree of impairment?
- can neural plasticity be distinguished from neurovascular dysfunction?

Conclusion

<u>Future work should take place in a larger stroke trial: longitudinal stroke rehab with age-matched normals</u>

- are there distinct BOLD indicators of CVD?
- can BOLD be related to degree of impairment?
- can neural plasticity be distinguished from neurovascular dysfunction?

<u>Optimisation of stroke recovery:</u>
to apply these answers to help monitor and develop stroke rehabilitation programmes

Acknowledgements

Supervisors:

- M. Hogan MD PhD (Neuroscience) *Ottawa Hospital Research Institute*
- A. Adler PhD (Biomedical Engineering) *Carleton University*

Co-investigators:

- I. Cameron PhD (MR Physics) *The Ottawa Hospital*
- T. Nguyen MD (Radiology) *The Ottawa Hospital*
- M. Sharma MA (Neurology) *The Ottawa Hospital*

Funding:

- Behavioural Research and Imaging Network (BRAIN)
- Ontario Research Fund
- Heart and Stroke Foundation Centre for Stroke Recovery

Pattern Recognition of Functional Neuroimage Data of the Human Sensorimotor System after Stroke

Camille Gómez-Laberge, M.A.Sc., B.Eng., B.Sc.

Ph.D. Candidate
Faculty of Engineering, Carleton University
Neuroscience Program, Ottawa Hospital Research Institute

May 13, 2010