An Active Inference Account of Executive Dysfunction in Alzheimer's Disease

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Computational Psychiatry Course, Zurich, August 29th – Sept 2nd 2016

Computational Psychiatry and Biomarkers in Alzheimer's Disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

CONCLUSIONS

Solanezumab, a humanized monoclonal antibody that binds amyloid, failed to improve cognition or functional ability. (Funded by Eli Lilly; EXPEDITION 1 and 2 ClinicalTrials.gov numbers, NCT00905372 and NCT00904683.)

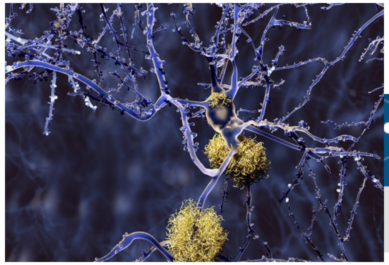
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

CONCLUSIONS

Bapineuzumab did not improve clinical outcomes in patients with Alzheimer's disease, despite treatment differences in biomarkers observed in *APOE* ε4 carriers. (Funded by Janssen Alzheimer Immunotherapy and Pfizer; Bapineuzumab 301 and 302 ClinicalTrials.gov numbers, NCT00575055 and NCT00574132, and EudraCT number, 2009-012748-17.)



theguardian

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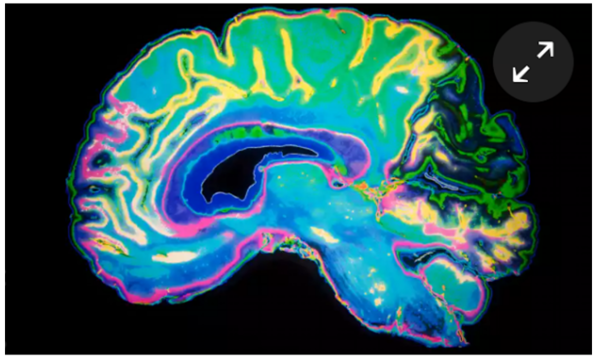
Alzheimer's The Observer

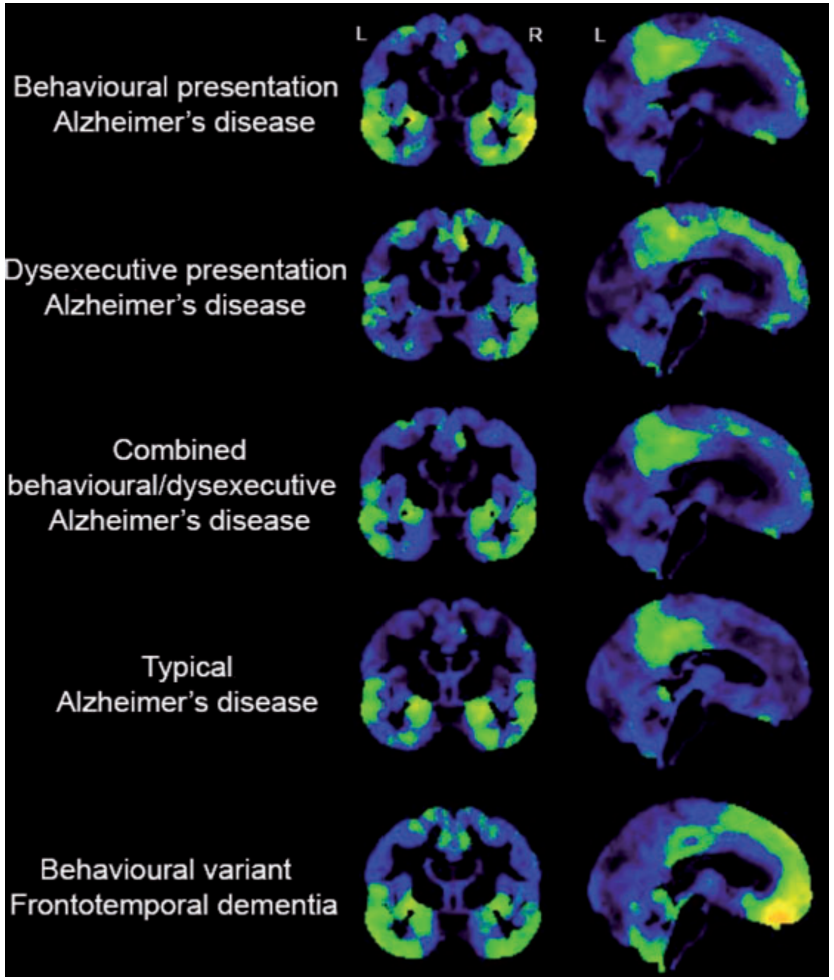
Scientists warn that new drugs will require earlier diagnosis of Alzheimer's

Announcement about success of solanezumab leads to calls for improved testing to identify those who would benefit from slowing of mental decline



New Alzheimer's treatments can slow the formation of plaques in the brain. Photograph: Alamy

Computational Psychiatry and Spectrums in Alzheimer's Disease



Ossenkoppele et al, Brain 2015

ADNI
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

"Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are not rare ... And associated with distinct clinical, genetic and cortical thinning characteristics"

Dickerson et al, 2011

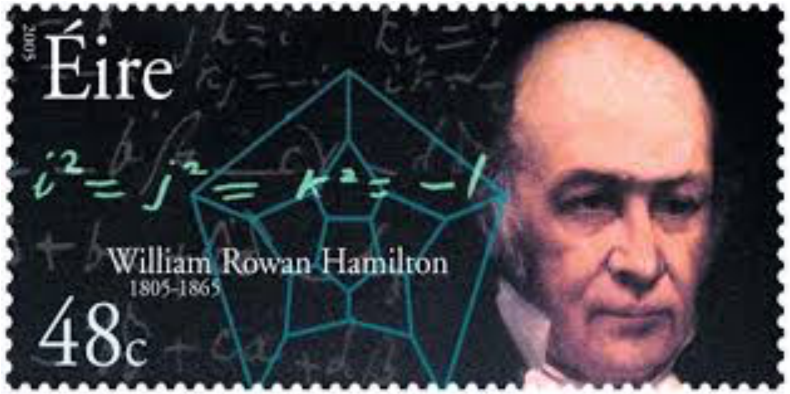
Outline

- Biomarkers from Active Inference
- A task of Executive Function – visual search in changing environments
- EEG – spectral correlates of predictability
- Optimizing Free Energy
  - – neural predictions under AI; the role of prior beliefs
  - – predictions predictions under these AI priors

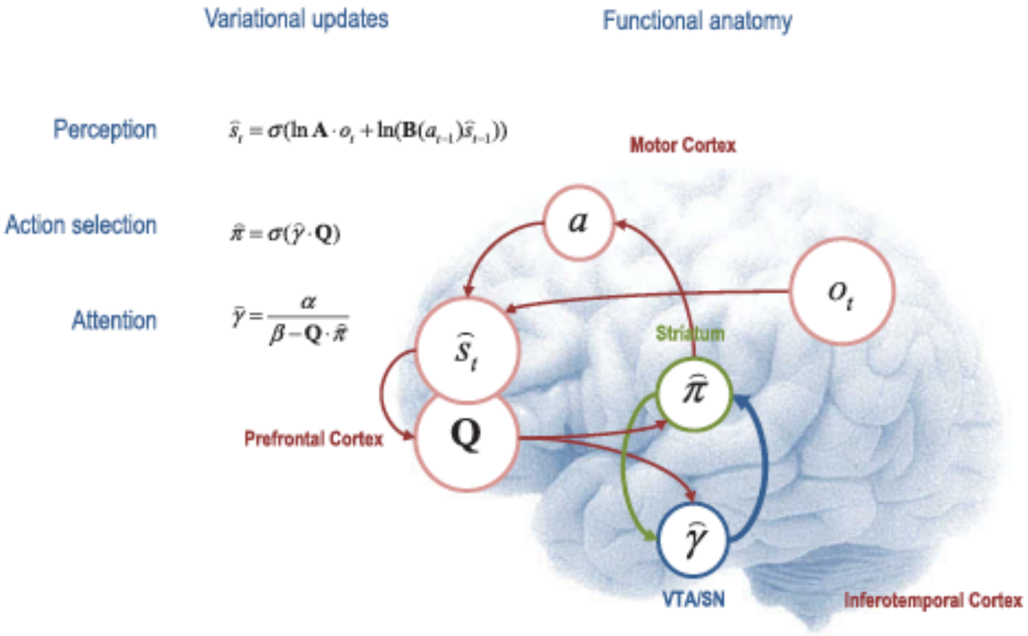
Active Inference: Actions are just samples from beliefs

Active Inference – Refresh

Normative Model

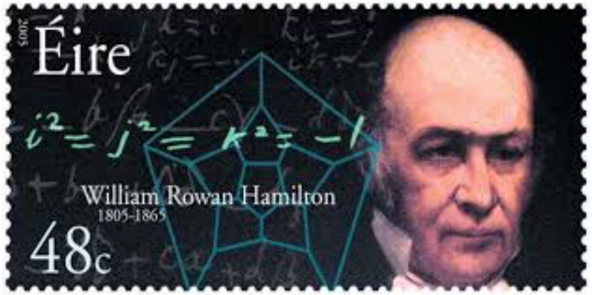


Process Model



Friston et al, 2015

Normative Model



The Free Energy Principle: minimize

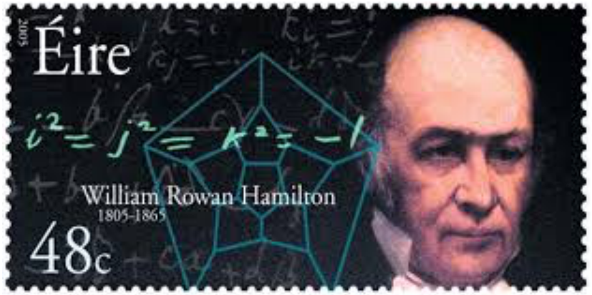
$$F_\tau(\pi) = E_Q[G(s_\tau, \pi)] - H[Q(s_\tau|\pi)] \qquad \tau > t$$

$$G(s_\tau, \pi) = -E_{Q(o_\tau|s_{\tau},)}[lnP(o_\tau, s_\tau|\pi\ )]$$

G: The Energy or surprise (negative log probability) of states and outcomes

Friston et al, 2005, 2015

Normative Model



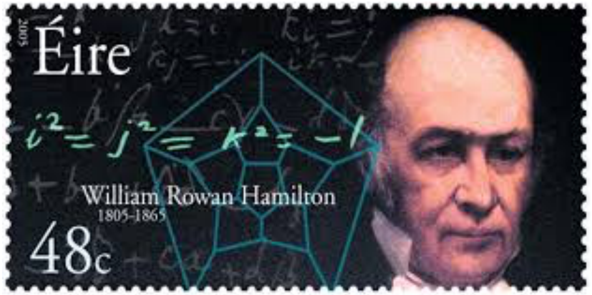
What’s in this objective function?

$$lnP(o_t\,|s_t) + lnP\left(s_t\middle|s_{t-1,}a_{t-1,}\right)\boldsymbol{s}_{t-1} + lnP(u|\gamma) + lnP(\gamma|\beta) - \pi.\,ln\pi - s_t.\,lns_t + const$$

Expected under approximate posterior Q

Friston et al, 2015

Normative Model



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log likelihood

Prior on state dependent on action

Likelihood of action conditioned on precision of control

Entropy of policy

Entropy of states

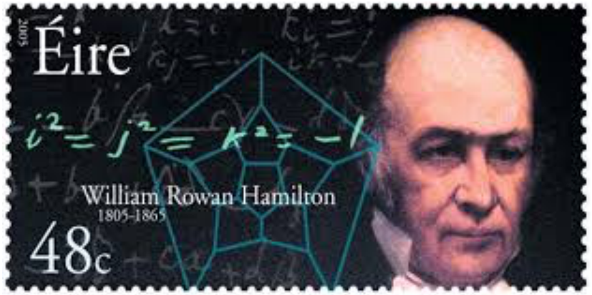
Likelihood of precision Conditioned on inverse temperature

Partially Observable

Markov

Friston et al, 2015

Normative Model



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Know your environment

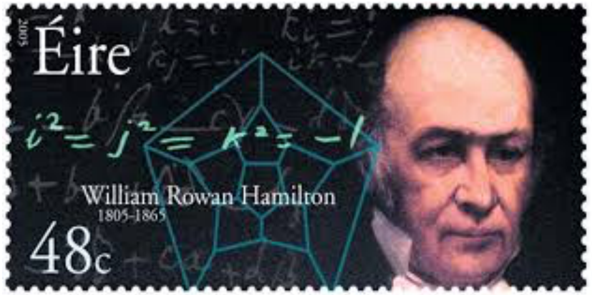
And push into the future

Judiciously,
intrepidly
Or timidly,

In a way that keeps
your options open

Friston et al, 2015

Normative Model



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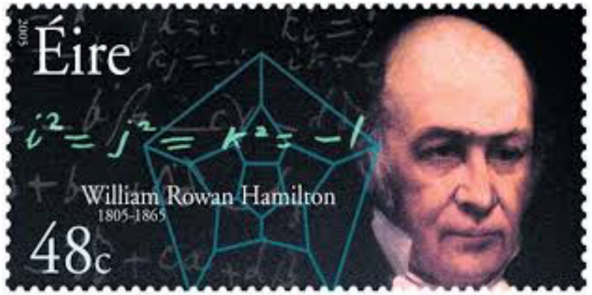
$$lnP(o_t\,|s_t) + lnP\left(s_t \middle| s_{t-1,} a_{t-1,}\right)\boldsymbol{s}_{t-1} + lnP(u|\gamma) + lnP(\gamma|\beta) - \pi.ln\pi - s_t.lns_t + const$$

Pushes you into the future: Value of a policy

$$lnP(u|\gamma) = \gamma\boldsymbol{U} = \gamma\left(U_{t+1}\,(\pi) + \cdots + U_T\,(\pi)\right)$$

Friston et al, 2015

Normative Model



Pushes you into the future (*u* describes the probability distribution from which action *a* is sampled)

$$lnP(u_t|\gamma) = \gamma \boldsymbol{U} = \gamma\big(U_{t+1}\,(\pi) + \cdots + U_T\,(\pi)\big)$$

Vector value of all policies at time t_n from time t

$$U_{t_n}\,(\pi) = (\mathrm{A}\ \mathrm{lnA}).\{\mathrm{B}(u_{t_n}\,|\pi)\ \ldots \mathrm{B}(u_t\,|\pi)s_t\}\ -(\ln(o_{t_n}|\pi) - \mathrm{lnC})o_{t_n}$$

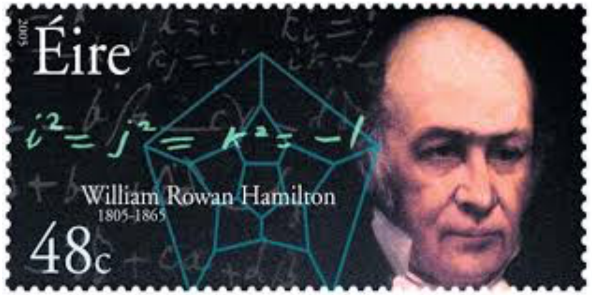
Observer

Transition Matrices

Divergence from where I want to be

Friston et al, 2015

Normative Model



A, B, C Requires specification for a particular experiment

$$U_{t_n}(\pi) = (\mathrm{A}\ \ln \mathrm{A}).\{\mathrm{B}(u_{t_n}|\pi) \ldots \mathrm{B}(u_t|\pi)s_t\} - (\ln(o_{t_n}|\pi) - \ln \mathrm{C})o_{t_n}$$

Observer

Transition Matrices

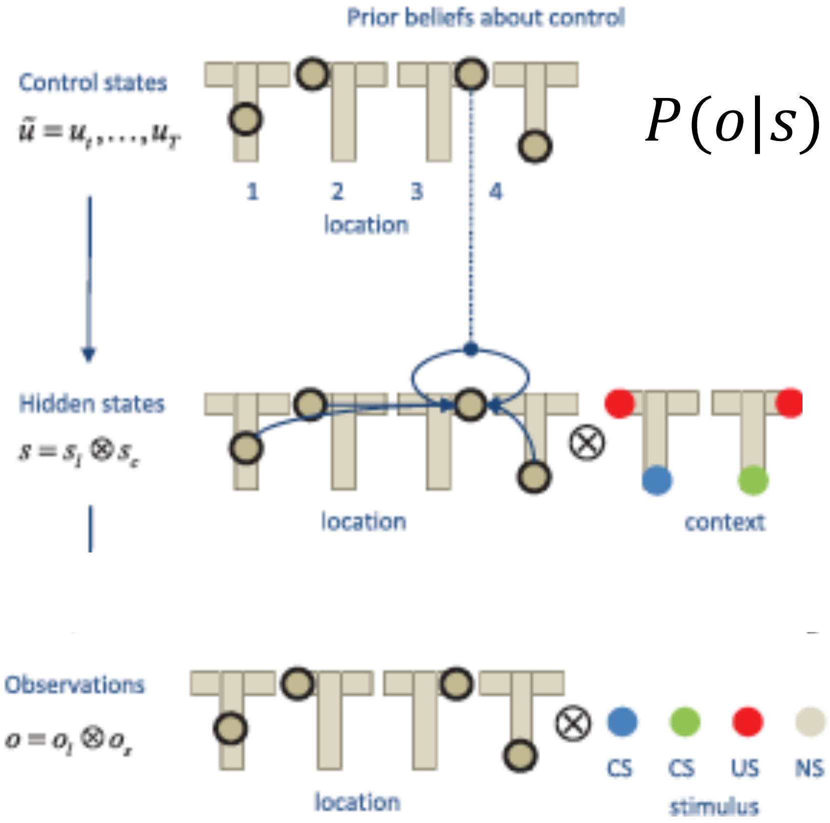
Divergence from where I want to be

Reduce Uncertainty

Achieve goal states

Friston et al, 2015

Example from Wednesday



$$B(u_t = 2) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \otimes I_2$$

Go to Left Arm

$$P(o|s) = A = [A1 \; \ddots \; A4]$$

A1= $\begin{bmatrix} 0.5 & 0.5 \\ 0.5 & 0.5 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}$ A2= $\begin{bmatrix} 1 & 0 \\ 0 & 1 \\ a & 1-a \\ 1-a & a \end{bmatrix}$

A3= $\begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 1-a & a \\ a & 1-a \end{bmatrix}$ A4= $\begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}$

$$P(o|m) = C = \sigma([1 \;\; 1 \;\; 1 \;\; 1]' \otimes I_2 \, [0 \;\; 0 \;\; c \;\; -c])'$$

Friston et al, 2015

‘EEG’ Process Model

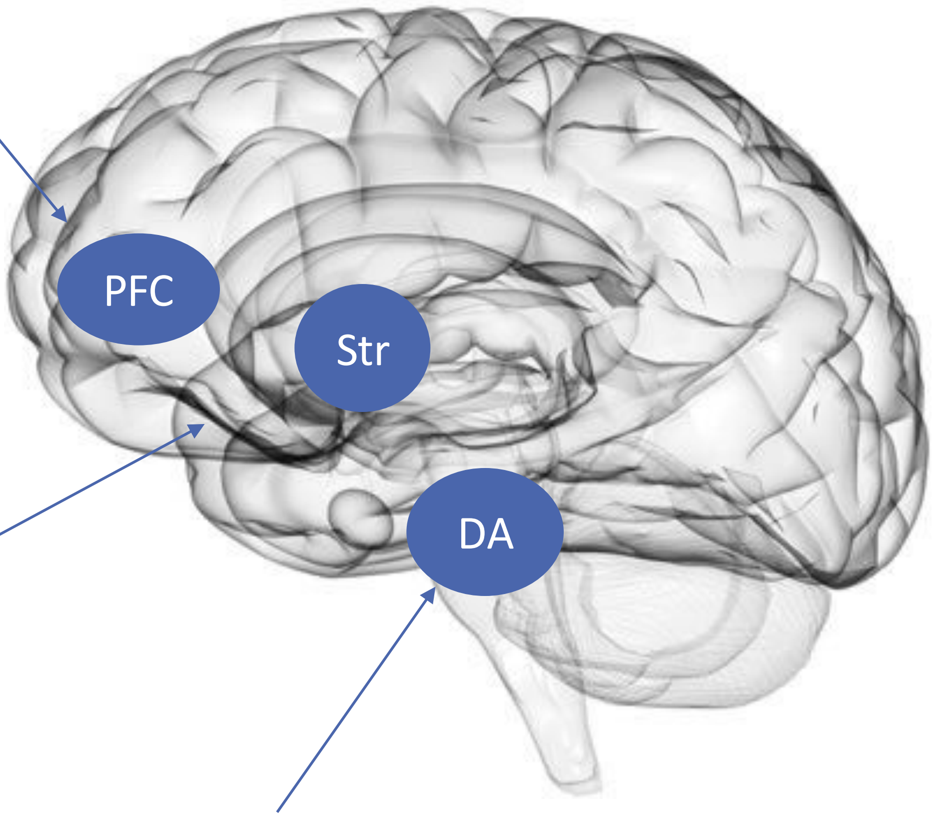
Variational Update Components in the Brain

‘EEG’ Process Model

Variational Update Components in the Brain

$$s_t = \sigma(ln\boldsymbol{A}o_t + \ln(B(a_{t-1})s_{t-1}))$$

Perception



$$\pi = \sigma(\gamma U)$$

Action Selection

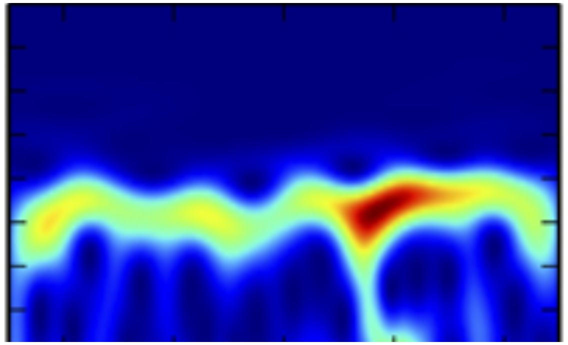
$$\gamma = \frac{\alpha}{\beta - U\pi}$$

Attention/Precision

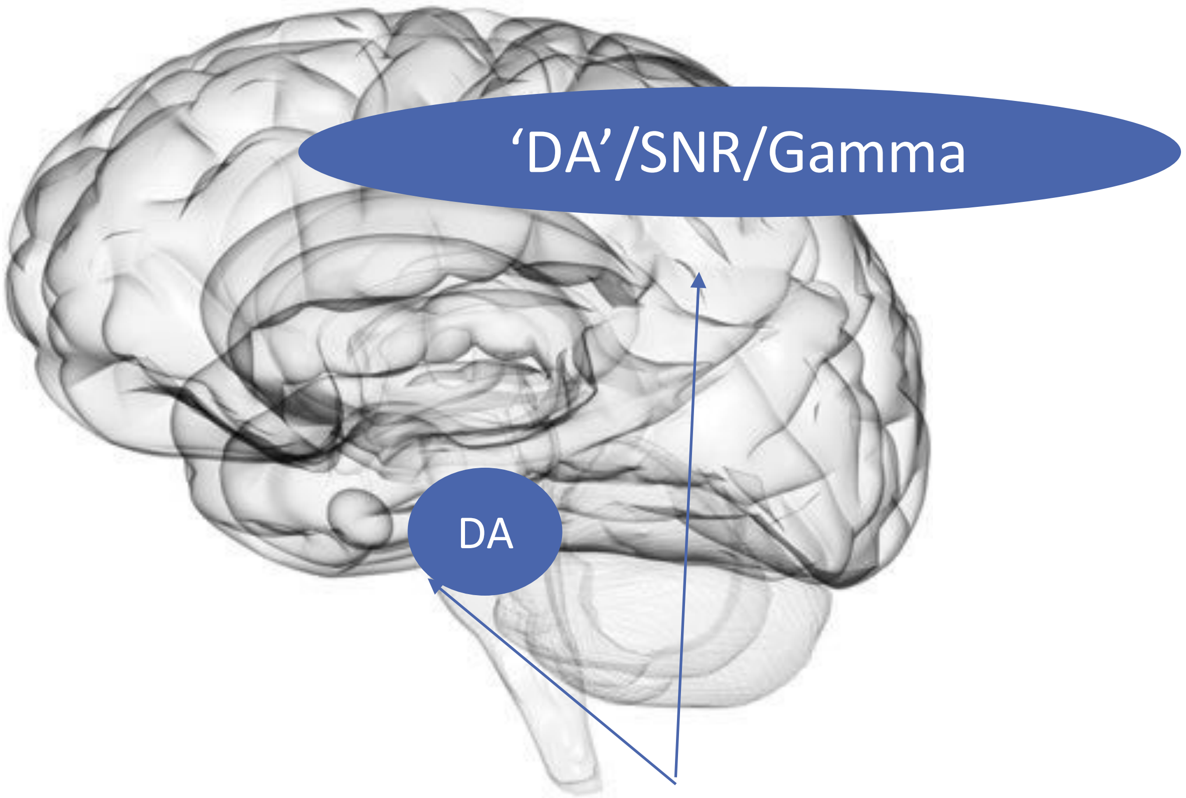
Friston et al, 2015

‘EEG’ Process Model

Variational Update Components in the Brain



32 – 80 Hz



Attention/Precision

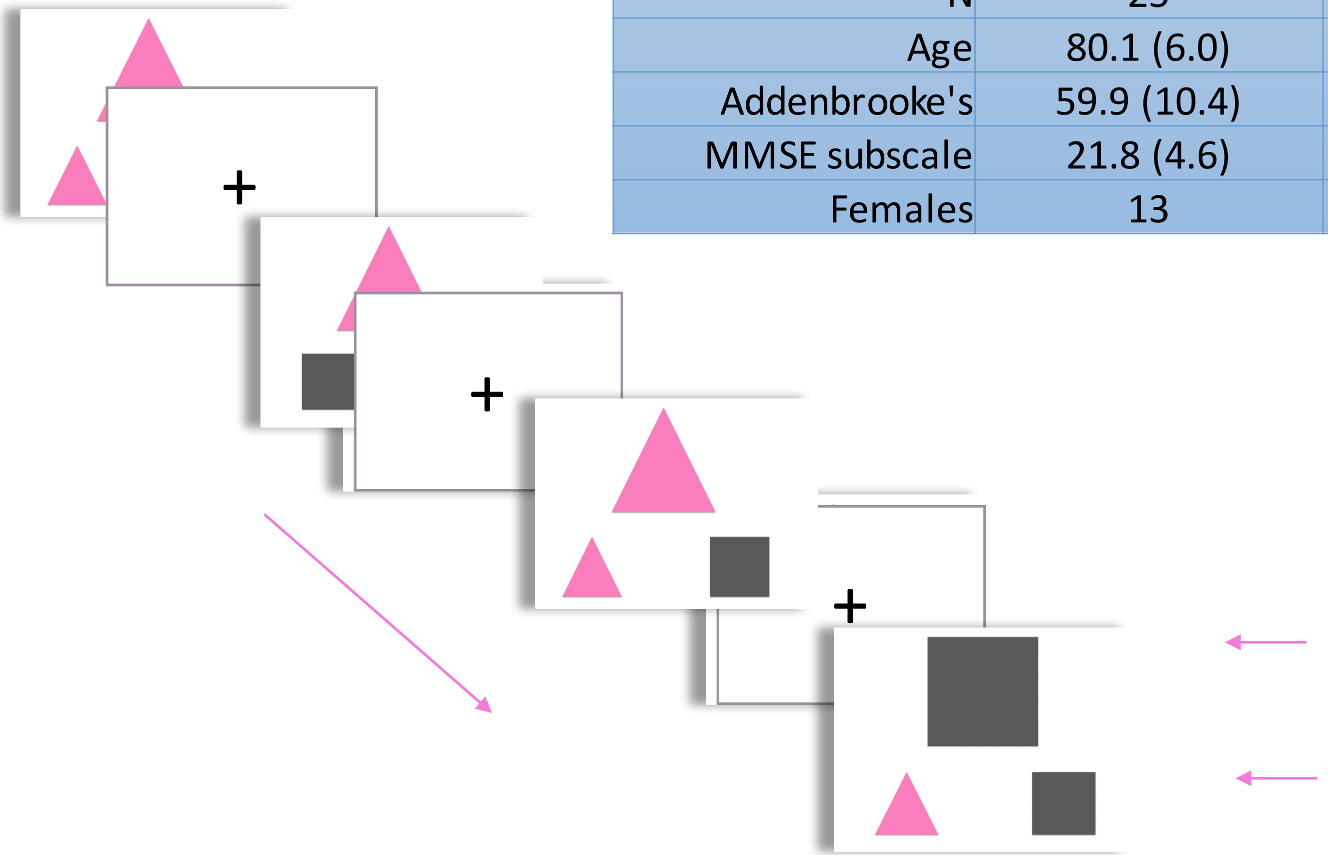
$$\gamma = \frac{\alpha}{\beta - U\pi}$$

Active Inference: Actions are just samples from beliefs

What do patients with AD believe? $\equiv$ How is Executive Function disrupted? c.f. Biomarkers

Visual Oddball Paradigm during EEG

	AD Mean (SD)	Older Controls Mean (SD)	Young Controls Mean (SD)
N	25	21	23
Age	80.1 (6.0)	73.7 (6.4)	23.8 (4.0)
Addenbrooke's	59.9 (10.4)	91.9 (4.1)	92.0 (5.5)
MMSE subscale	21.8 (4.6)	29.6 (0.6)	29.7 (0.6)
Females	13	12	13

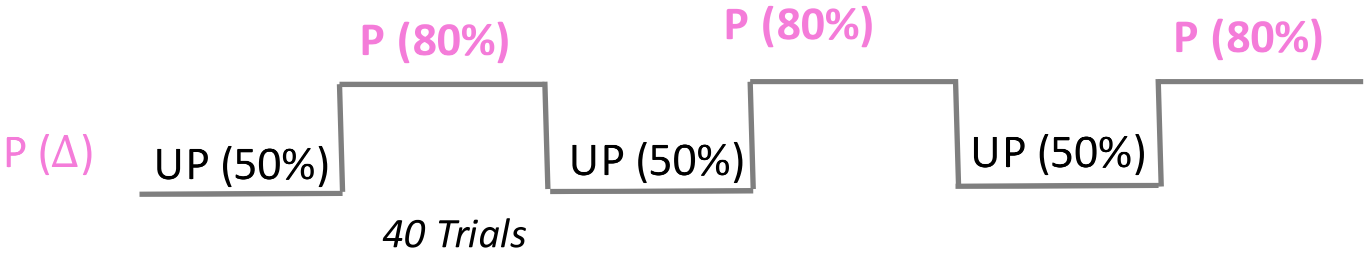


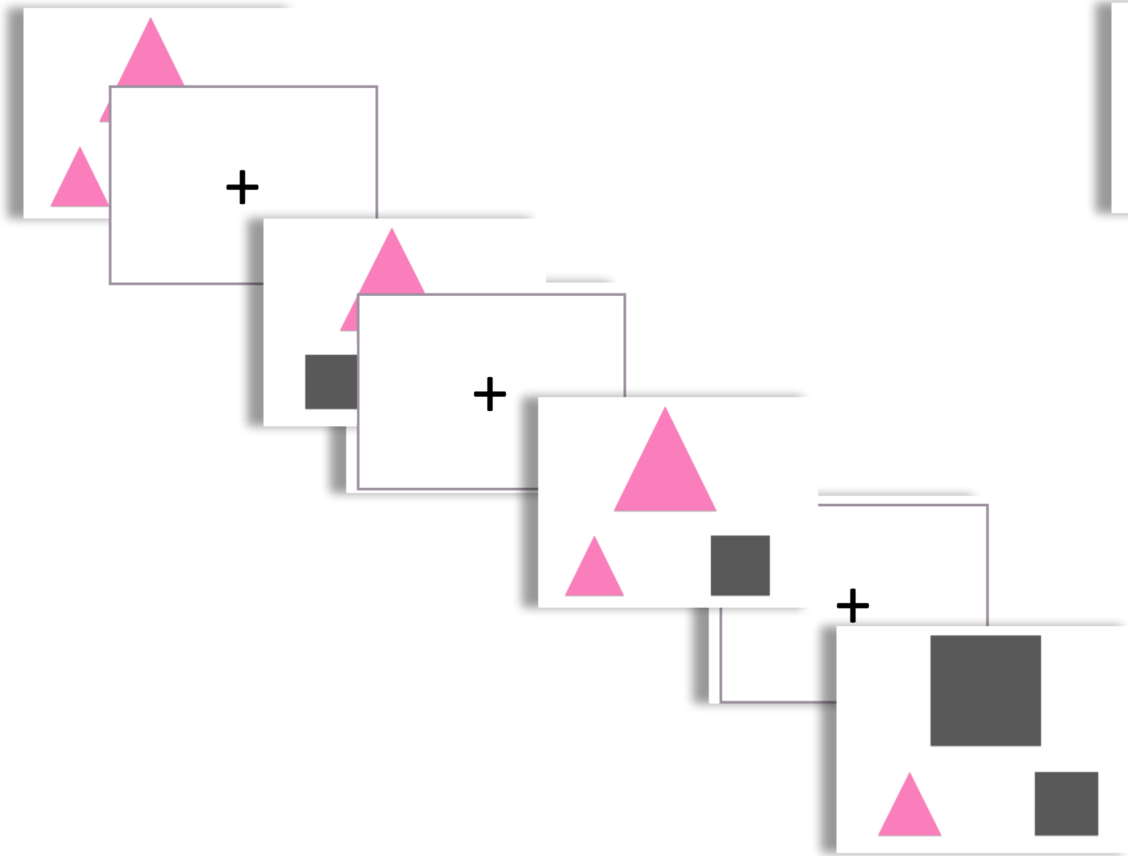
Target

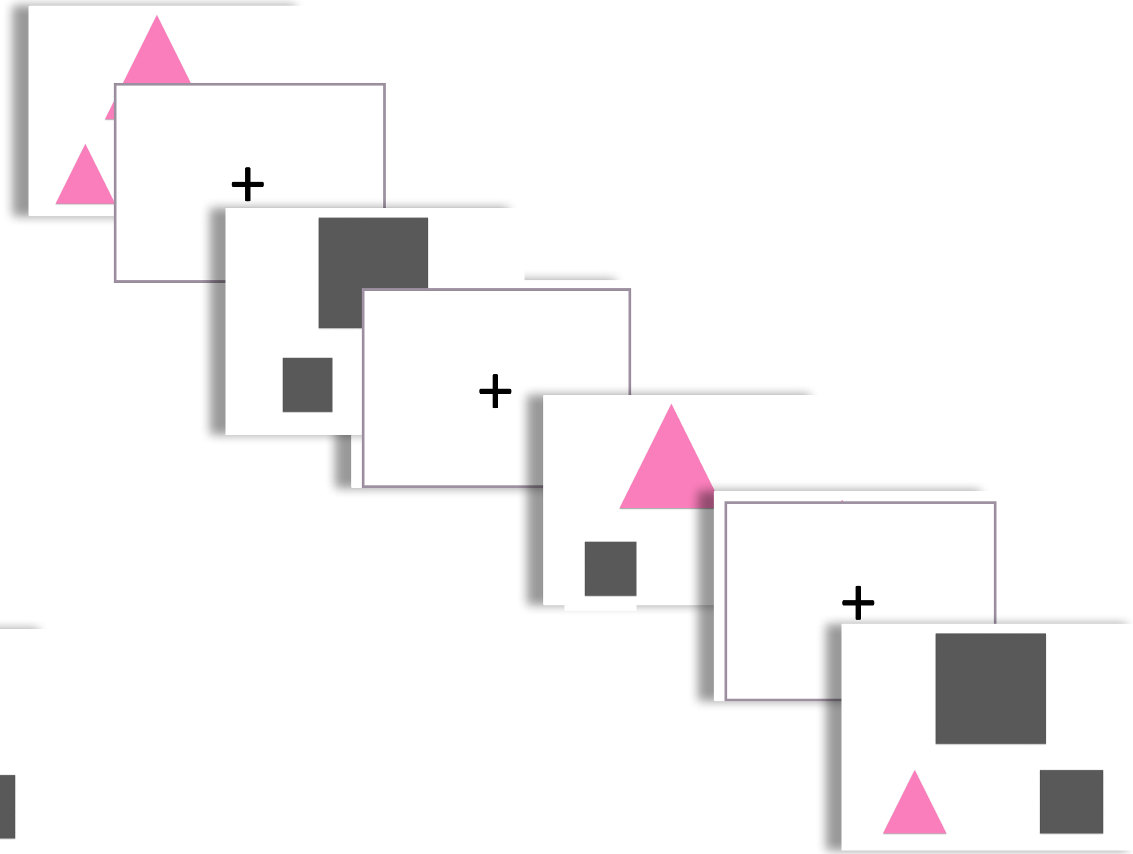
Detection Left/Right Button Press Response

Visual Oddball Paradigm

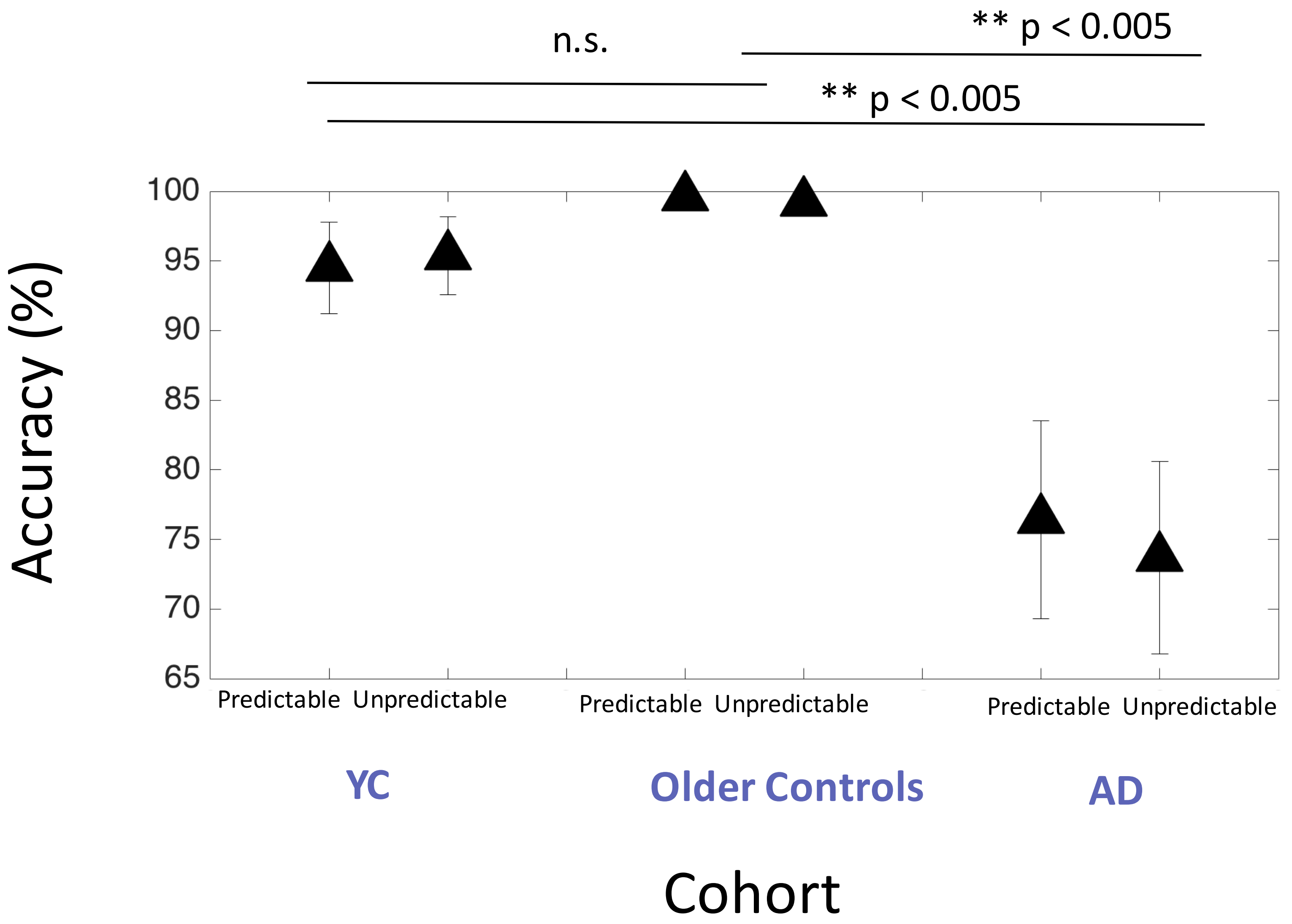
- 3 Predictable, 3 Unpredictable Blocks







Performance: Accuracy



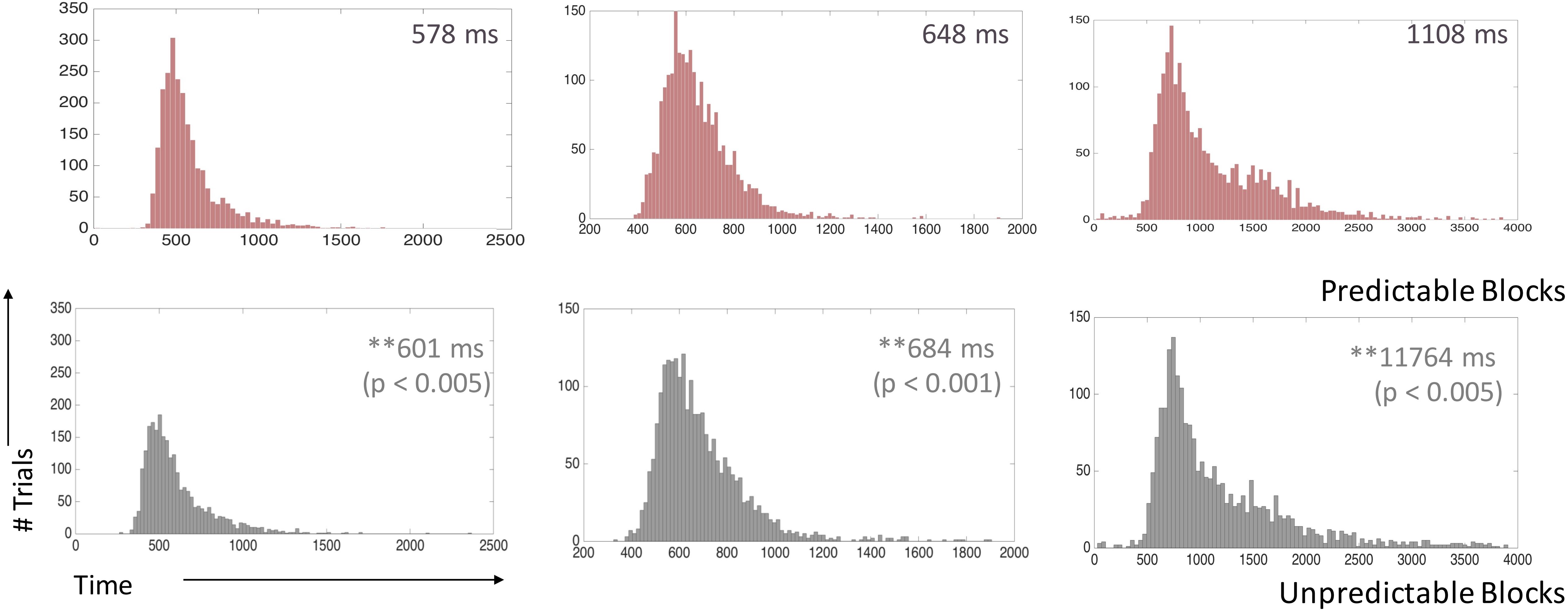
Reaction Times

Young Controls | Age-Matched Controls | AD Patients

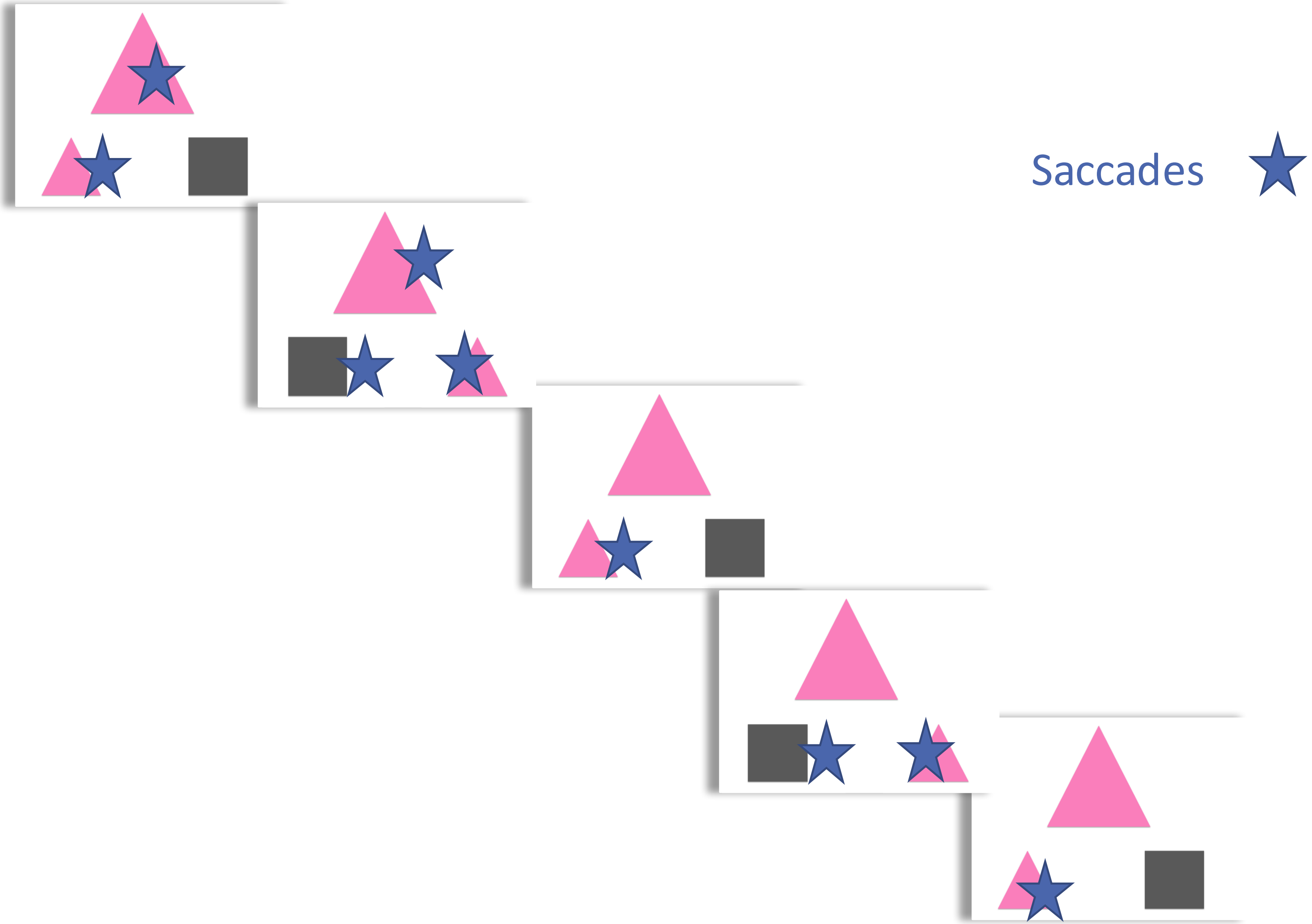
RT: 589 ± 43 msec (Mean ± S.E.M.)

RT: 666 ± 34 msec

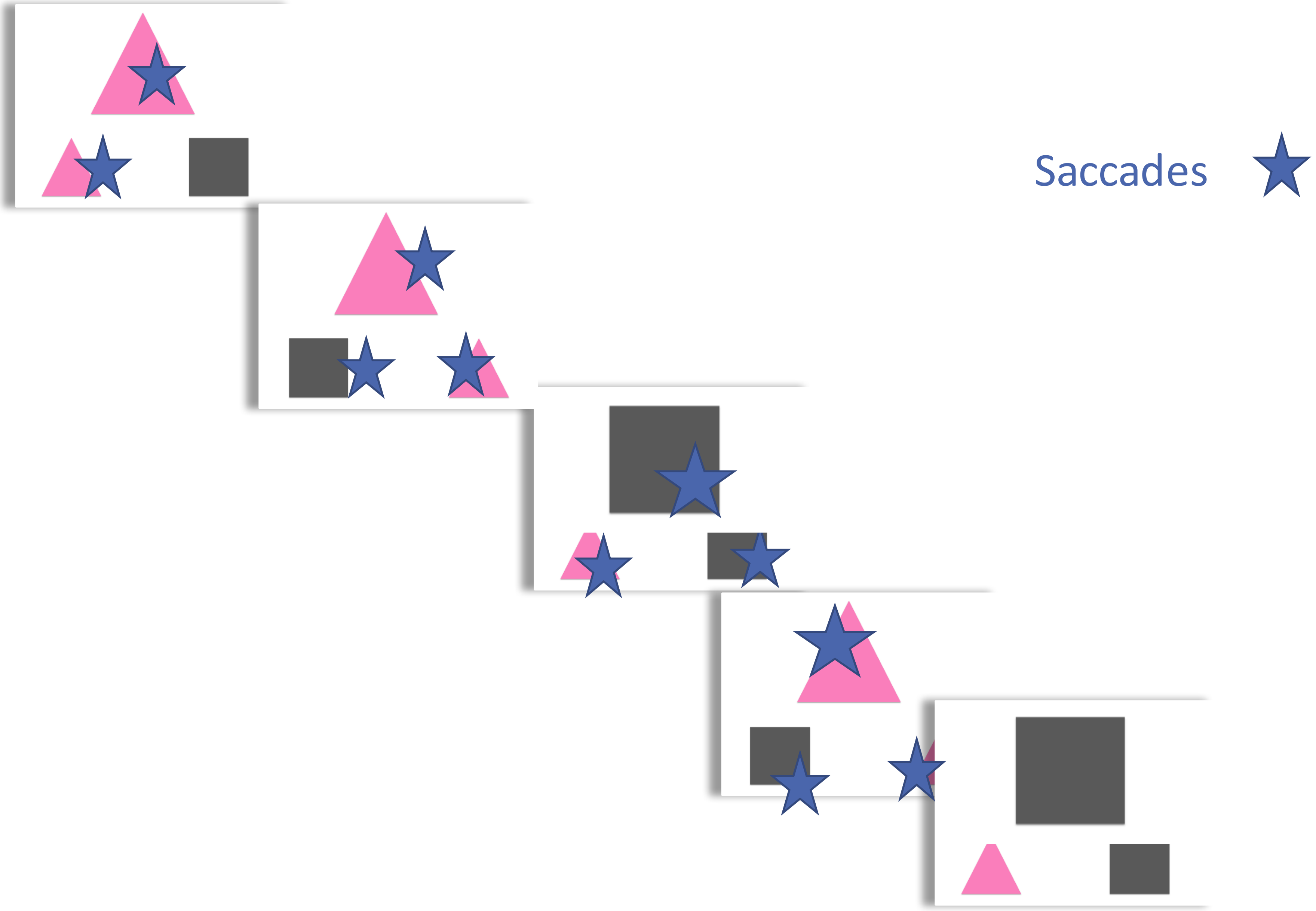
RT: 1141 ± 123 msec



Assumption: Speeded RTs on Predictable 80-20 Blocks



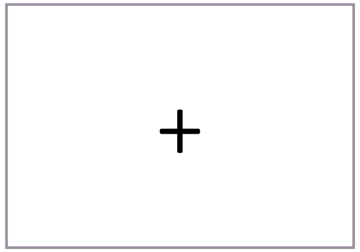
Assumption: Vs. RTs on Unpredictable 50-50 Blocks



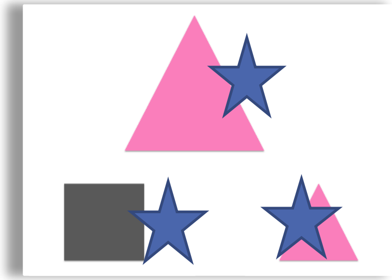
Proposition: This visual oddball paradigm can be represented as a POMDP

Formulating the POMDP

Hidden States: *s*



Both Informative and Uninformative Early Cue



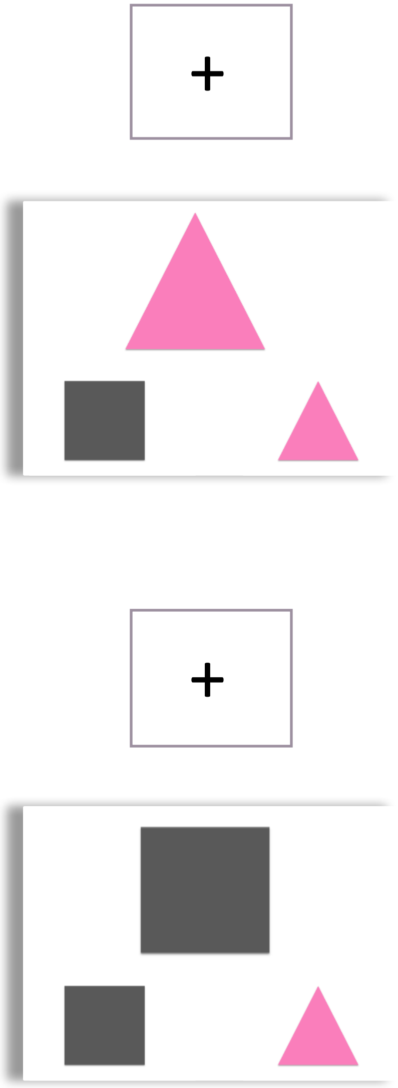
Informative Cue

Triangle or Square Response

Formulating the POMDP

8 Hidden States: *s*

1. Early Cue, Triangle Target (EC1)
2. Early Cue, Square Target Square Target (EC2)
3. Unconditioned Stimulus, Triangle Target (US1)
4. Unconditioned Stimulus Square Target (US2)
5. Conditioned Stimulus Square, Triangle Target (CSS1)
6. Conditioned Stimulus Square Square Target (CSS2)
7. Conditioned Stimulus Triangle, Triangle Target (CST1)
8. Conditioned Stimulus Triangle, Square Target (CST2)



Formulating the POMDP

$p(o|s)$: Observation Matrix (A)
Unpredictable Environment (50-50)

Not sure where I begin: act to reduce uncertainty

- Target triangle
- Target square
- Reward Triangle
- Reward Square
- Target triangle
- Target square
- Reward Triangle
- Reward Square ...

$$
A = \begin{array}{cccccccc}
(EC1) & (EC2) & (US1) & (US2) & (CSS1) & (CSS2) & (CST1) & (CST2) \\
\end{array}
$$

$$
\begin{bmatrix}
0.5 & 0.5 & 0 & \dots & & & & \\
0.5 & 0.5 & & & & & & \\
0 & 0 & & & & & & \\
0 & 0 & & & & & & \\
0 & & 0 & 0 & & & & \\
 & & 0 & 0 & & & & \\
\vdots & & 0.99 & 0.01 & & & & \\
 & & 0.01 & 0.99 & & & & \\
 & & & & 0 & 0 & & \\
 & & & & 0 & 0 & & \\
 & & & & 0.01 & 0.99 & & \\
 & & & & 0.99 & 0.01 & & \\
 & & & & & & 1 & 0 \\
 & & & & & & 0 & 1 \\
 & & & & & & 0 & 0 \\
 & & & & & & 0 & 0
\end{bmatrix}
$$

Formulating the POMDP

$p(o|s)$: Observation Matrix (A)

Predictable Environment (80-20)

Pretty sure where I begin: can act to Get my reward

$$A = \begin{bmatrix}
0.8 & 0.2 & 0 \; \dots & & & & & \\
0.2 & 0.8 & & & & & & \\
0 & 0 & & & & & & \\
0 & 0 & & & & & & \\
0 & & 0 & 0 & & & & \\
 & & 0 & 0 & & & & \\
\vdots & & 0.99 & 0.01 & & & & \\
 & & 0.01 & 0.99 & & & & \\
 & & & & 0 & 0 & & \\
 & & & & 0 & 0 & & \\
 & & & & 0.01 & 0.99 & & \\
 & & & & 0.99 & 0.01 & & \\
 & & & & & & 1 & 0 \\
 & & & & & & 0 & 1 \\
 & & & & & & 0 & 0 \\
 & & & & & & 0 & 0
\end{bmatrix}$$

Formulating the POMDP

$p(s_{t+1}|s_t, u)$:
Transition Matrix (B)

Same in predictable and unpredictable environment

$$B(u_t = 1) = \begin{bmatrix} 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \otimes I_2$$

Begin Trial

$$B(u_t = 2) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \otimes I_2$$

Press Triangle

$$B(u_t = 3) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 \end{bmatrix} \otimes I_2$$

Press Square

$$B(u_t = 4) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 \end{bmatrix} \otimes I_2$$

Saccade to CS

Given a model of the task

$$lnP(u_t|\gamma) = \gamma\boldsymbol{U} = \gamma\left(U_{t+1}\,(\pi) + \cdots + U_T\,(\pi)\right)$$

$$U_{t_n}\,(\pi) = (\mathrm{A}\ \mathrm{lnA}).\{\mathrm{B}(u_{t_n}\,|\pi)\ldots\mathrm{B}(u_t\,|\pi)s_t\} - (\mathrm{ln}(o_{t_n}|\pi) - \mathrm{lnC})o_{t_n}$$

Only two sets of priors

$$lnP(u_t|\gamma) = \gamma \boldsymbol{U} = \gamma\left(U_{t+1}(\pi) + \cdots + U_T(\pi)\right)$$

$$U_{t_n}(\pi) = (\mathrm{A}\ \mathrm{lnA}).\{\mathrm{B}(u_{t_n}|\pi) \ldots \mathrm{B}(u_t|\pi)s_t\} - (\ln(o_{t_n}|\pi) - \mathrm{lnC})o_{t_n}$$

Priors on Outcome

I will be right

I will be wrong

$$P(o|m) = C = \sigma([1\ \ 1\ \ 1\ \ 1]'\otimes I_2\,[0\ \ 0\ \ c\ \ -c])'$$

Priors on Precision

I am confident in my actions

$\alpha\ high, \beta$ low

I don't have any control

$\alpha\ low, \beta$ high

$$P(\gamma|m) = \Gamma(\alpha, \beta)$$

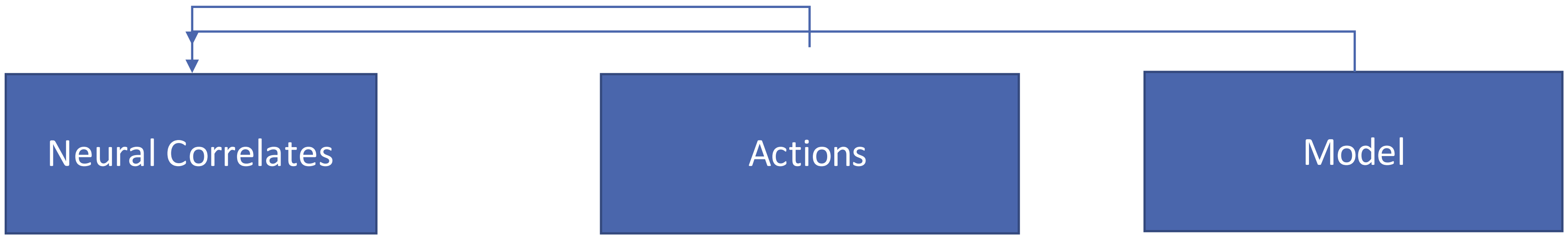
Given: A, B, C

1. Simulate Behavioural Performance (actions) for various priors (C)

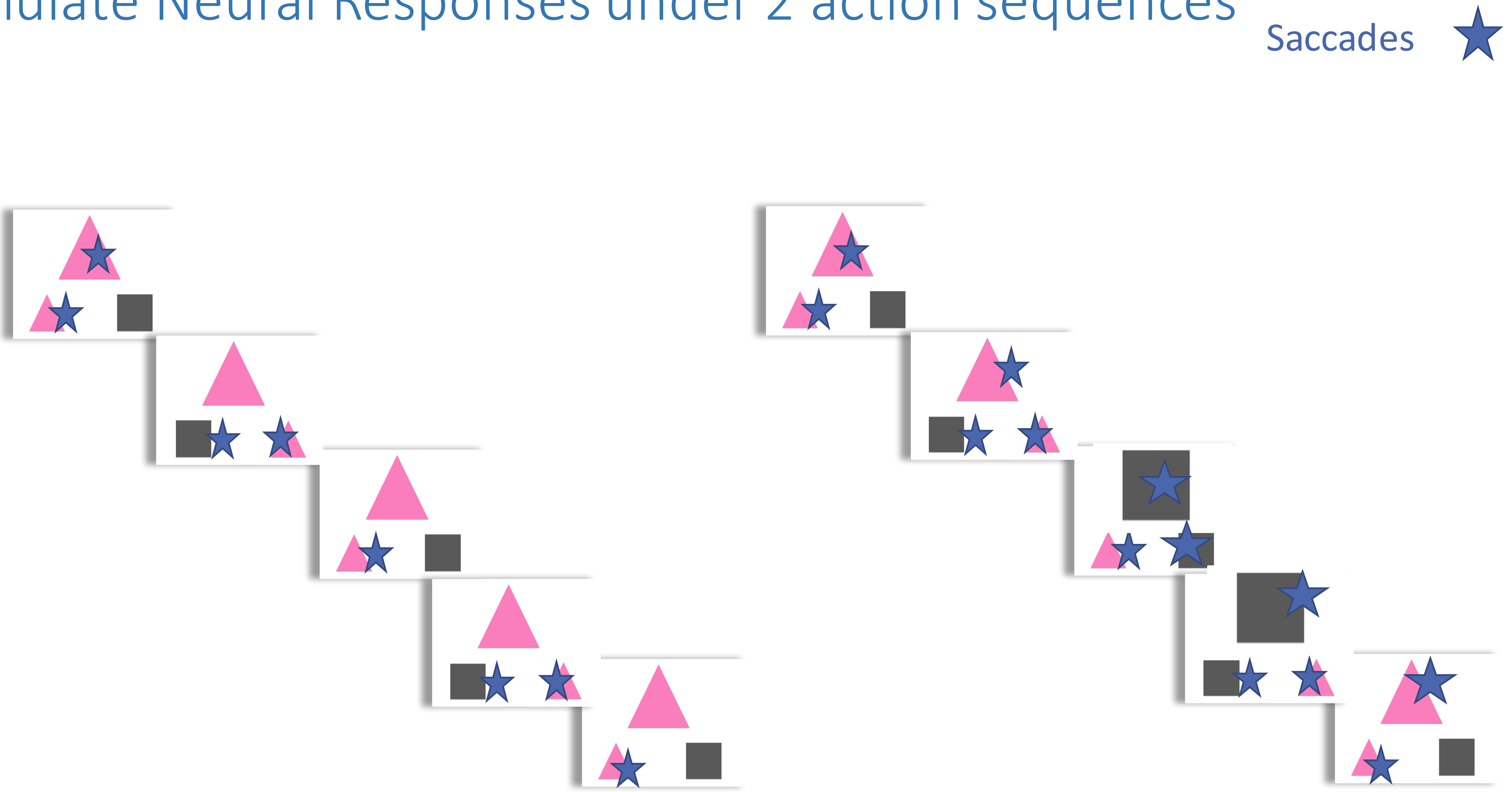
2. Simulate Behavioural Performance (actions) for various levels of precision (γ, α, β)

3. Given actions simulate within trial (saccade, saccade, response) variational updates:
   i.e. updates on s and γ to produce neural predictions

Thus: Assuming distinct action sequence for Unpredictable and Predictable trials (based on RTs) we will generate neural correlates of within trial updates under different prior beliefs



Simulate Neural Responses under 2 action sequences



Predicted Neural Correlates

Priors on Outcomes

Priors on Precision

With
$c = 0.5$
$\alpha = 64$
$\beta = 4$

Distinct Neural Predictions for

Unpredictable Vs.

Predictable Blocks

Predicted Neural Correlates

Priors on Outcomes

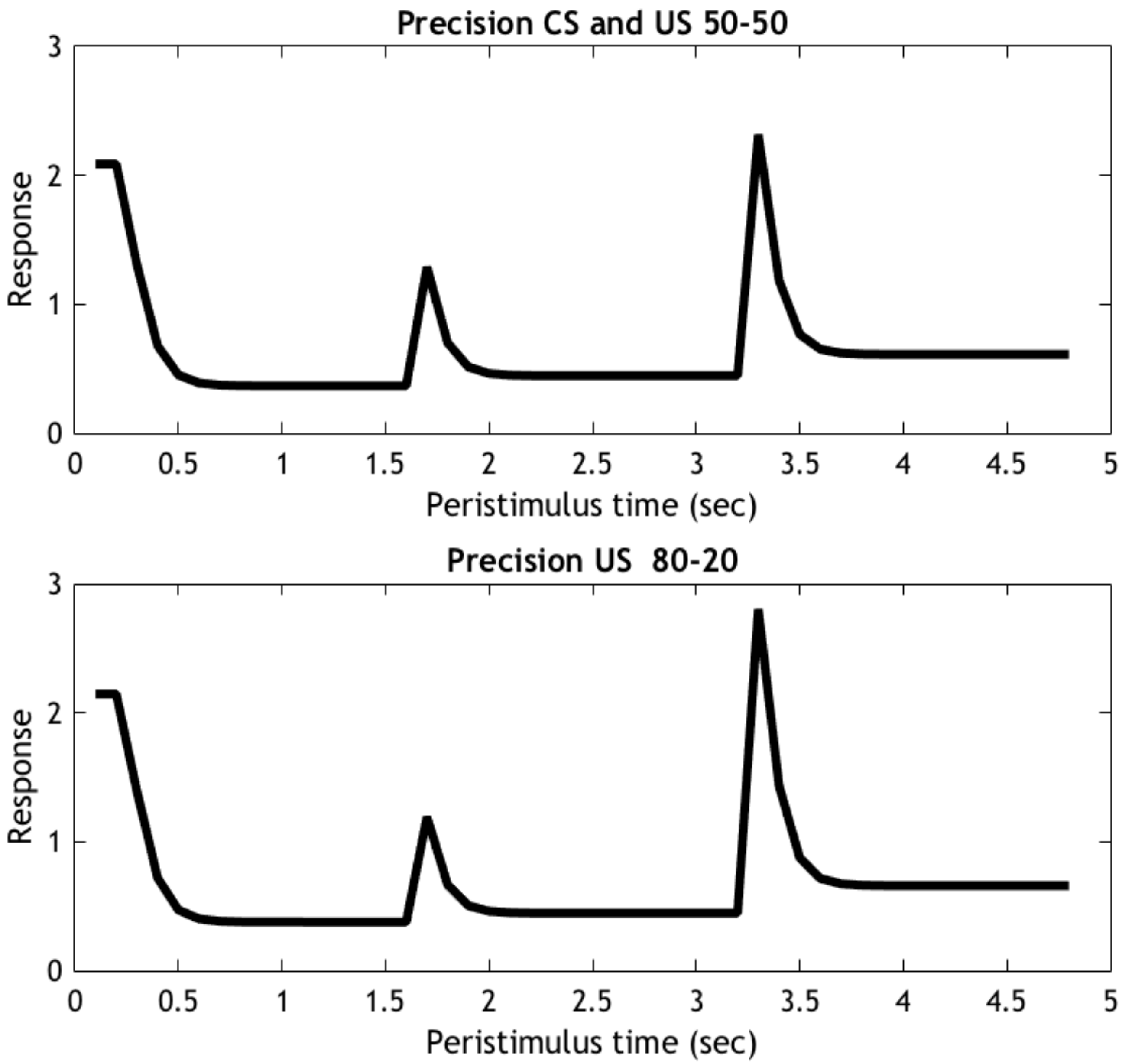
Priors on Precision

With
c = 0.5
$\alpha = 64$
$\beta = 4$

Distinct Neural Predictions for

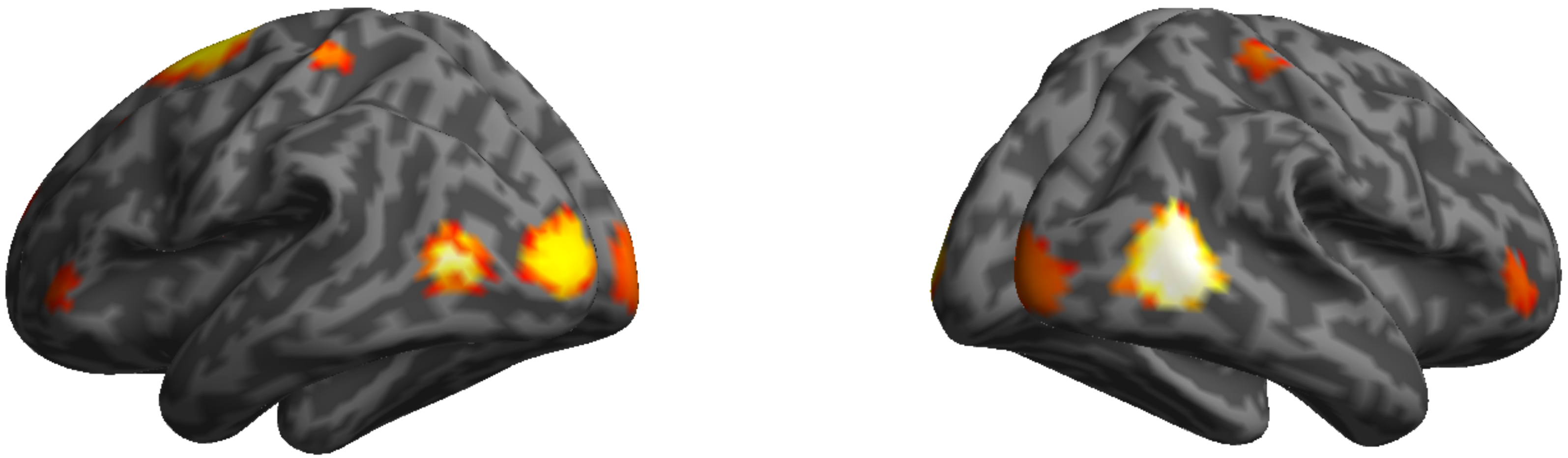
Unpredictable Vs.

Predictable Blocks



Hypothesis: Correlates of model-based brain dynamics are present in real brain dynamics

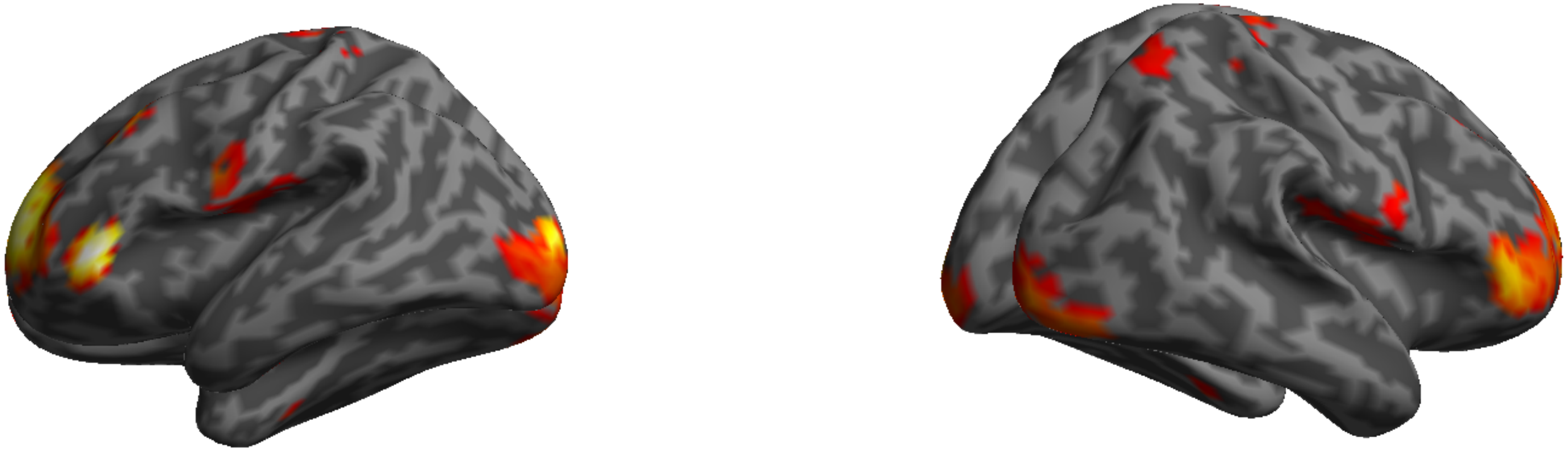
Source Localization: Identifying ROIs



64 Channel EEG: Source localize induced power from 1- 45 Hz over -50 to 500 msec PST

SPM's Multiple Sparse Priors, Group Inversion all Young only, Canonical Render, $p < 0.001$ unc

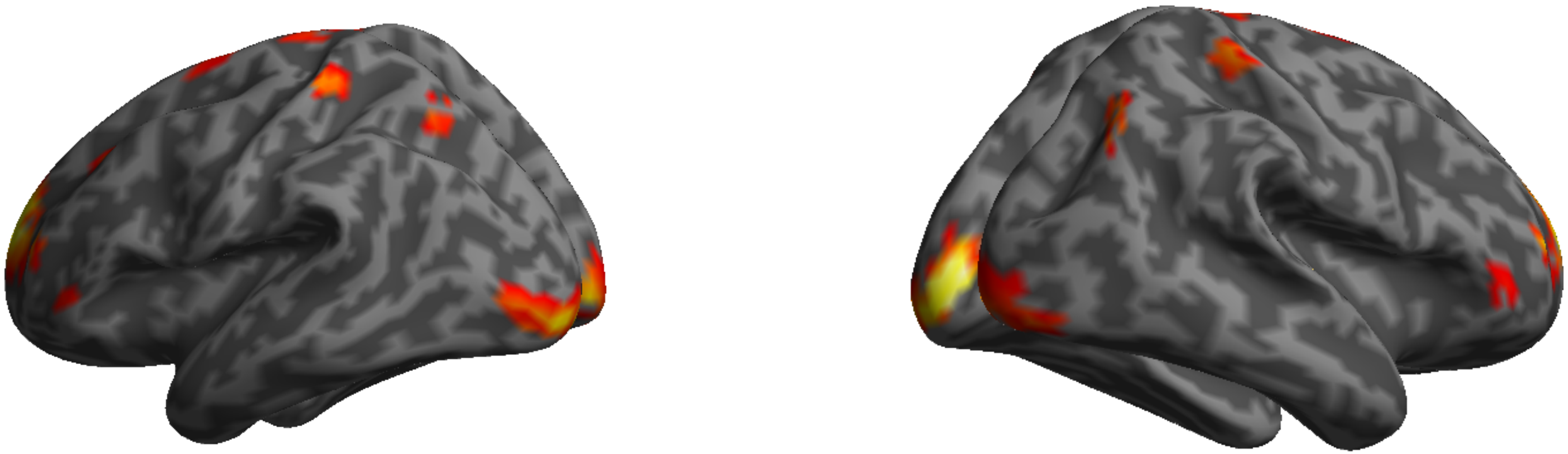
Source Localization: Identifying ROIs



Age-Matched Controls: One sample *t* test over all trials using induced power from 1- 45 Hz over -50 to 500 msec PST

SPM's Multiple Sparse Priors, Group Inversion all Age-matched only, $p < 0.005$ unc

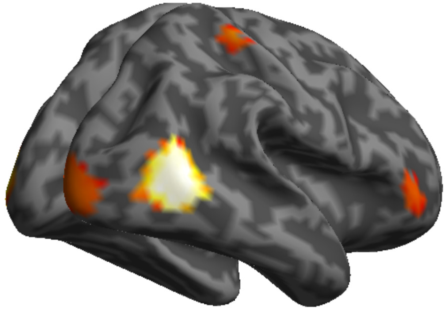
Source Localization: Identifying ROIs

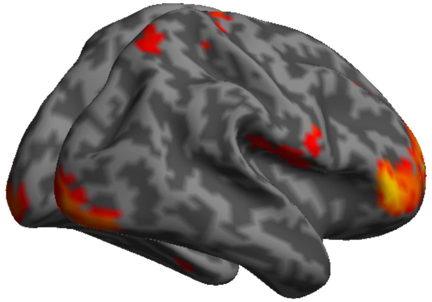


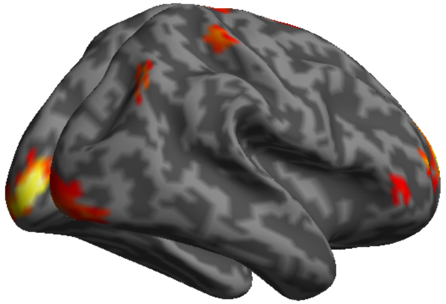
Patients with AD: One sample *t* test over all trials using induced power from 1- 45 Hz over -50 to 500 msec PST

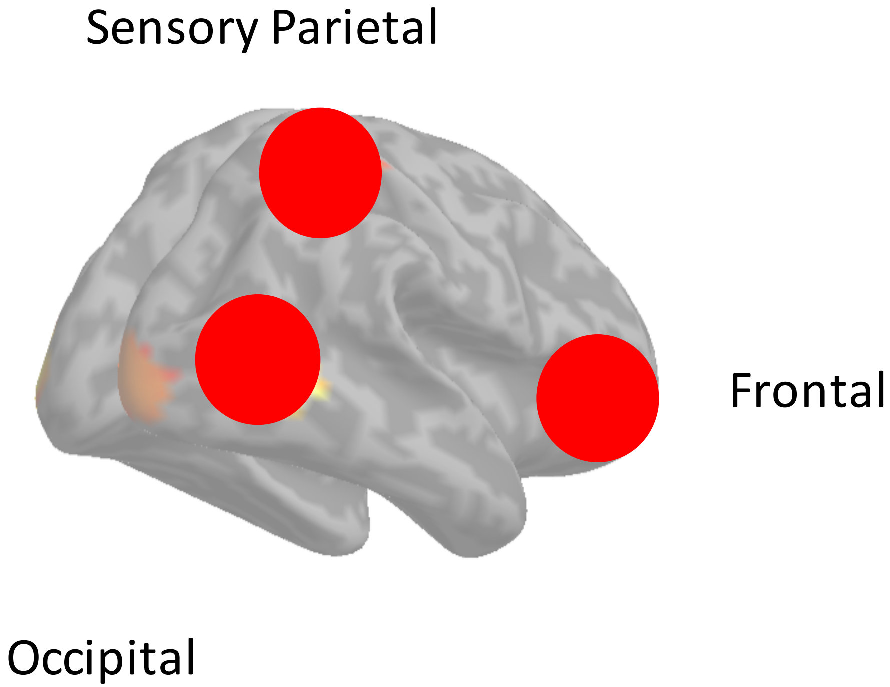
SPM's Multiple Sparse Priors, Group Inversion all AD only, $p < 0.001$ unc

Chosen ROI's

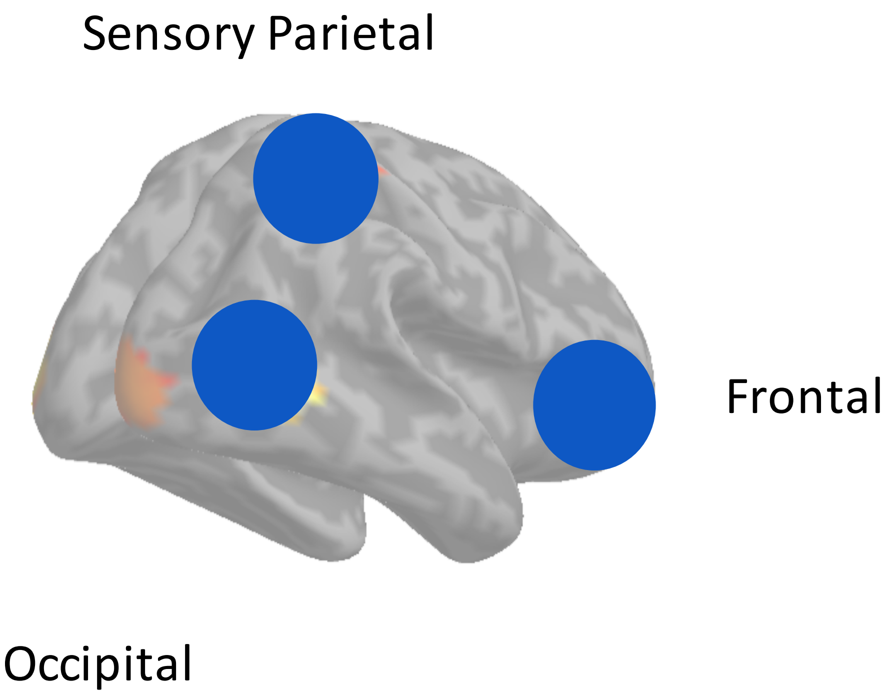


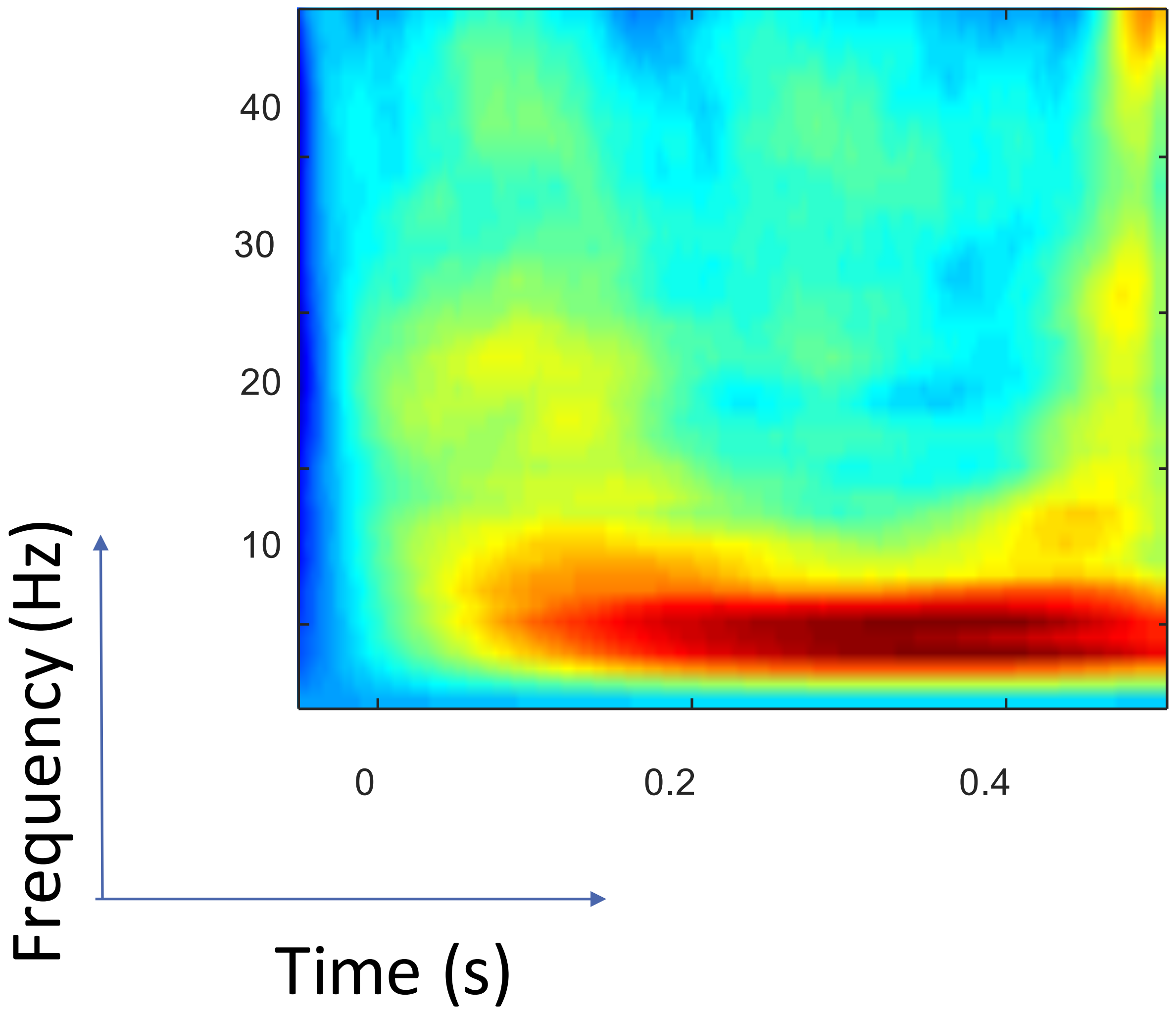




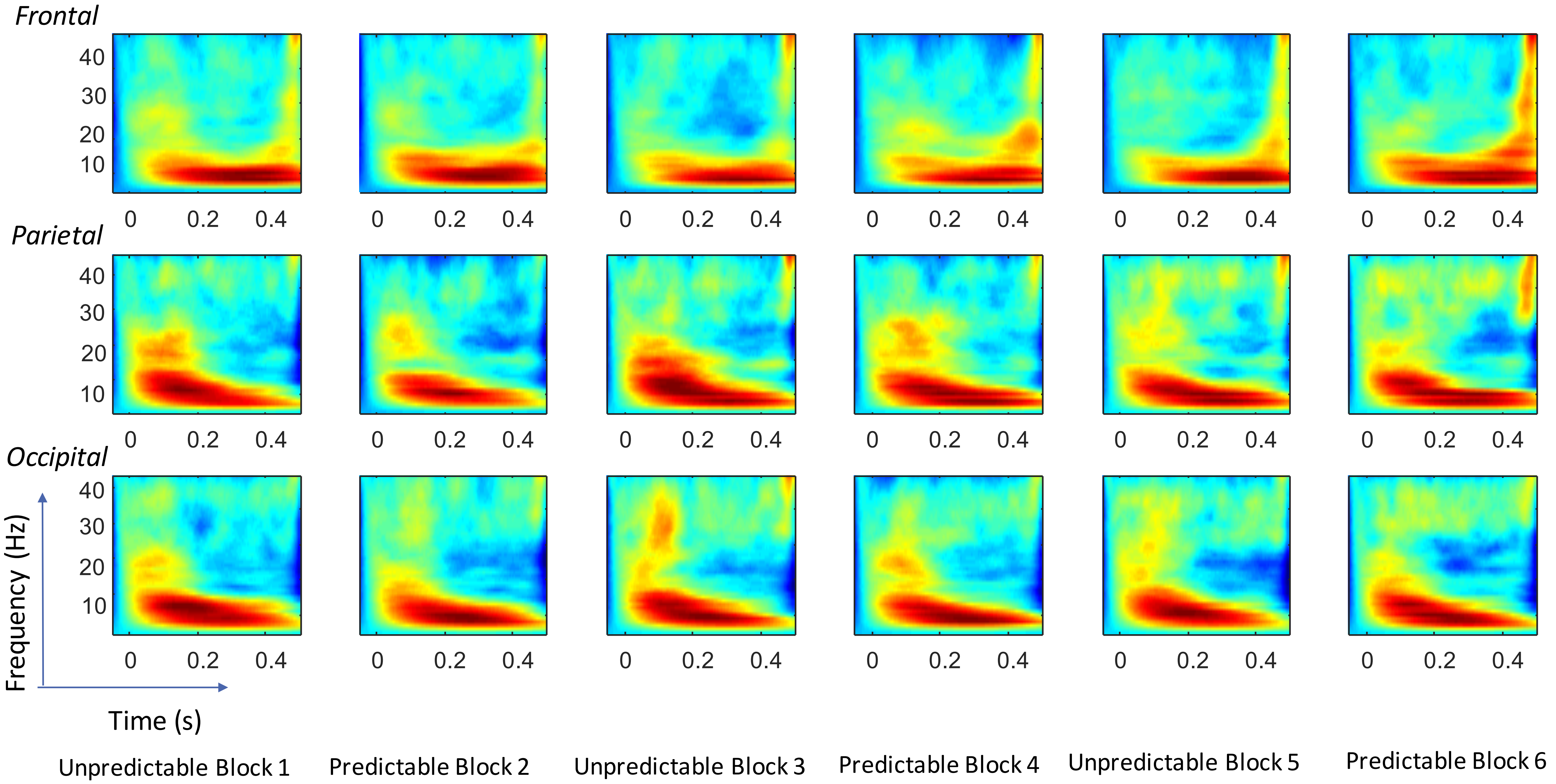


Within Trial Effects using T-F Analysis





Time Frequency Representation, Extracted Sources

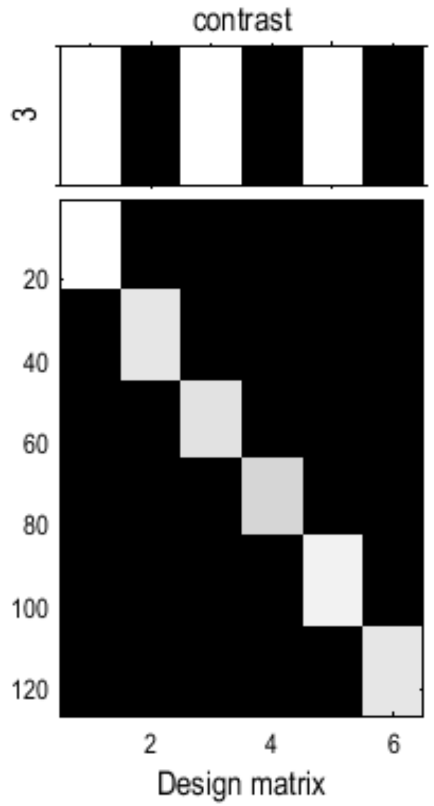


Time Frequency Representation, Extracted Sources

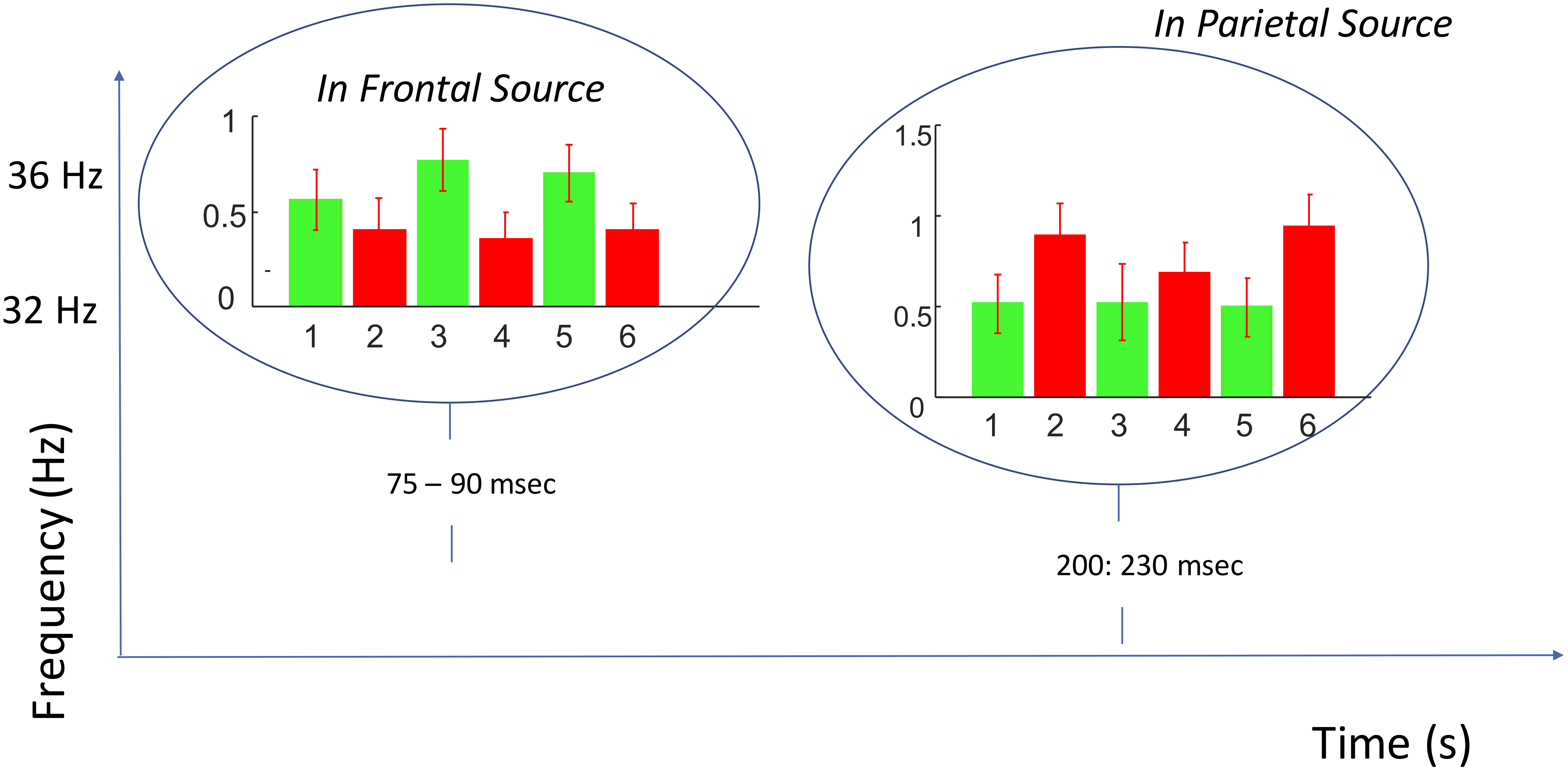
All cohorts displayed a
significant effect of predictability on RT

Testing AD in the presence of an effect

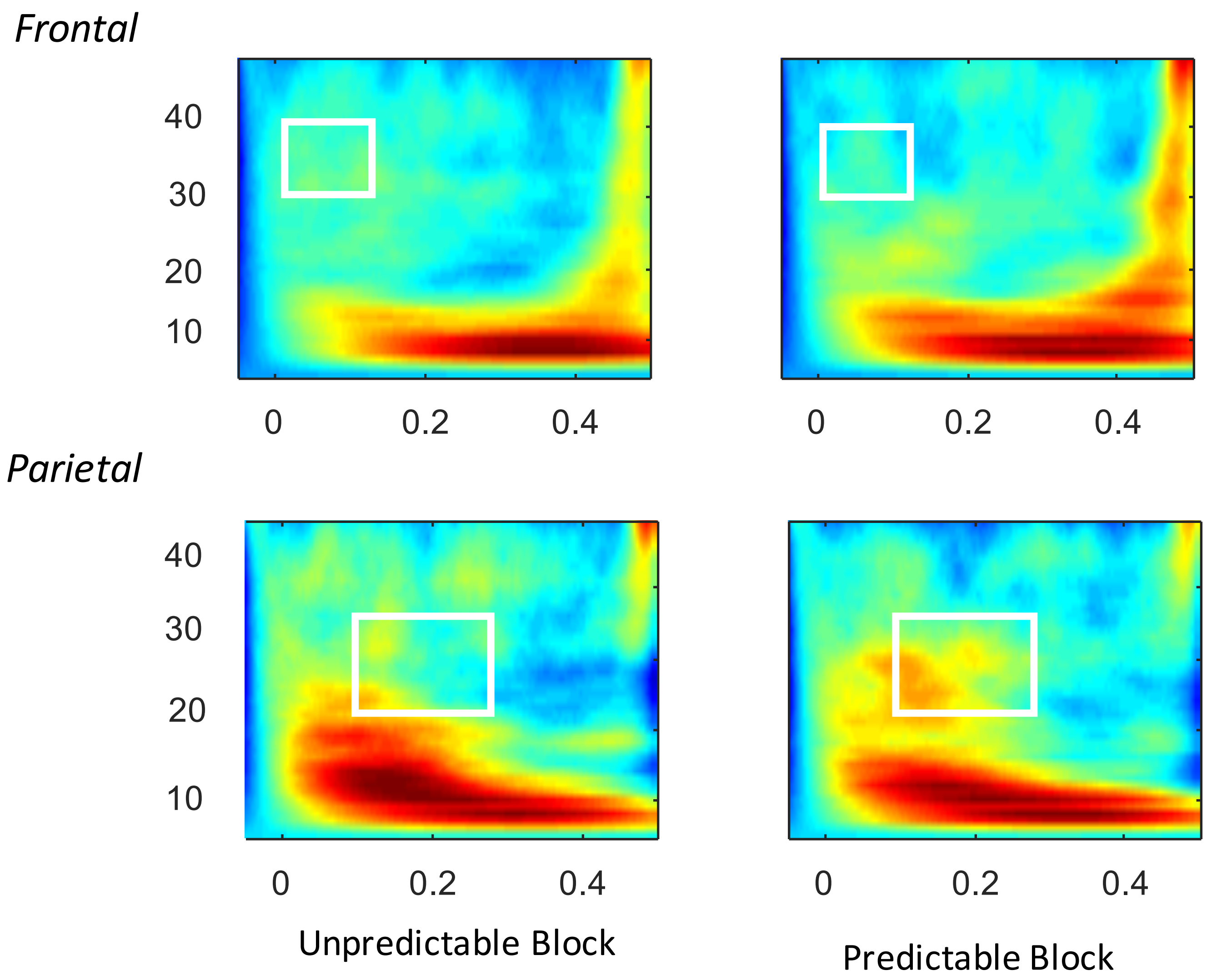
......For each region test
for effects of predictability



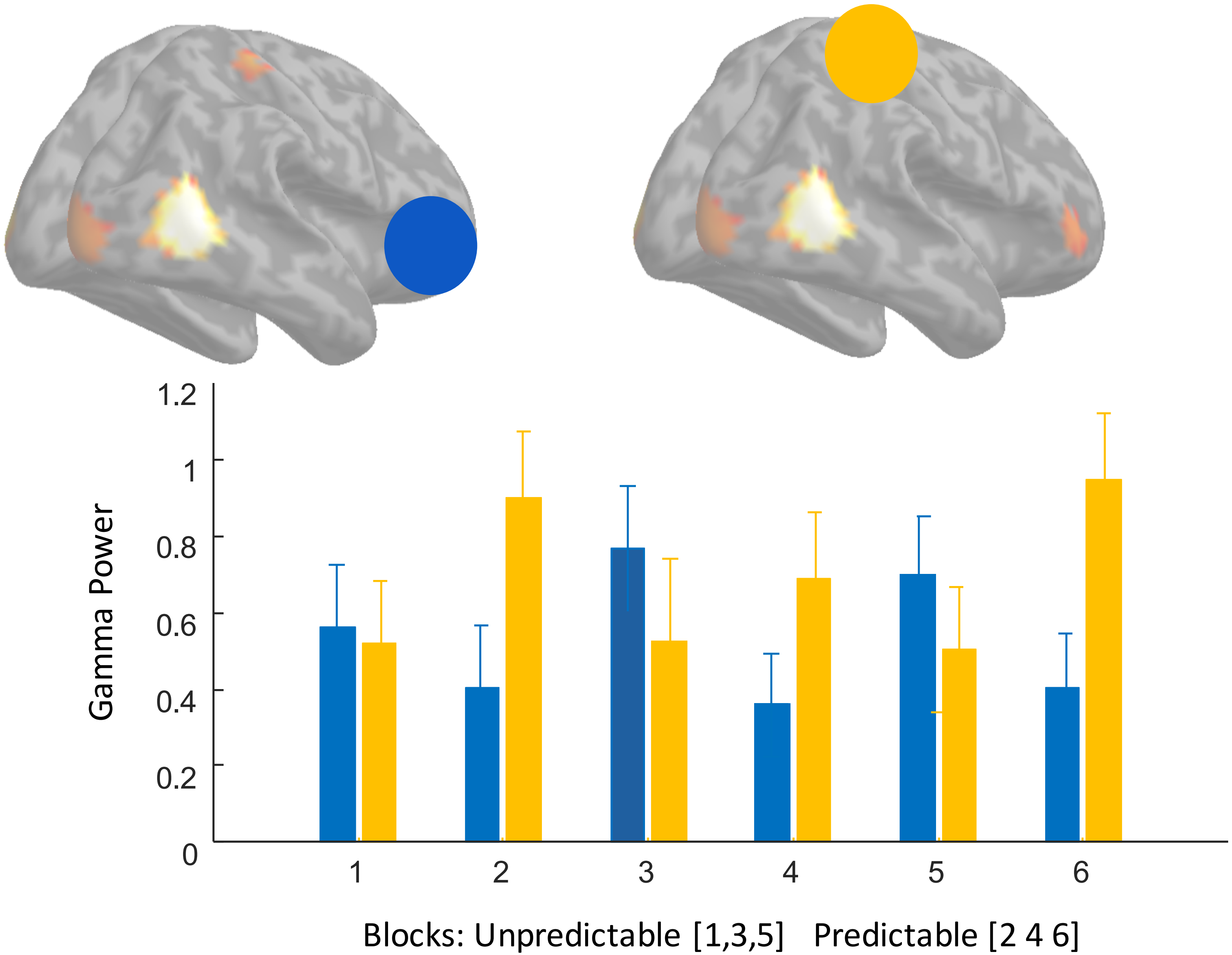
Significant Main Effects of Predictability



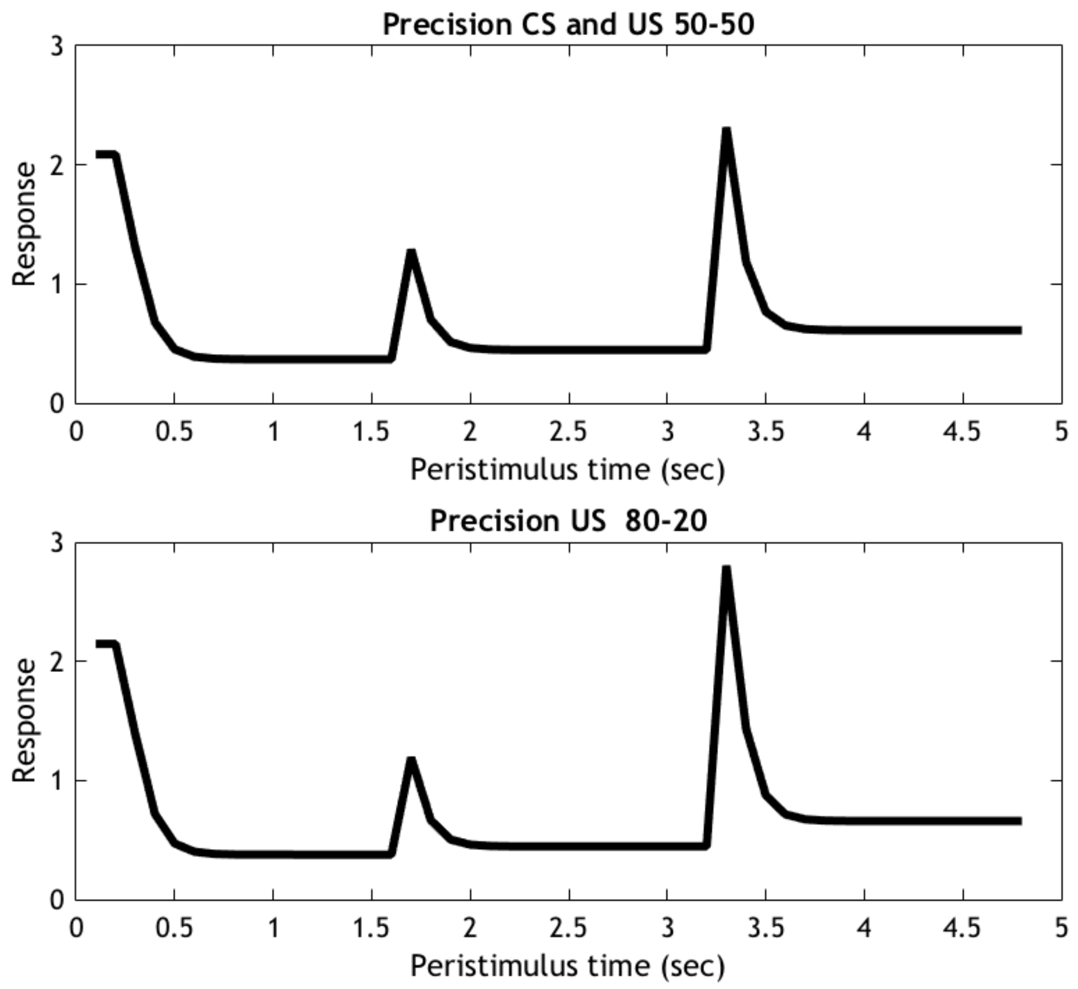
Time Frequency Representation, Extracted Sources

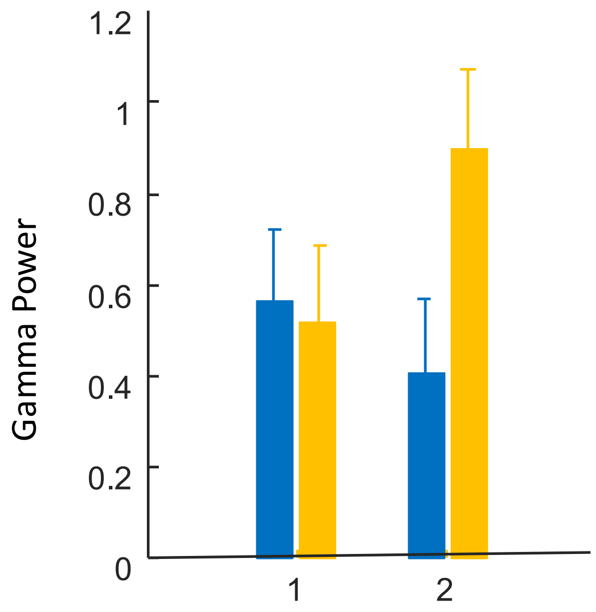


Gamma Correlates of Predictability…



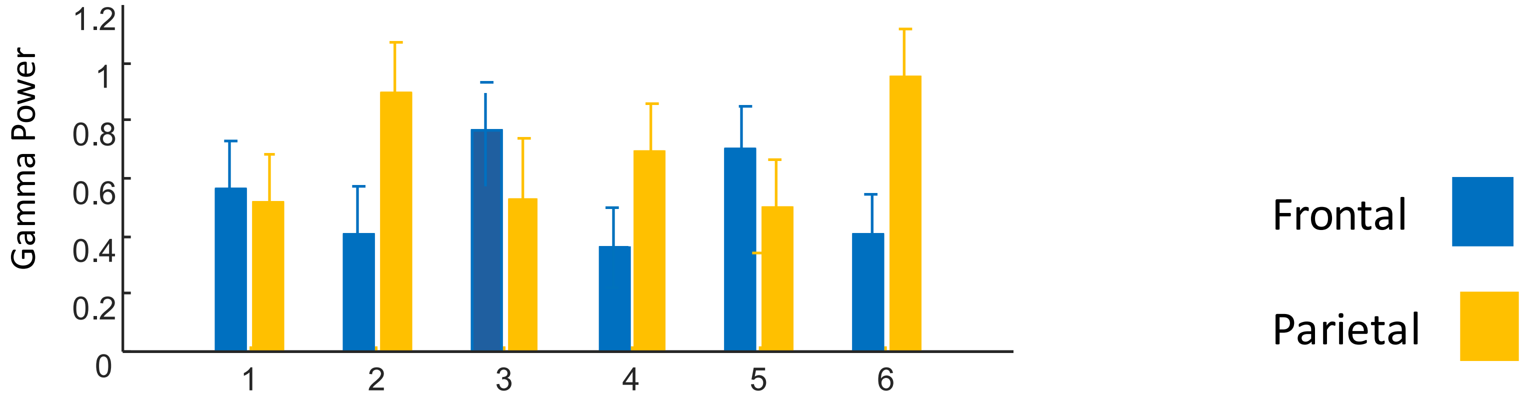
We predicted distinct precision signatures

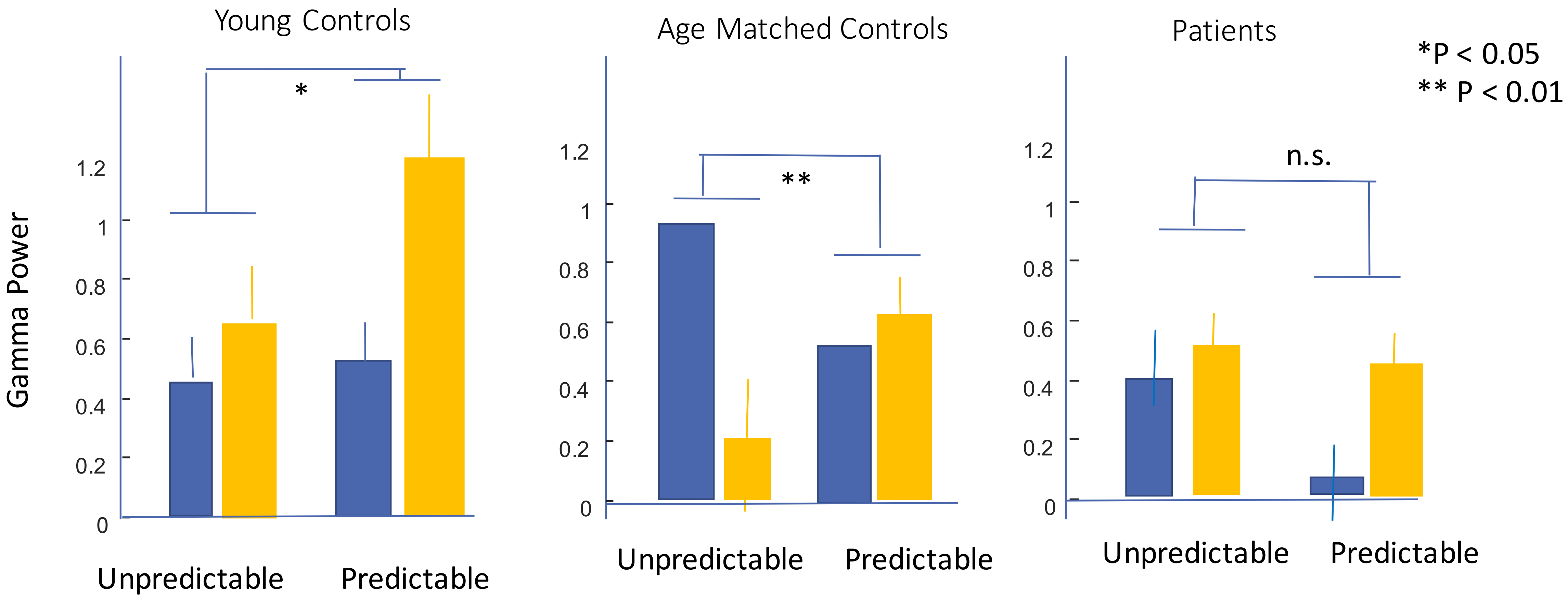




Hypothesis: Group differences in these brain dynamics reflect differences in variational updates caused by different priors on outcomes and precision

Group Differences





Precision & Priors: Young Controls

Priors on Outcome

I will be right

I will be wrong

$$P(o|m) = C = \sigma([1\quad 1\quad 1\quad 1]'\otimes I_2\,[0\quad 0\quad c\quad -c])'$$

Priors on Precision

I am confident in my actions

$\alpha\ high, \beta$ low

I don't have any control

$\alpha\ low, \beta$ high

$$P(\gamma|m) = \Gamma(\alpha,\beta)$$

With

$c = 0.5, \alpha = 64, \beta = 4$

Precision & Priors: Young Controls

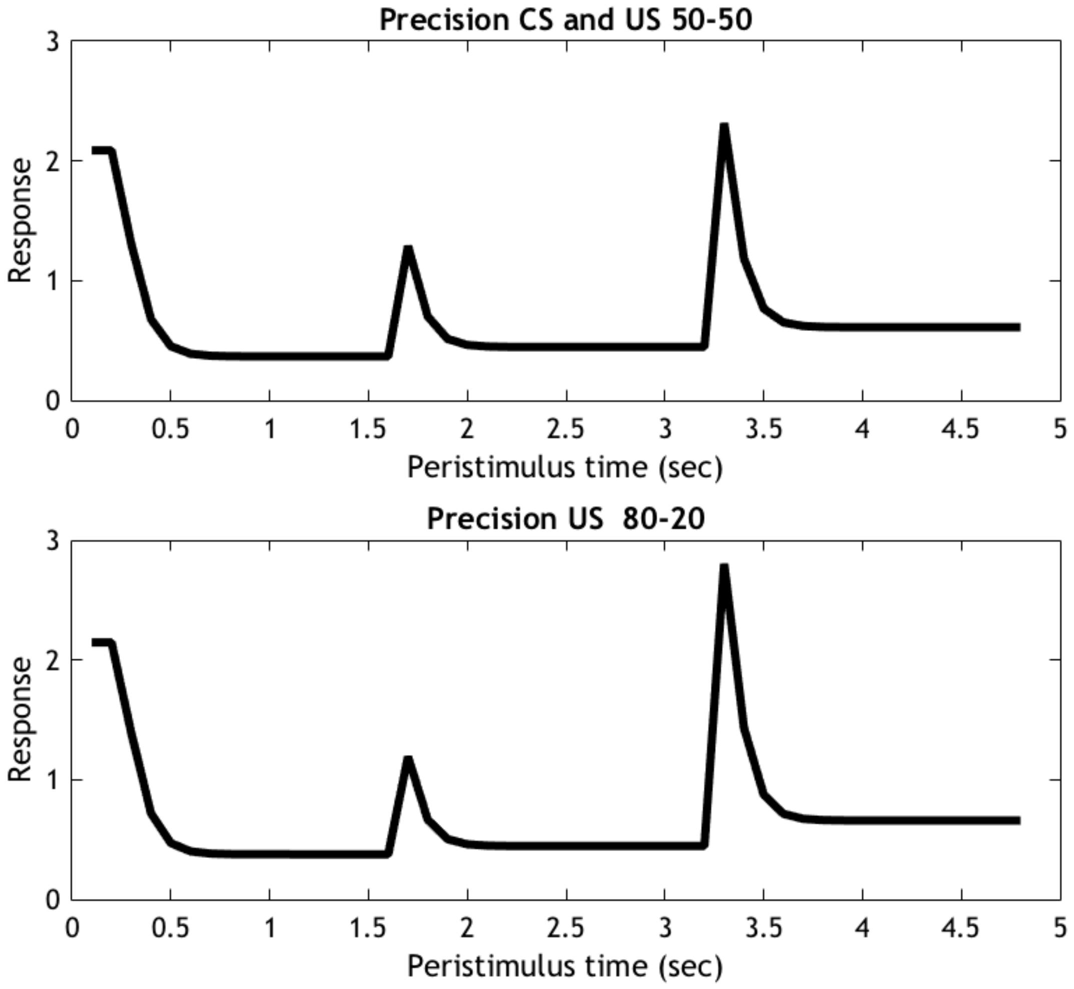
With

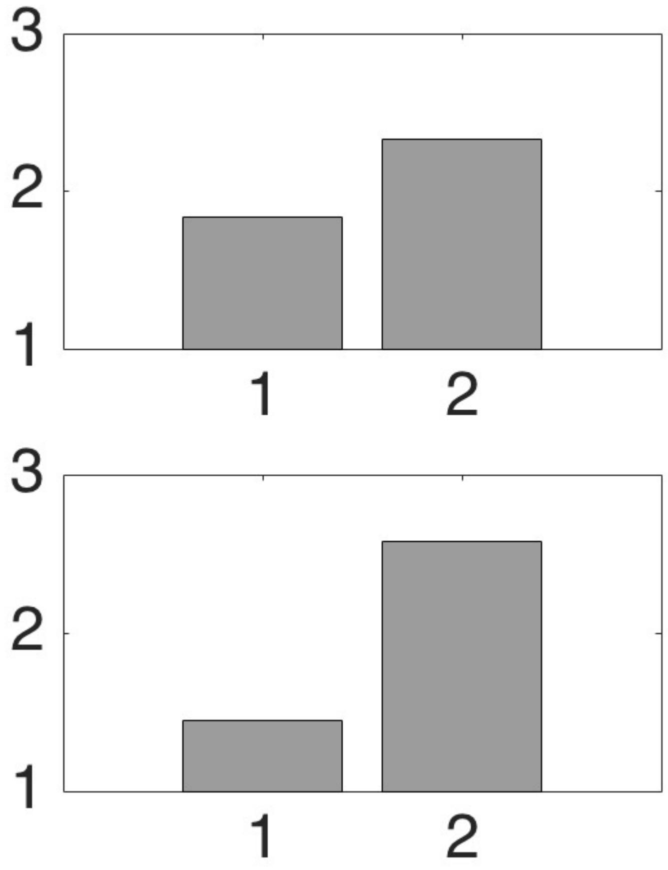
$c = 0.5, \alpha = 64, \beta = 4$

Predicted Gamma Burst

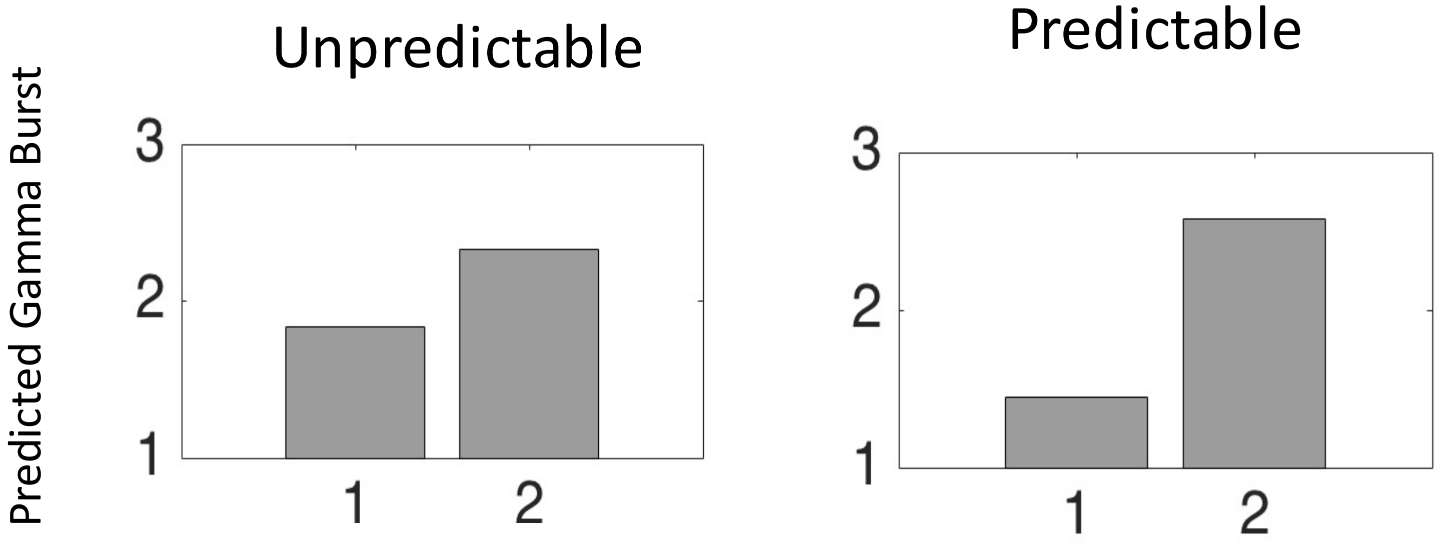
Unpredictable

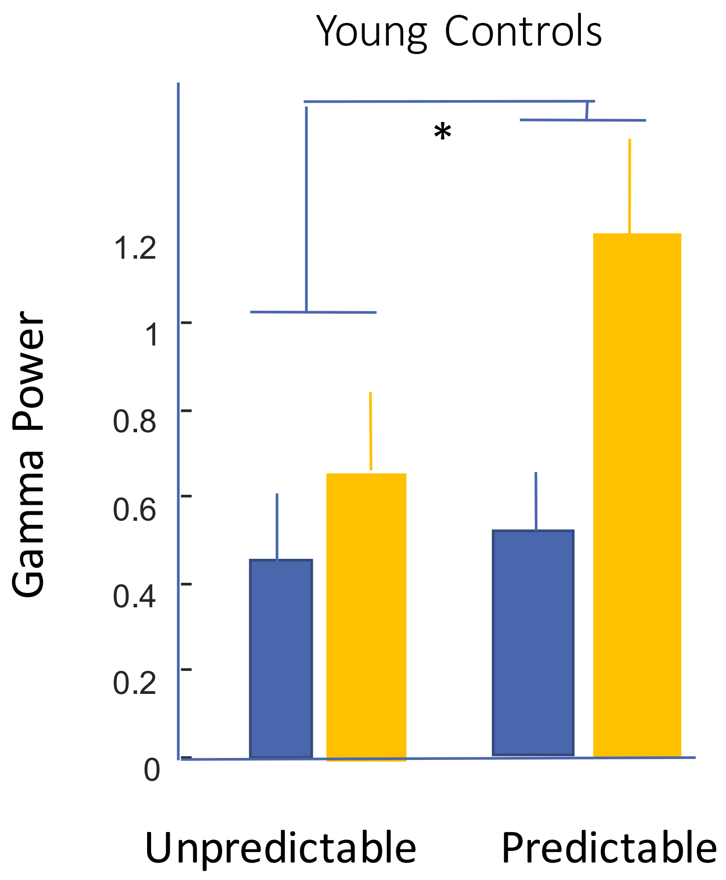
Predictable





Precision & Priors: Young Controls





With

$c = 0.5, \alpha = 64, \beta = 4$

Precision & Priors: **Older Controls** vs Younger Controls

Priors on Outcome (goals)

With
$\boldsymbol{c = 2, \alpha = 64, \beta = 3}$

Vs. Young Controls
$c = 0.5, \alpha = 64, \beta = 4$

I WILL be right

I will be right

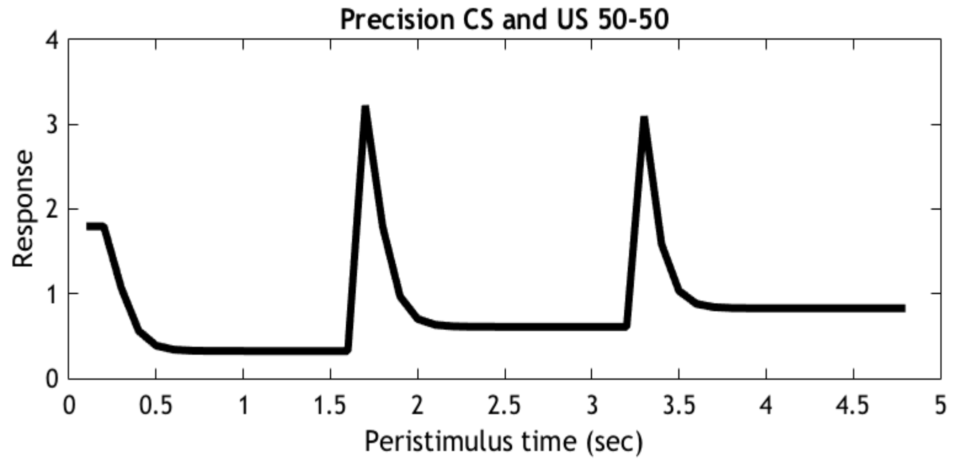
Update precision more slowly

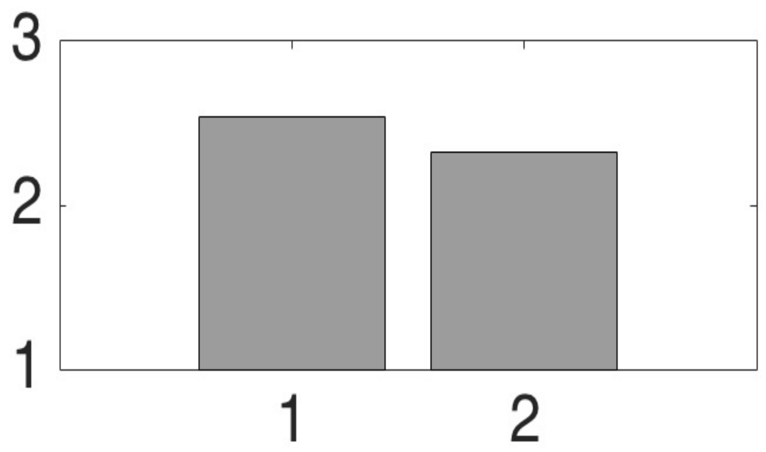
Precision & Priors: Older Controls

With
$c = 2, \alpha = 64, \beta = 3$

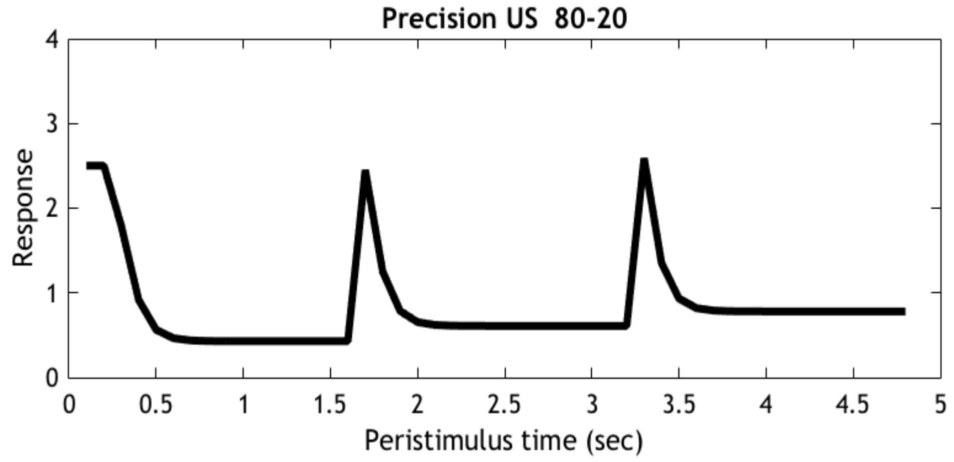
Predicted Gamma Burst

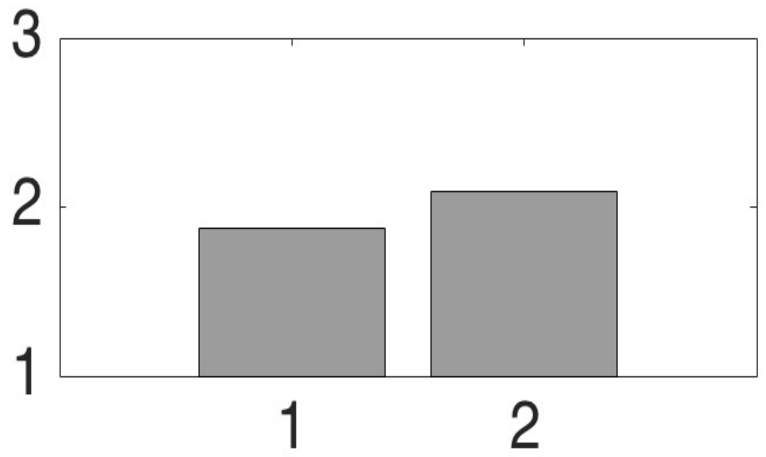
Unpredictable



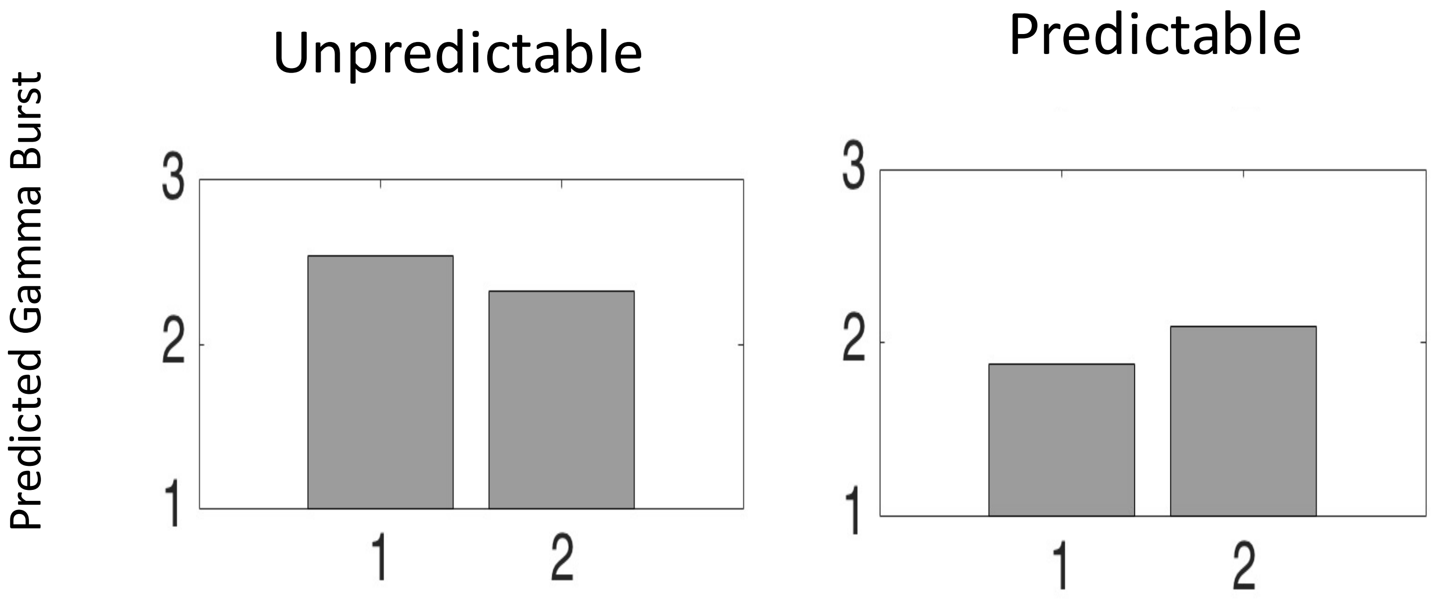


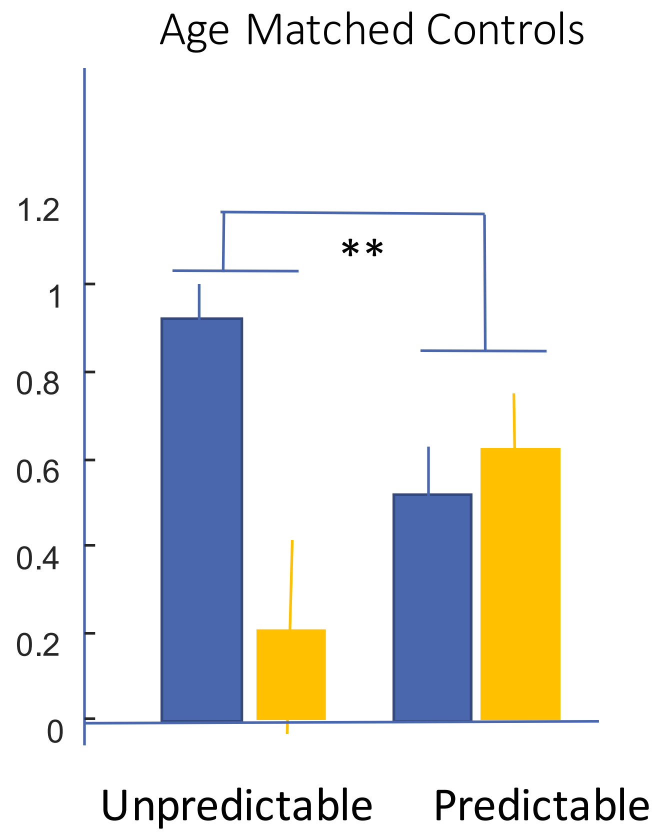
Predictable





Precision & Priors: Older Controls





With

$c = 2, \alpha = 64, \beta = 3$

Precision & Priors: **Alzheimer's Disease** vs Age-matched Controls

Priors on Precision

With

$\boldsymbol{c = 0.5, \alpha = 8, \beta = 3}$

Vs. Age-matched

$c = 2, \alpha = 64, \beta = 3$

I don't have any control

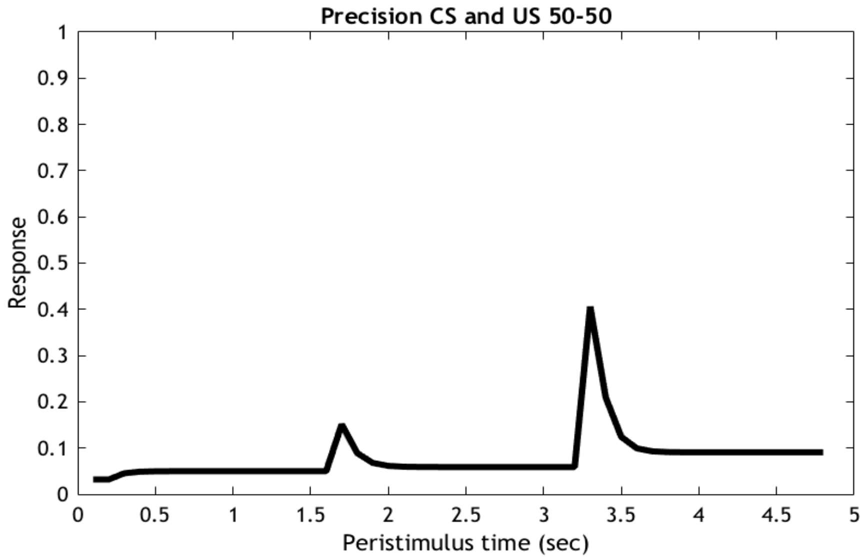
I am confident in my actions

Precision & Priors: AD Patients

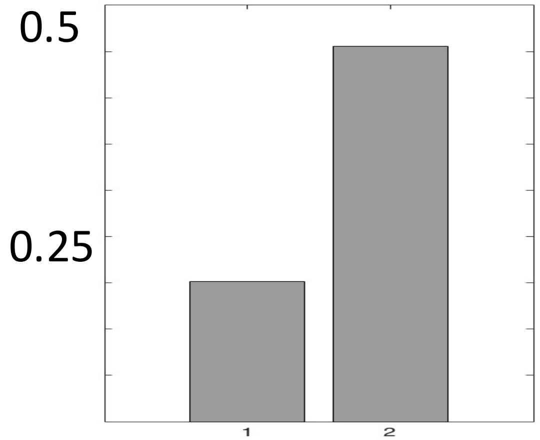
With

$c = 0.5, \alpha = 8, \beta = 3$

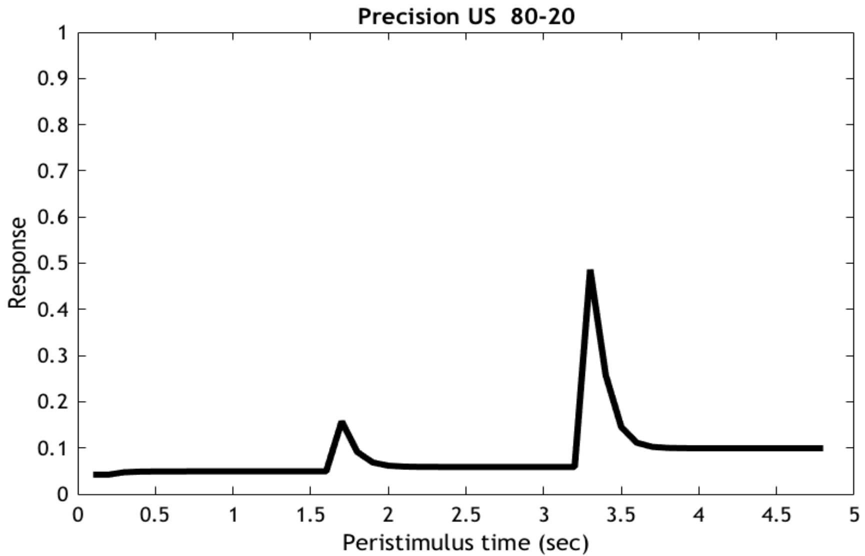
Unpredictable

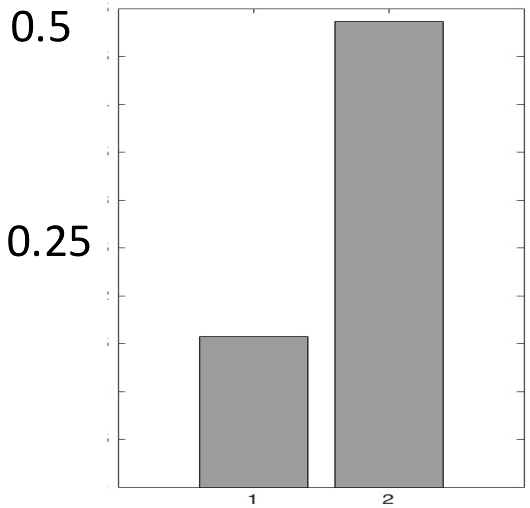


Predicted Gamma Burst

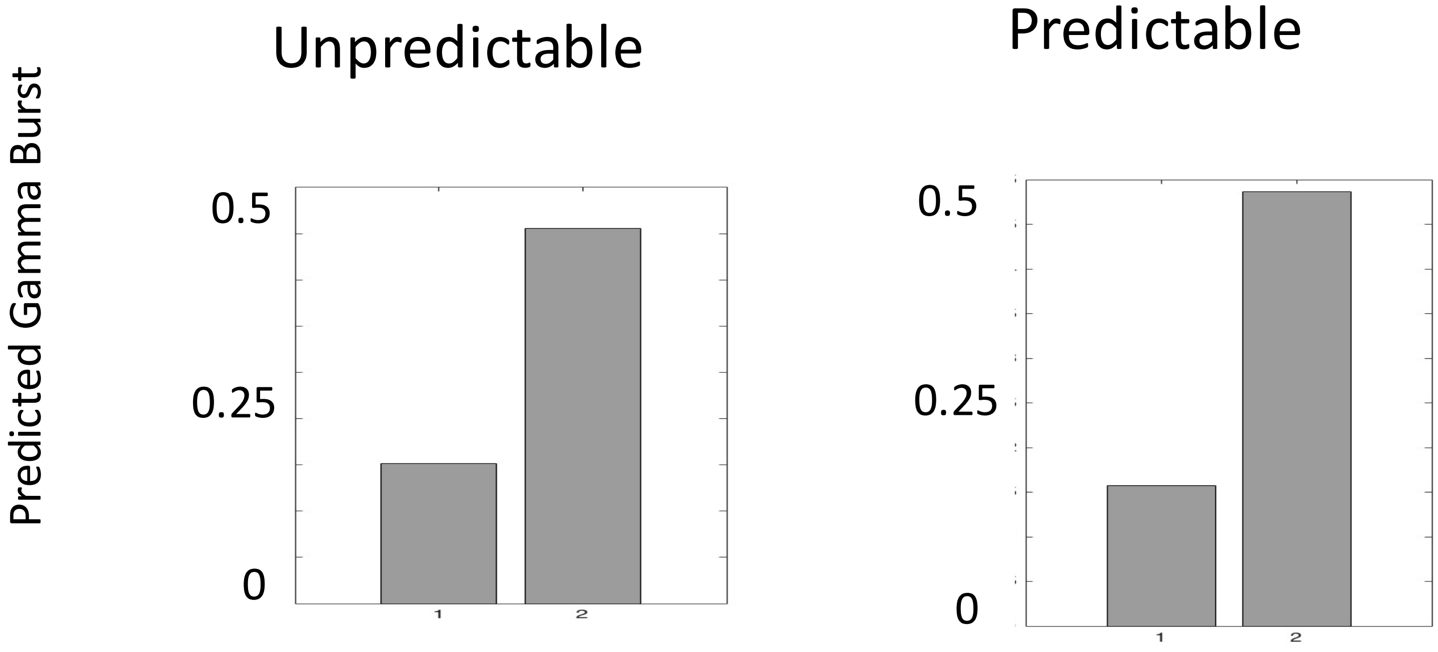


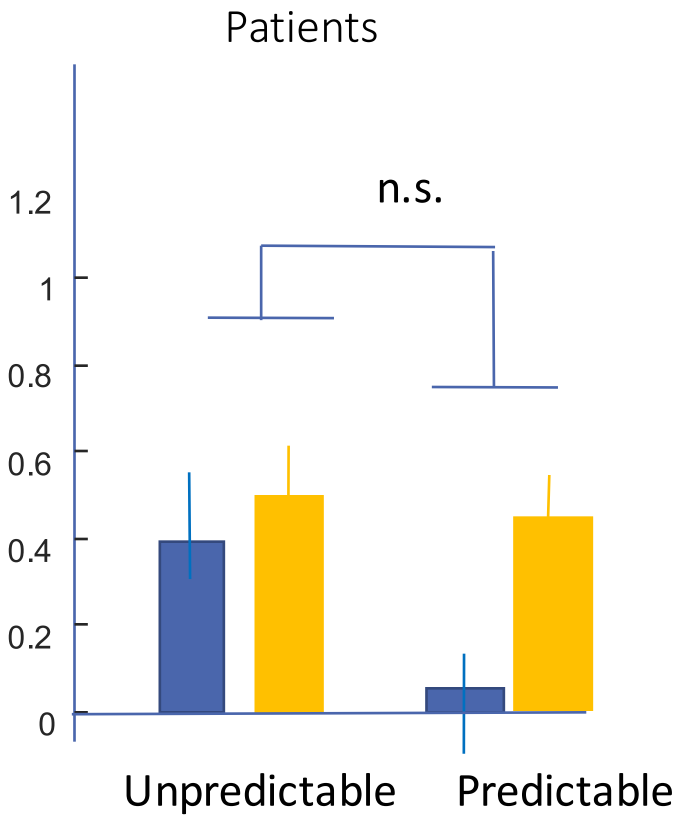
Predictable





Precision & Priors: AD Patients

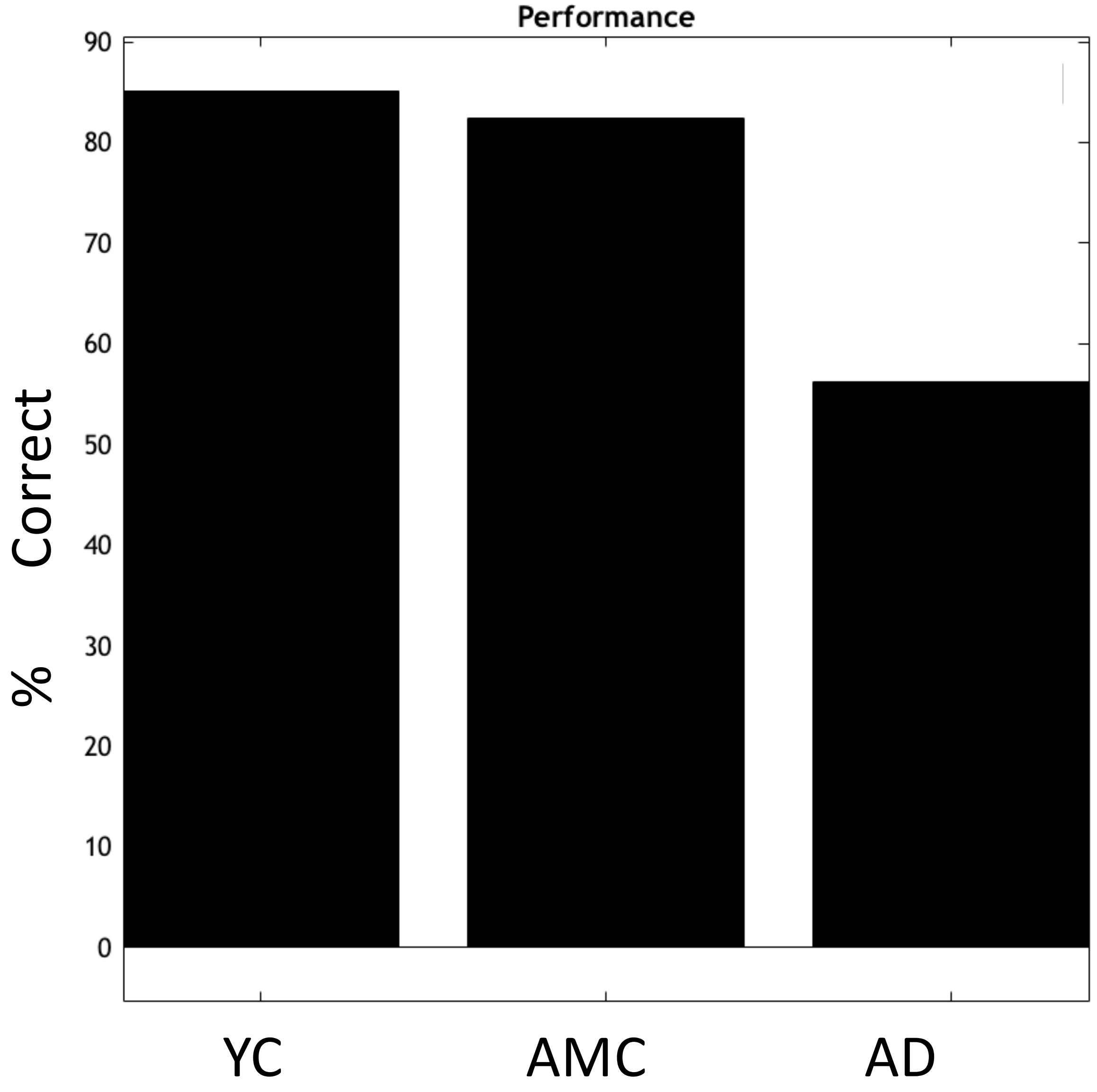




With

$c = 0.5, \alpha = 8, \beta = 3$

Simulate performance under these priors



Conclusions, limitations

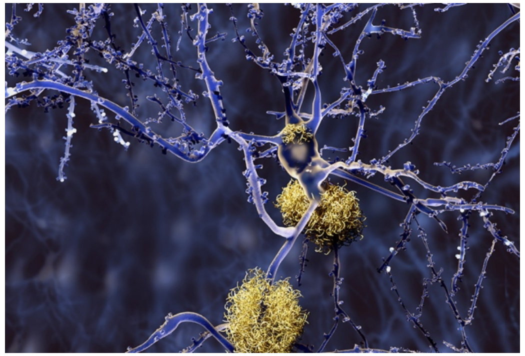
Different priors on outcomes and precision – predict group differences in brain dynamics.

These dynamics are in the gamma band which has been associated with precision.

Different priors on outcomes and precision - derived from brain dynamics - predict group differences in behaviour. Can predict behaviour on other tasks

But used identical models of the task for all cohorts; could change A,B for AD and perform Bayesian Model Comparison & did not account for learning.

Computational Psychiatry and Spectrums in Alzheimer’s Disease



Without the model:

Abnormal gamma responses in AD patients in frontal cortex may ‘cause’ behavioural decline in executive function

With the model:

Abnormal gamma responses suggest failure to resolve uncertainty (due to low belief in control) and could suggest DA treatment to induce higher prior precisions

Thank you