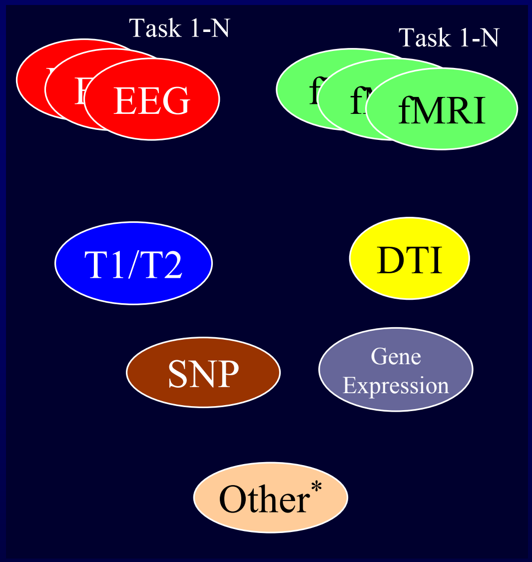
Combining fMRI, ERP and SNP data with ICA: Introduction and examples

Vince D. Calhoun, Ph.D.

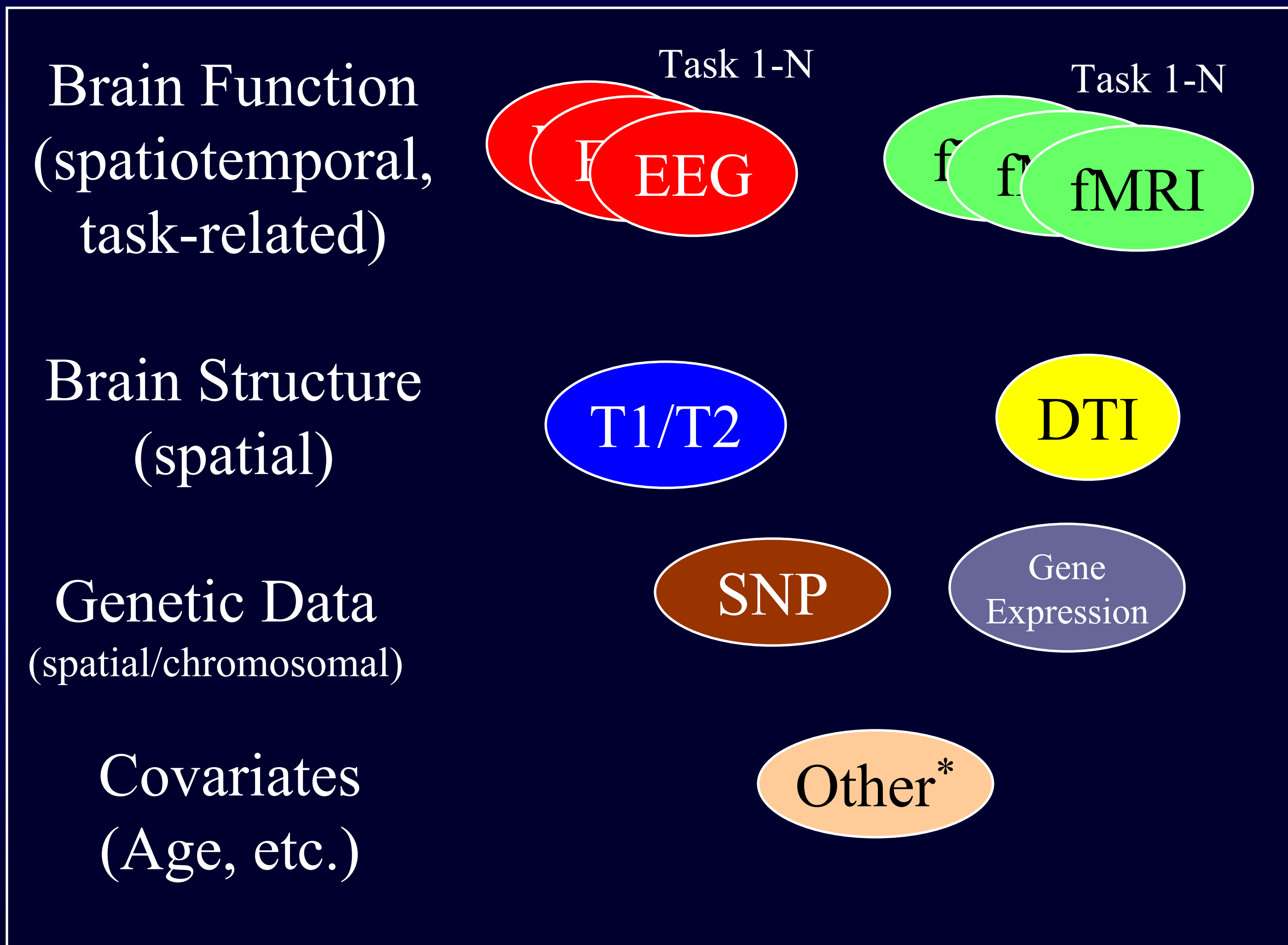
Director, Image Analysis & MR Research
The Mind Research Network
Associate Professor, Electrical and Computer Engineering
The University of New Mexico

Outline

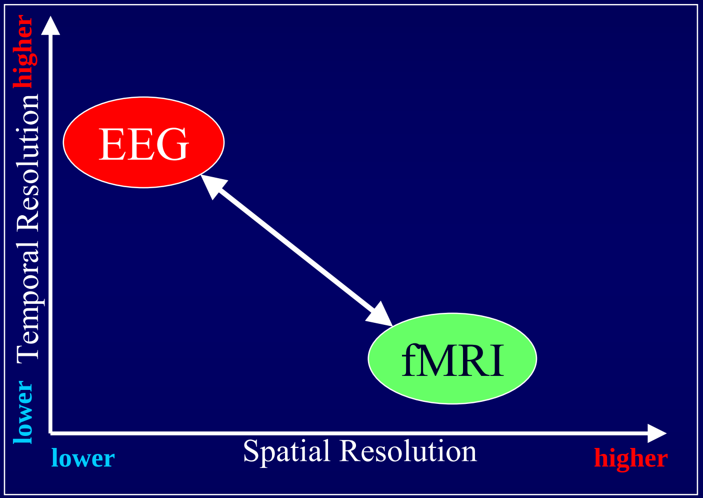
- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions



Multimodal Data Collection

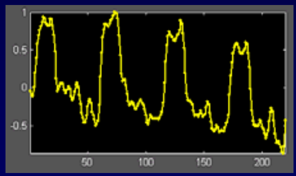


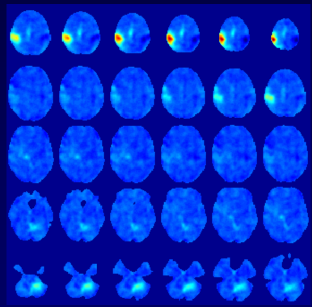
A Role For Data Fusion?:

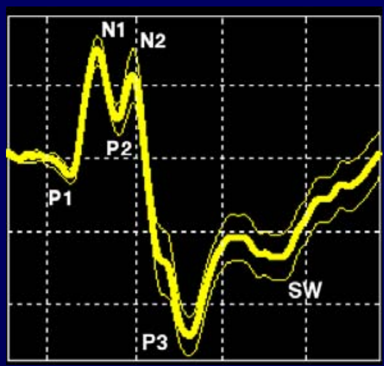


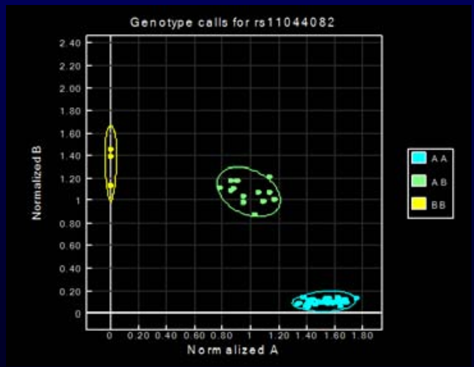
Outline

- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions

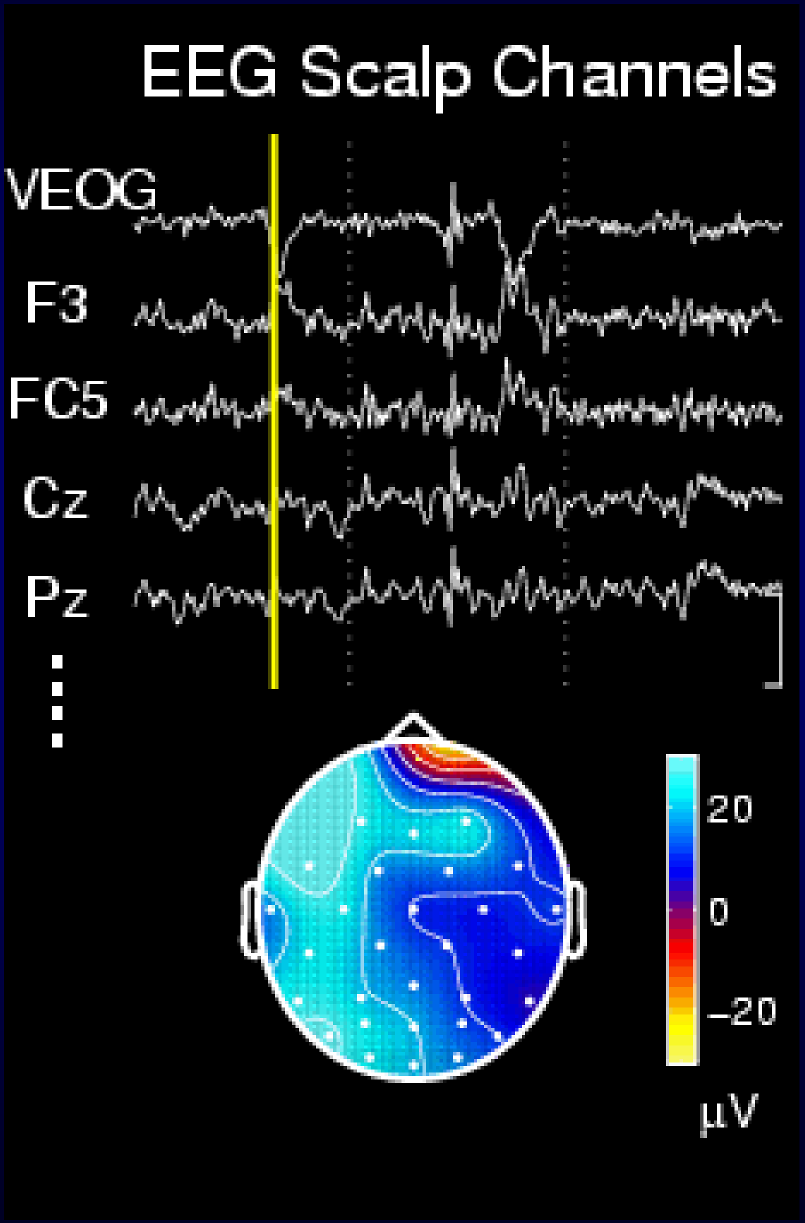




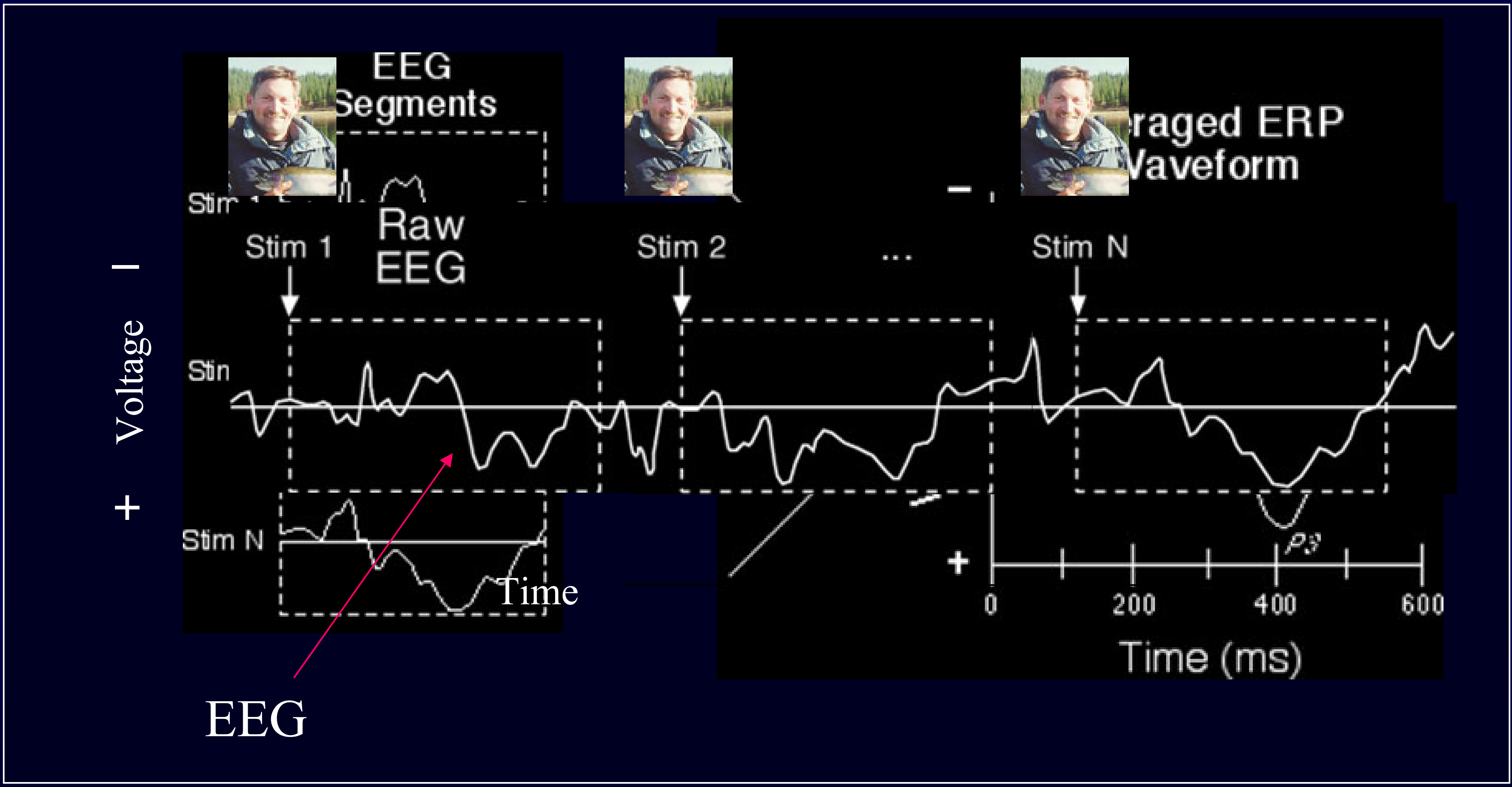




EEG/ERP



Event-related Potentials (ERPs)



Genetic Variation

ACTTG**C**ATCCG
ACTTG**T**ATCCG

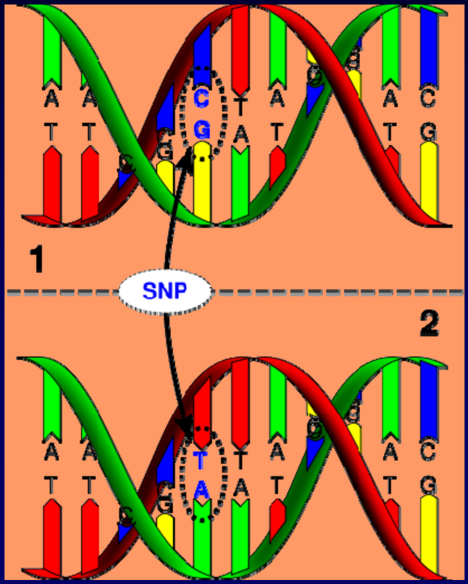
Single Nucleotide Polymorphism (SNP)

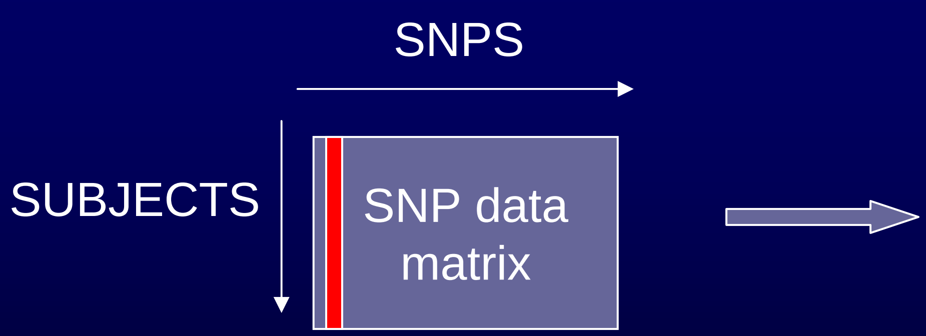
ACTTG**CA**TCCG
ACTTG--TCCG

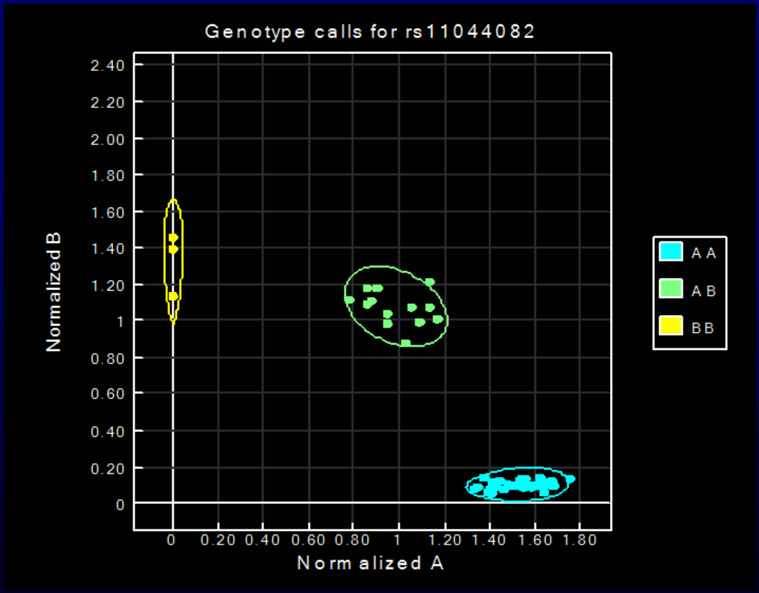
Insertion/Deletion (Indel)

ACTTG**GCGCGC**TCCG
ACTTG**GCGC**--TCCG
ACTTG**GC**----TCCG

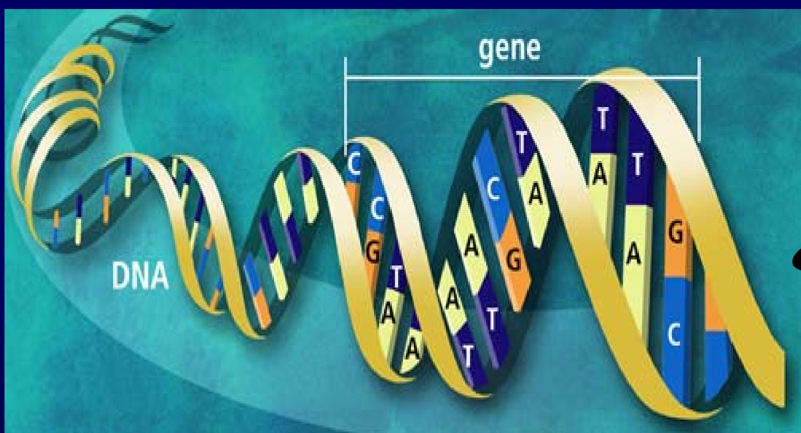
Short Tandem Repeat (STR)

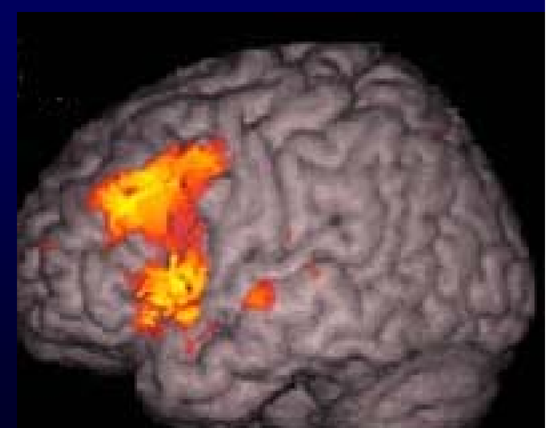






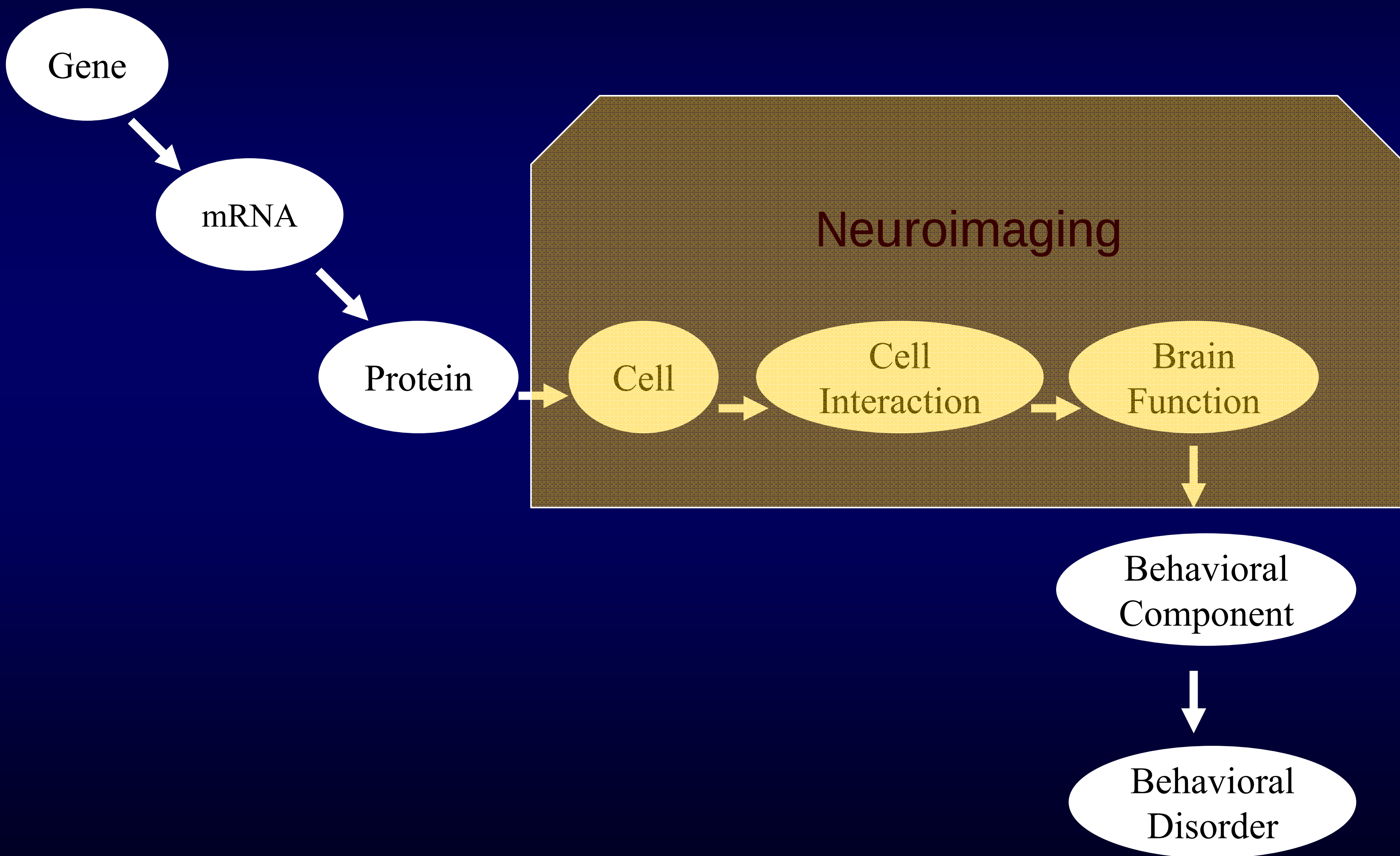
The Link between brain function and genetic coding





The First Challenge

A conceptual slide to drive home the point…



Outline

- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions

Separate vs. Joint Estimation

Linear mixtures with shared mixing parameter

$$x_{i,v}^{(E)} = \sum_{c=1}^{C} a_{ic} s_{c,v}^{(E)} \text{ and } x_{i,v}^{(F)} = \sum_{c=1}^{C} a_{ic} s_{c,v}^{(F)}$$

In a non-joint analysis, we maximize the likelihood functions for each modality separately…

$$p\left(x^{(E)}; w\right) \quad p\left(x^{(F)}; w\right) \quad w = 1/a$$

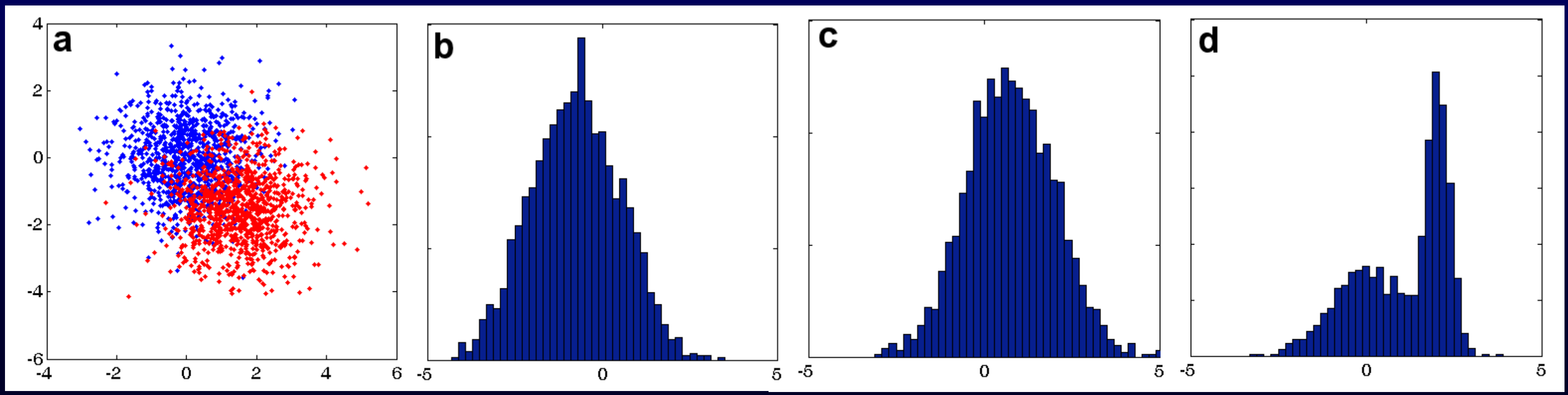
Resulting in two unmixing parameters, that then have to somehow be fused together

$$w_1^* = \arg\max_{w_1} \log p\left(x^{(E)}; w_1\right)$$

$$w_2^* = \arg\max_{w_2} \log p\left(x^{(F)}; w_2\right)$$

In contrast: for a joint analysis we maximize the joint likelihood function, resulting in a single fused unmixing parameter

$$w^* = \arg\max_{w} \log p\left(x^{(E)}, x^{(F)}; w\right)$$

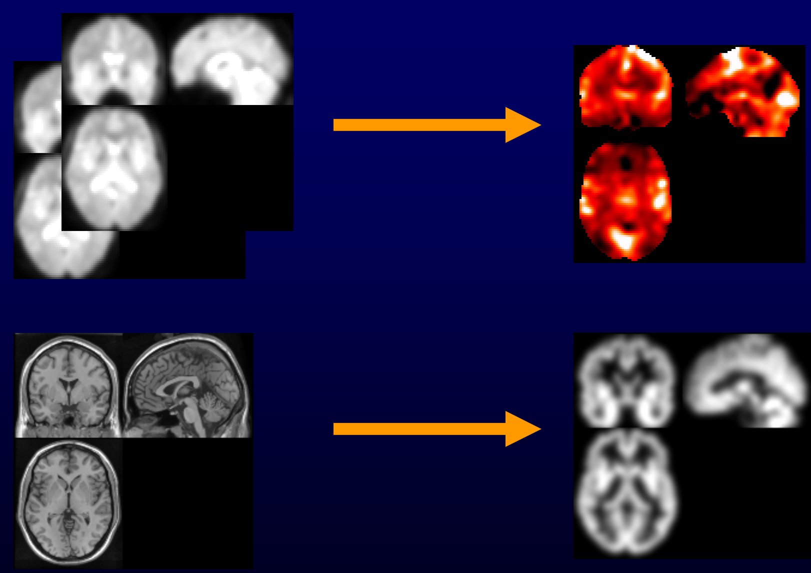


Feature Data

- What is a feature?
  - Lower dimensional data containing information of interest
  - Examples: An image of activation amplitudes, A gray matter segmentation image, fractional anisotropy image
- Advantages
  - Less-computationally complex/easier to model
  - Takes advantages of existing analytic approaches
  - Can be used to examine inter-relationships between multiple data types at the subject level

fMRI

sMRI



Feature Data

- What are the features?
  - Examples: An image of activation amplitudes, A gray matter segmentation image, fractional anisotropy image
- Advantages
  - Less-computationally complex/easier to model
  - Takes advantages of existing analytic approaches
  - Examines inter-subject covariation of multiple data types

Modality	***Core-Feature***
fMRI SB task	Recognition related activity
	Encode-related activity
fMRI AOD task	Target-related activity
	Novel-related activity
sMRI	GM concentration
	WM concentration
	CSF concentration
EEG AOD task	Target-related ERP
	Novel-related ERP

Modality	*Raw data size*	*Feature size*	*Compression ratio*
fMRI	260 MB	1.3 MB	1:200
DTI	200 MB	10 MB	1:20
sMRI	46 MB	28 MB	1:1.6
EEG	25MB	.45MB	1:56

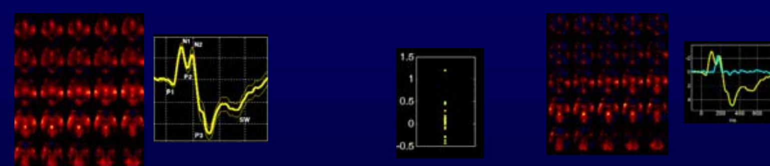
Feature	Effect Size (d)
fMRI	2.1 (SB Encode)
sMRI	0.6 (GM)
DTI	0.8 (FA)
ERP	2.2 (Target Cz)

Possible approaches for joint analyses

- Voxel-based
  - Correlation [Worsely 1998]
  - *Straightforward, but difficult to visualize*
- Region-based
  - Interregional correlation [Horwitz, et al, 1984]
  - Structural equation modeling [McIntosh and Gonzalez-Lima 1994; Friston et al., 2003, McIntosh & Gonzalez-Lima, 1991, Buchel & Friston, 1997]
  - Multiple regression and extensions [e.g., Kalman filters, Buchel & Friston, 1998]
  - Bayes networks, Dynamic Causal Modeling [Dynamic Causal Modeling, Friston, Penny, et al, 2003]
  - *Useful for model testing, does not take into account all brain regions*
- Transformation-based
  - *A natural set of tools for this problem include those that transform data matrices into a smaller set of modes or components*
  - Singular value decomposition [Friston et al., 1993; Friston et al., 1996]
  - Partial Least Squares [McIntosh, Bookstein, et al, 1996]
  - Canonical Variates Analysis [Strother et al, 1995]
  - Independent Component Analysis [McKeown et al, 1998, Calhoun et al, 2001, Beckmann, et al., 2002]

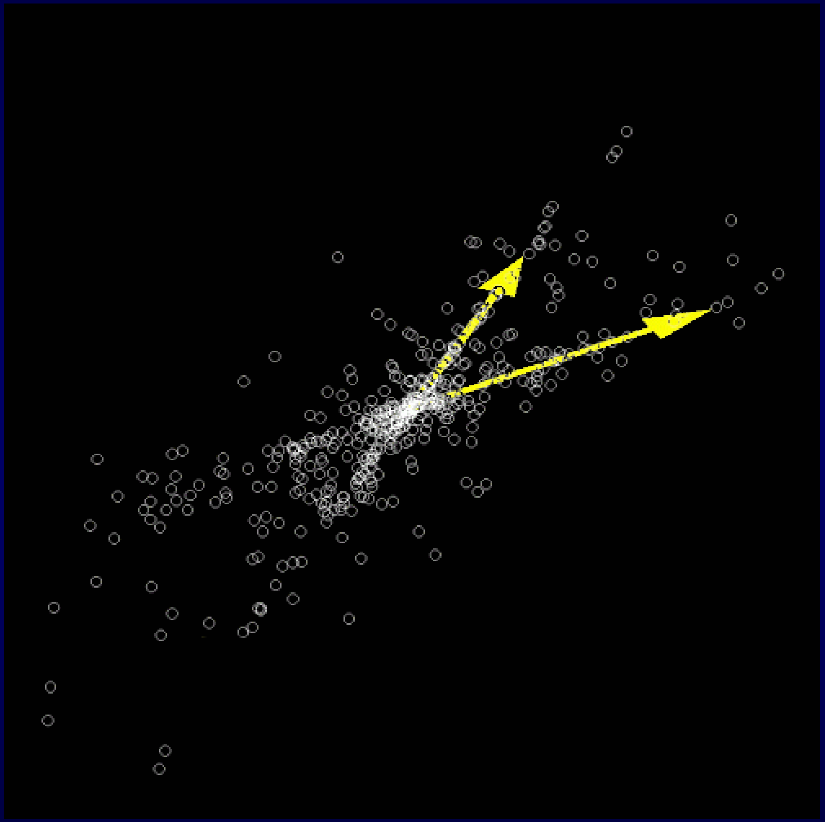
Outline

- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions



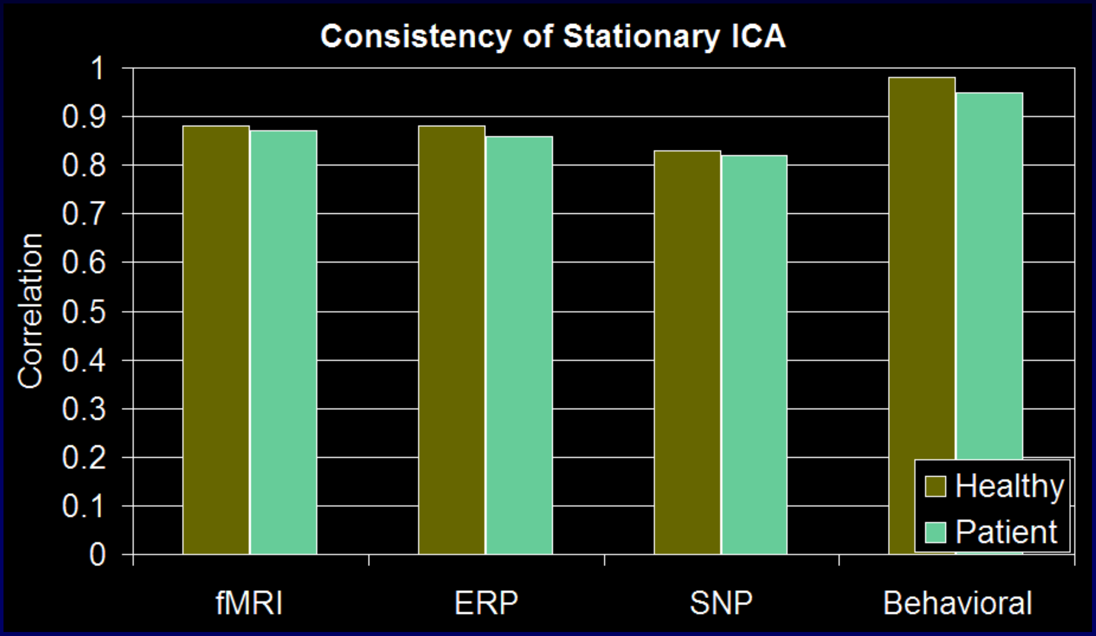
$$[\mathbf{x}_{\text{mod}\,1} \quad \mathbf{x}_{\text{mod}\,2}] = \mathbf{A} \times [\mathbf{s}_{\text{mod}\,1} \quad \mathbf{s}_{\text{mod}\,2}]$$

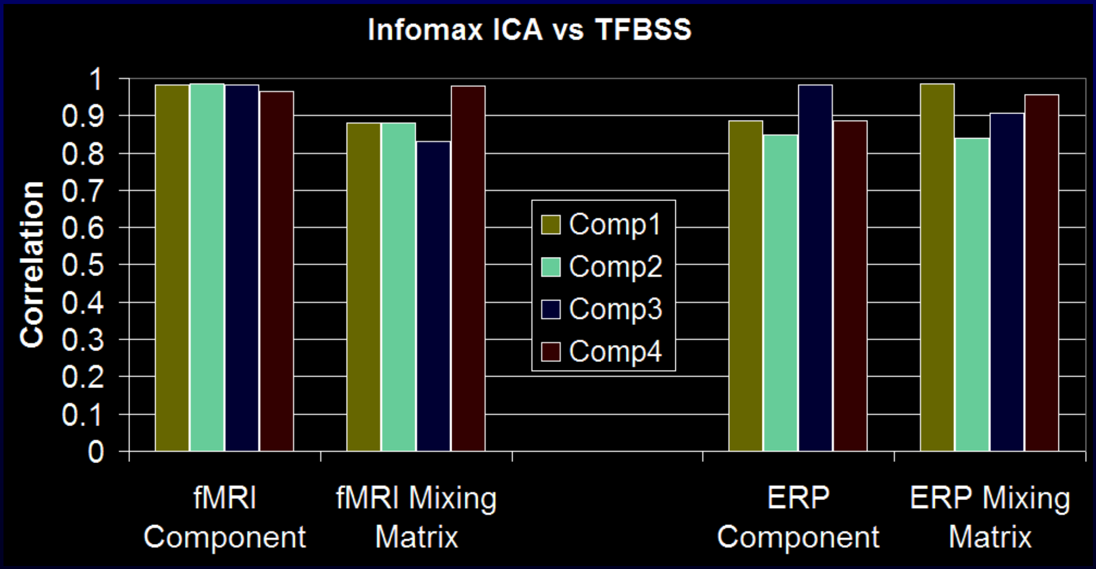
Blind Source Separation (ICA)



ICA finds directions which maximize independence (using higher order statistics)

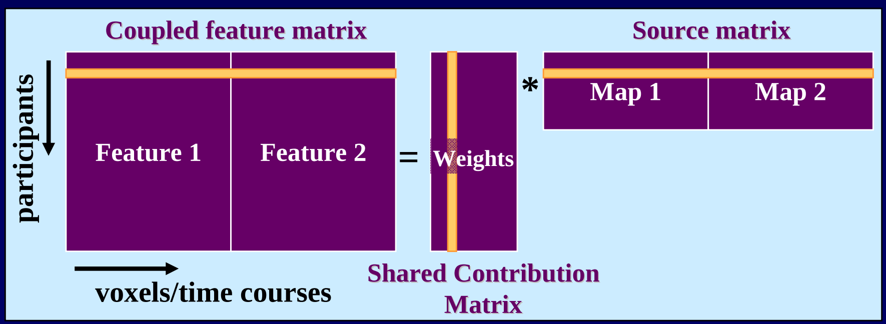
Stationarity





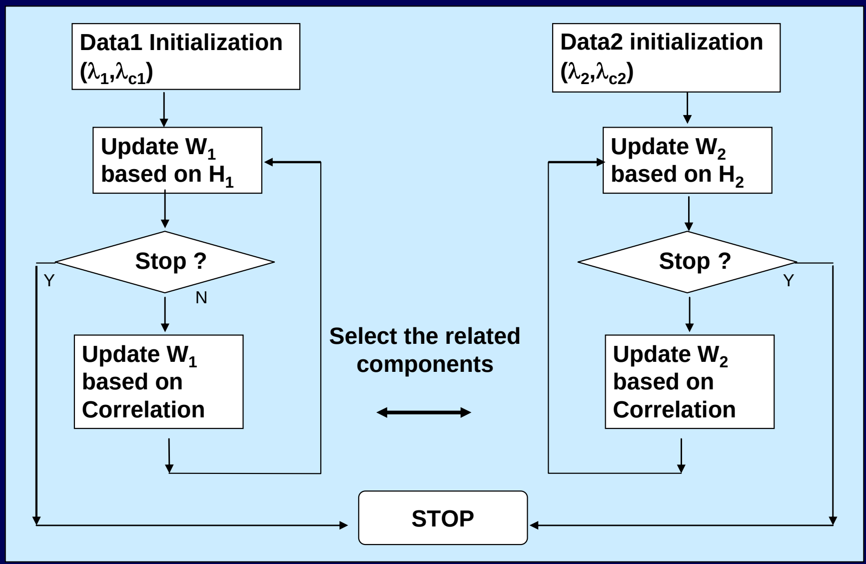
a Joint ICA

Shared Feature Profile

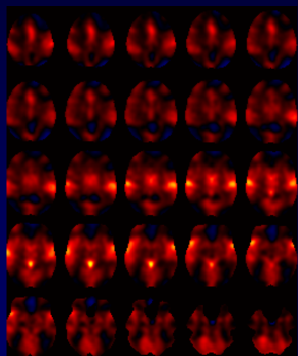
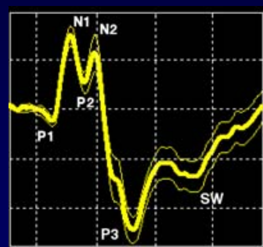


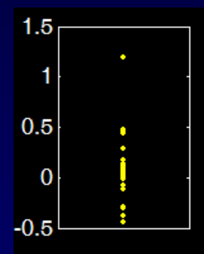
b Parallel ICA

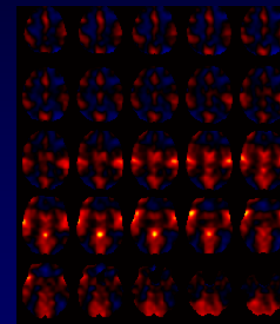
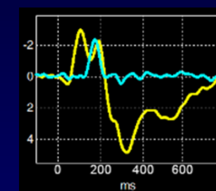
Distinct but linked Feature Profile



Joint ICA



$$\begin{bmatrix} \mathbf{x}_{\text{mod}\,1} & \mathbf{x}_{\text{mod}\,2} \end{bmatrix} = \mathbf{A} \times \begin{bmatrix} \mathbf{s}_{\text{mod}\,1} & \mathbf{s}_{\text{mod}\,2} \end{bmatrix}$$

Generative Model:

$$\begin{bmatrix} x_i^F & x_i^E \end{bmatrix} = \mathbf{A} \begin{bmatrix} s_c^F & s_c^E \end{bmatrix}$$

Update Equation:

$$\Delta \mathbf{W} = \eta \left\{ \mathbf{I} - 2\mathbf{y}^F \left(\mathbf{u}^F \right)^T - 2\mathbf{y}^E \left(\mathbf{u}^E \right)^T \right\} \mathbf{W}$$

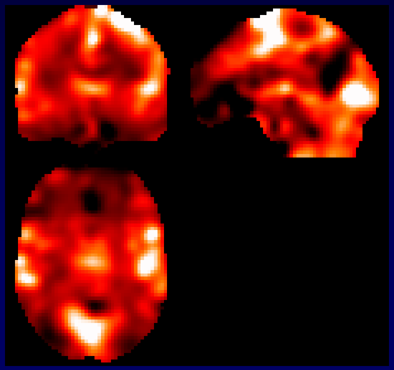
sMRI/fMRI: Calhoun VD, Adali T, Giuliani N, Pekar JJ, Pearlson GD, Kiehl KA. (2006): A Method for Multimodal Analysis of Independent Source Differences in Schizophrenia: Combining Gray Matter Structural and Auditory Oddball Functional Data. Hum.Brain Map. 27(1):47-62.

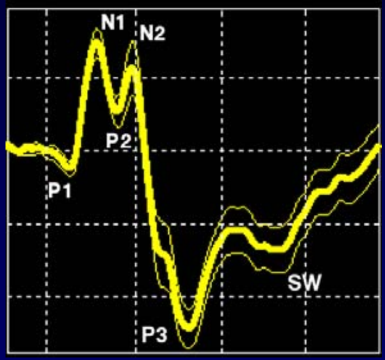
fMRI/fMRI: Calhoun VD, Adali T, Kiehl KA, Astur RS, Pekar JJ, Pearlson GD. (2006): A Method for Multi-task fMRI Data Fusion Applied to Schizophrenia. Hum.Brain Map. 27(7):598-610.

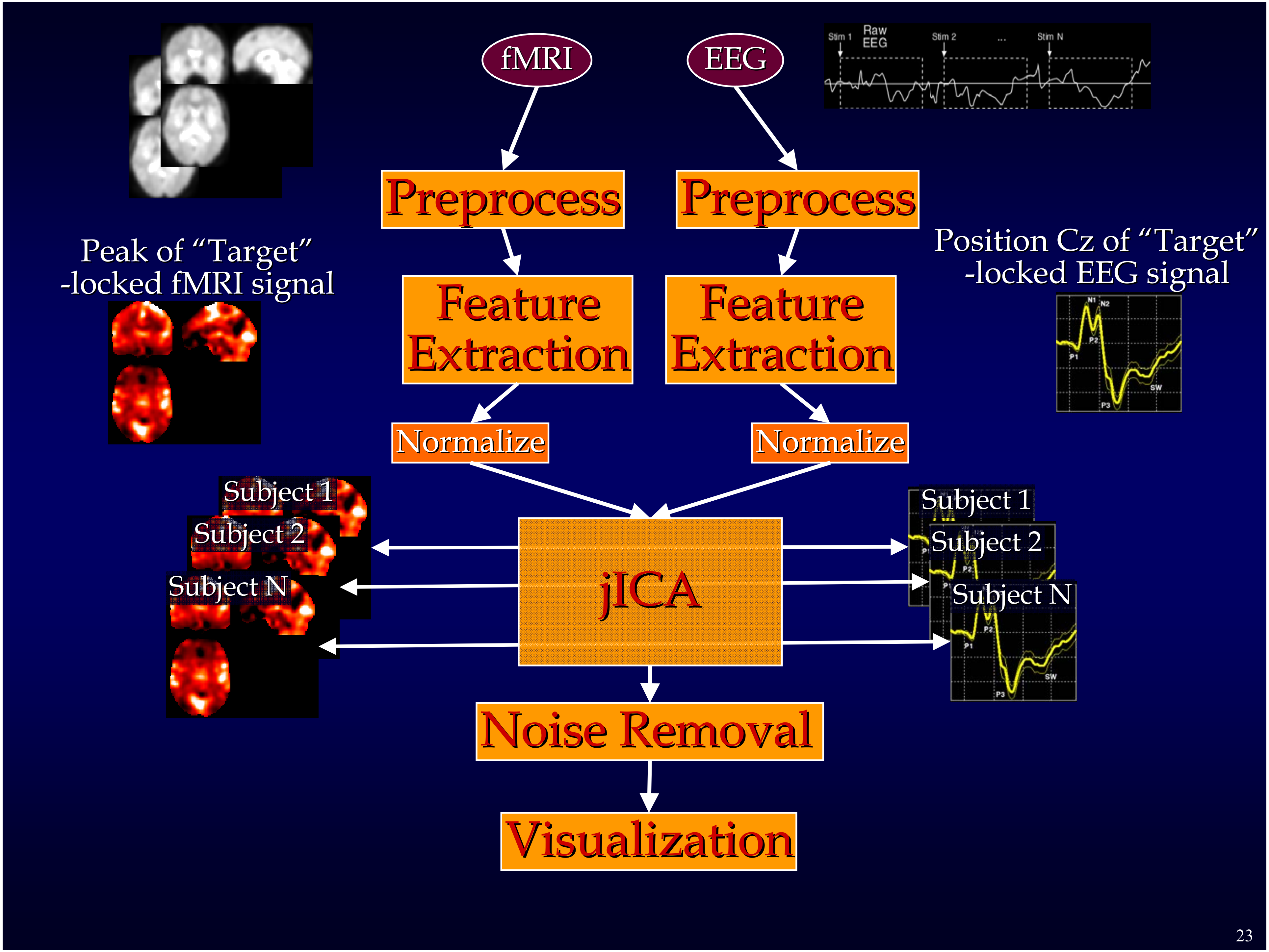
EEG/fMRI: Calhoun VD, Pearlson GD, Kiehl KA. (2006): Neuronal Chronometry of Target Detection: Fusion of Hemodynamic and Event-related Potential Data. NeuroImage 30(2):544-553.

Outline

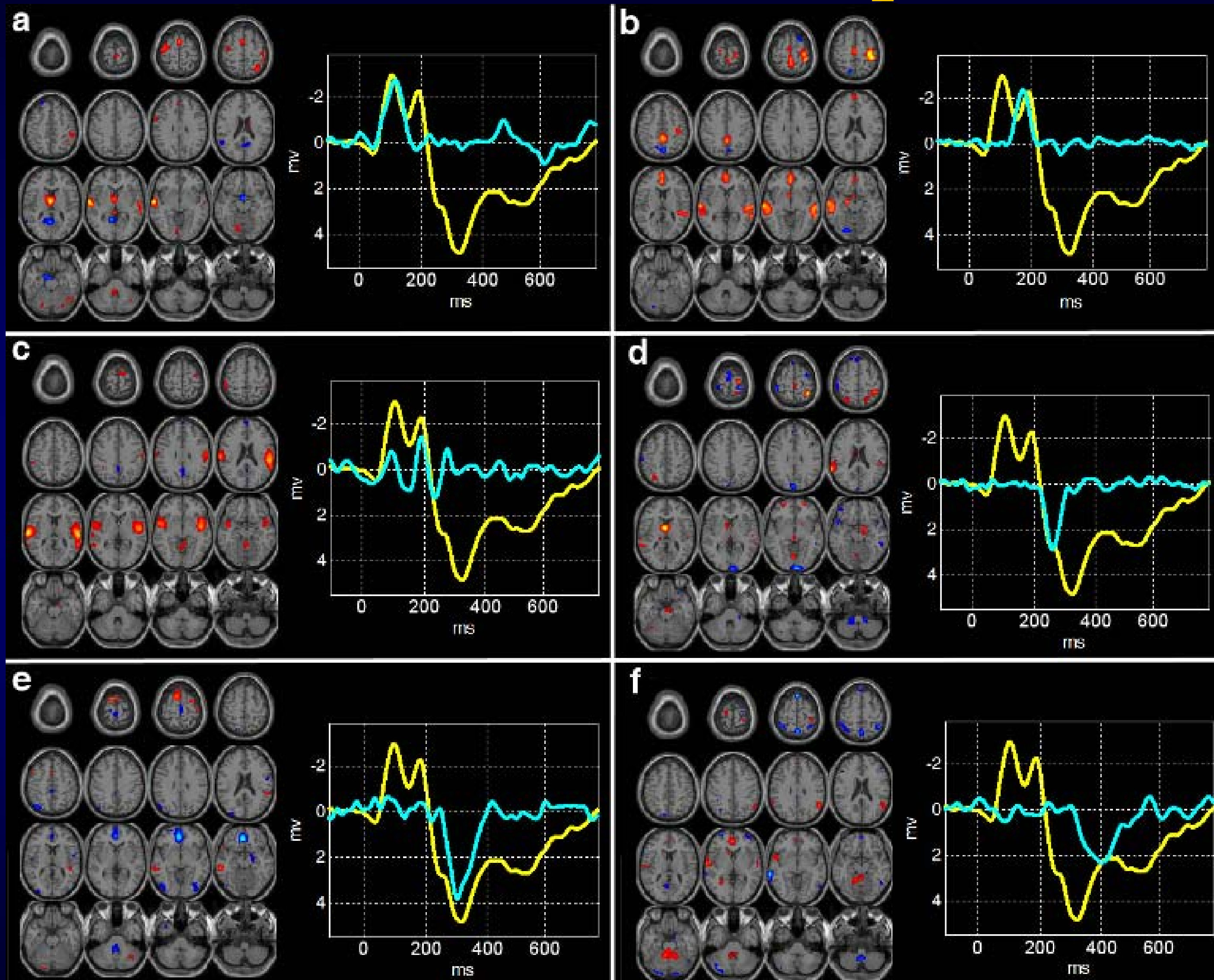
- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions





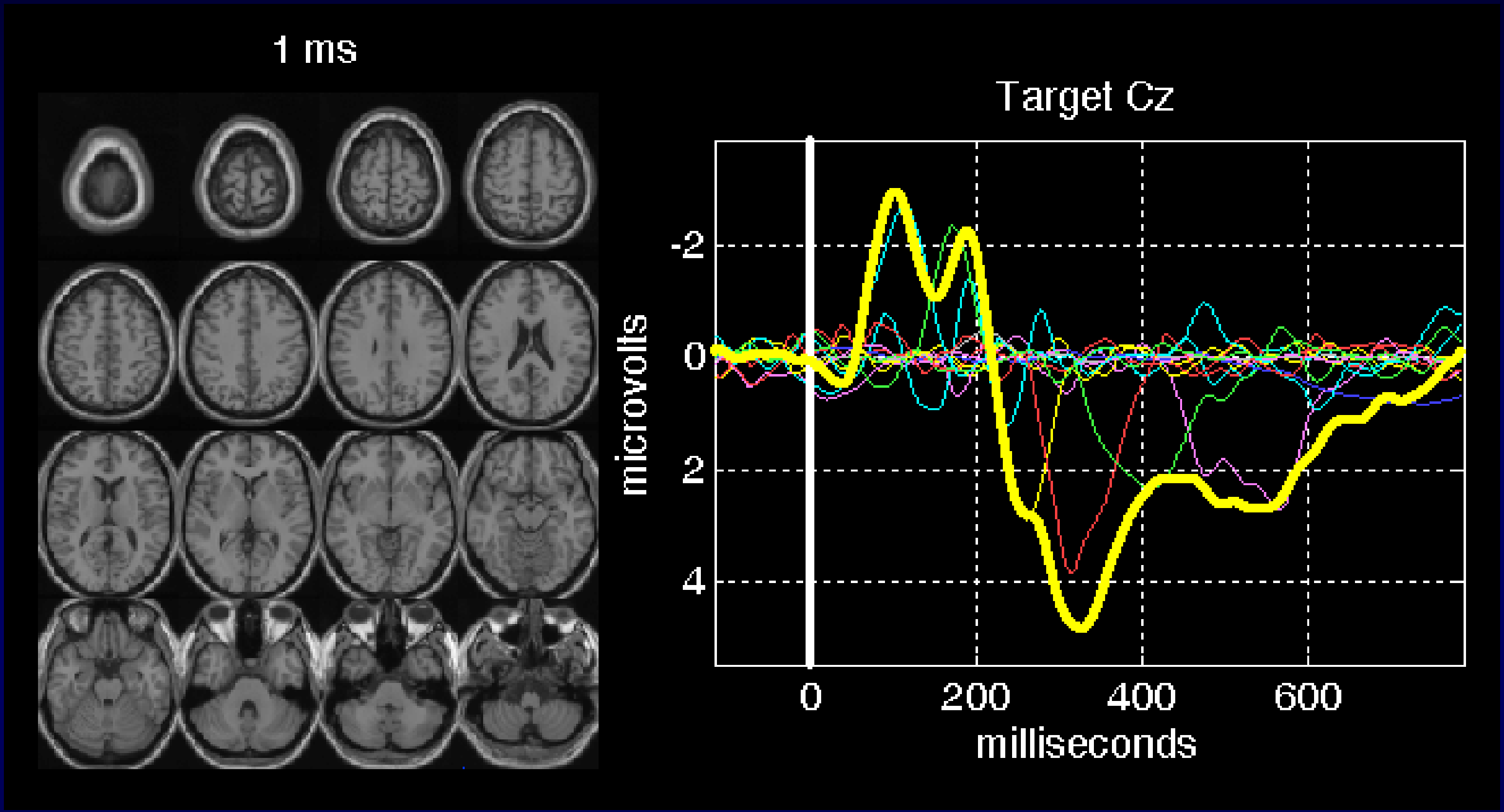

fMRI
EEG
Stim 1
Raw EEG
Stim 2
...
Stim N
Preprocess
Preprocess
Peak of "Target" -locked fMRI signal
Position Cz of "Target" -locked EEG signal
Feature Extraction
Feature Extraction
N1
N2
P1
P2
P3
SW
Normalize
Normalize
Subject 1
Subject 2
Subject N
jICA
Subject 1
Subject 2
Subject N
Noise Removal
Visualization

Joint ERP/fMRI Components



Calhoun, V.D., Pearlson, G.D., and Kiehl, K.A. (2006). Neuronal Chronometry of Target Detection: Fusion of Hemodynamic and Event-related Potential Data. NeuroImage 30, 544-553.

FMRI Snapshots (movie)



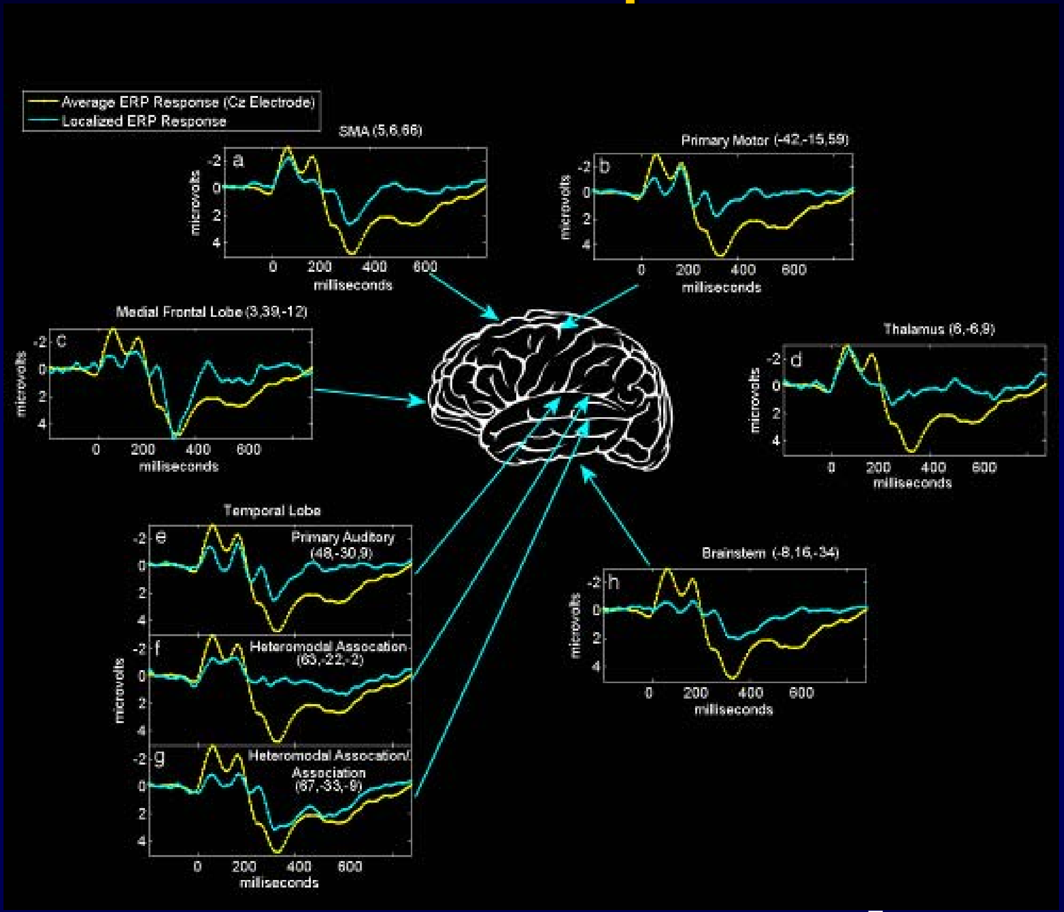
ERP (temporal) Components: $\mathbf{T} = \begin{bmatrix} \mathbf{t}_1 & \ldots & \mathbf{t}_N \end{bmatrix}$

FMRI (spatial) Components: $\mathbf{S} = \begin{bmatrix} \mathbf{s}_1 & \ldots & \mathbf{s}_N \end{bmatrix}$

FMRI Image Snapshot: $\mathbf{M}_F(t) = |\mathbf{T}| \times \mathbf{S}^T(t)$

Calhoun, V.D., Pearlson, G.D., and Kiehl, K.A. (2006). Neuronal Chronometry of Target Detection: Fusion of Hemodynamic and Event-related Potential Data. NeuroImage 30, 544-553.

ERP Snapshots

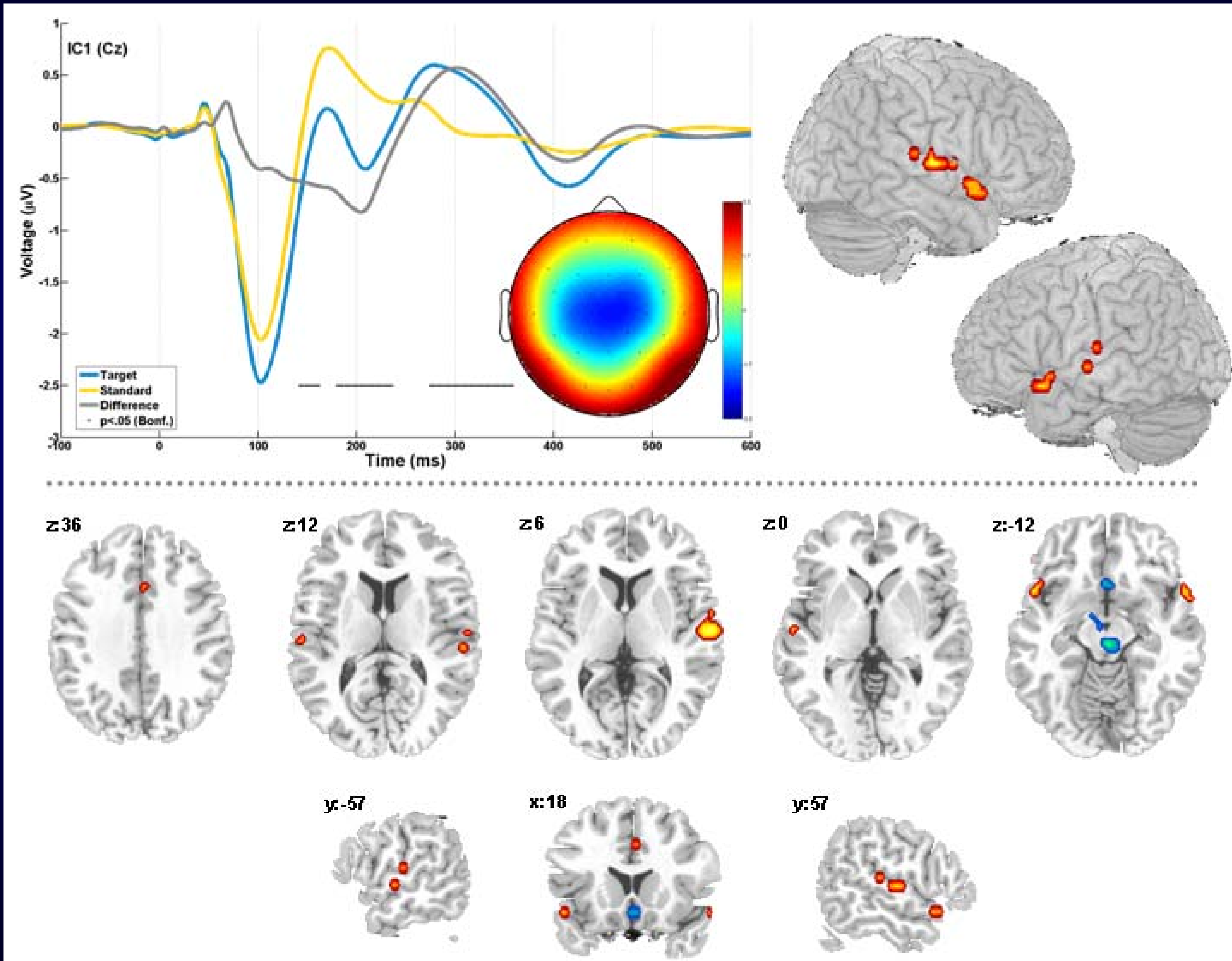


ERP (temporal) Components: $\mathbf{T} = \begin{bmatrix} \mathbf{t}_1 & \dots & \mathbf{t}_N \end{bmatrix}$

FMRI (spatial) Components: $\mathbf{S} = \begin{bmatrix} \mathbf{s}_1 & \dots & \mathbf{s}_N \end{bmatrix}$

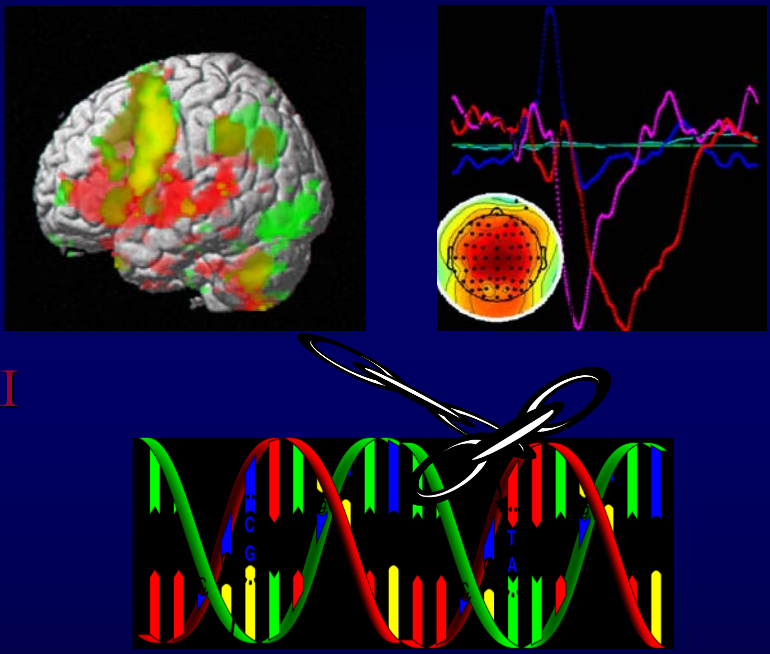
ERP Timecourse Snapshot: $\mathbf{M}_E(v) = \mathbf{T} \times |\mathbf{S}|^T(v)$

Calhoun, V.D., Pearlson, G.D., and Kiehl, K.A. (2006). Neuronal Chronometry of Target Detection: Fusion of Hemodynamic and Event-related Potential Data. NeuroImage 30, 544-553.


IC1 (Cz)
Voltage (µV)
Time (ms)
Target
Standard
Difference
p<.05 (Bonf.)
-100
0
100
200
300
400
500
600
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
z:36
z:12
z:6
z:0
z:-12
y:-57
x:18
y:57

Outline

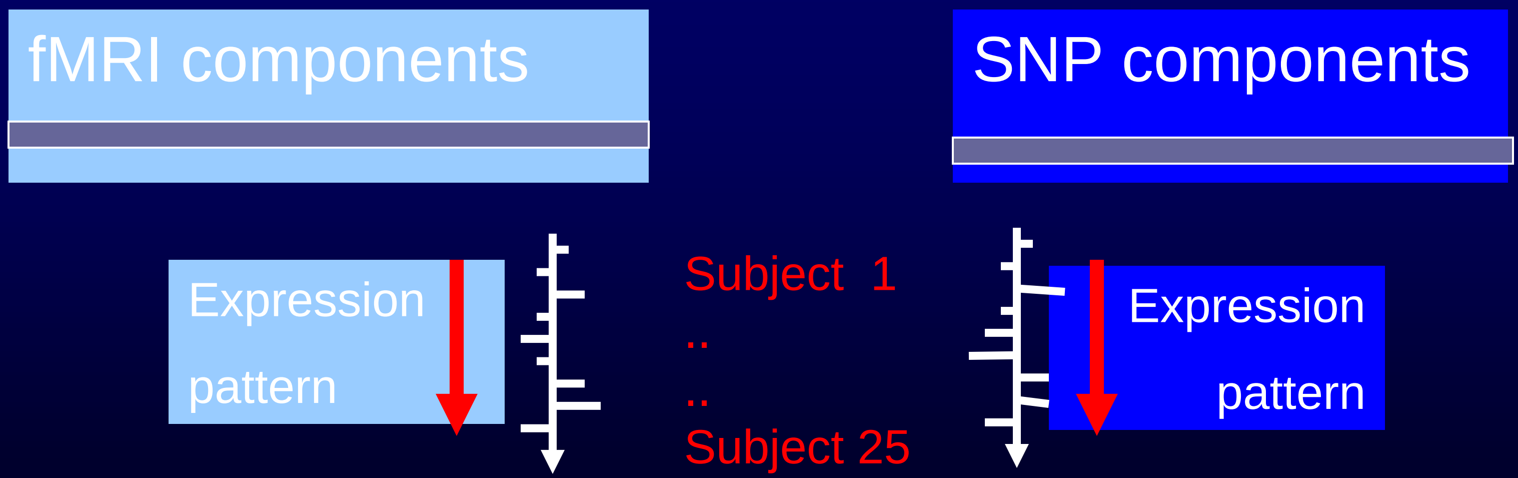
- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions



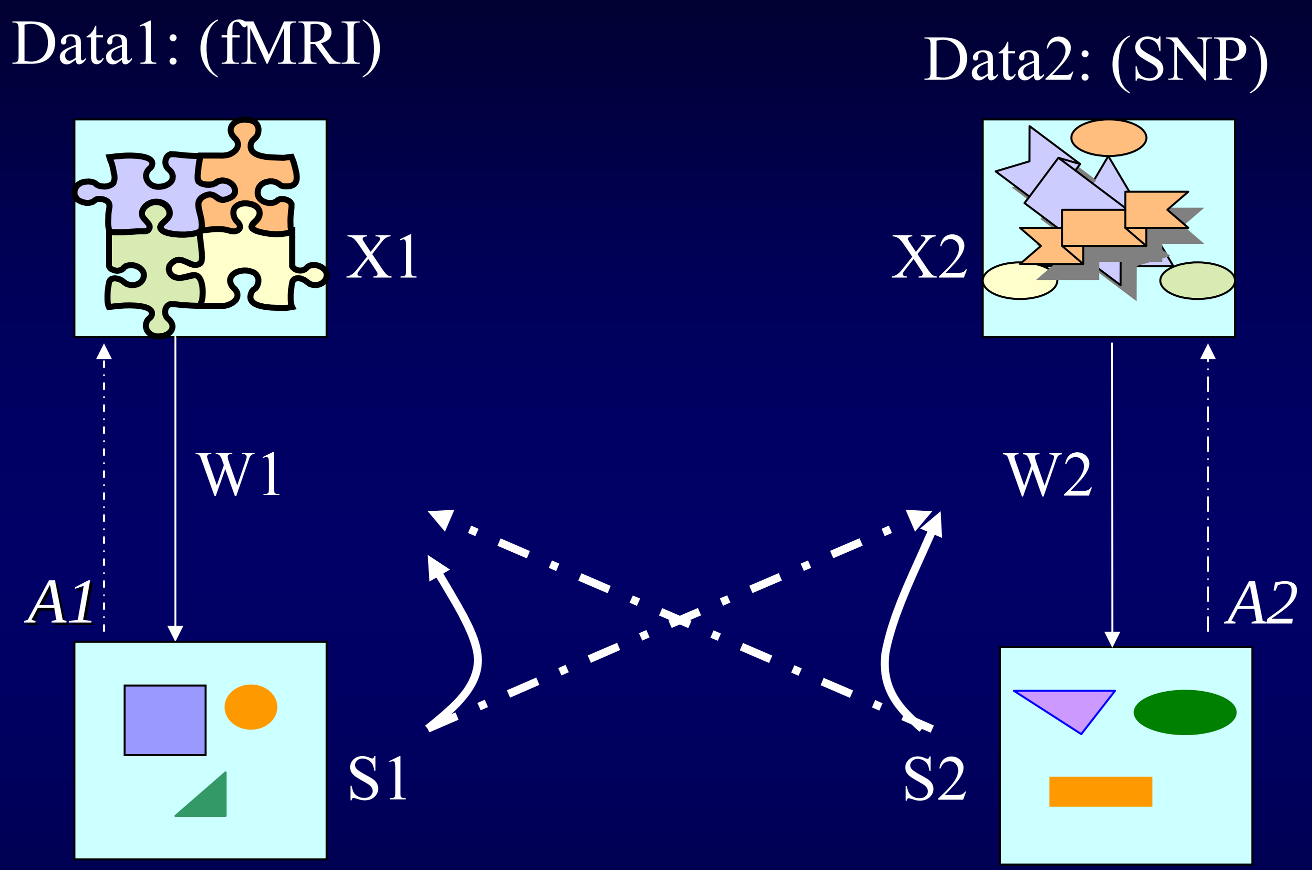
fMRI/SNP connection

- fMRI component: *specific brain regions with common independent brain functionality*.
- SNP component: *a linearly weighted group of SNPs functioning together*.
- Relationship assumption

  If an association of SNPs partially define a certain brain function in specific brain regions, Then, the linked fMRI and SNP components should share a similar pattern of existence across subjects.



Parallel ICA structure

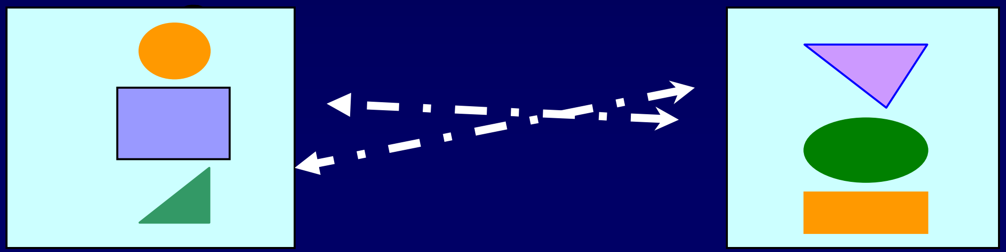


- MAX : {H(**Y1**) + H(**Y2**) }, <Infomax>
- Subject to: arg max g{W1,W2 ŝ1,ŝ2 },

$$g(\cdot)=\text{Correlation}(A_1,A_2)^2=\frac{\text{Cov}(a_{1i},a_{2j})^2}{\text{Var}(a_{1i})\times\text{Var}(a_{2j})}$$

Dynamic parallel ICA optimization

- Dynamically constrained components:



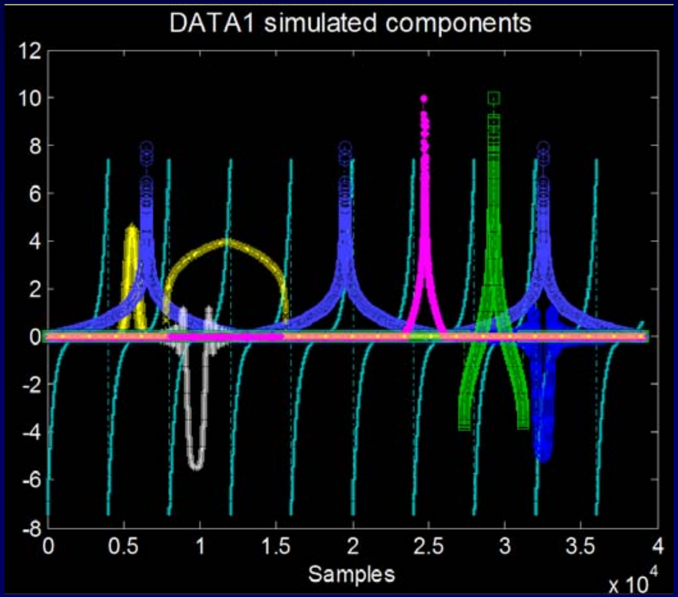
X1→ŝ1 X2→ŝ2

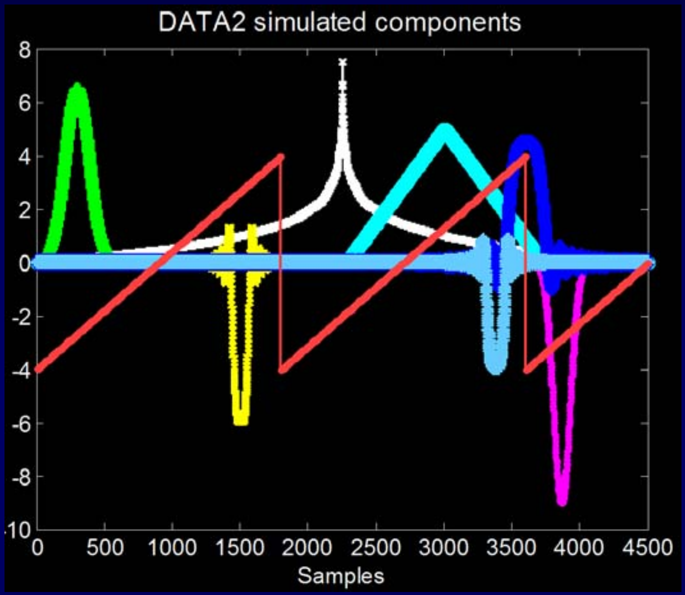
- Adaptive constraint strength:
  - Effects on Entropy H(.)

Simulation data

- DATA1
- A1

- DATA2
- A2





True component: 8/8; True correlation:0.8

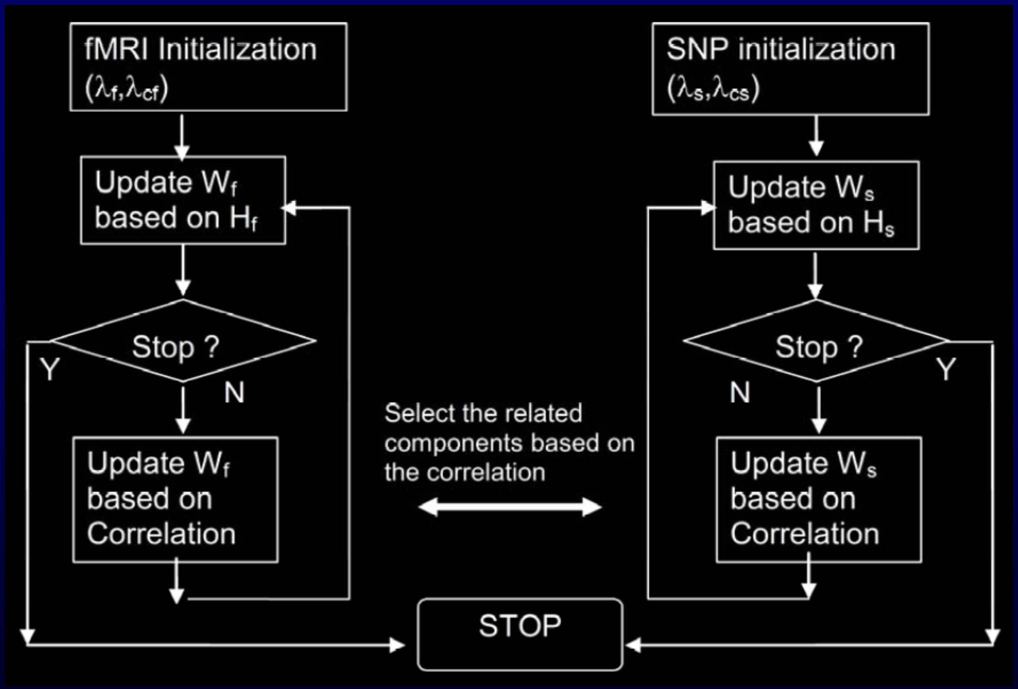
Data1	*Data2*	*Parallel ICA connection*	*Regular ICA connection*
8	4	0.4149	0.4148
	8	0.8275	0.6635
	16	0.8240	0.6639
4	8	0.1739	0.1738
8		0.8492	0.6636
16		0.8953	0.6636

True Correlation	*Parallel ICA correlation*	*Regular ICA correlation*
1.00	0.9278	0.8606
0.80	0.7911	0.7348
0.60	0.5850	0.5205
0.45	0.4603	0.4138

Parallel ICA

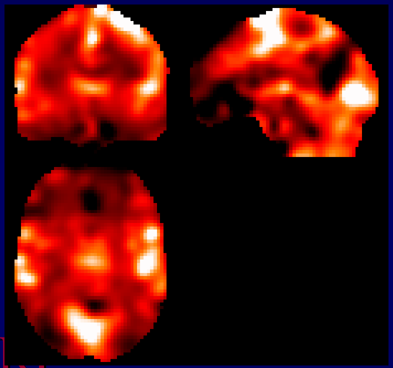
1. independent components/factors of each modality
2. Inter-relationship between modalities

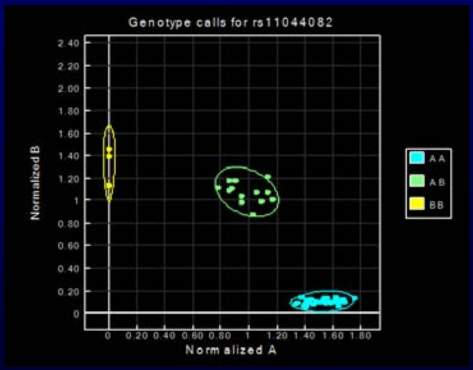
The algorithm is based on classic ICA, aiming to extract independent sources and enhance the connections between modalities.



Outline

- Motivation
- Data Description
  - fMRI
  - ERP
  - Genetic
- Features & Joint Estimation
- Joint ICA
  - Example 1: ERP/fMRI
  - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
  - SNP/FMRI
  - SNP/ERP
- Conclusions



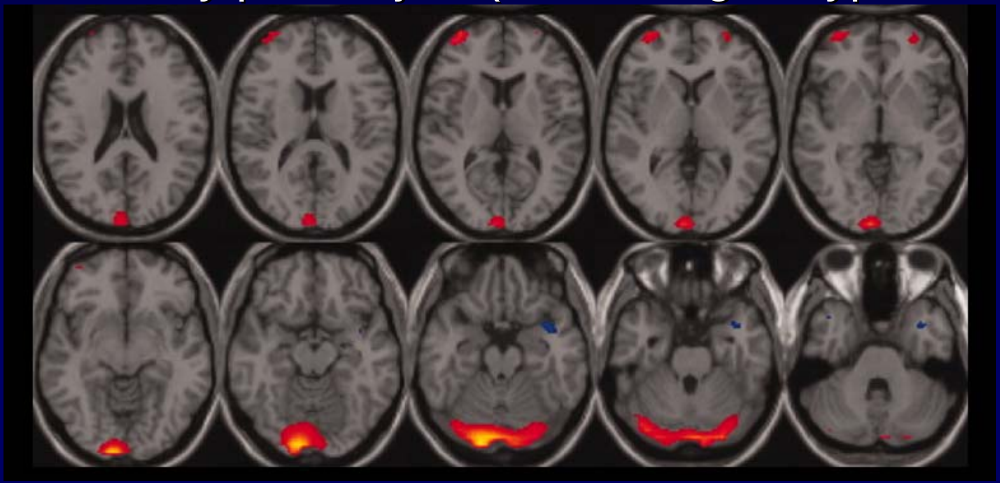


Example 1: SNP/fMRI Fusion

Data Description: 20 Sz & 43 Healthy controls (Caucasian)

fMRI: one image per subject (Target activation in Auditory Oddball task

SNP: one array per subject (384 SNP genotypes - -> 367 SNPs)

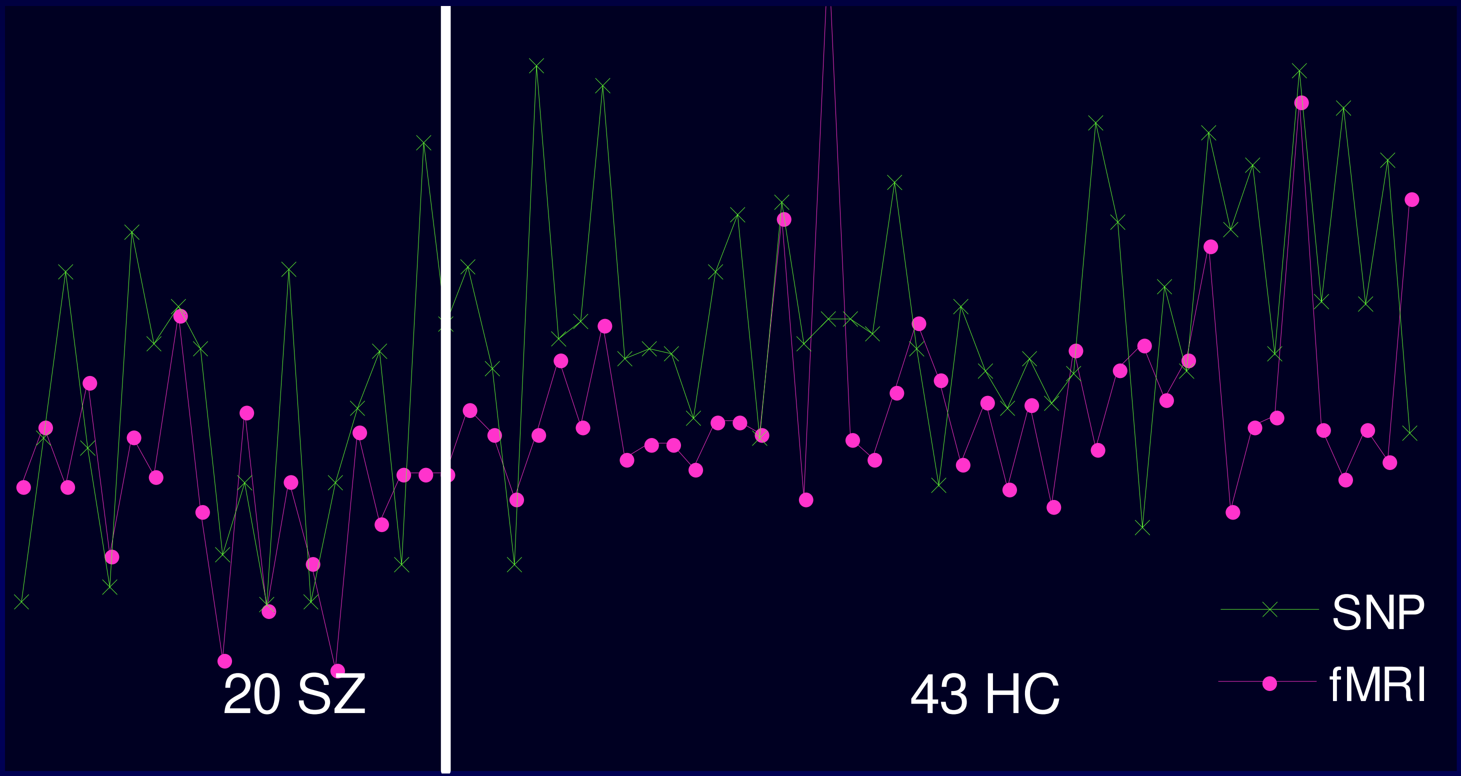


Control vs Patient
$p<0.001$

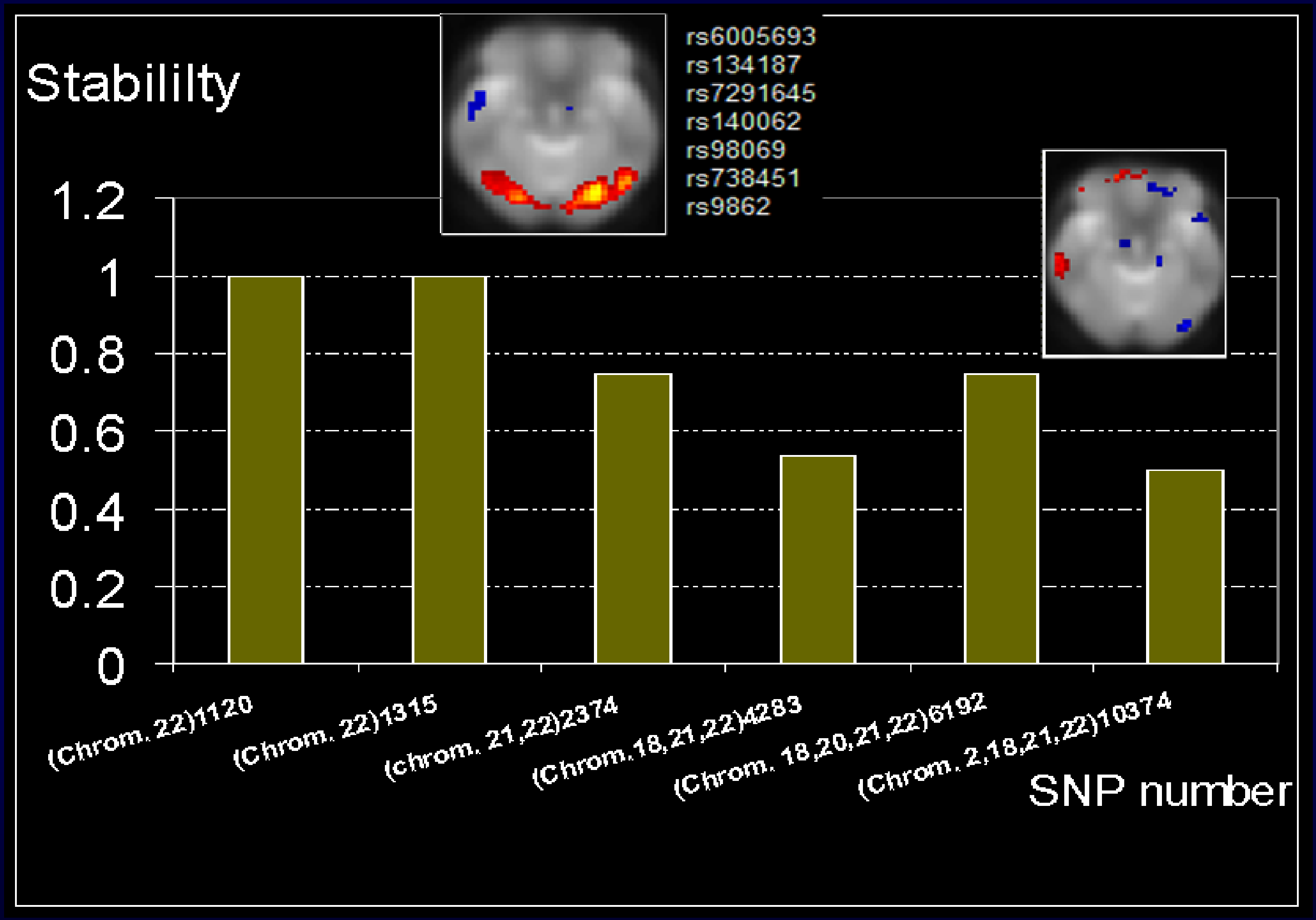
SNP	*Z score*	*Gene*
Rs1466163	-4.08	AADC: aromatic L-amino acid decarboxylase
Rs2429511	3.97	ADRA2A: alpha-2A adrenergic receptor gene
Rs3087454	**-3.09**	**CHRNA7: alpha 7 nicotinic cholinergic receptor**
Rs821616	**2.96**	**DISC1: disrupted in schizophrenia 1**
Rs885834	**-2.78**	**CHAT: choline acetyltransferase**
Rs1355920	**-2.77**	**CHRNA7: cholinergic receptor, nicotinic, alpha 7**
R4765623	2.73	SCARB1: scavenger receptor class B, member 1
Rs4784642	-2.71	GNAO1: guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O
Rs2071521	2.58	APOC3: apolipoprotein C-III
Rs7520974	2.55	CHRM3: muscarinic-3 cholinergic receptor

J. Liu, G. D. Pearlson, A. Windemuth, G. Ruano, N. I. Perrone-Bizzozero, and V. D. Calhoun, "Combining Fmri and Snp Data to Investigate Connections between Brain Function and Genetics Using Parallel Ica," Hum.Brain Map., In Press.

Subject loading associated with linked SNP and fMRI components



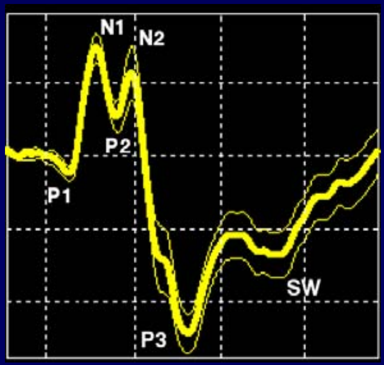
Sample size vs Number of SNPs

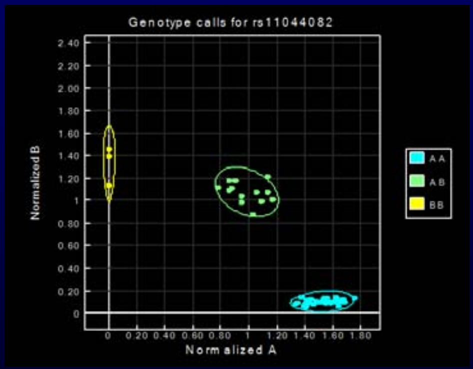


Data collected at UCI

Outline

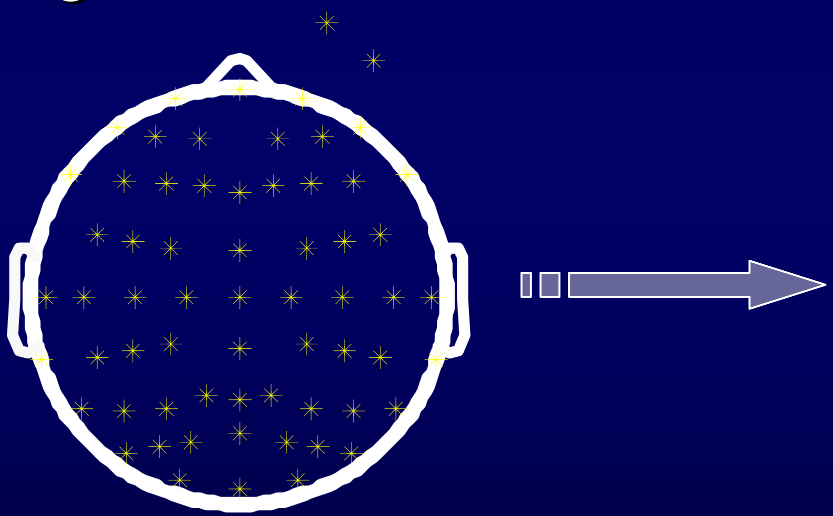
- Motivation
- Data Description
    - fMRI
    - ERP
    - Genetic
- Features & Joint Estimation
- Joint ICA
    - Example 1: ERP/fMRI
    - Example 2: Multielectrode ERP/fMRI
- Parallel ICA
    - SNP/FMRI
    - SNP/ERP
- Conclusions

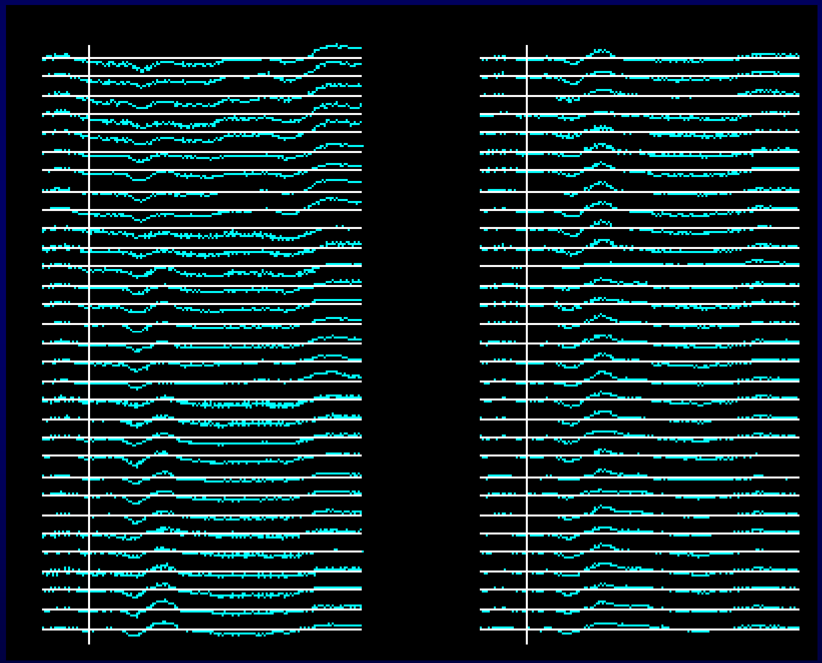




Example 2: Genetics and P3 ERP generation

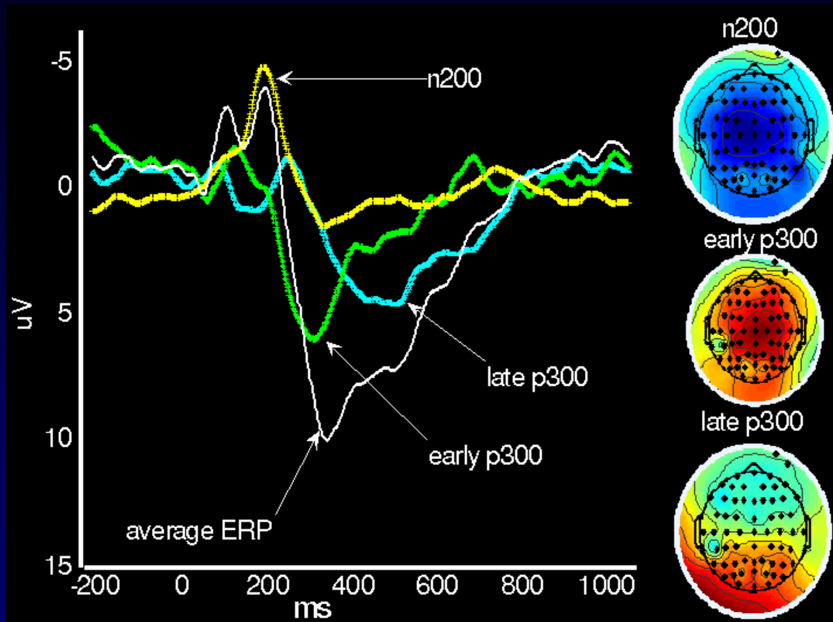
- Subjects: 41 healthy subjects(24 female, 17 male)
- EEG collected during AOD task, target/novel ERPs extracted





- Blood sample collected, genotyped 384 SNPs from 222 genes 6 physiological systems.

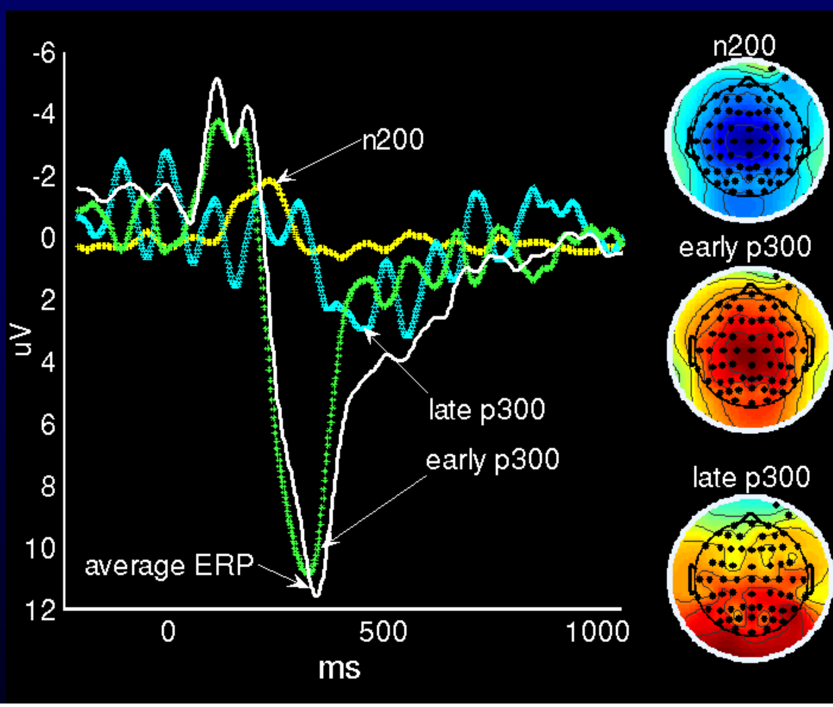
Target Stimuli



0.55

SNPs	Genes
rs1800545	ADRA2A
rs7412	APOE
rs1128503	ABCB1
rs6578993	TH
rs1045642	ABCB1
rs2278718	MDH1
rs4784642	GNAO1
rs521674	ADRA2A

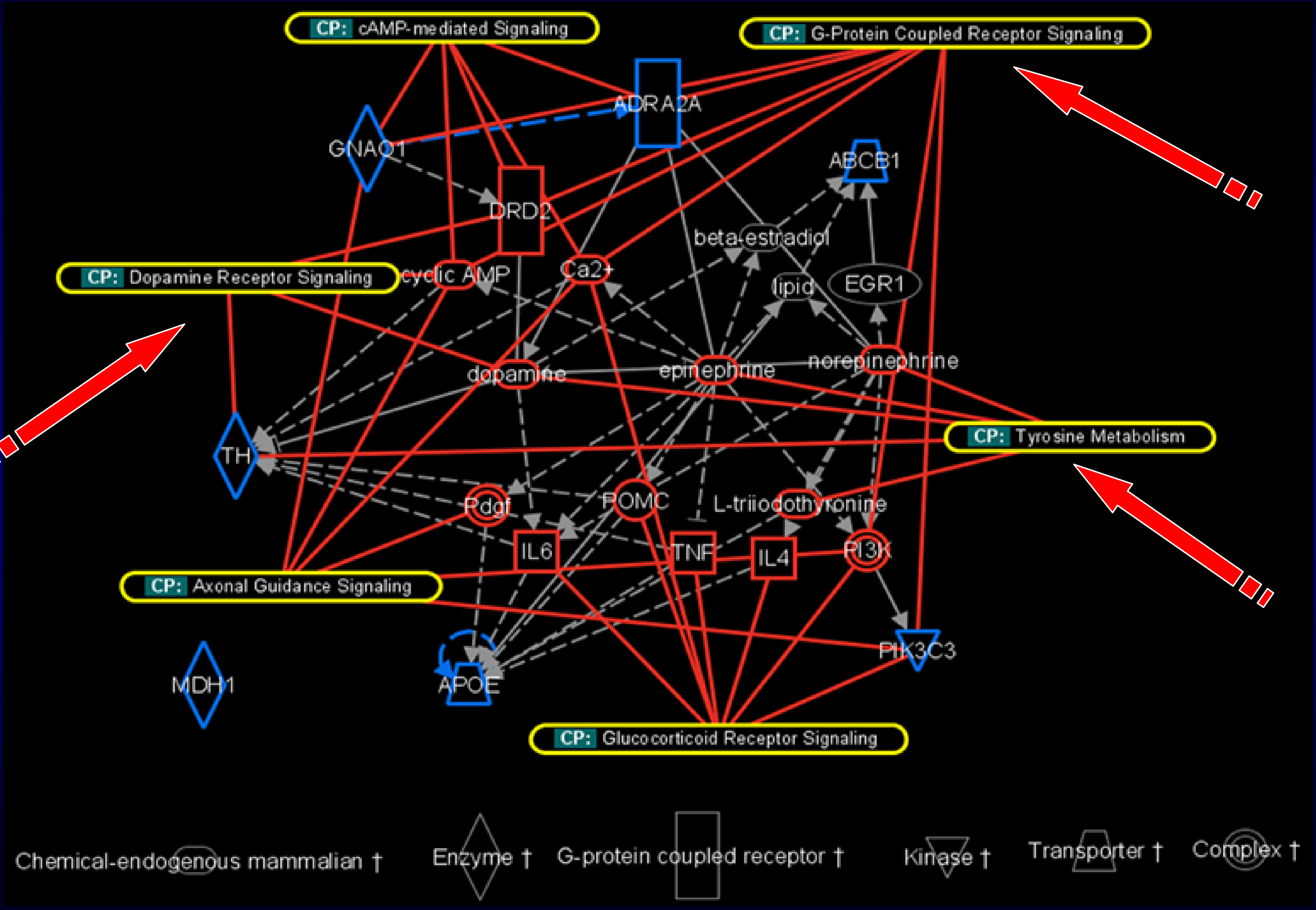
Novel Stimuli



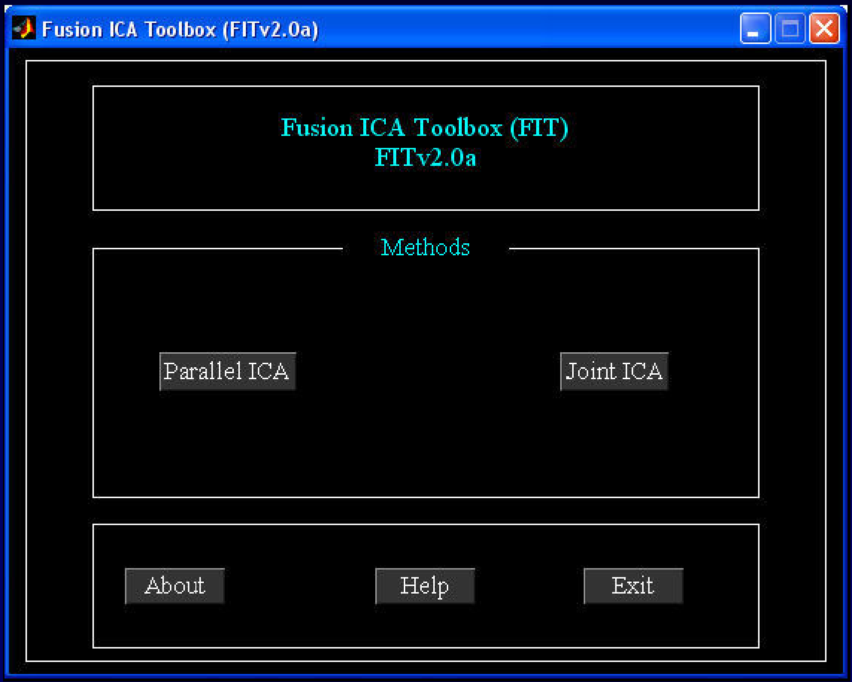
0.47

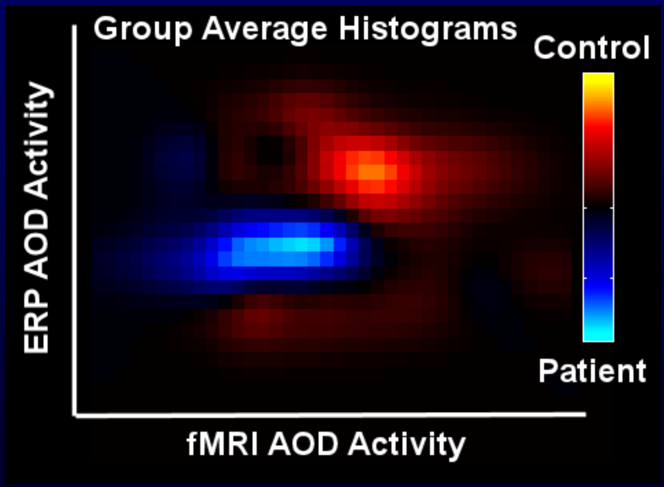
SNPs	Genes
rs1800545	ADRA2A
rs7412	APOE
rs6578993	TH
rs2278718	MDH1
rs1128503	ABCB1
rs429358	APOE
rs3813065	PIK3C3
rs4121817	PIK3C3
rs521674	ADRA2A

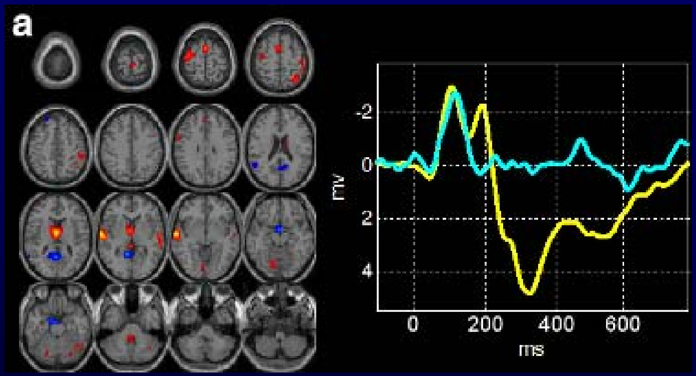
Pathway Analysis



Fusion ICA Toolbox (FIT)







250+ unique downloads
http://icatb.sourceforge.net

Funded by NIH 1 R01 EB 005846

Thank You!