Connectivity measures across multiple modalities in Parkinson's disease

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UBC

Outline

- **Motivation**
  - Parkinson's disease (PD)
  - Problems with standard fMRI analyses in PD
- **Brain Imaging techniques**
  - 3D Moment Invariant descriptors of activation
    - fMRI
    - PET
  - Replicator Dynamics
  - PCfdr method for Bayesian Network learning
  - Robust, group LASSO for fMRI connectivity
- **Electrophysiology techniques**
  - EEG source connectivity
- **Multivariate ← → Multivariate comparisons**
  - Multiblock PLS & EEG-EMG coupling
  - ICA-PLS methods

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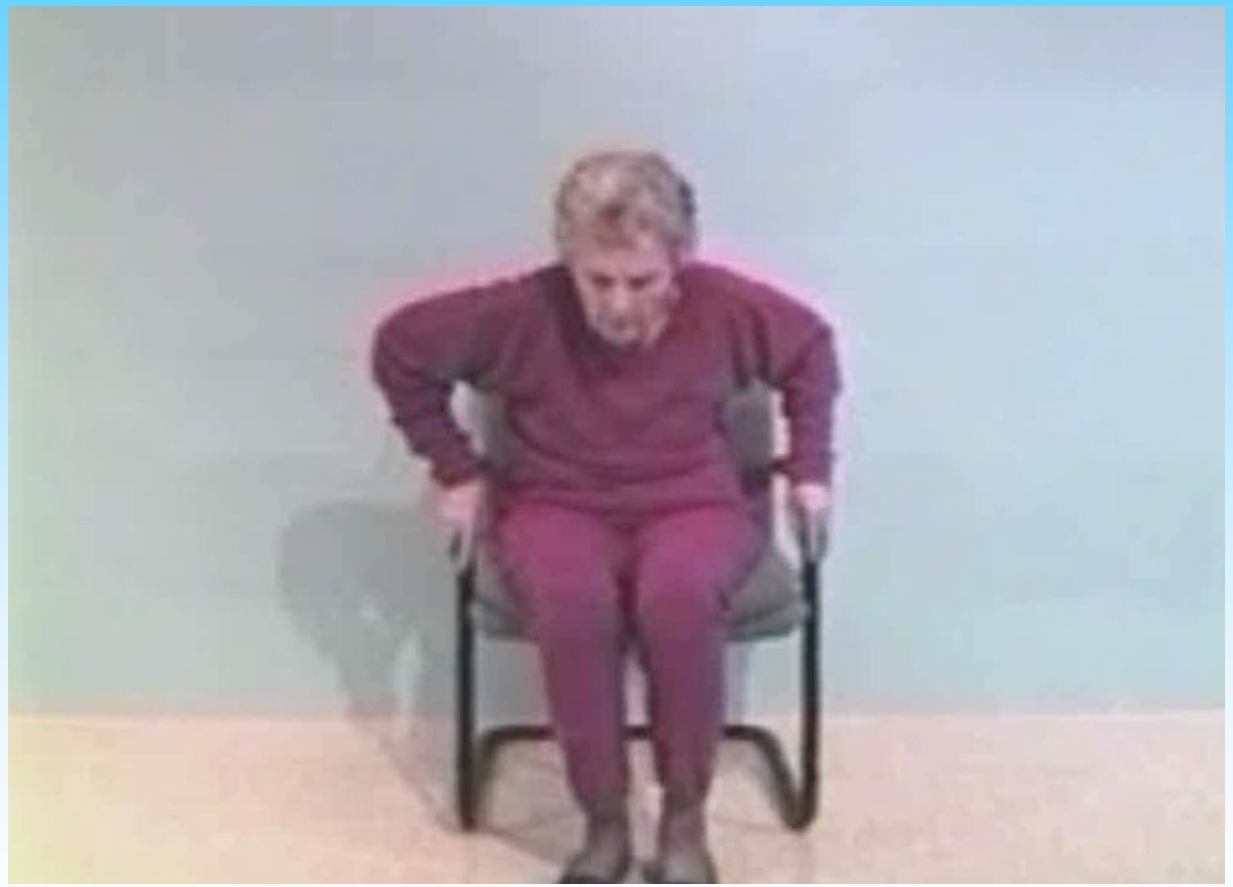
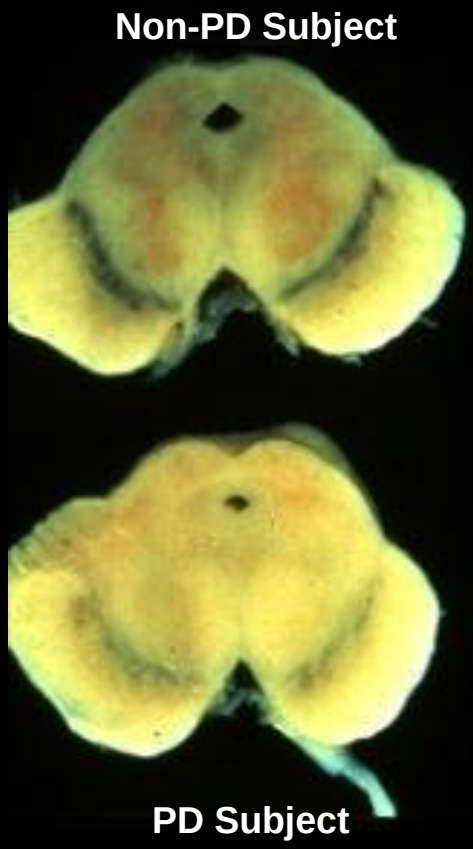
What is Parkinson's Disease?

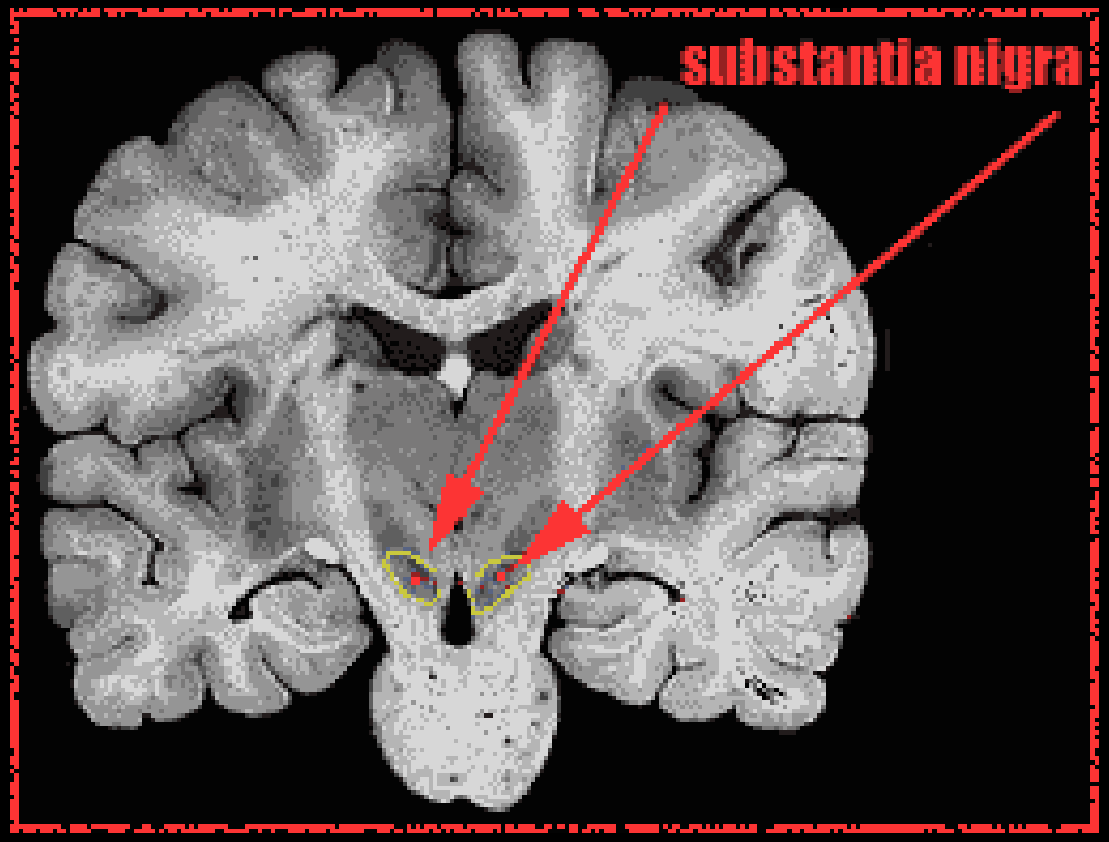


- Tremor
- Stiffness
- Slow movement
- Balance problems

Adapted From: Principles and Practice of Movement Disorders, 5th Ed. Jankovic et al.

Prominent loss of dopaminergic cells in the Substantia Nigra



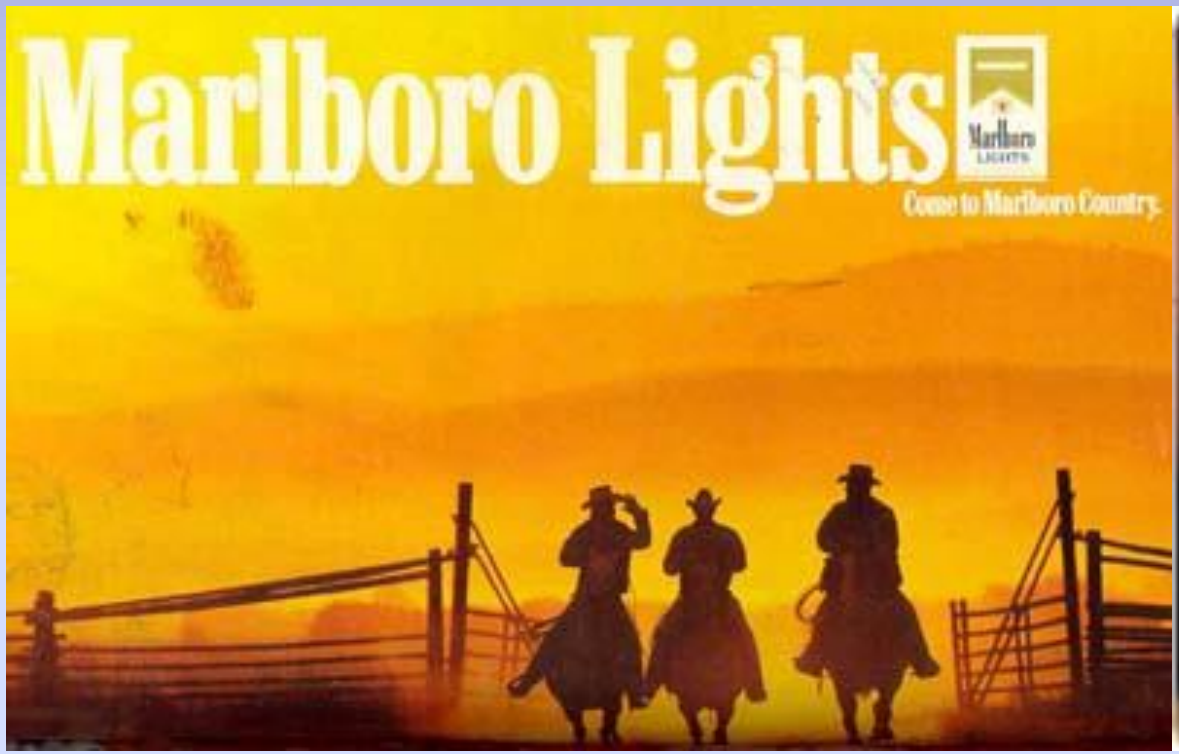


Clinical symptoms don’t become evident until a majority of dopaminergic cells are lost!!

What causes Parkinson's?
→ *Environmental factors*

- California –1983
- Attempted to create MPPP, a drug similar to heroin
- In fact created MPTP, a potent neurotoxin which results in something similar to Parkinson's when injected intravenously

Is anything associated with ***NOT*** developing Parkinson's Disease?



What causes Parkinson's?

- Probably some complex interaction between genetic susceptibility genes and environmental factors that we don't yet fully understand

Early Sign: Loss of Sense of Smell (anosmia)

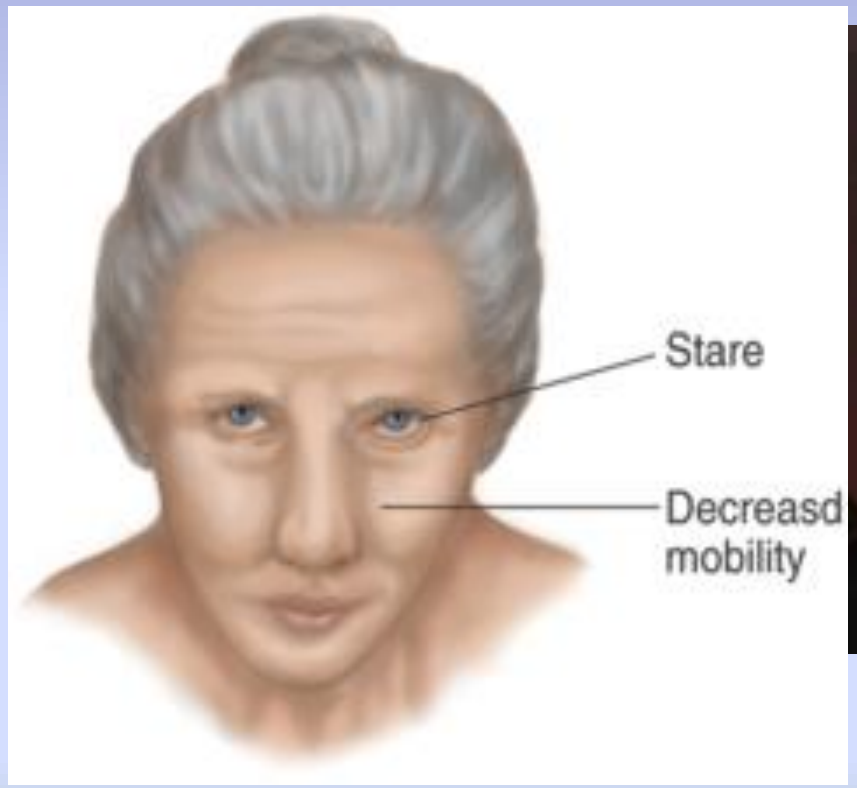
?

Early Sign: Depression and Anxiety

Early Sign: Sleep Disturbances

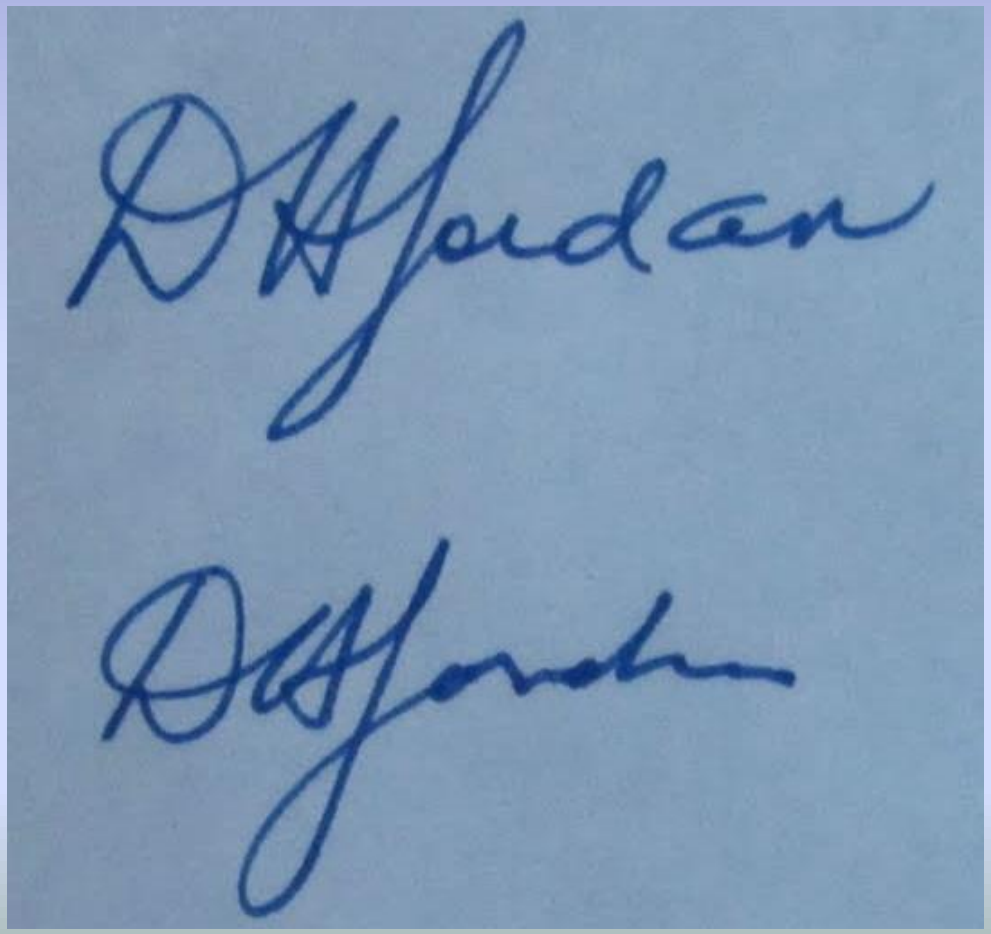
Early Sign: Sleep Disturbances
REM Sleep Behaviour Disorder -- RBD

Early Sign: Masked Facies



http://www.vigconic.com/vineuro/eng/user.php
http://quizlet.com/10504538/examination-of-the-neck-head-flash-cards/

Early Sign: Small Handwriting (micrographia)



http://wpgchap.blogspot.sg

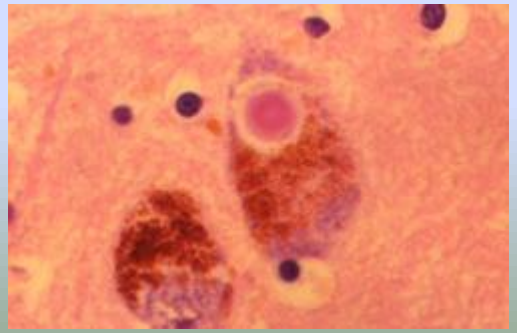
Early Sign: Stiffness / Neck Pain

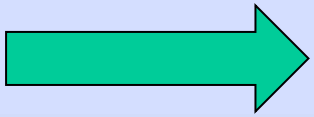
http://www.buzzle.com/articles/frozen-shoulder-treatment.html

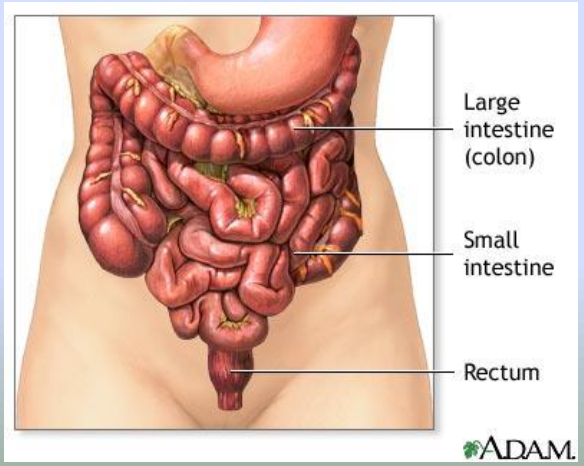
Early Sign: constipation

- **Risk of Parkinson's disease increased if < 1 bowel movement / day at middle age**
- Lewy bodies are seen not just in the brain, but in the nervous system of gut
- Surprising relationship between genetic risks for Parkinson's disease and Crohn's disease

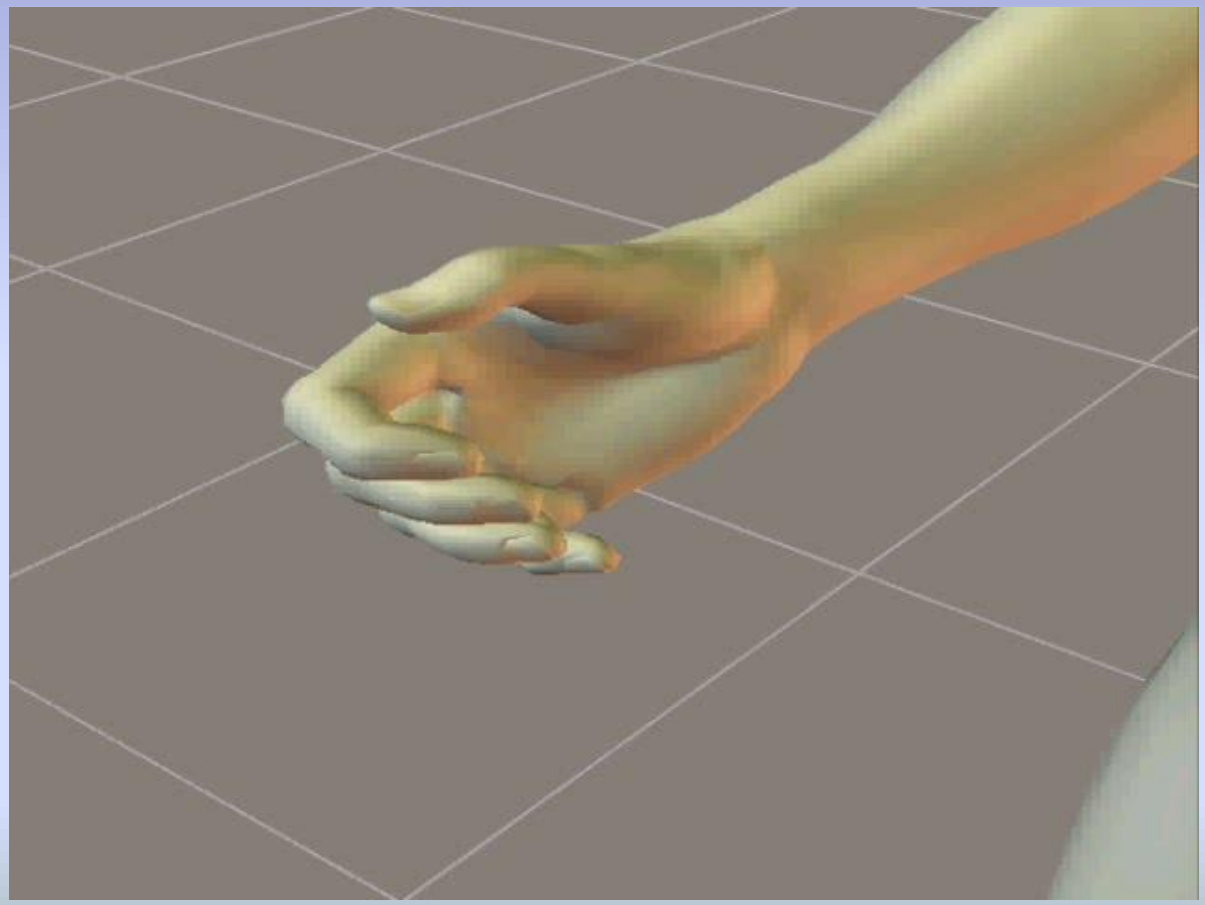
Lewy Body



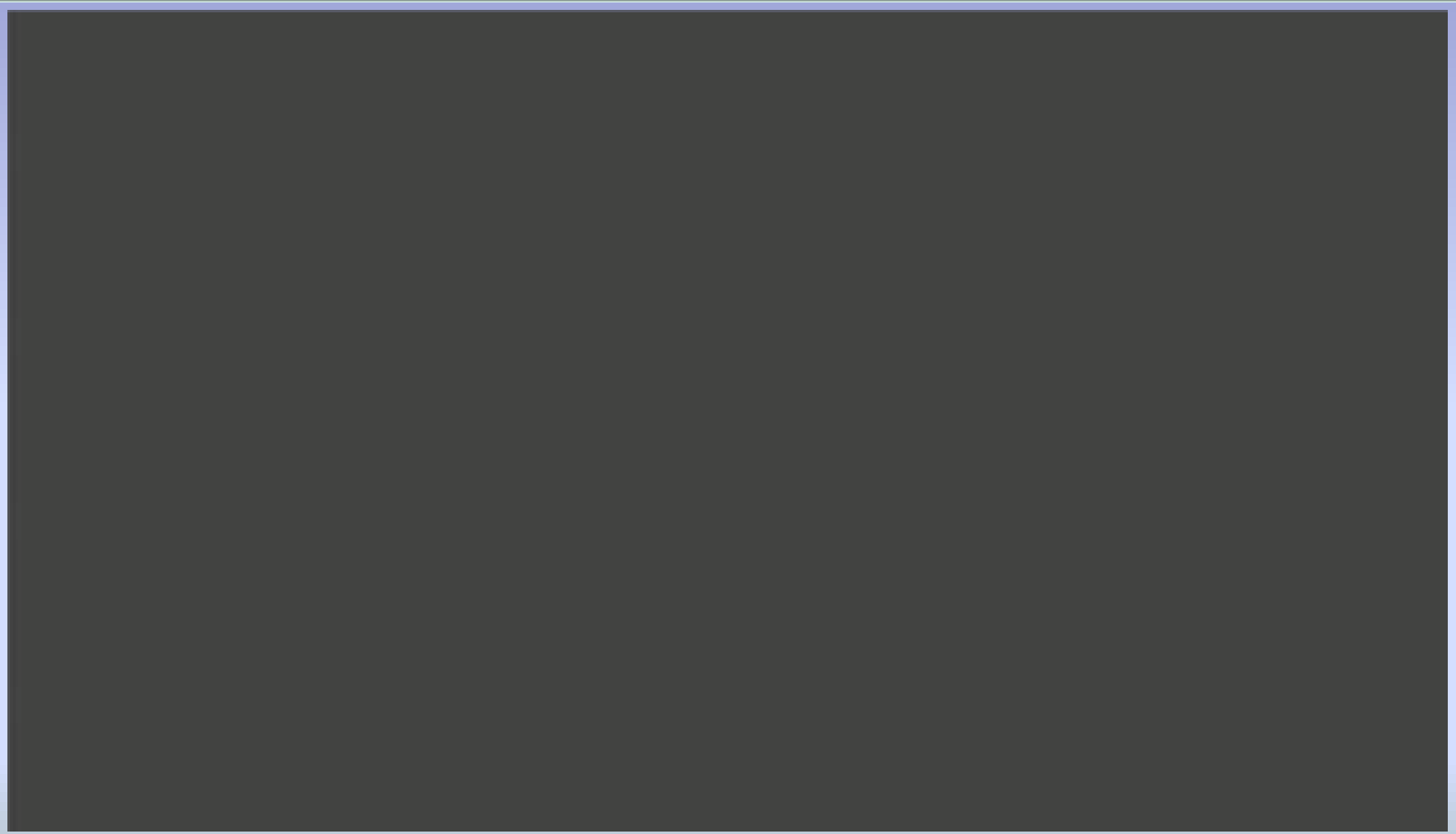




Early Sign: Tremor at rest

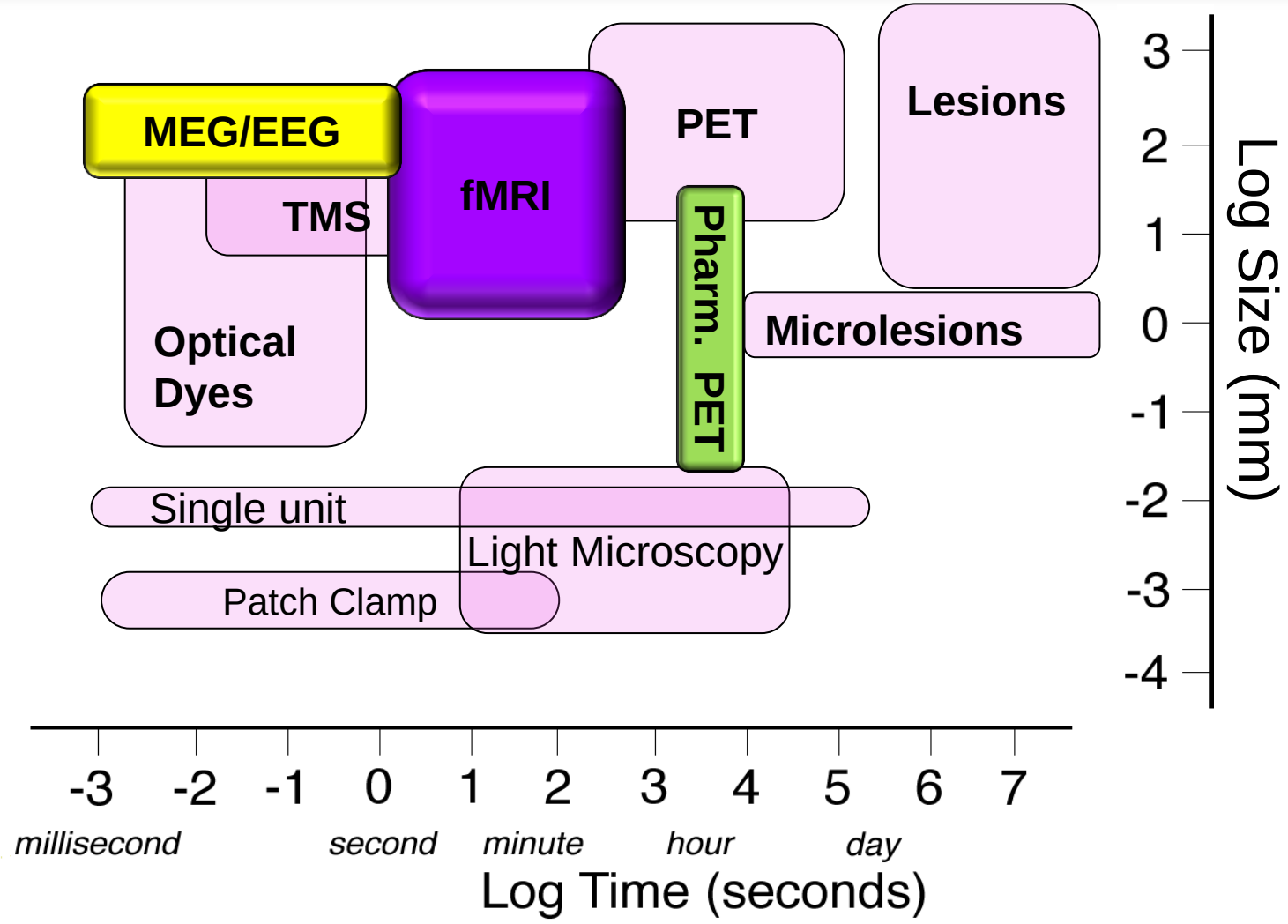


Parkinson's tremor

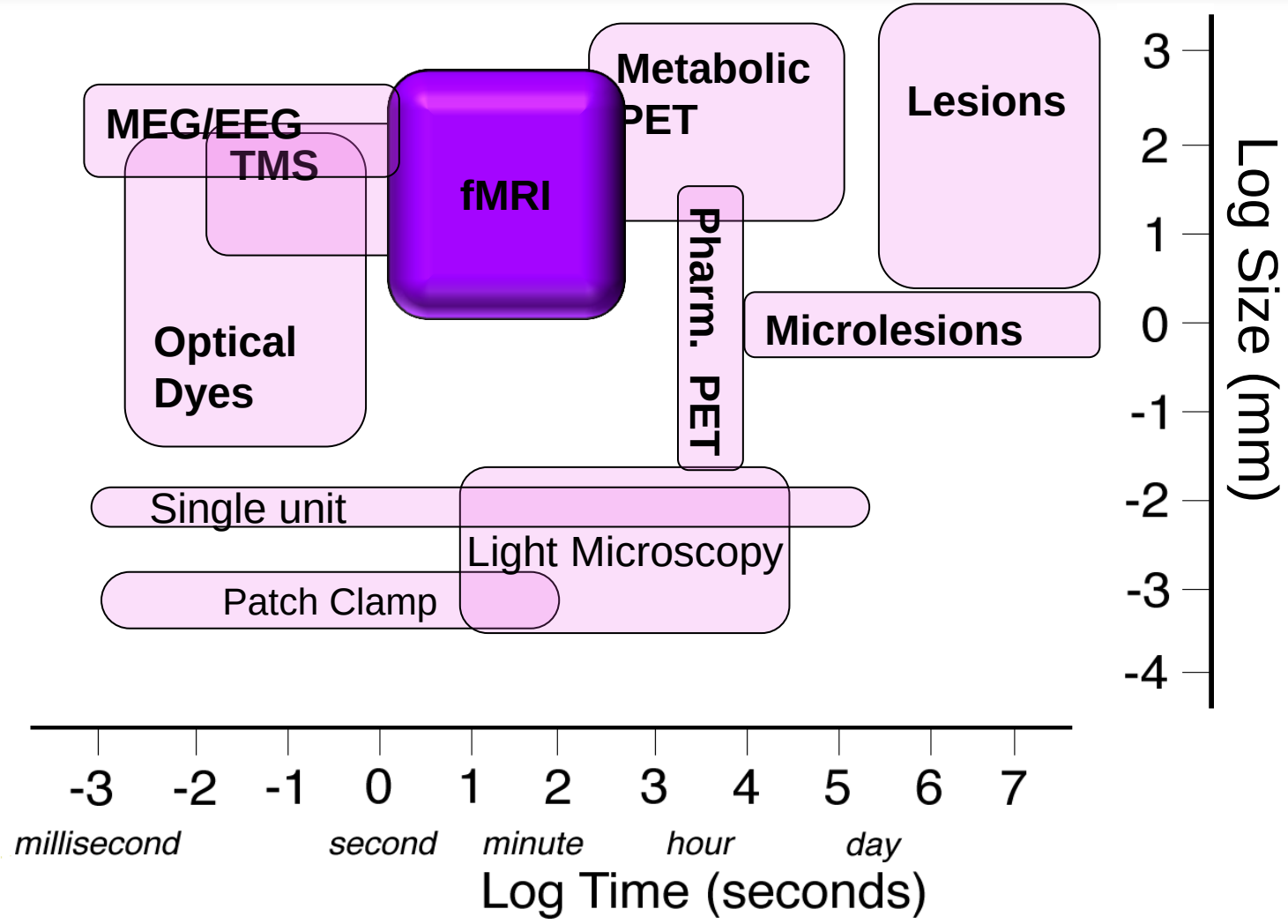


Early Sign:
Decreased Arm Swing

Techniques to probe brain function

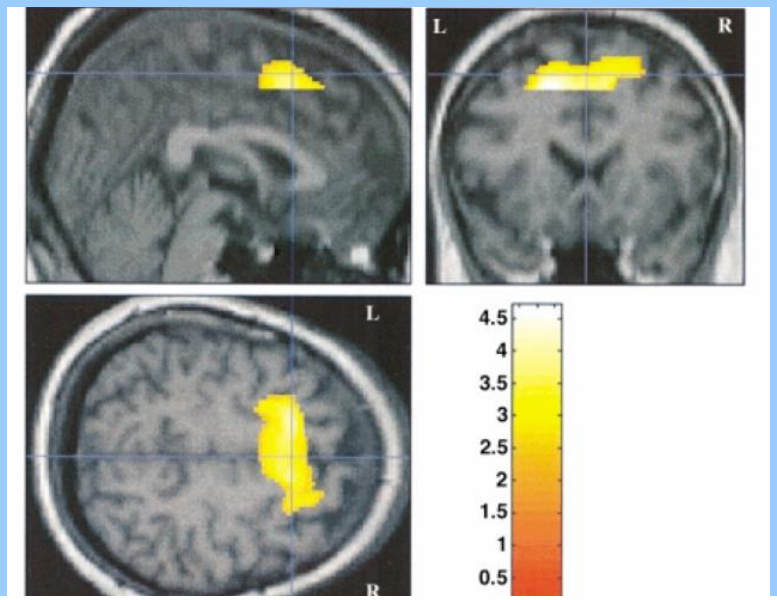


Techniques to probe brain function

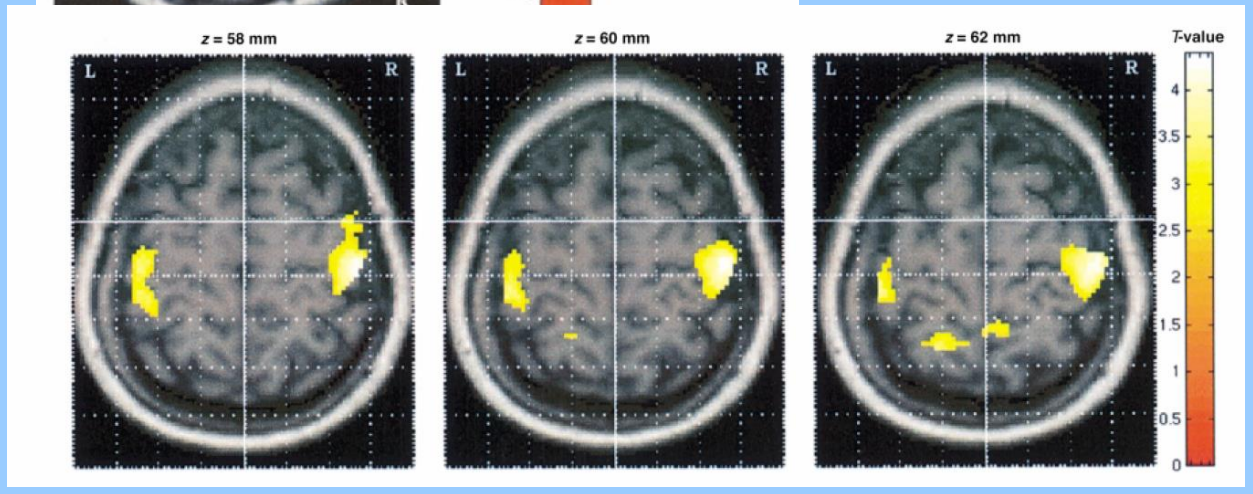


Parkinson's Disease: Clinical Effects of L-dopa treatment can be dramatic

Surprisingly subtle changes in activation due to L-dopa !



- **Areas that show *decreased* activation in Parkinson's.**



- **Areas that show *increased* activation in Parkinson's.**

Haslinger et al. Brain 2001

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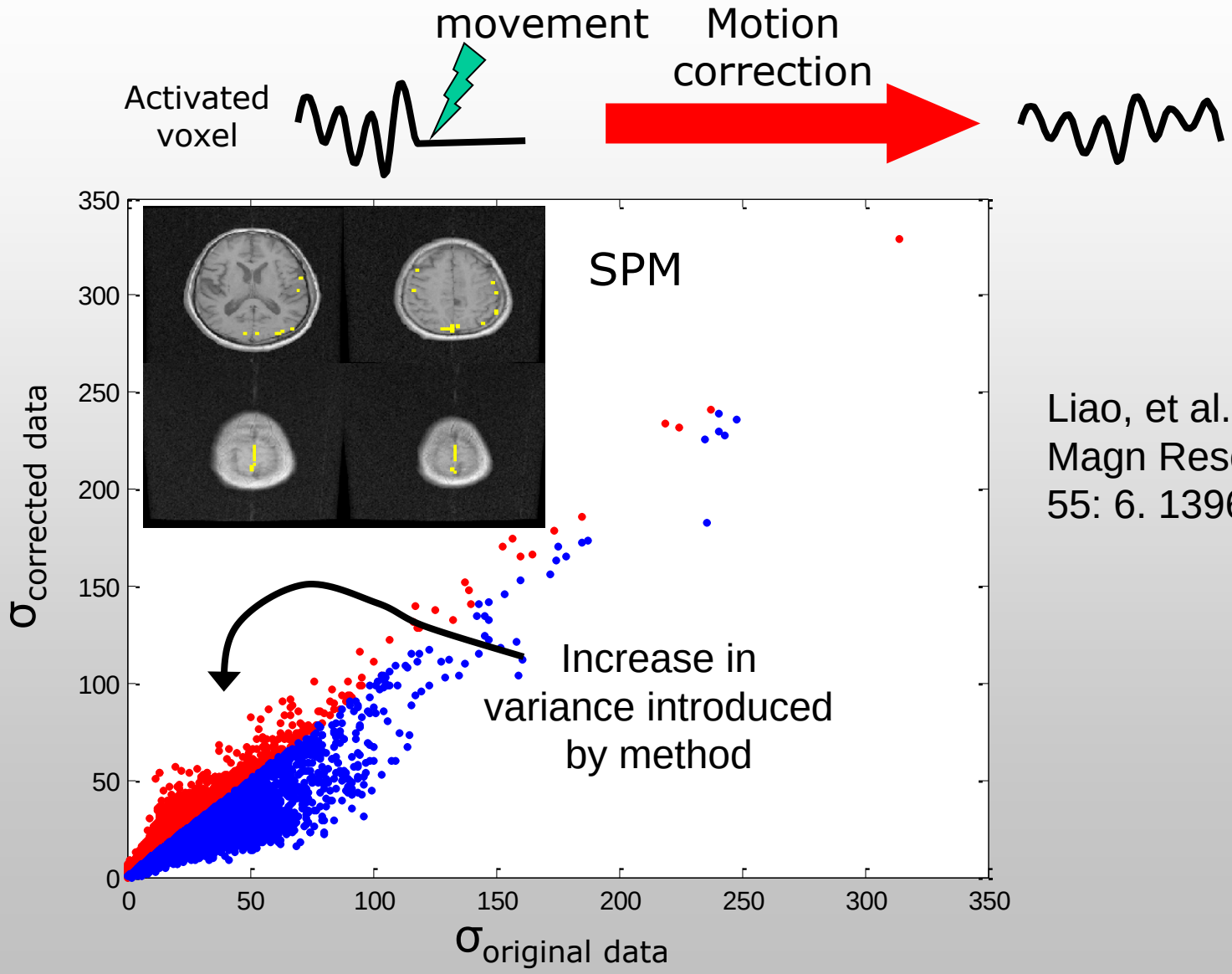
Why are traditional fMRI analyses so insensitive to medication effects in Parkinson's ?

- **Task activation manifests itself differently than changes in BOLD amplitude at discrete loci**
- **Increased inter-subject variability**
- **Increased movement artifact**

Most motion correction algorithms INTRODUCE variability in the data

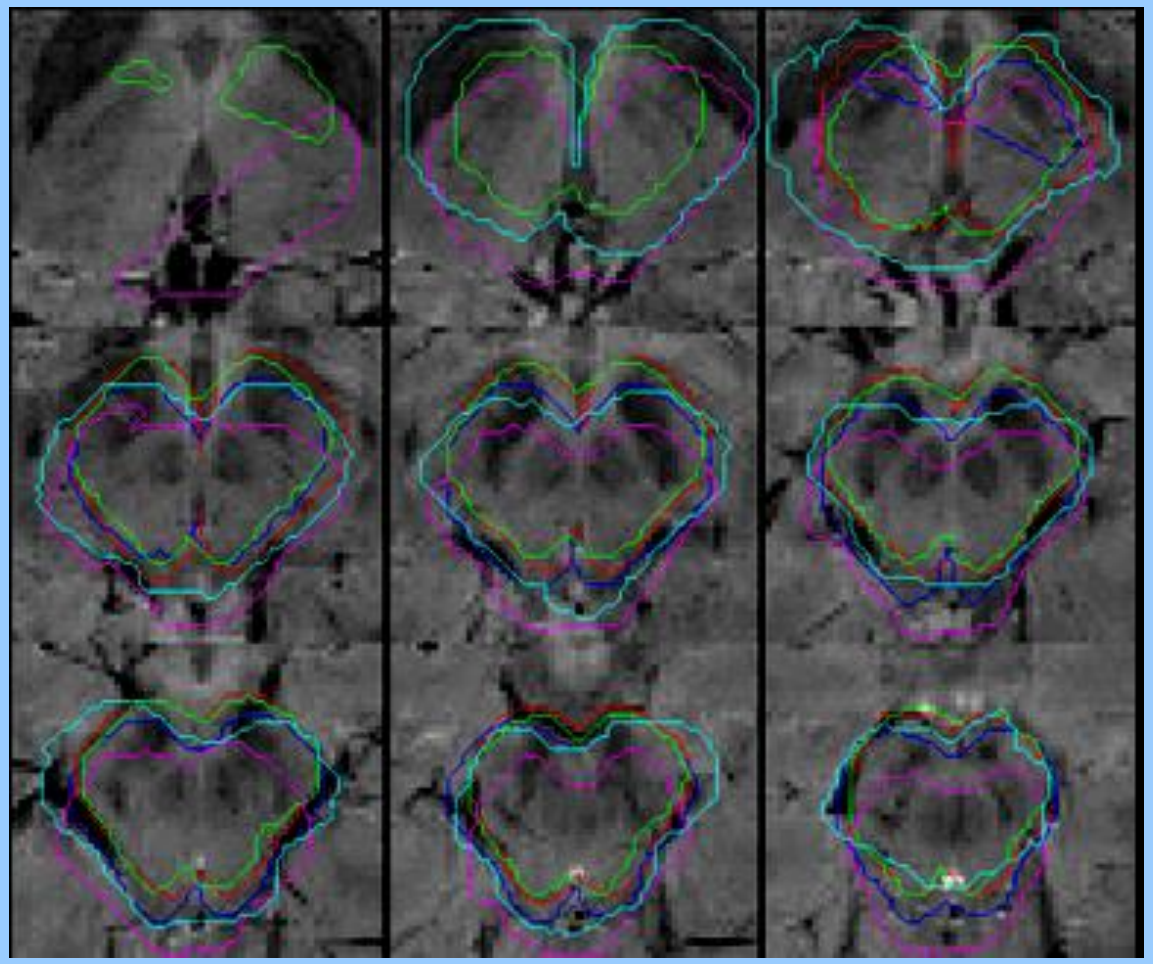


Liao, et al. (2006)
Magn Reson Med
55: 6. 1396-1413 Jun

Why we don’t routinely register brains for our studies …

Midbrain of 5 control subjects

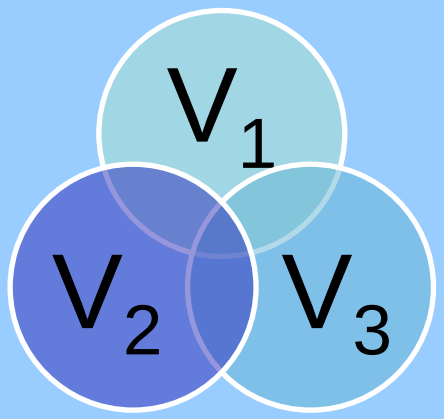
Standard Affine

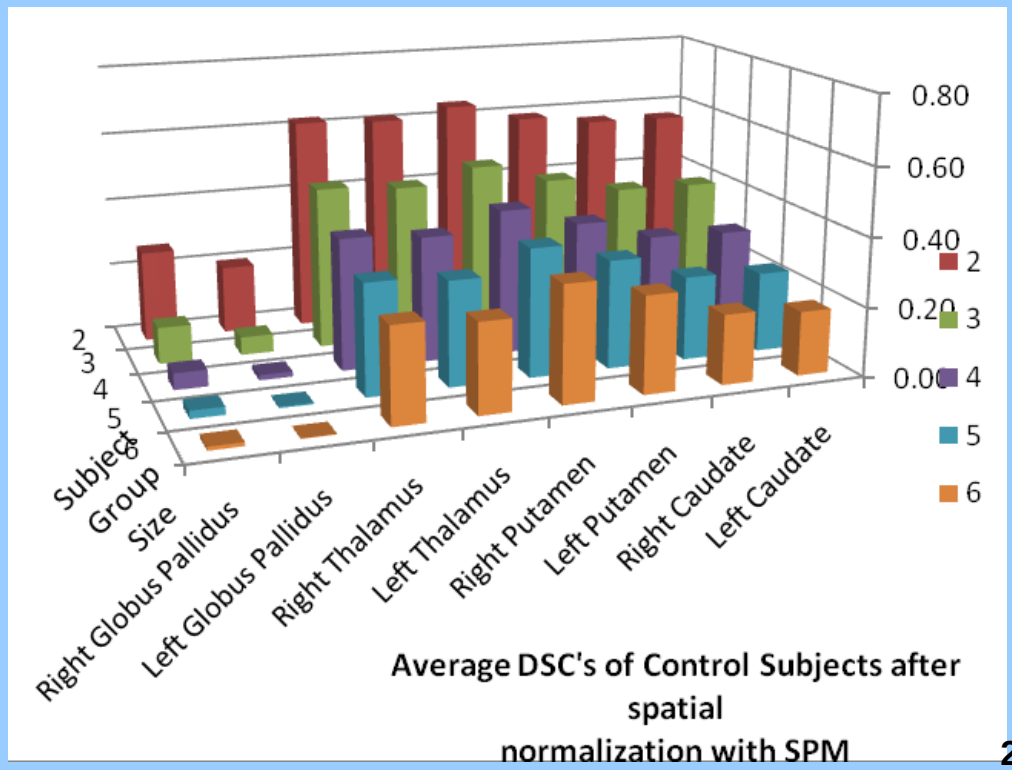


Measurement of Residual Anatomical Variability after Registration

- Dice Similarity Coefficient (DSC)
  - DSC=1 Exact alignment
  - DSC=0 No overlap

$$DSC = \frac{n \times \bigcap_{i=1}^{n} V_i}{\sum_{i=1}^{n} V_i}$$





c/o Prof. Faisal Beg, SFU

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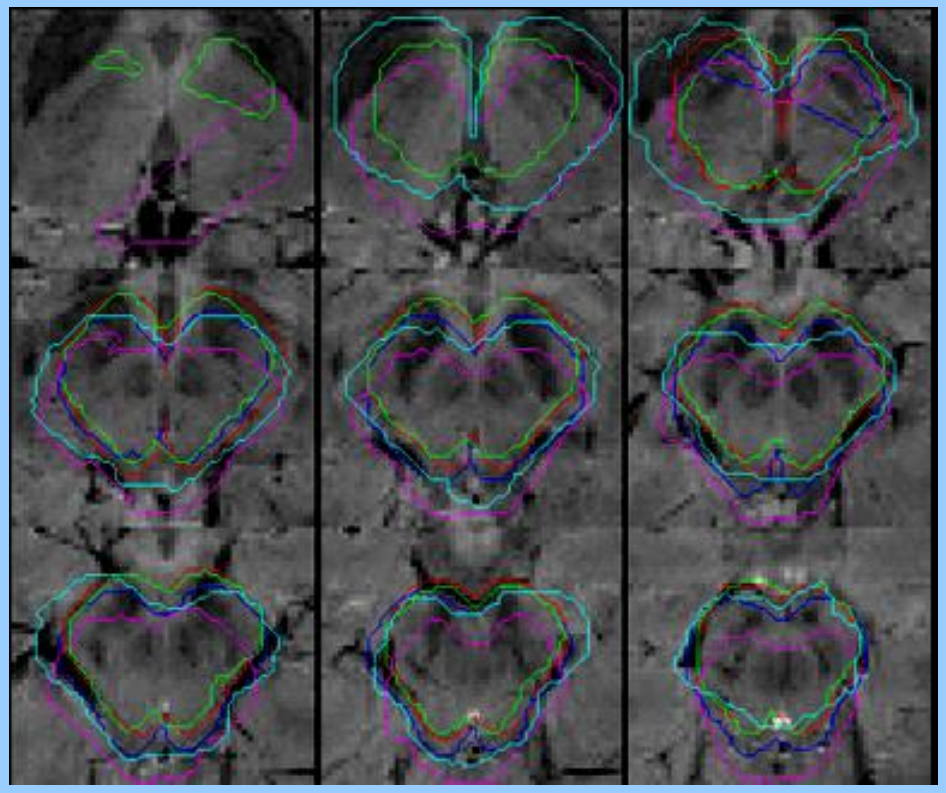
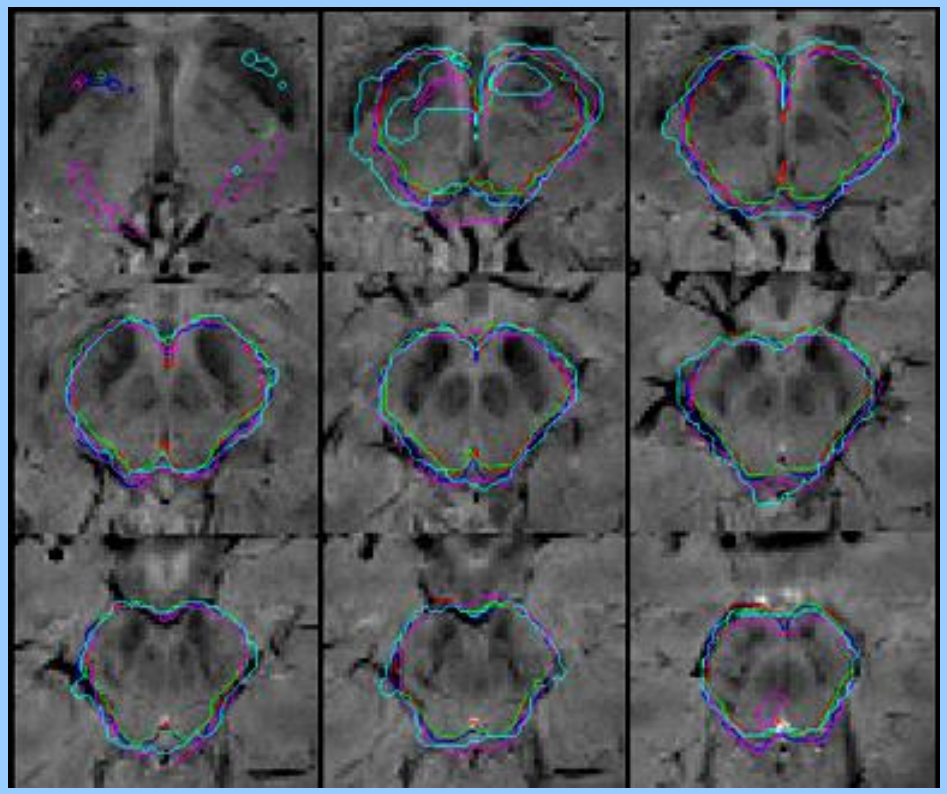
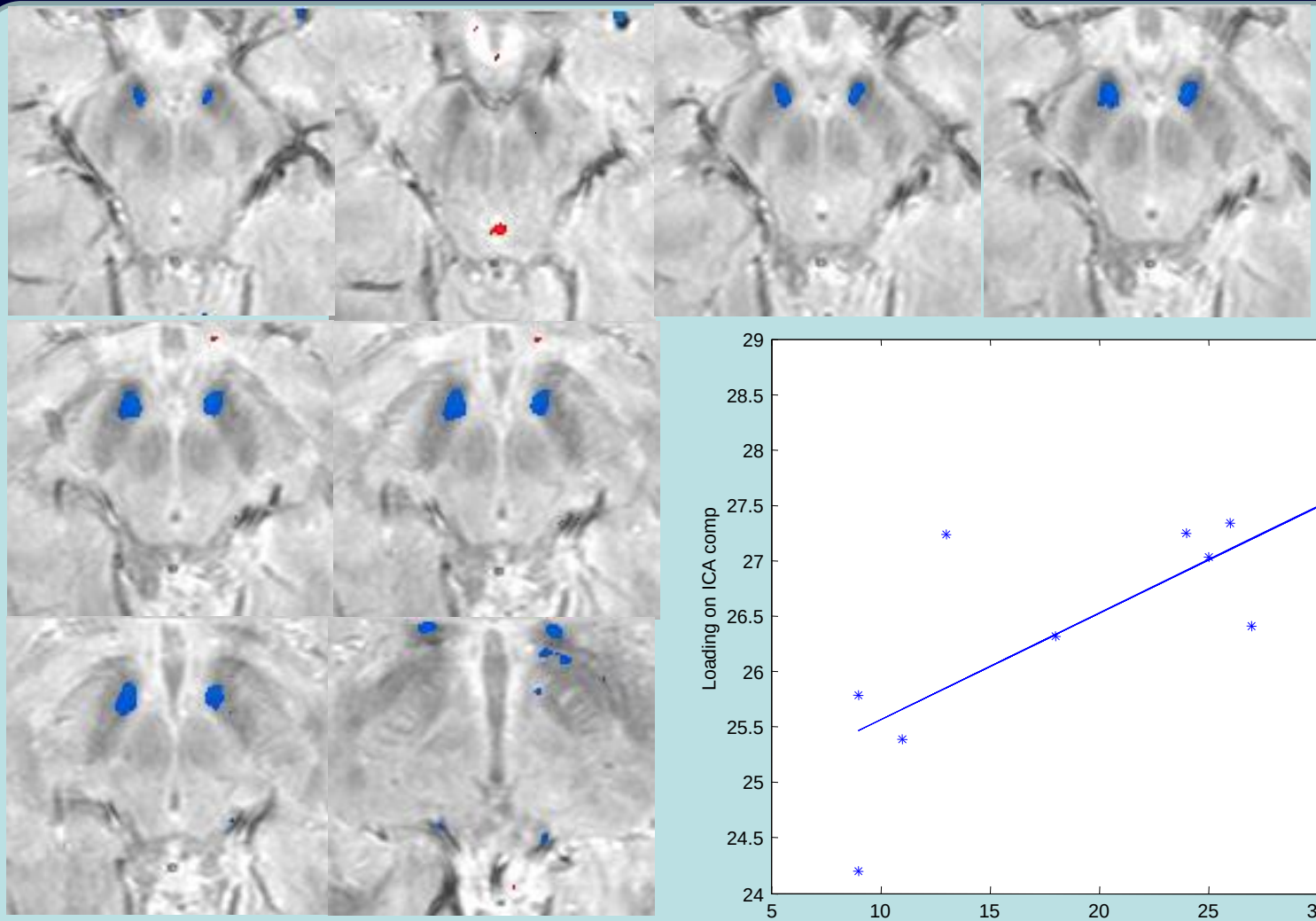


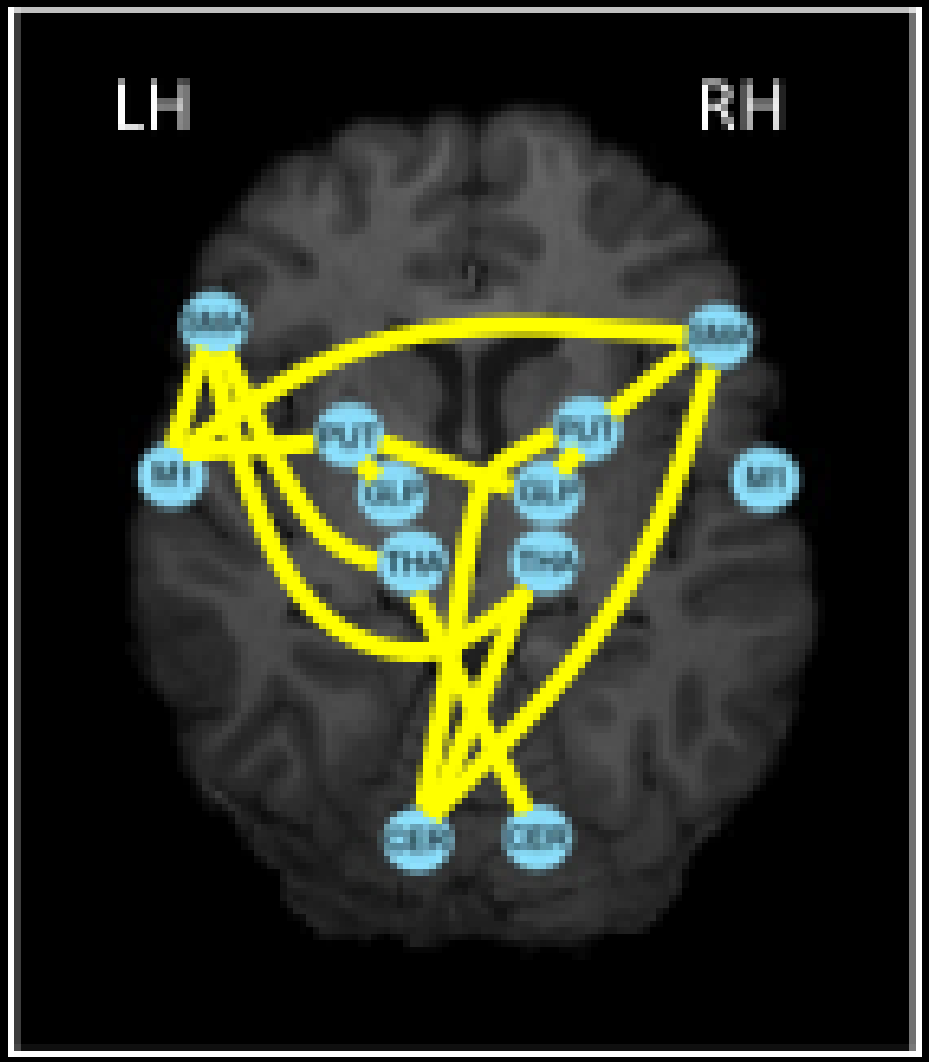
Multi-structure LDDMM



Susceptibility Weighted Imaging (SWI): Correlation with Parkinson's Disease Severity



Determine measures in native (unwarped)space



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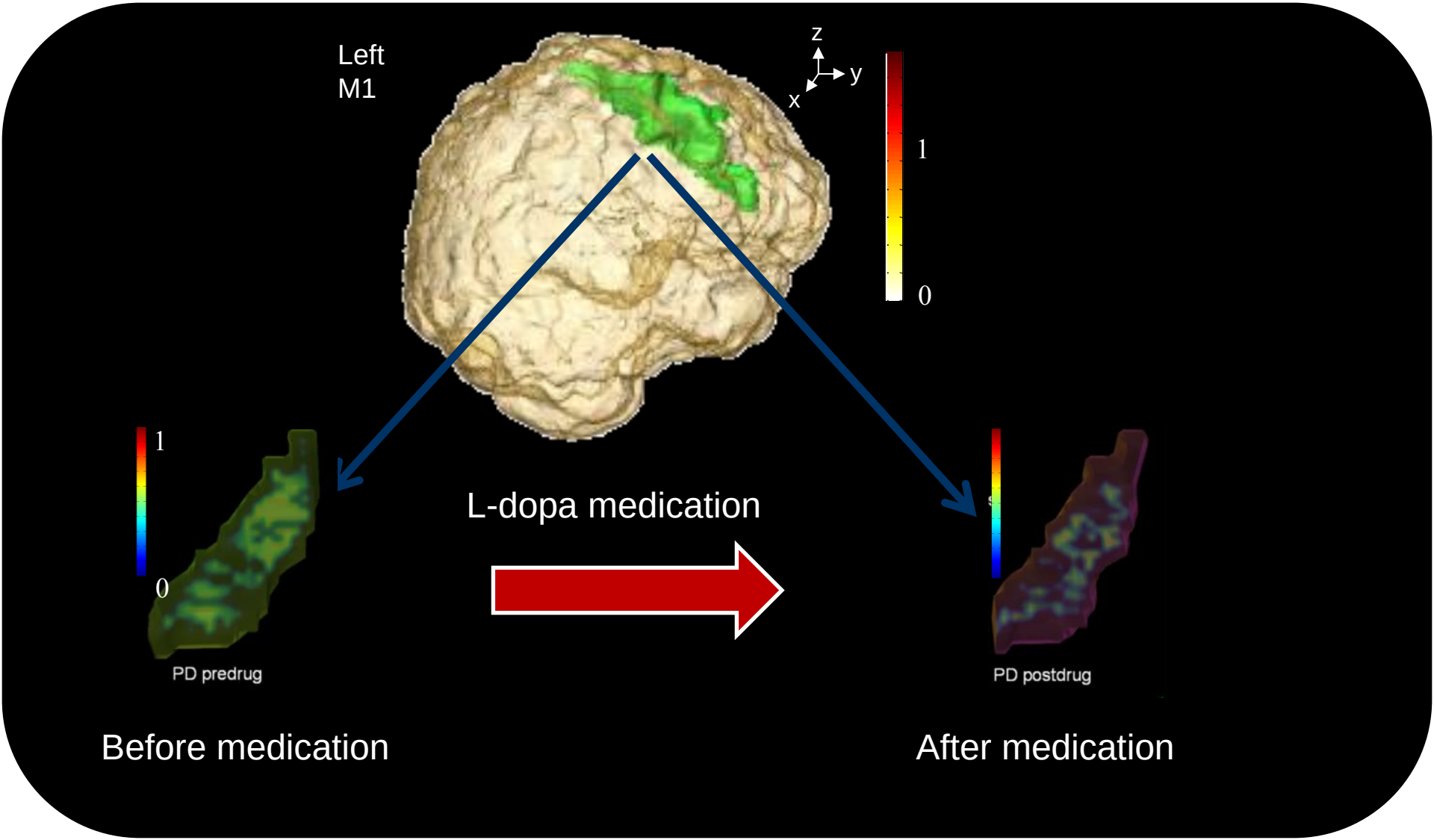
Spatial effects of L-dopa medication on fMRI activation maps



Examining the shape ("3D texture") of fMRI activation

For a 3D distribution, in our case a fMRI t-statistics within a specific ROI, the moments of order *n=p+q+r* are given by:

$$\mu_{pqr} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} x^p y^q z^r \rho(x,y,z)dxdydz$$

where *(x,y,z)* are the spatial coordinates of each voxel and *f(x,y,z)* is the value of voxel with coordinates *(x,y,z)* within the ROI.

To obtain **invariance to position**:

$$\mu_{pqr} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} (x-\bar{x})^p (y-\bar{y})^q (z-\bar{z})^r \rho(x,y,z)dxdydz$$

For **invariance to size**, we normalize as: $\eta_{pqr} = \dfrac{\mu_{pqr}}{\mu_{000}^{\frac{p+q+r}{3}+1}}$

For **invariance to rotation,** central moments can be combined in specific ways, for example :

$$J_1 = \eta_{200} + \eta_{020} + \eta_{002}$$

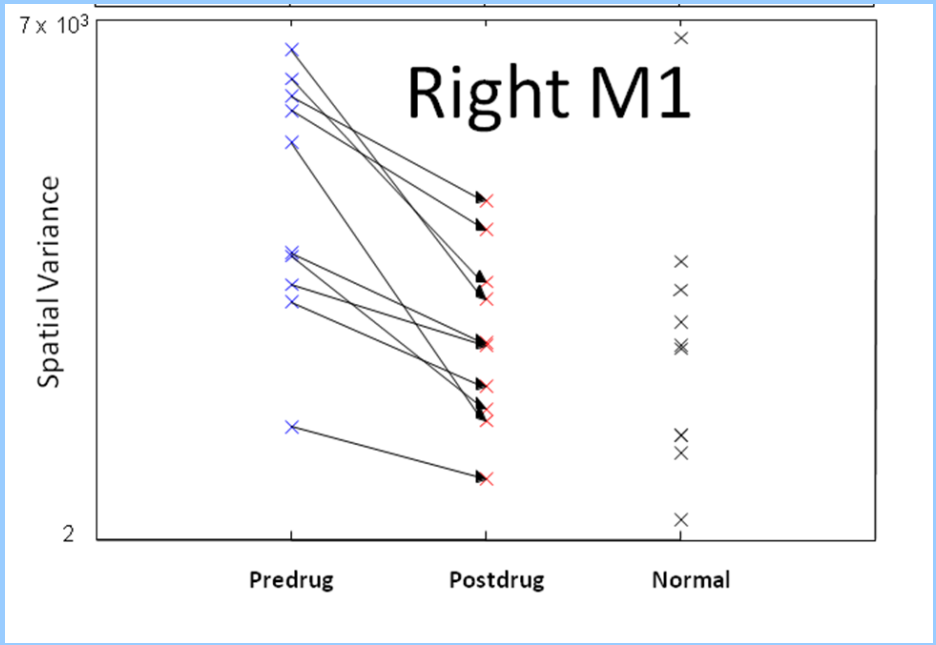
$$J_2 = \eta_{200}\eta_{020} + \eta_{200}\eta_{002} + \eta_{020}\eta_{002} - \eta_{101}^2 - \eta_{110}^2 - \eta_{011}^2$$

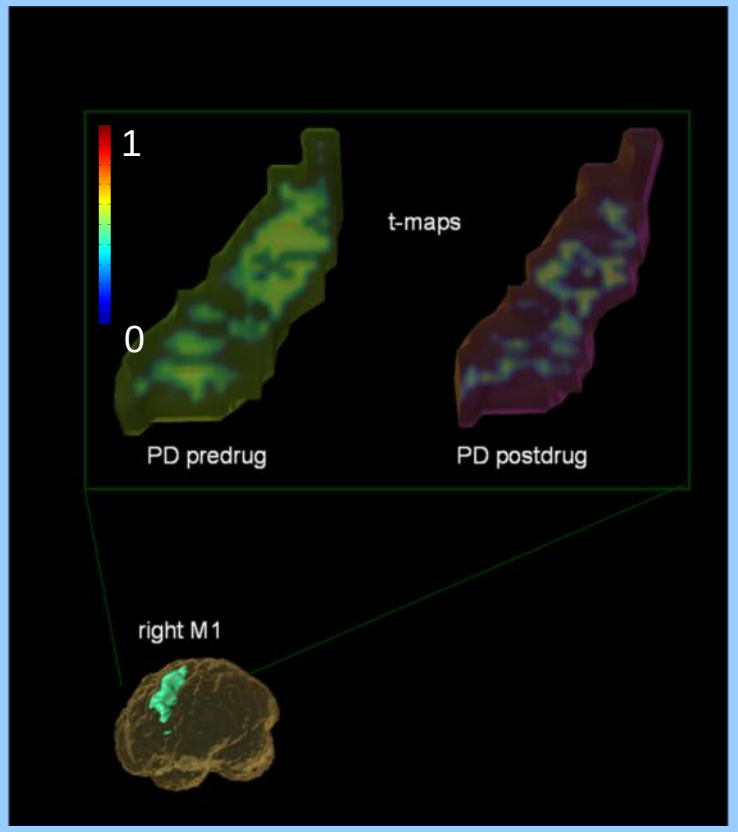
$$J_3 = \eta_{200}\eta_{020}\eta_{002} - \eta_{002}\eta_{110}^2 + 2\eta_{110}\eta_{101}\eta_{011} - \eta_{020}\eta_{101}^2 - \eta_{200}\eta_{011}^2$$

Ng et al. ***IEEE Transactions on Medical Imaging***, 2009.

Focusing Effect of L-dopa assessed by spatial variance

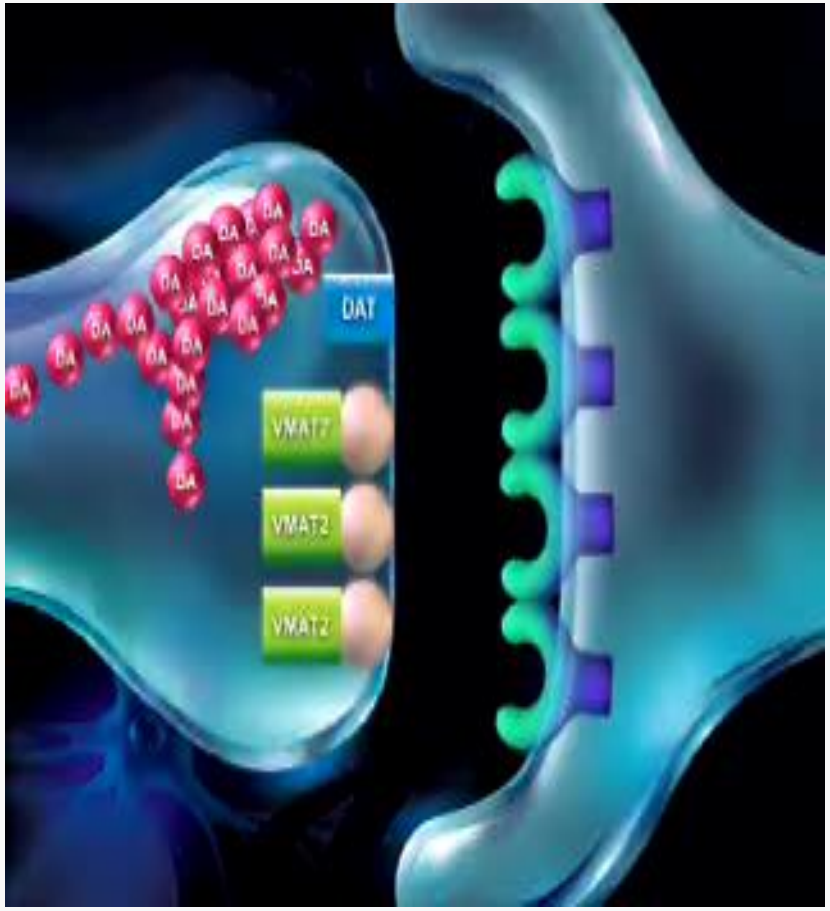
PD subjects increase their area of activation compared to normal controls. This increased area normalizes after L-dopa

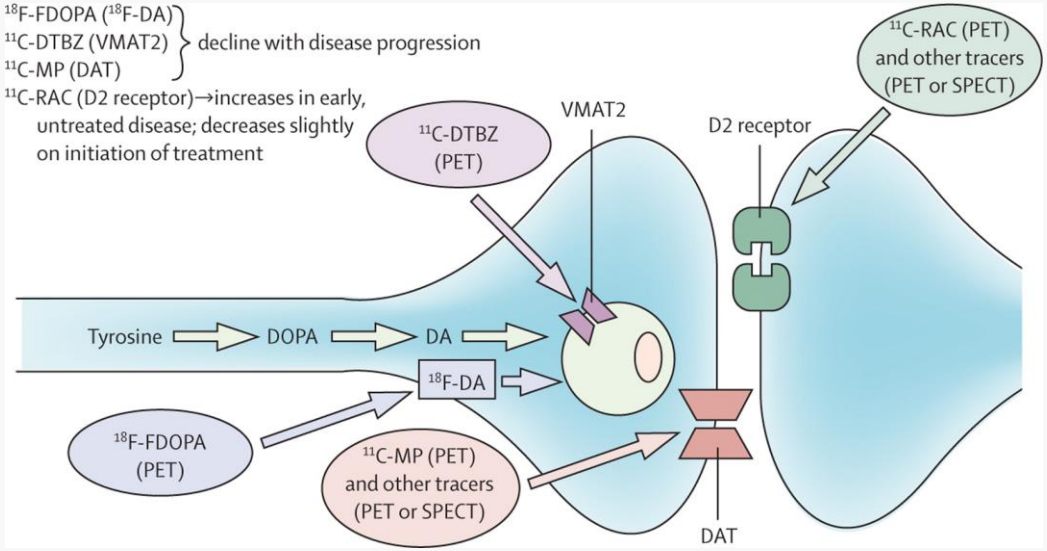




Ng, Palmer, Abugharbieh & McKeown. Focusing Effects of L-dopa in Parkinsons Disease. ***Human Brain Mapping*** *(2009).*

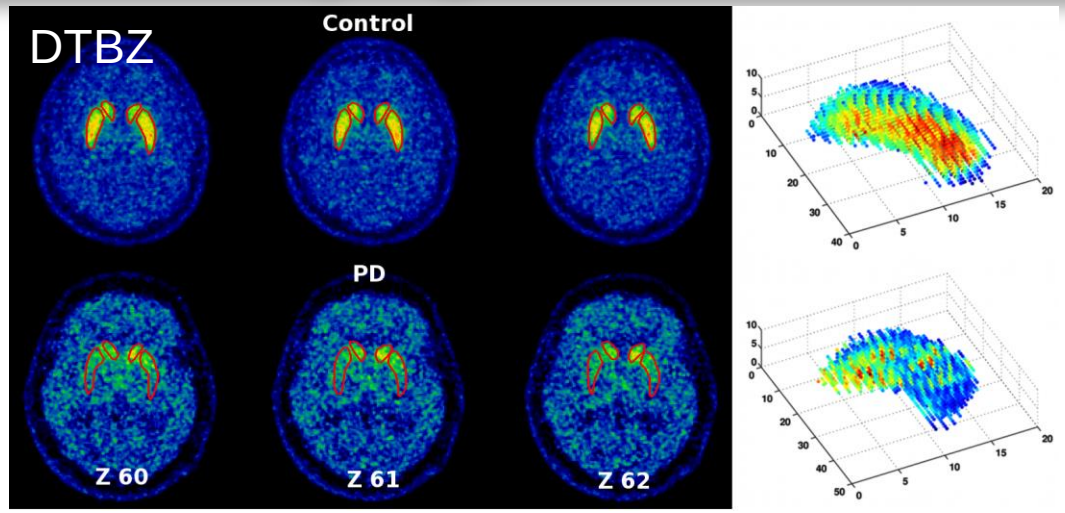
PET imaging of the dopamine system

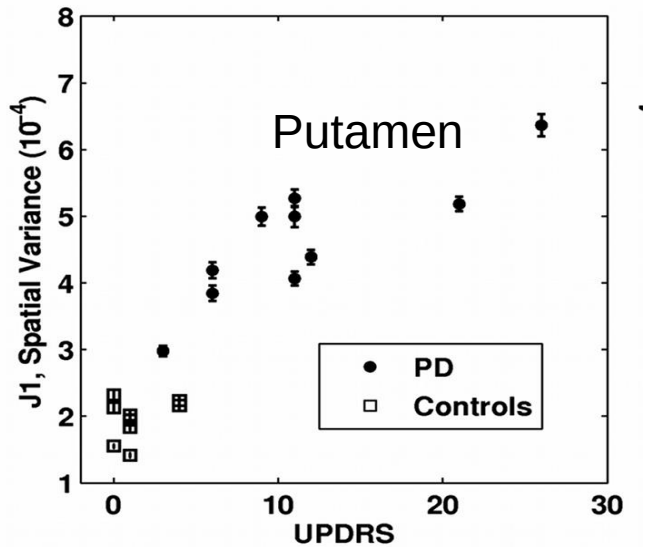




A J Stoessl, W R W Martin, M J McKeown, V Sossi (2011) Advances in Imaging In Parkinson's Disease **Lancet Neurology** 10: 11. 987-1001

3D Moment Invariants – application to PET imaging in Parkinson's disease





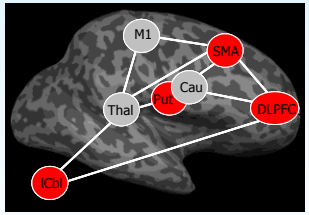
Gonzalez et al. Neuroimage. 2013 Mar;68:11-21.

Areas of activation *vs* connectivity

Late 19th Century two opposing view of normal brain function:

1. **Each cortical area was associated with a particular function (Gall)**

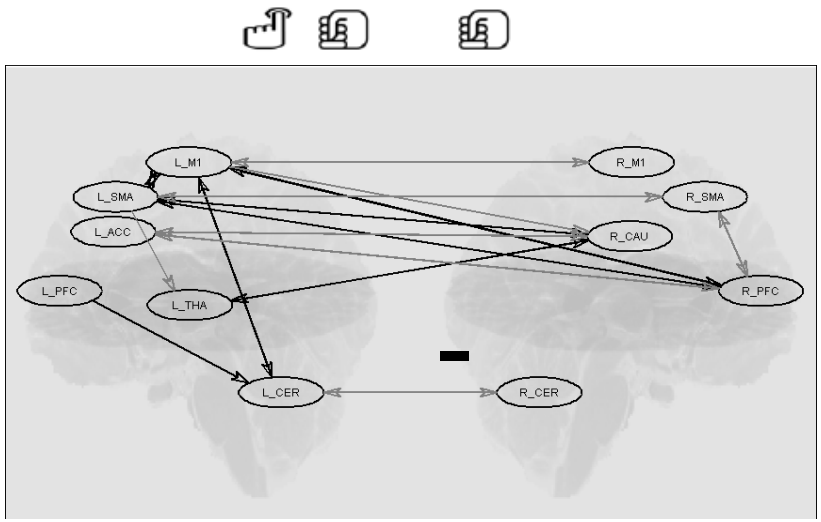
2. **Normal function required the collaboration between different brain areas (Wernicke)** *"Any psychic process … could not be localized, but tested on the mutual interactions of these fundamental psychic elements mediated by means of the … association fibres"*



L-dopa normalizes impaired connectivity

Differences in connectivity patterns (based on an MAR model) between PD and normal controls during performance of bimanual movements

PD Subjects Off Medication



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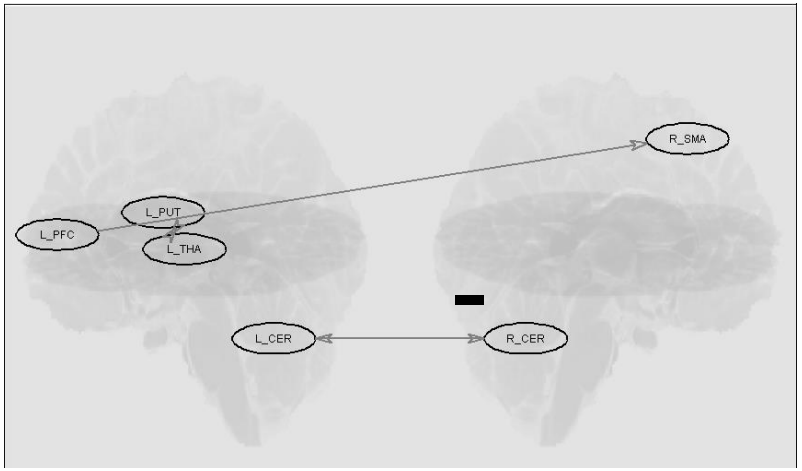

PD Off-med: grey lines (decreased cf controls) mostly decoupling from rest between homologous regions, black lines (increased cf controls) show **increased cerebellar connectivity**.

S J Palmer, L Eigenraam, T Hoque, R G McCaig, A Troiano, M J McKeown (2009) ***Levodopa-sensitive, dynamic changes in effective connectivity during simultaneous movements in Parkinson's disease***. Neuroscience 158: 2. 693-704 Jan

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Replicator Dynamics – one way to assess co-varying regions forming networks

Based on theoretical biology

- Have a number of species, ***w***
- Define a static 'fitness' matrix, ***C***, which represents interaction between species
- How does the population evolve over generations?

Replicator Dynamics – one way to assess co-varying regions forming networks

Let w(k) be a vector with the jth element being the probability that allele *j* remains in the gene pool during the kth generation and *C* be a 'fitness' matrix with each element reflecting the fitness of a genotype (a pairwise combination of alleles), w(k) can be estimated as follows :

$$w(k+1) = \frac{w(k).*Cw(k)}{w(k)^T Cw(k)}$$

where .* represents element-wise multiplication.

The above equation is a local maximizer of the following optimization problem:

$$\arg\max_{w} w^T Cw, \quad subject\ to \left\|w\right\|_1 = 1, w \geq 0$$

This provides an elegant solution to the challenging problem of non-negative, sparse PCA.

Ng et al. ***IEEE Trans Med Imaging***. 2012 Mar;31(3):576-85.

Group Replicator Dynamics

- Let $W(k)$ be a $N_r \times N_s$ matrix with $w^i(k)$ of each subject along the columns,
  - $W_c(k)$ be the same as $W(k)$ but with the subject mean removed from each row.

To encourage networks comprising the same ROIs, the weight vector of each subject i, $w^i(k)$, is adjusted so that the group entropy is minimized:

$$W(k) = W(k) - \lambda\left((W_c(k)W_c(k)^T)^{-1}W_c(k)\right)$$

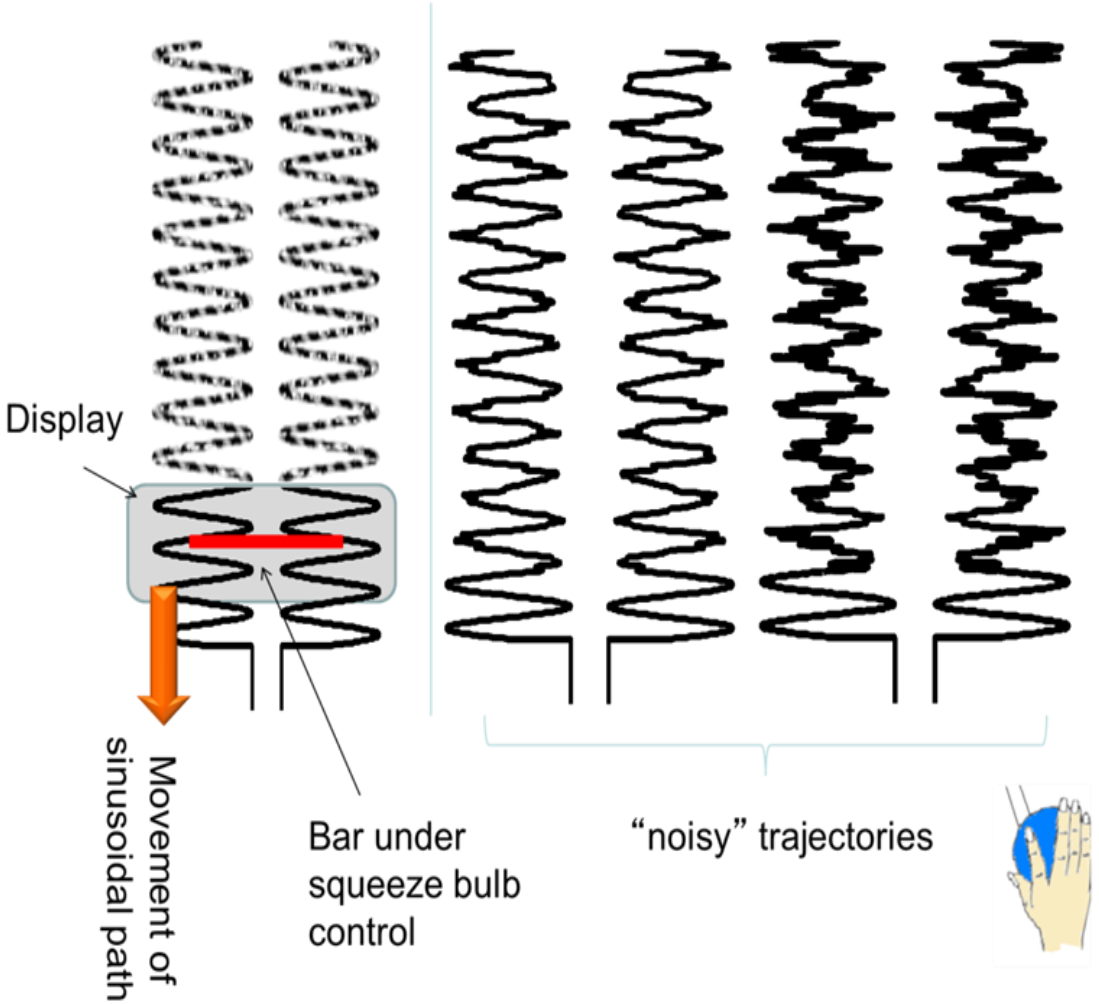
where λ governs the degree of group support.

- This results in highly coherent networks that comprise the same ROIs across subjects but with subject-specific ROI weightings.

➢ If we consider ROIs as nodes of a graph and elements of C_i as edge weights, we can remove only those edges present in the dominant network, which enables the same ROI to be in multiple networks.

Ng et al. ***IEEE Trans Med Imaging***. 2012 Mar;31(3):576-85.

Group Replicator Dynamics in Parkinson's Disease



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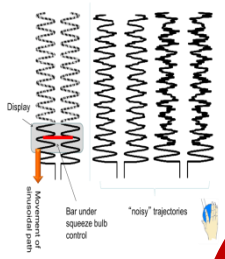
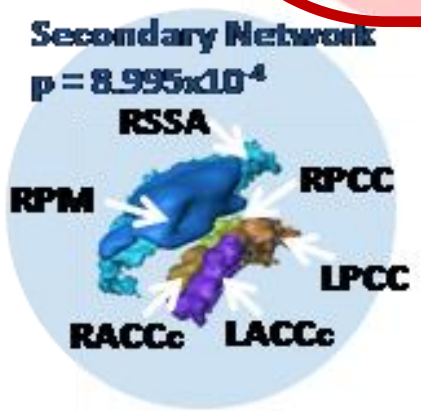
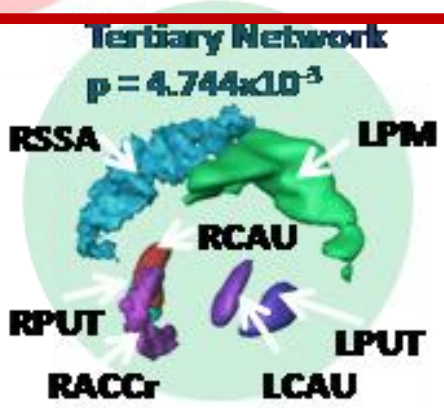
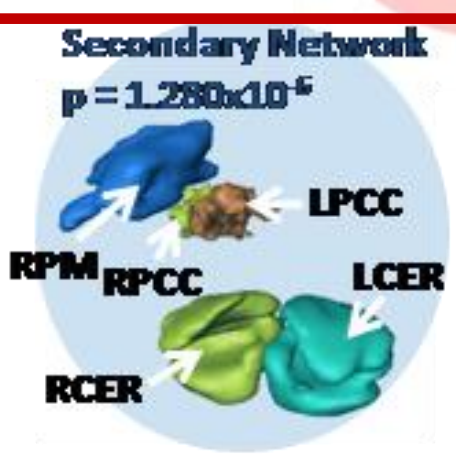


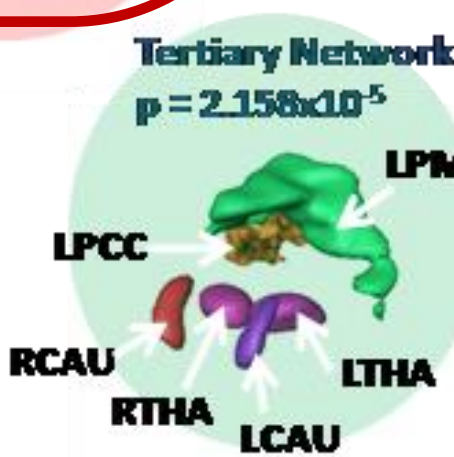
Tremor-predominant Parkinson's

Akinetic Rigid Parkinson's









Ng et al. ***IEEE Trans Med Imaging***. 2012 Mar;31(3):576-85.

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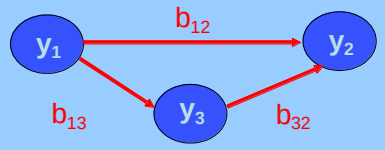
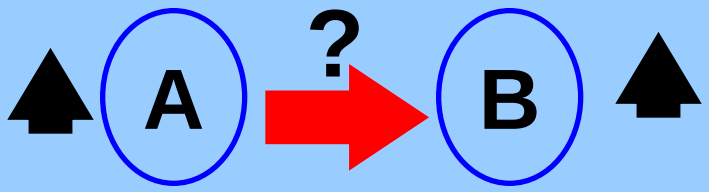
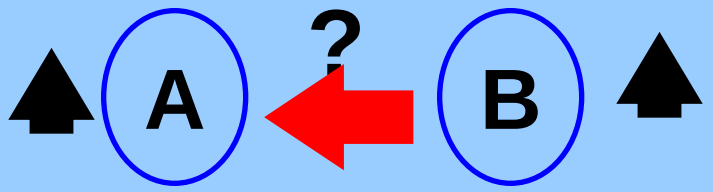
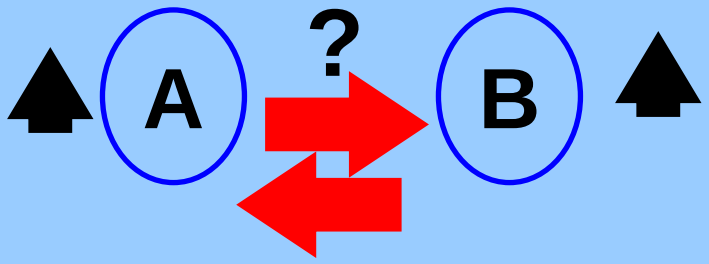
Problems with Inferring Connectivity

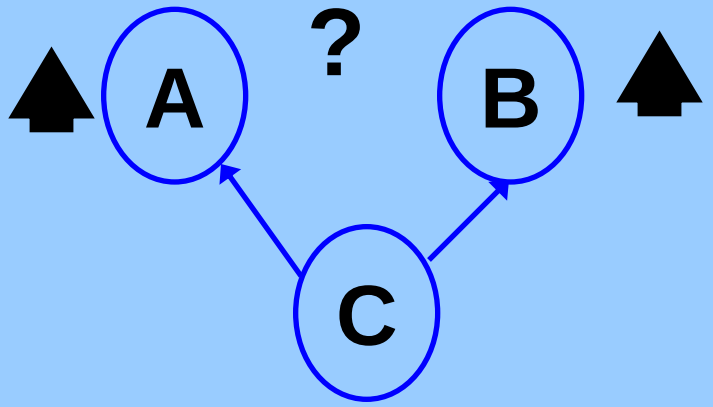


Problems of covariance vs. causality









Thomas Bayes

Issues Related to Bayesian Network Learning

- Accuracy.
  - ♦ How many connections are actually true?
  - ♦ How many true connections can be detected?

Error rate control : FDR

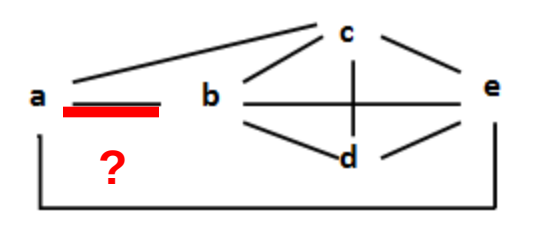
- Efficiency.
  - ♦ Exploratory studies must search through a huge number of possible models to find one or a few that are best supported by data.

Group Level PCfdr algorithm

- Generality (deal with the inter-subject variability issue).
  - ♦ Biomedical research usually involves a group of subjects.

The PCfdr algorithm for Bayesian Network (BN) Learning

- PC algorithm is a fast BN learning method.



Estimate the *p-value* between a and b given vertex set C , $p_{a \perp b|C}$ based on partial correlation coefficients.

If $p_{a \perp b|C}$ is larger than the threshold, then remove the edge between a and b.

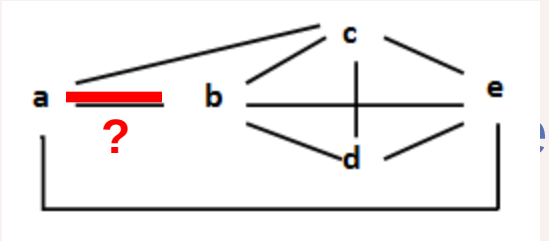
- False Discovery Rate (FDR) control procedure.

Given *p-values* of multiple-hypothesis testing, it adaptively sets a threshold to control the FDR under user-specified level q.

PCfdr algorithm : Combine PC algorithm with the FDR control .

Li, J and Wang, ZJ. (2009). Controlling the false discovery rate of the association/causality structure learned with the PC algorithm. ***The Journal of Machine Learning Research***, 10, 475-514.

Extending the PCfdr algorithm to the group level by embedding the mixed effect model



Estimate the *p-value* between a and b given vertex set C **at the group level**

$$Z_i = Z_g + e_i + \varepsilon_i$$

subject level

group level

$e_i \propto N(0, \sigma_g^2)$ → Inter-subject variance

$\varepsilon_i \propto N(0, \sigma_i^2)$ → Within-subject variance

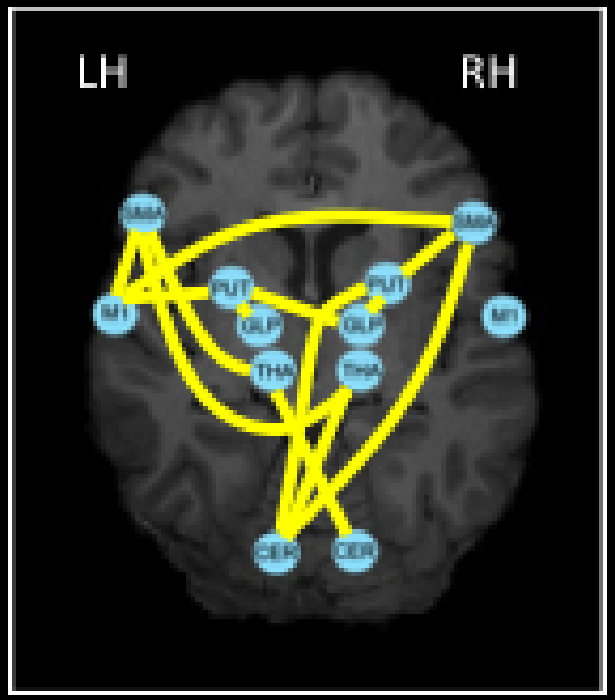
Unbalanced case: Restricted Maximum Likelihood (ReML) approach

Balanced case: t-test

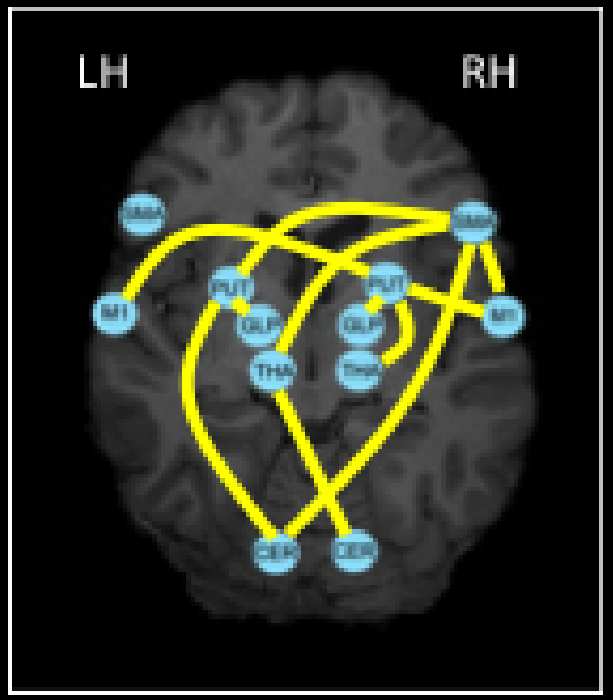
A Liu, J Li, Z J Wang, M J McKeown (2012) A Computationally-Efficient, Exploratory Approach to Brain Connectivity Incorporating False Discovery Rate Control, A Priori Knowledge and Group Inference ***Computational and Mathematical Methods in Medicine*** (in press)

Altered connectivity in PD subtypes may represent a type of compensation

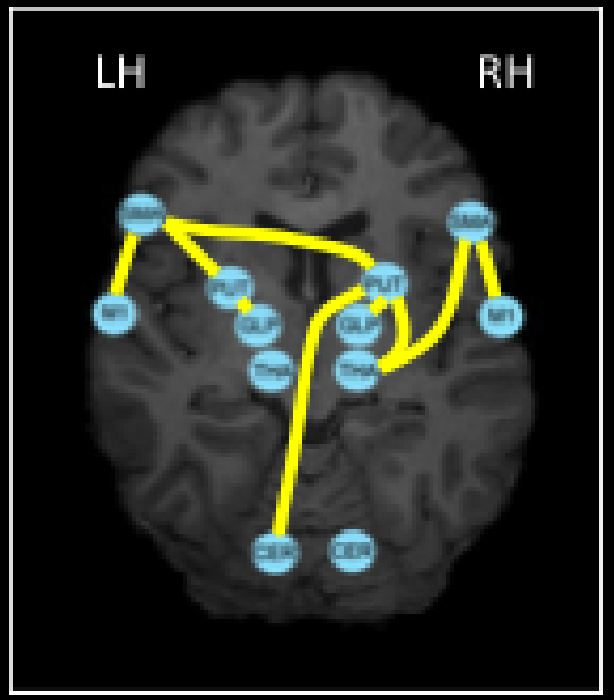
Normal



PD-Tremor



PD-Rigid



S J Palmer, J Li, Z J Wang, M J McKeown (2010) Joint amplitude and connectivity compensatory mechanisms in Parkinson's disease. Neuroscience 166: 4. 1110-1118 Apr

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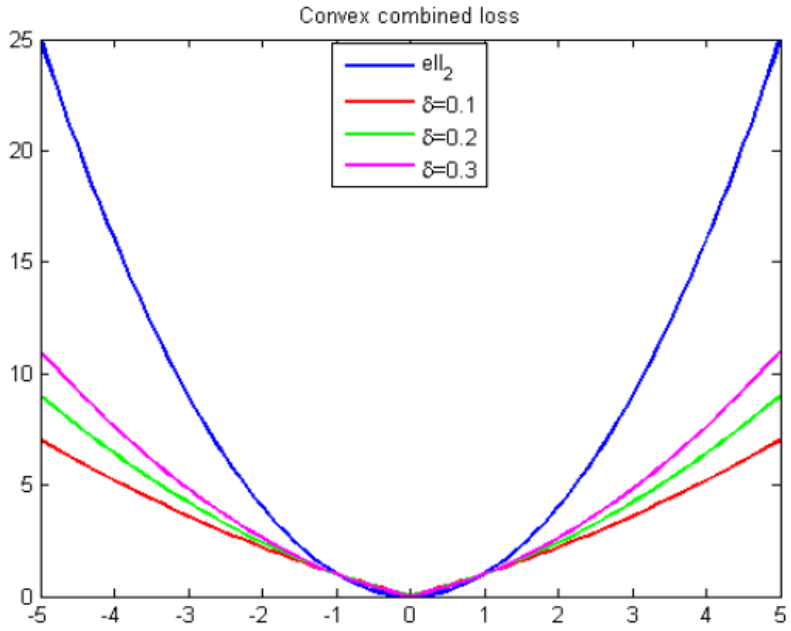
Robust LASSO

- We propose the convex combined loss of ℓ_1 and ℓ_2 norms.
- Special cases:
  - $\delta = 1 \implies$ ordinary LASSO
  - $\delta = 0 \implies$ *Regularized Least Absolute Deviation* (RLAD).
- More flexibility: the convex combined weight can be tuned to achieve the minimal asymptotic variance.
- Adaptive robust LASSO: allowing unequal penalty weights for different coefficients.



The proposed convex combined loss function is defined as

$$L(\mathbf{u}; y_i, \mathbf{x}_i) = \delta \left(y_i - \mathbf{u}^* \mathbf{x}_i\right)^2 + (1 - \delta) \left|y_i - \mathbf{u}^* \mathbf{x}_i\right| .$$

Xiaohui Chen, Z Jane Wang, Martin J McKeown (2010) **Asymptotic Analysis of Robust LASSOs in the Presence of Noise with Large Variance** *IEEE Transactions on Information Theory* 56: 10. 5131 - 5149 Oct

Group robust LASSO for connectivity utilizing an SEM & AR(1) model

$$\begin{pmatrix} \mathbf{y}_{1,j} \\ \mathbf{y}_{2,j} \\ \vdots \\ \mathbf{y}_{S,j} \end{pmatrix} = \underbrace{\operatorname{diag}\left(\left\{(Y^{(0)}_{s,-j}, Y^{(1)}_{s})\right\}_{s=1}^{S}\right) \begin{pmatrix} \beta^{(0)}_{1,j} \\ \beta^{(1)}_{1,j} \\ \beta^{(0)}_{2,j} \\ \beta^{(1)}_{2,j} \\ \vdots \\ \beta^{(0)}_{S,j} \\ \beta^{(1)}_{S,j} \end{pmatrix} + \begin{pmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \\ \vdots \\ \mathbf{e}_S \end{pmatrix}}_{\stackrel{\text{def}}{=} \mathbf{X}\beta + \mathbf{e}} \quad (6)$$

where

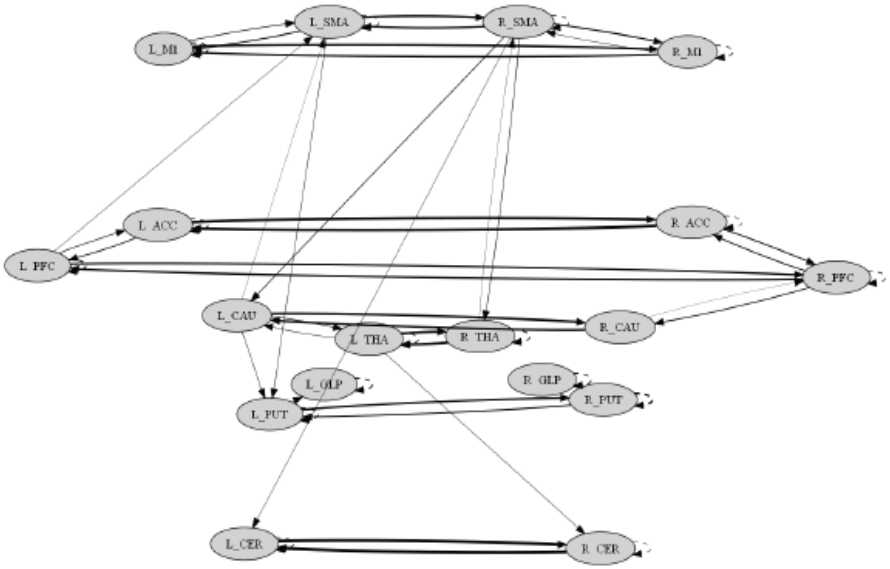
$$\operatorname{diag}\left(\left\{(Y^{(0)}_{s,-j}, Y^{(1)}_{s})\right\}_{s=1}^{S}\right) = \begin{pmatrix} Y^{(0)}_{1,-j} & Y^{(1)}_{1} & & & & \\ & & Y^{(0)}_{2,-j} & Y^{(1)}_{2} & & \\ & & & & \ddots & \\ & & & & Y^{(0)}_{S,-j} & Y^{(1)}_{S} \end{pmatrix}.$$

Try to predict a given ROI's time course under the assumptions of:

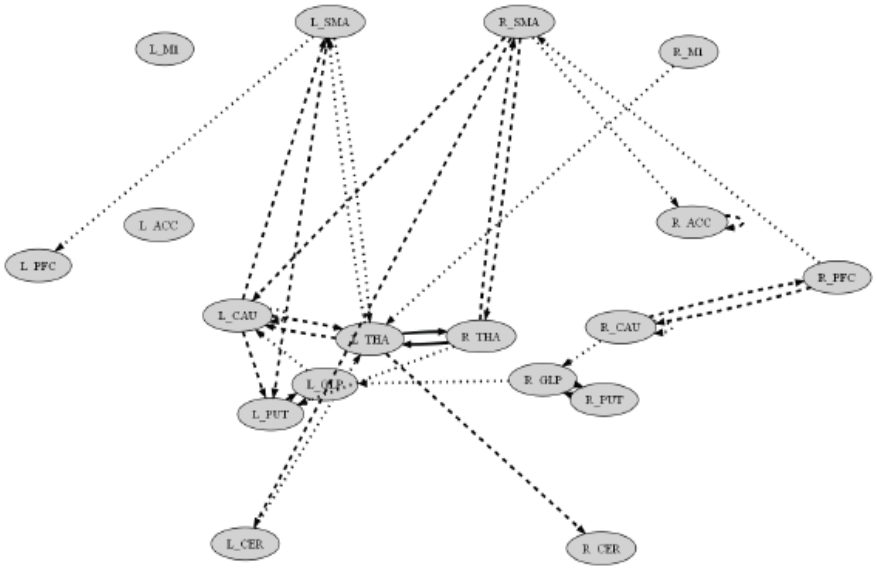
1) Each subject within a given group has the same connectivity (but connection strengths can vary).
2) Use current timepoint from all other ROIs and previous timepoint from all ROIs in model

Xiaohui Chen, Z Jane Wang,Martin J McKeown (2010) fMRI Group Studies of Brain Connectivity via A Group Robust LASSO *International Conference on Image Processing, September 26-29, Hong Kong.*

Group Robust Lasso for fMRI Group Analysis



(r) Normal Group



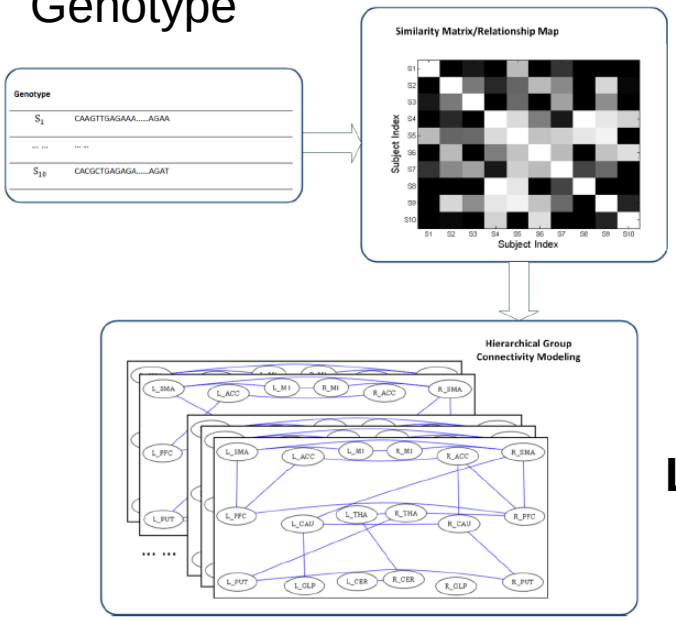
(s) Dashed: in normal; dotted: in PD

- Reciprocal connections
- Left↔right shift
  - Normal: R_SMA – R_THA
  - PD: L_SMA – L_THA
- Missing connections in PD: R_PFC – R_CAU

Incorporating genetic/clinical information into network computations

Genotype

Similarity matrix



$$f(B) = \sum_{i=1}^{S} \|Y(i) - X(i)B(i)\|_F^2 + \lambda \sum_{i=1}^{S} \|B(i)\|_{l_1} +$$
$$\gamma \sum_{e_{lm} \in E} W(e_{lm}) \|B(l) - B(m)\|_{l_1}$$
$$= \sum_{j=1}^{S} \sum_{i=1}^{n} (Y_i(j) - \sum_{k=1}^{K} X_{ik}(j) B_k(j))^2 + \lambda \sum_{j=1}^{S} \sum_{k=1}^{K} |B_k(j)| +$$
$$\gamma \sum_{e_{lm} \in E} W(e_{lm}) \sum_{k=1}^{K} |B_k(l) - B_k(m)|$$

Loss

Penalty

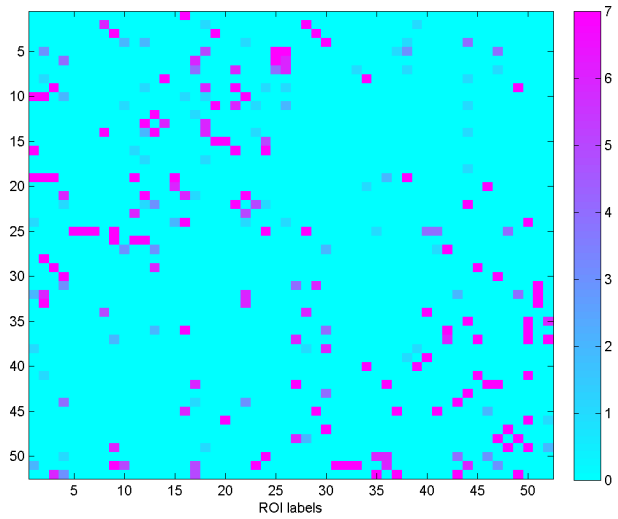
Influence of similarity

Liu et al, in preparation

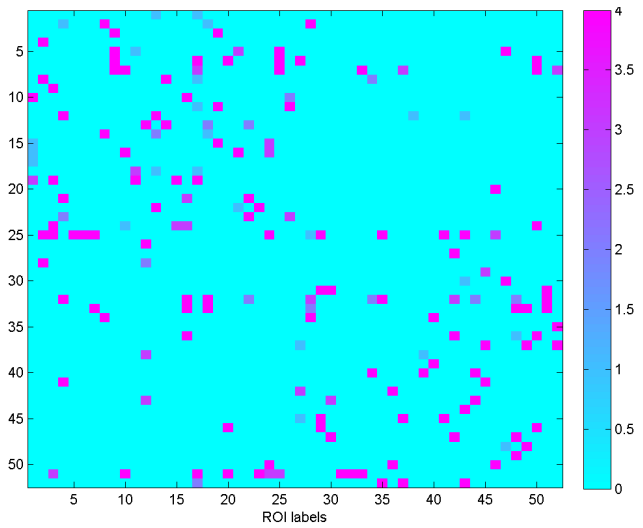
Results

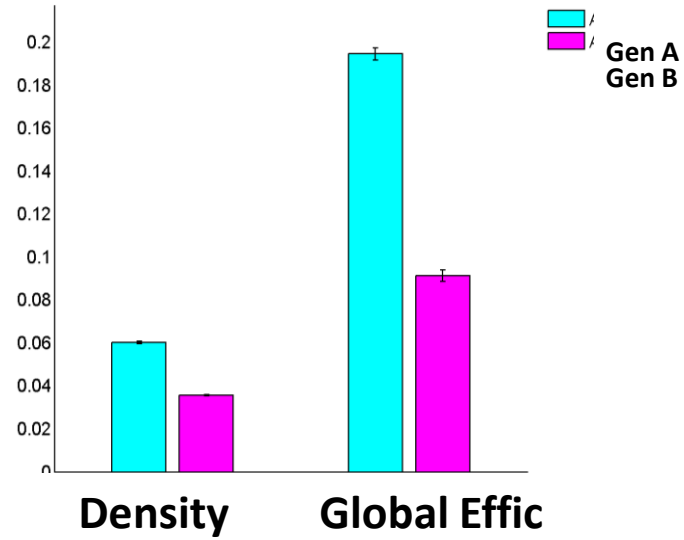
Connectivity Patterns

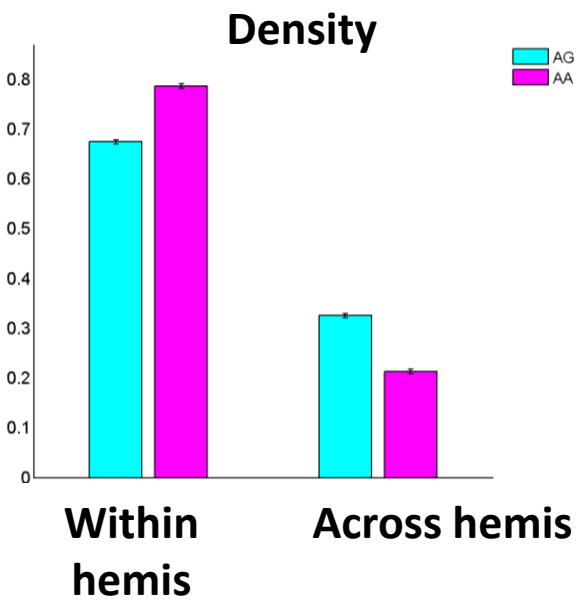
Genotype A



Genotype B







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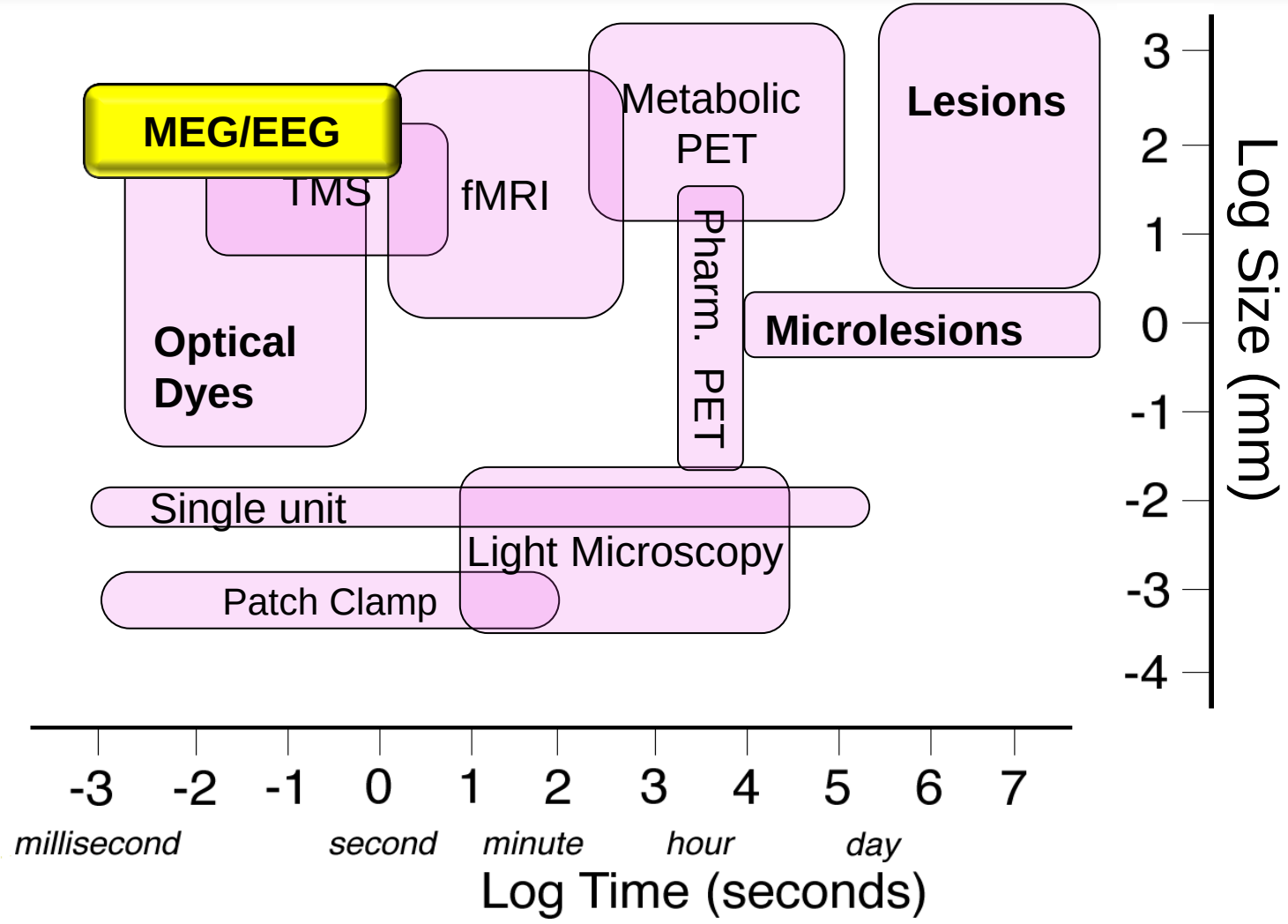
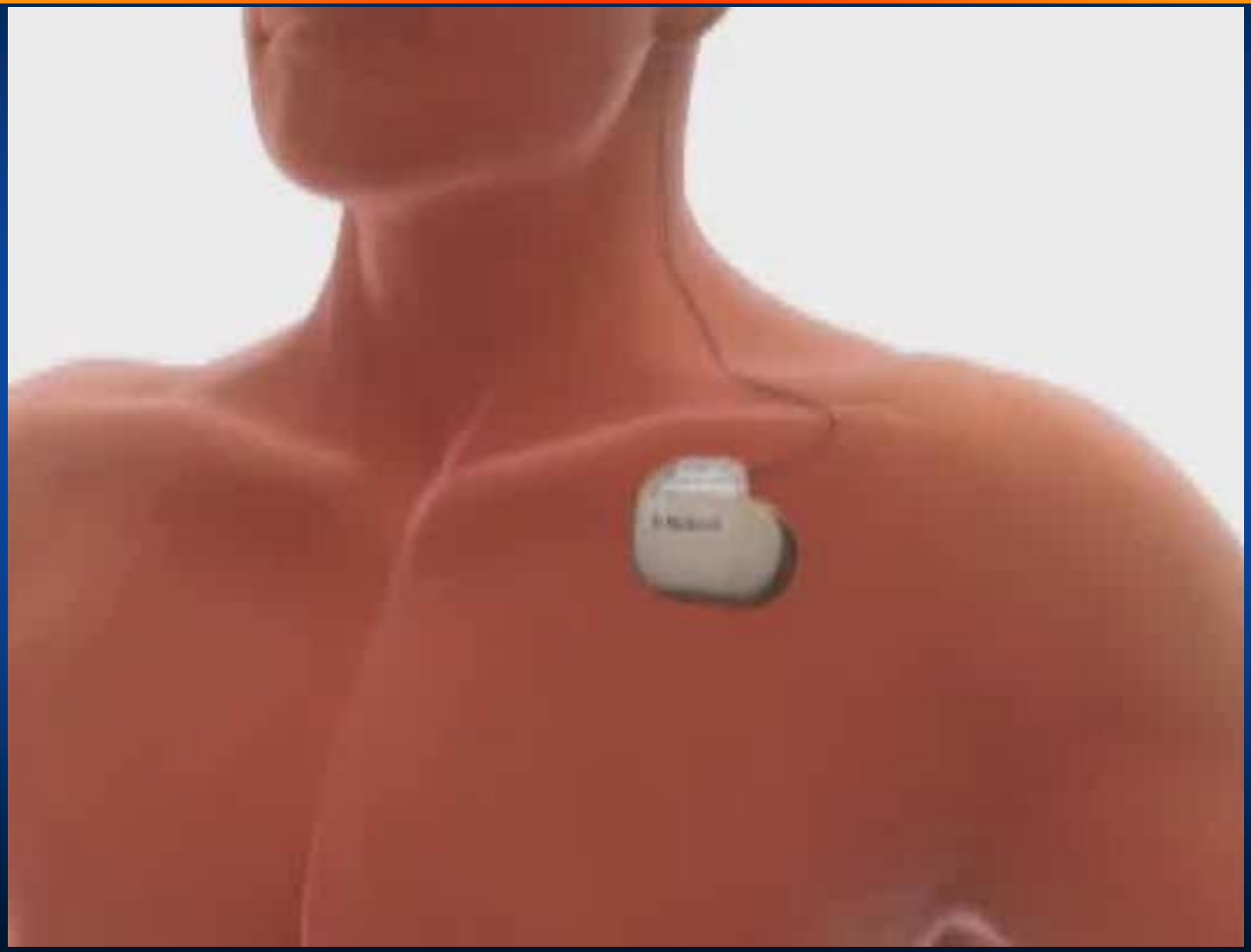
Techniques to probe brain function



Treatment of Parkinson's Disease: SURGERY



http://www.youtube.com/watch?v=FAfcXakF56Q

Existing EEG Connectivity Measures

Linear | Bivariate | Directional

Nonlinear | Multivariate | Non-directional

Coherence	Linear	Bivariate	Non-directional
Mutual Information	Nonlinear	Bivariate	Non-directional
Granger Causality	Linear	Bivariate	Directional
Multivariate AR-based Measures	Linear	Multivariate	Directional

more robust to noise and computationally efficient

more accurate as it accounts for all the covariance structure information from the full data set (Humans poor pattern recognizers in high dimensional states)

more biologically meaningful as it models causal relationships

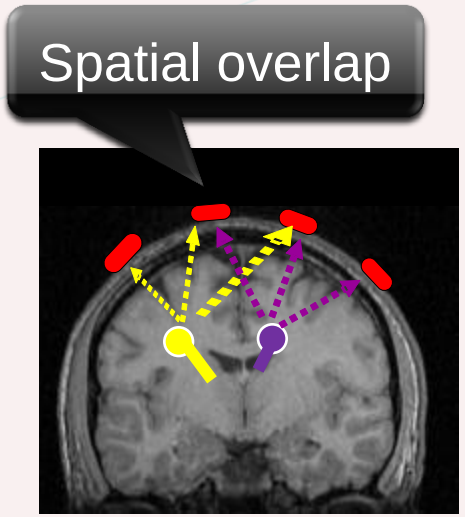
Common Challenges in EEG Connectivity Analysis (1)

1) **Poor "signal-to-noise" ratio**
   - Only a small fraction of signal content is task-related
   - Noise include measurement noise, eye and movement and non-task-related background brain activities

     ➔ EEG pre-processing or correlate EEG with the task

2) **Poor spatial resolution**
   - Exacerbated by volume conduction.
   - Electrical activity of a current source is propagated radially to the scalp and picked up by multiple sensors.
   - Leads to spurious correlations between sensor recordings.

     ➔ Source extraction



Common Challenges in EEG Connectivity Analysis (2)

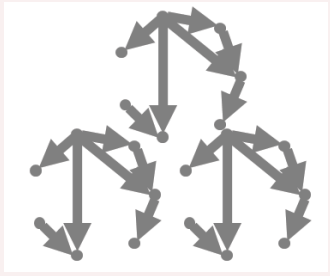
3) Numerical instability in mAR estimation

- high EEG dimension + high mAR model order
- e.g. consider a 10th-order mAR model with 20 channels
  → ~4000 parameters to be estimated
  → unstable when # samples << # parameters

➔ Enforce sparsity

4) Inter-subject variability in group pattern inference

Pool-all-subjects Approach

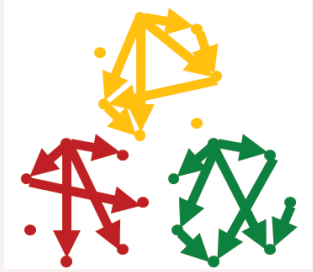


Structure: the Same
Parameters: the Same

➔ Group analysis methods

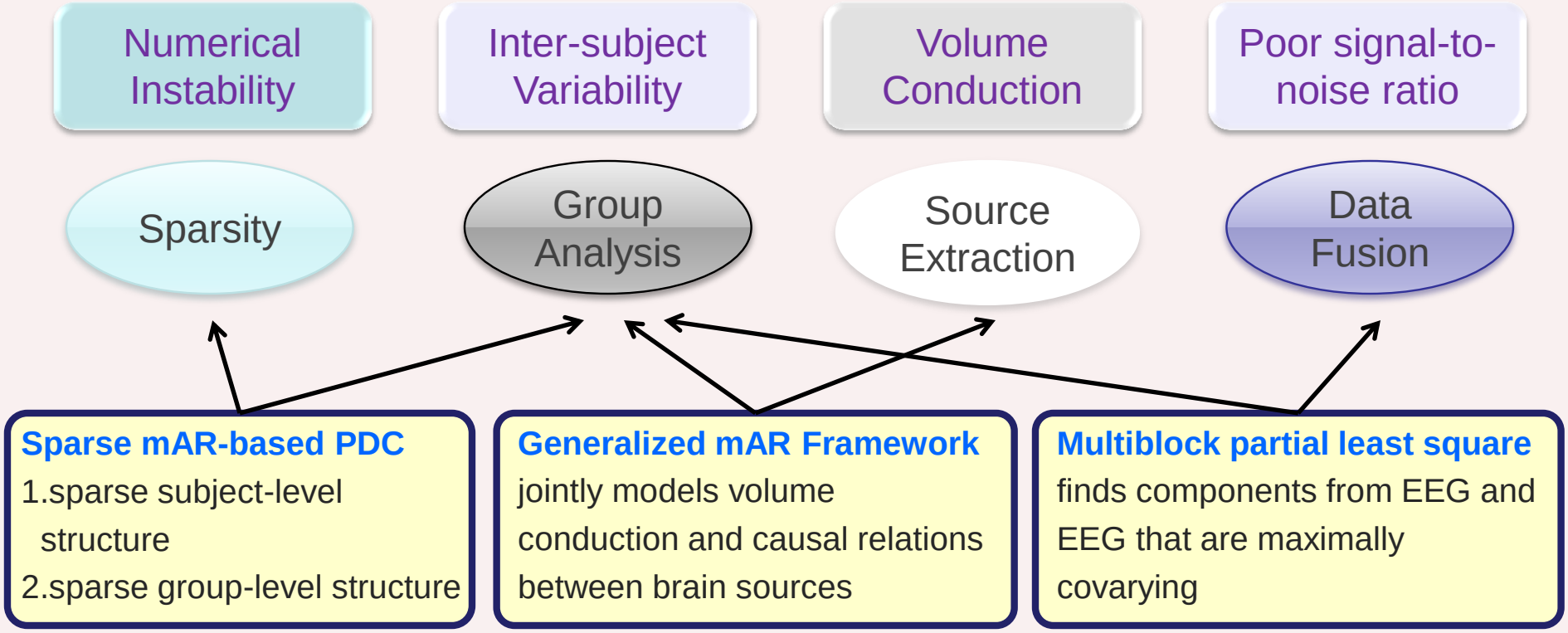
Uniformity ⟷ **Diversity**

Individual-structure Approach



Structure: Different
Parameters: Different

Addressing Problems in the EEG:



➔ Apply to normal and PD subjects to assess effects of disease and medication on motor-related brain connectivity

Partial Directed Coherence

Partial directed coherence (PDC) provides a frequency measure of directional, direct connectivity between multichannel signals based on an multivariate AR (mAR) model.

Time Domain

$$x(t) = \sum_{p=1}^{P} A_p x(t-p) + e(t)$$

Fourier Transform

Frequency Domain

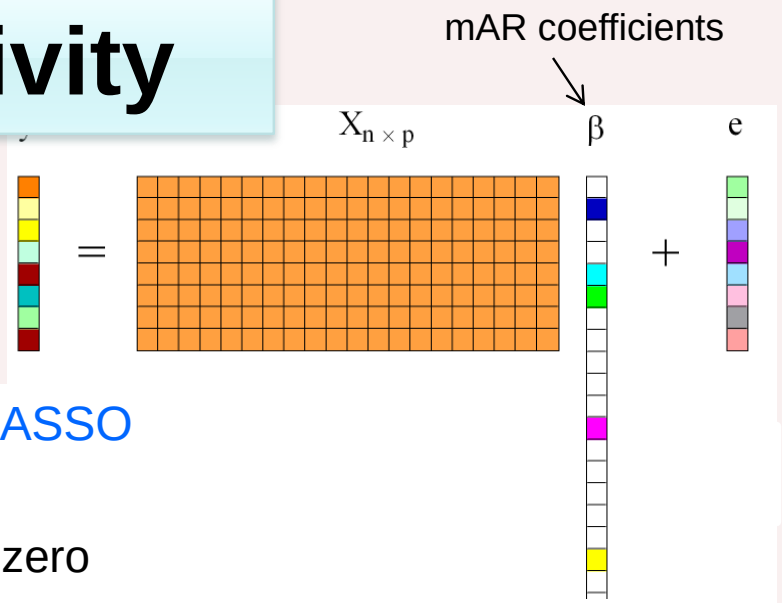
$$\bar{A}(f) = I - \sum_{p=1}^{P} A_p e^{-i2\pi fp}$$

PDC index: $$\pi_{i \leftarrow j}(f) = \frac{\bar{a}_{i,j}(f)}{\sqrt{\sum_{d=1}^{D} \left|\bar{a}_{d,j}(f)\right|^2}}$$

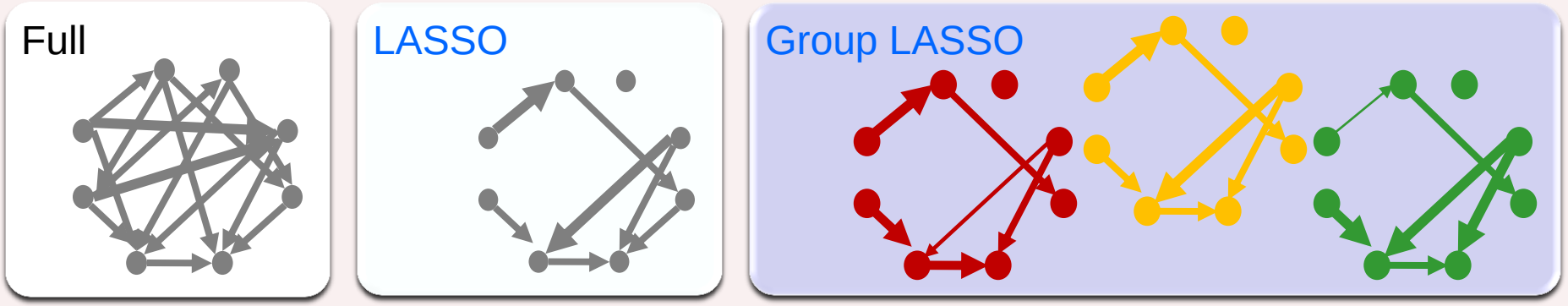
- PDC values range between 0 (no influence) and 1 (high influence).
- Represent the relative strength of influence of signal j on signal i, discounting the effects of all other signals

Sparsity in Connectivity

$$x(t) = \sum_{p=1}^{P} A_p x(t-p) + e(t)$$

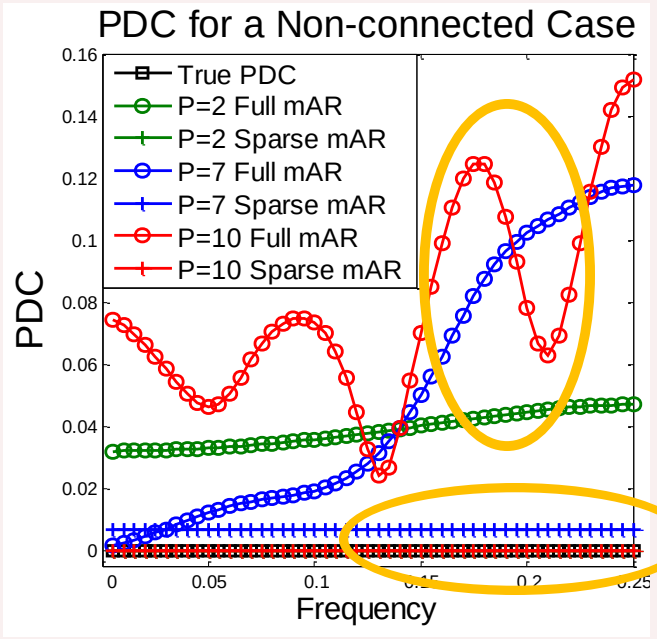


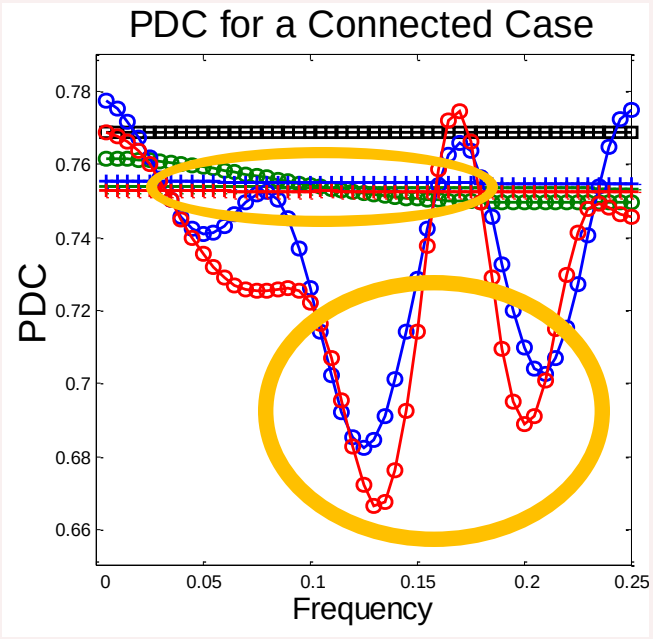
1. **Sparsity on subject-level structure** using LASSO
   - penalizes L1 norm of β
   - favours a solution where most coefficients are zero
2. **Sparsity on group-level structure** using Group LASSO
   - gLASSO divides β into sub-vectors, one for each connection (element *i*, *j* at lag *p)* containing all subjects, and penalizes the sum of their L2 norms
   - each sub-vector is either all zero or all nonzero (but can have different values)



Sparsity in Connectivity - Simulations

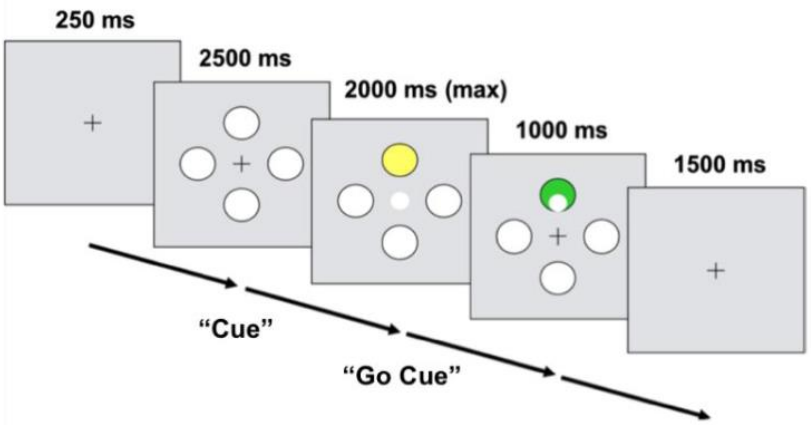
Simulated a 18-channel, 2nd order mAR model (648 coefficients) with 11 non-zero coefficients. Data length = 2000.

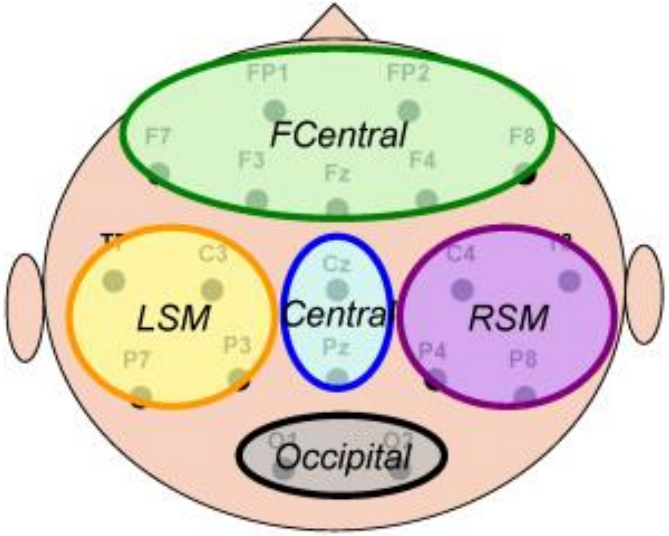




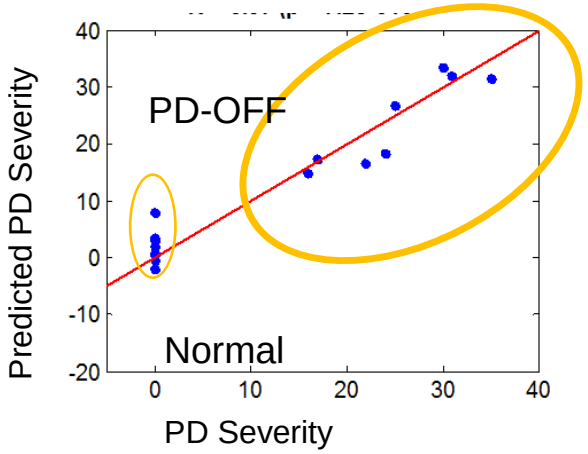
- Regular mAR: The estimated PDC noticeably deviates from the true PDC. The deviation increases as the model order increases.
- Sparse mAR: Regardless the choice of model order, the estimated PDC are very close to true PDC at all frequencies. ➔ address the issue of order selection

Sparsity in Connectivity – Real Data

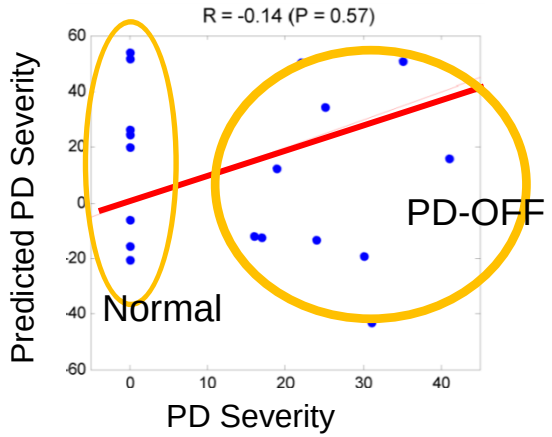




Predict PD Severity using PDC



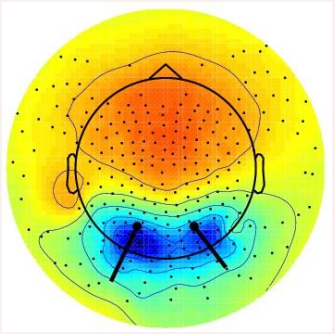
Predict PD Severity using Univariate Spectral Power



G Tropini, J Chiang, Z J Wang, E Ty, MJ. McKeown (2011) Altered Directional Connectivity in Parkinson's Disease During Performance of a Visually Guided Task .***Neuroimage*** 56: 4. 2144-2156

Source-level Connectivity in the EEG

- Volume conduction causes spurious correlations between sensors
  ➔ analyze EEG connectivity in “source” domain.
- An ill-conditioned inverse problem ➔ has no unique solution.
- Dipole Modeling:
  - Cons: computationally complex and sensitive to: assumed number of active dipoles, head model used, etc.



- Blind Source Separation: Independent Component Analysis (ICA)
  ➔ observed signals are linear mixtures of mutually independent sources

  Cons: brain sources are temporally cross-correlated which contradicts with the independence assumption of ICA

➔ Propose a state-space mAR framework to allow joint modeling of volume conduction and causal relationships between sources

G. Gómez-Herrero, M. Atienza, K. Egiazarian, and J. Cantero, “Measuring directional coupling between EEG sources,” Neuroimage, vol. 43, no. 3, pp. 497–508, 2008.

GmAR Source Separation Framework

M-dimensional EEG data vector

Mixing matrix modeling the effects of volume conduction. Columns of C represents the projection from sources to scalp electrodes.

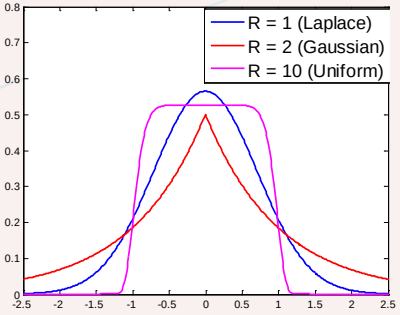
Electrode level: $x(t) = Cs(t)$

Source level: $s(t) = \sum_{p=1}^{P} A_p s(t-p) + v(t)$

Residual process whose elements are assumed to be mutually independent and follows a generalized Gaussian distribution.

M-dimensional brain sources

mAR coefficient matrix, which captures the causal relation-ships between brain sources



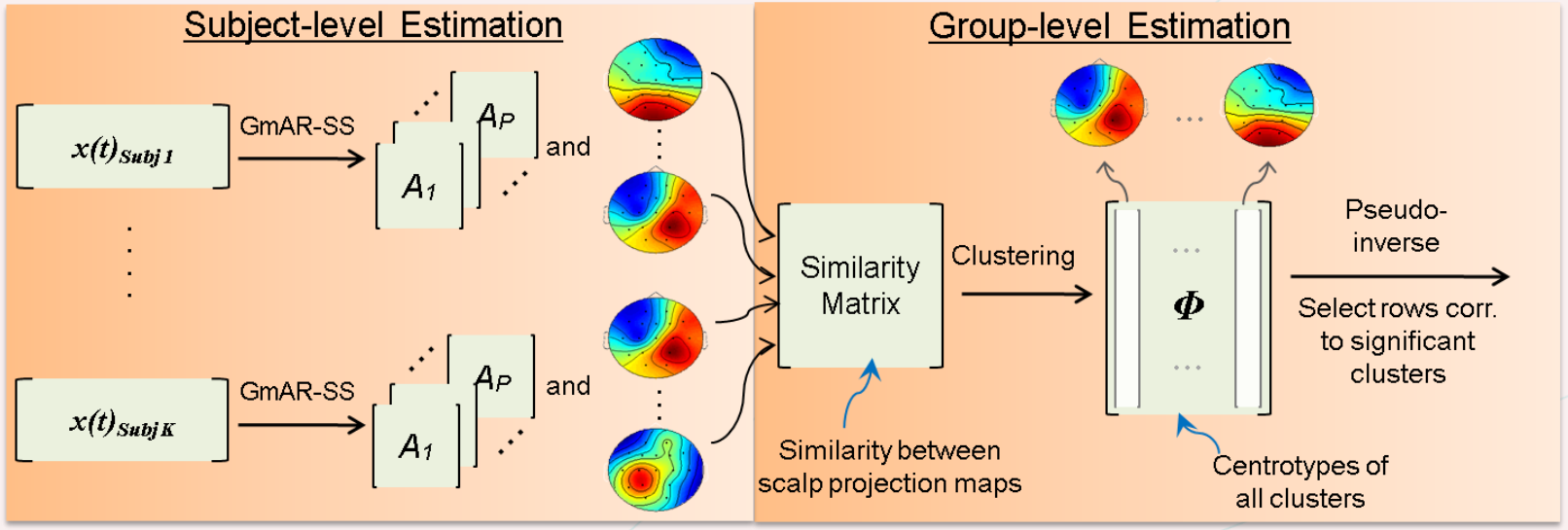
Generalized Gaussian

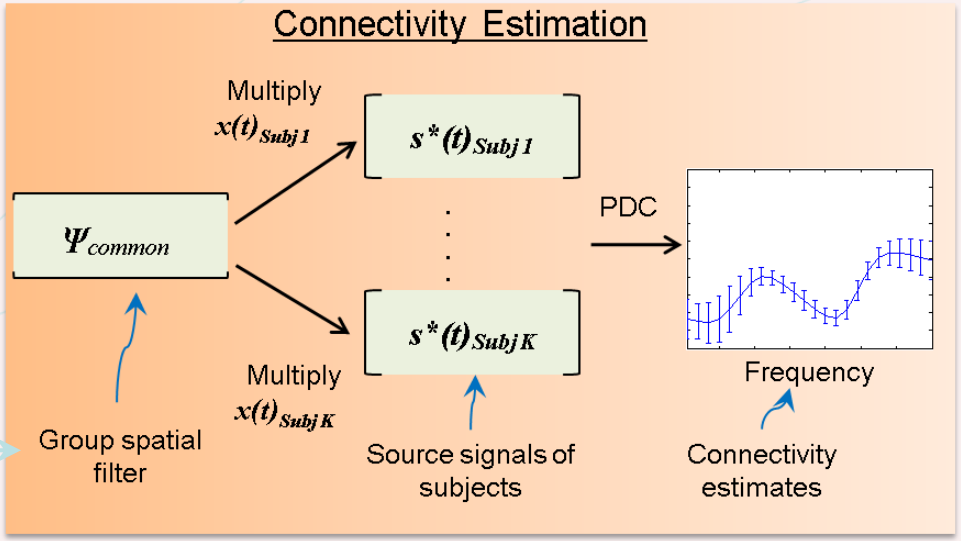
$p(x \mid R, w)$

➔ Use a maximum likelihood method to estimate C, $s(t)$ and A_p given $x(t)$

GmAR Source Separation – Group Analysis

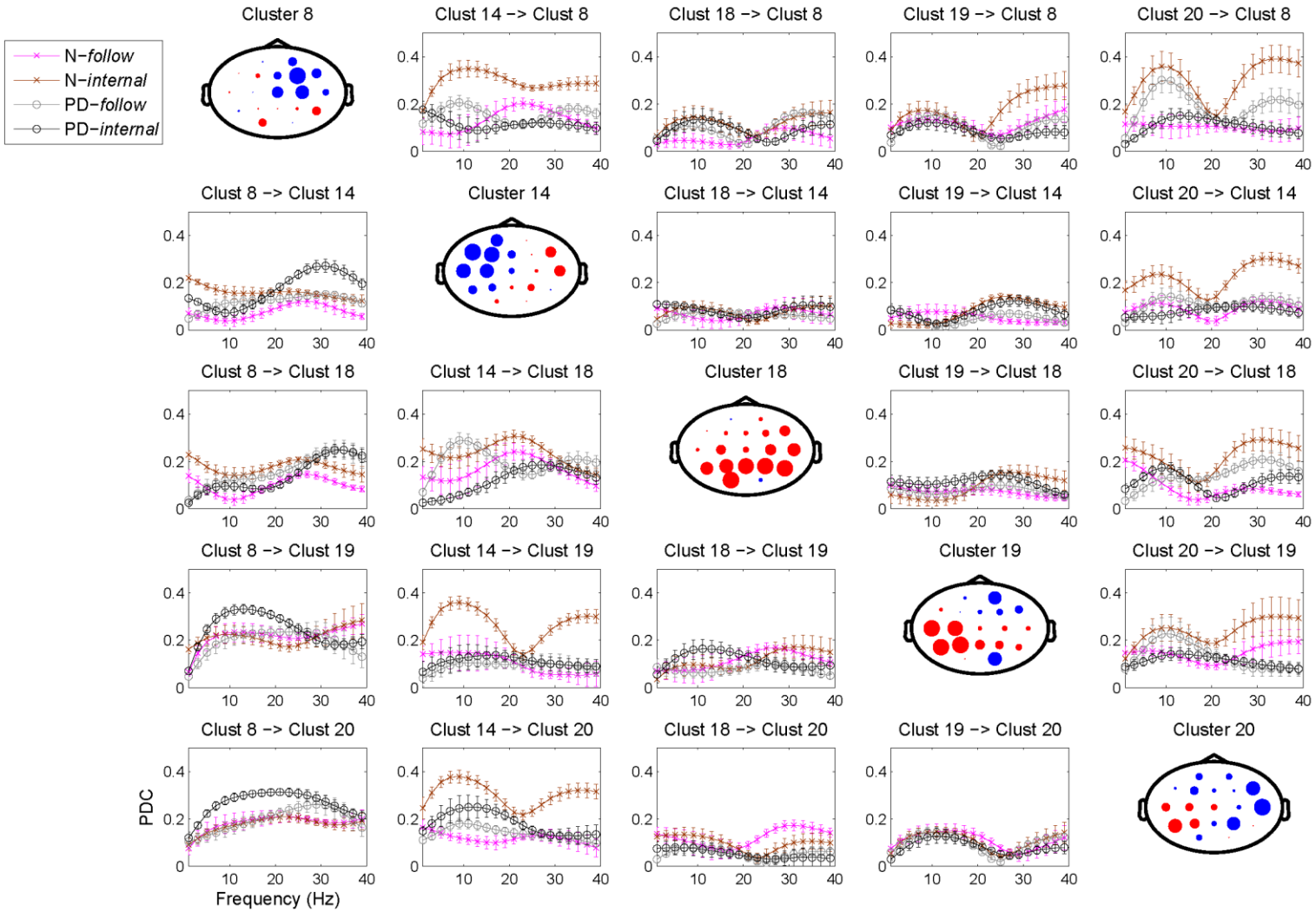
How to combine the extracted sources across subjects? ➔ Clustering





Group-level unmixing matrix

GmAR-SS Application Parkinson's EEG



Chiang, Z J Wang, M J McKeown (2011) A Generalized Multivariate Autoregressive (GmAR)-Based Approach for EEG Source Connectivity Analysis ***IEEE Transactions on Signal Processing*** 60: 453-465.

Outline

- **Motivation**
  - Parkinson's disease
  - Problems with standard fMRI analyses
- Brain Imaging techniques
  - 3D Moment Invariant descriptors of activation
    - fMRI
    - PET
  - Replicator Dynamics
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  - Robust, group LASSO for fMRI connectivity
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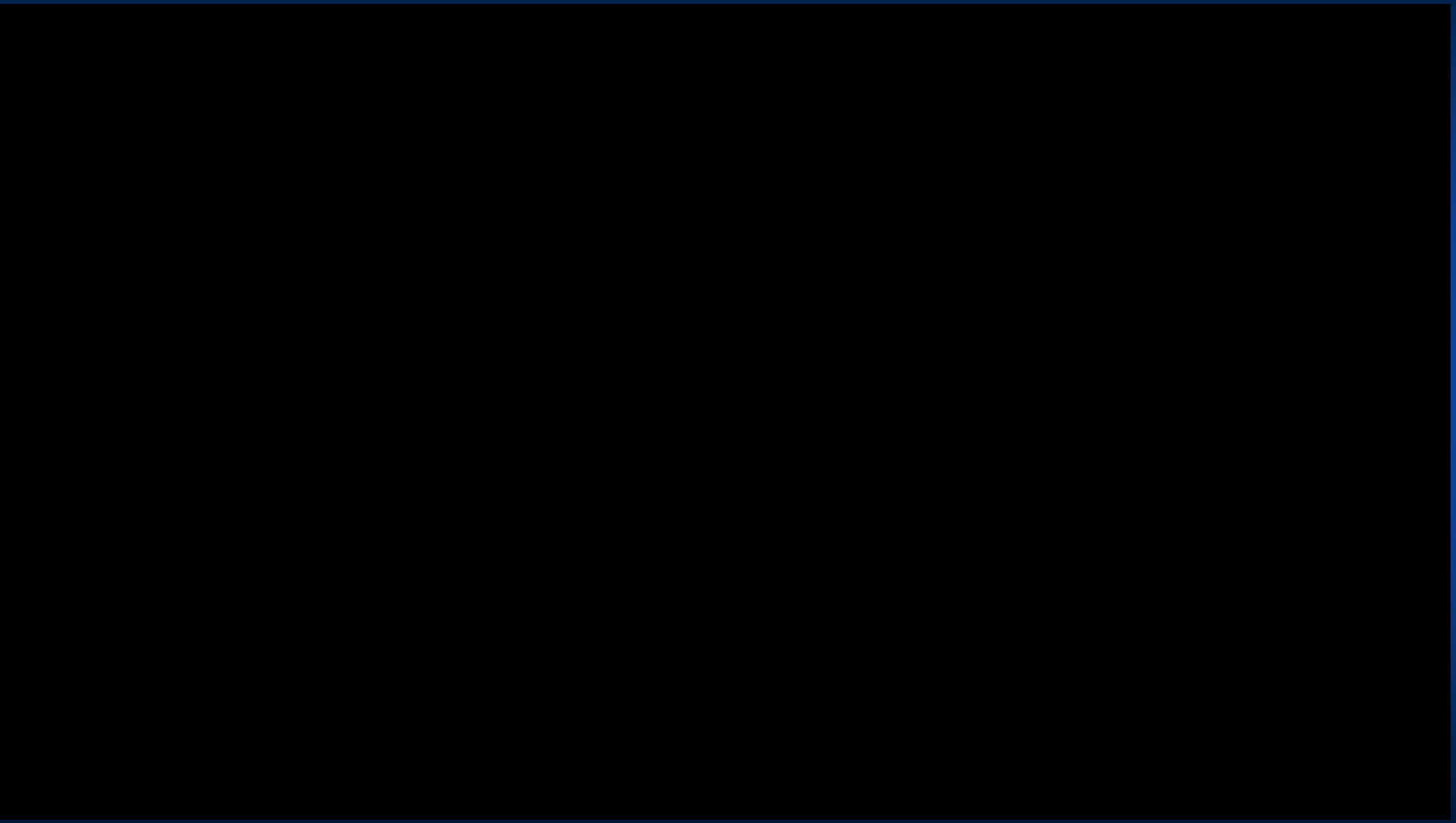
- **Multivariate ← → Multivariate comparisons**
  - Multiblock PLS & EEG-EMG coupling
  - ICA-PLS methods

How do we get people with Parkinson's to exercise ?

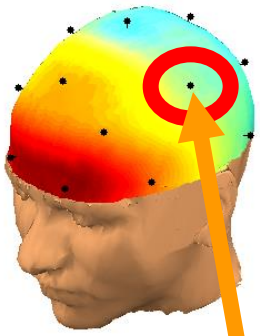
Courtesy of Dr. Bin Hu, University of Calgary

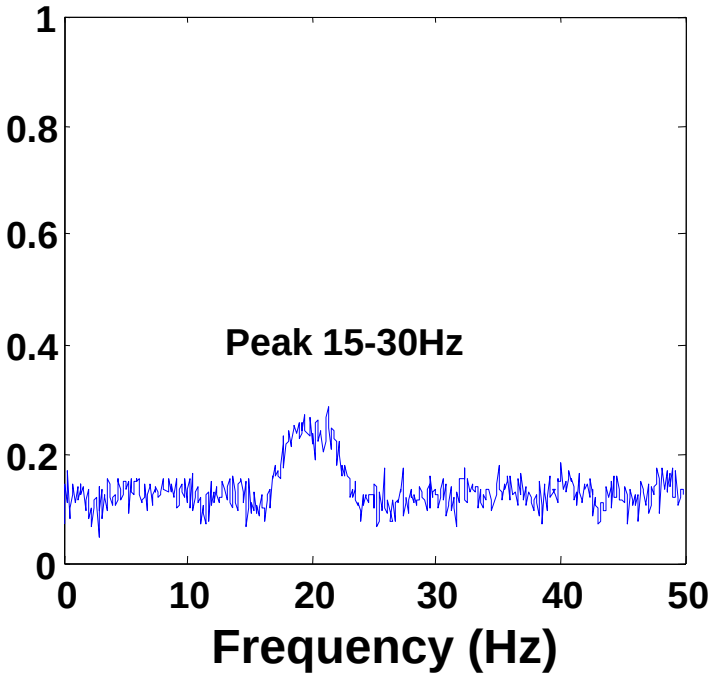
Encouraging the “right type” of exercise

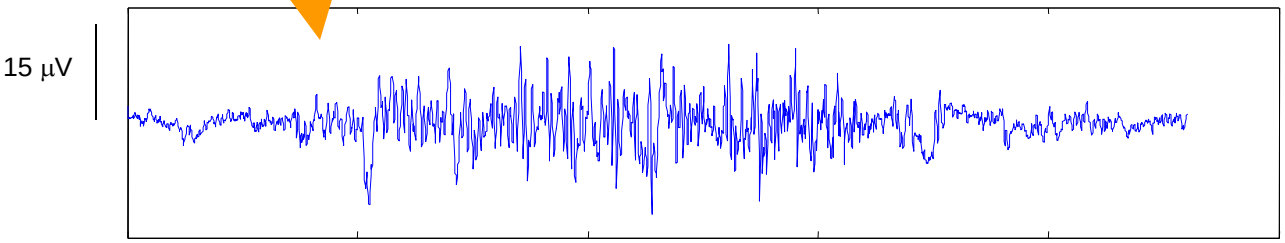


Mall walking

EEG-EMG coherence



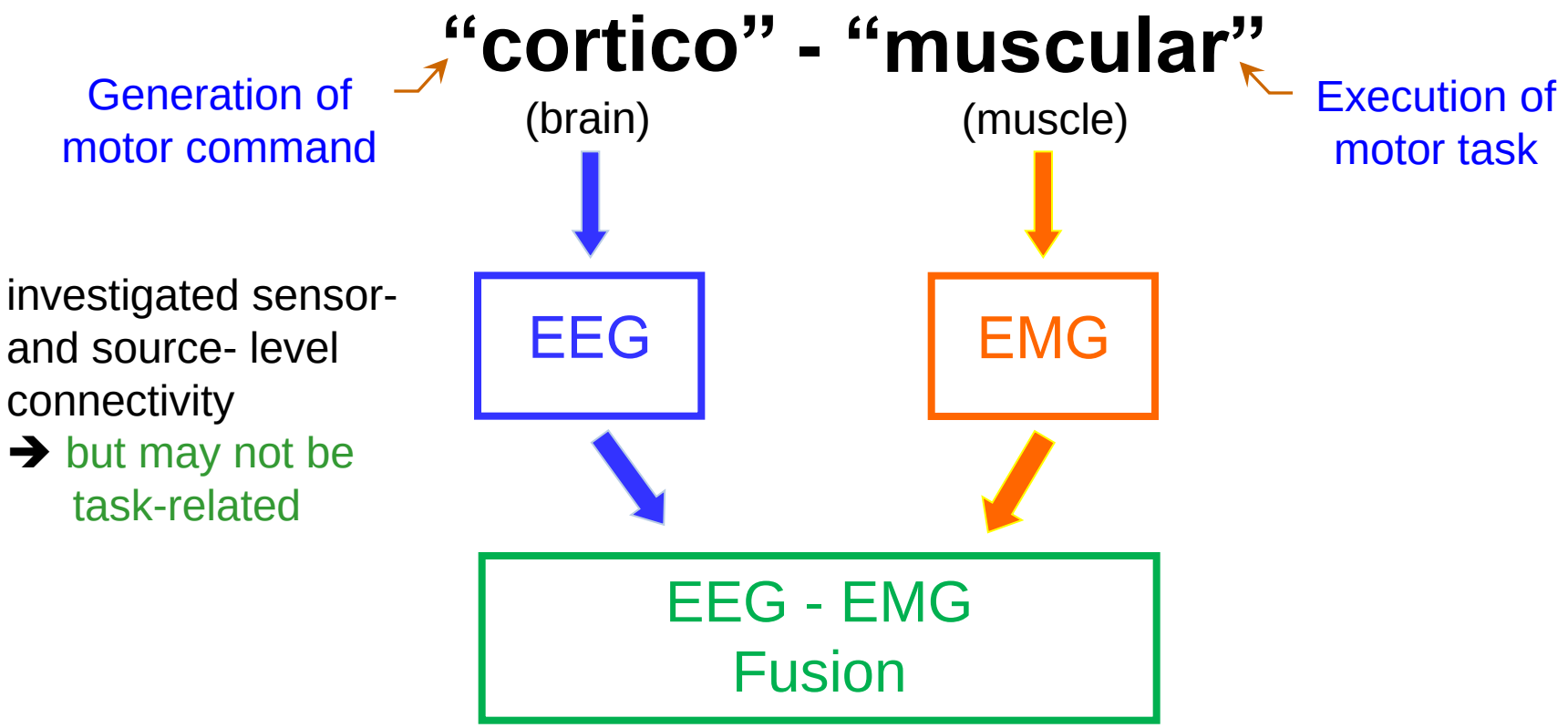




Note:

1) **Typically only compare 1 EEG channel and 1 sEMG channel at once**
2) **Must average over long duration of contraction to get significant coherence**

Cortico-muscular Interactivity



investigated sensor- and source- level connectivity

➔ but may not be task-related

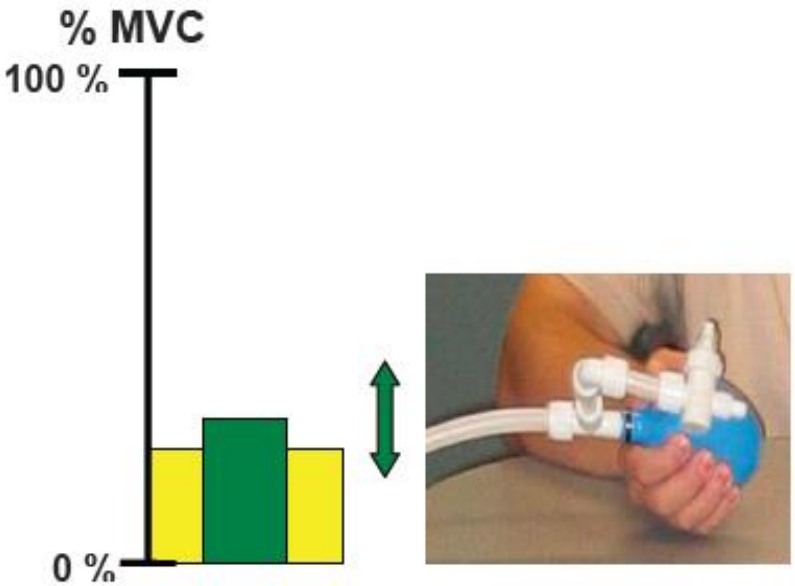
Identify source components from scalp (EEG signals) that are maximally correlated to muscle activity (EMG signals)

Cortico-muscular Interactivity

- Traditional approaches to studying motor control:
  - Look at rectified EMG signals
  - Identify active brain regions via EEG/MEG/LFP during sustained muscle contraction.
- Corticomuscular (EEG/EMG) coupling is typically analyzed using coherence technique.
- Issues with coherence technique:
  - Only a small fraction of the EEG signal content is related to motor control ➔ low coherence value.
  - Coherence replies on pairwise comparisons. However, the mapping between the brain and musculature is many-to-many, as opposed to one-to-one.

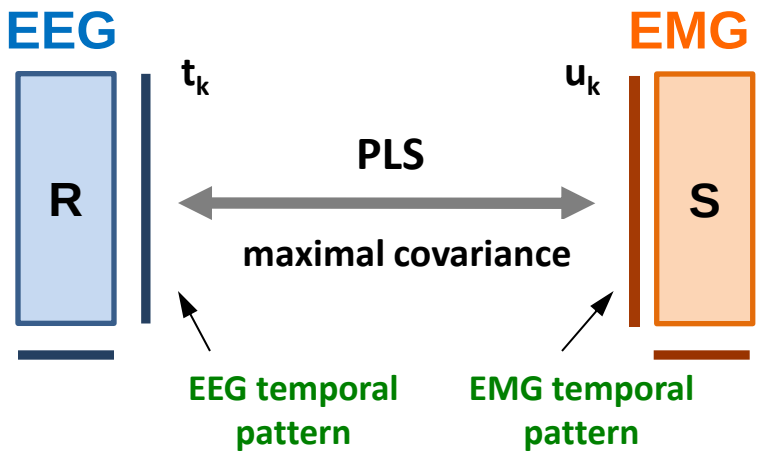
➔ We propose the Partial Least Square (PLS) method – which aims at finding components in two datasets that are maximally covarying.

Experimental Setup



Squeezing task: The subject was instructed to follow the target bar (yellow) as close as possible. The force exerted by the subject was shown by green bar.

Multiblock PLS for EEG-EMG Fusion (2)

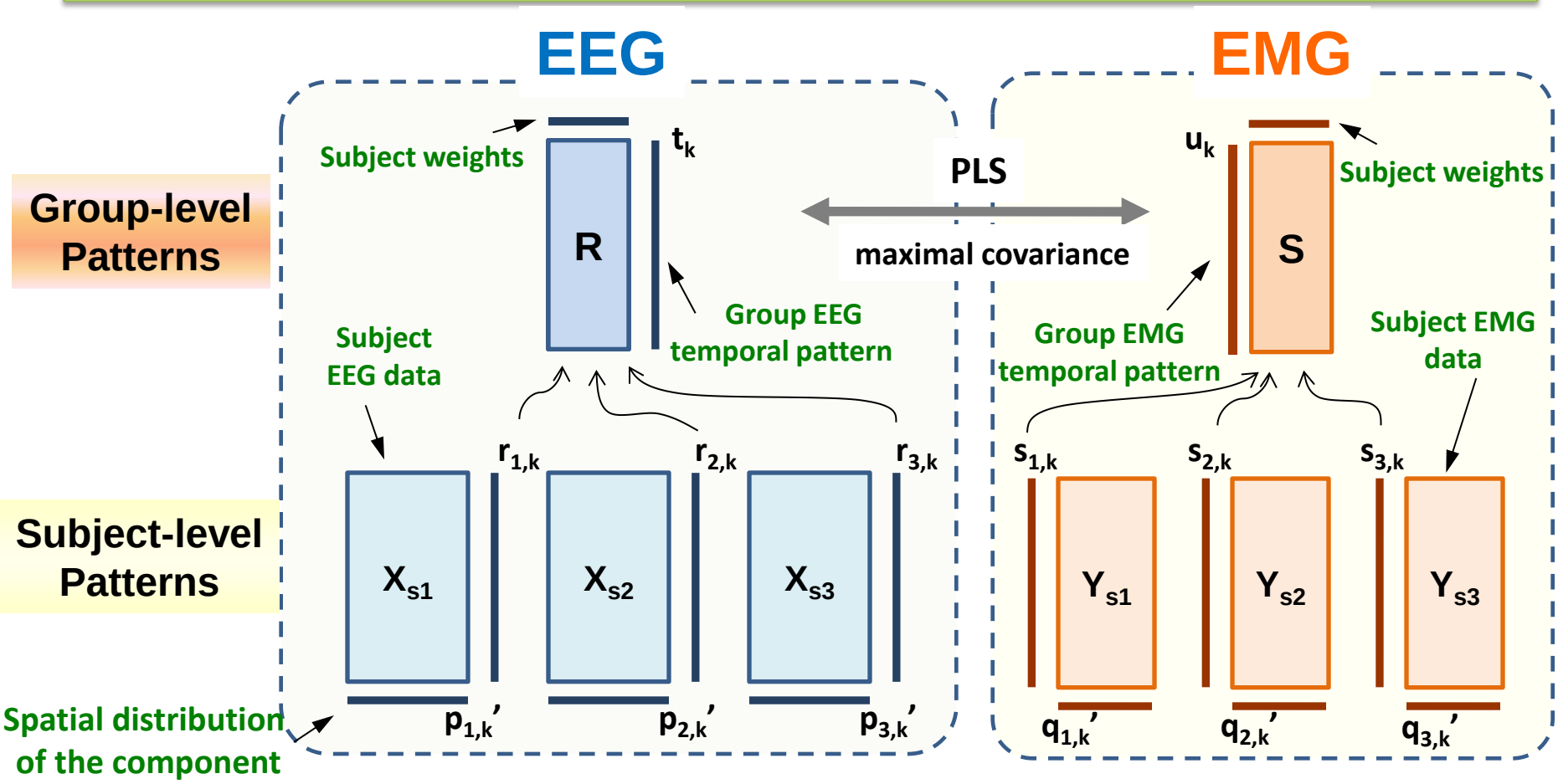


- Inter-subject variability makes the standard approach of simply pooling data from different subjects problematic.

- To address this, we introduce the idea of multiblock PLS (mbPLS) which is a two-level, multiple-block extension of the regular PLS.
  - groups data of each subject into individual "subject blocks"
  - aggregates subject-level decompositions to form "super blocks" at the second layer
  - extracts group-level components which exhibit high covariance between predictor block (EEG) and response block (EMG) .

➢ allows for some individual variations across subjects, but also, at a second level, allows group inferences to be made.

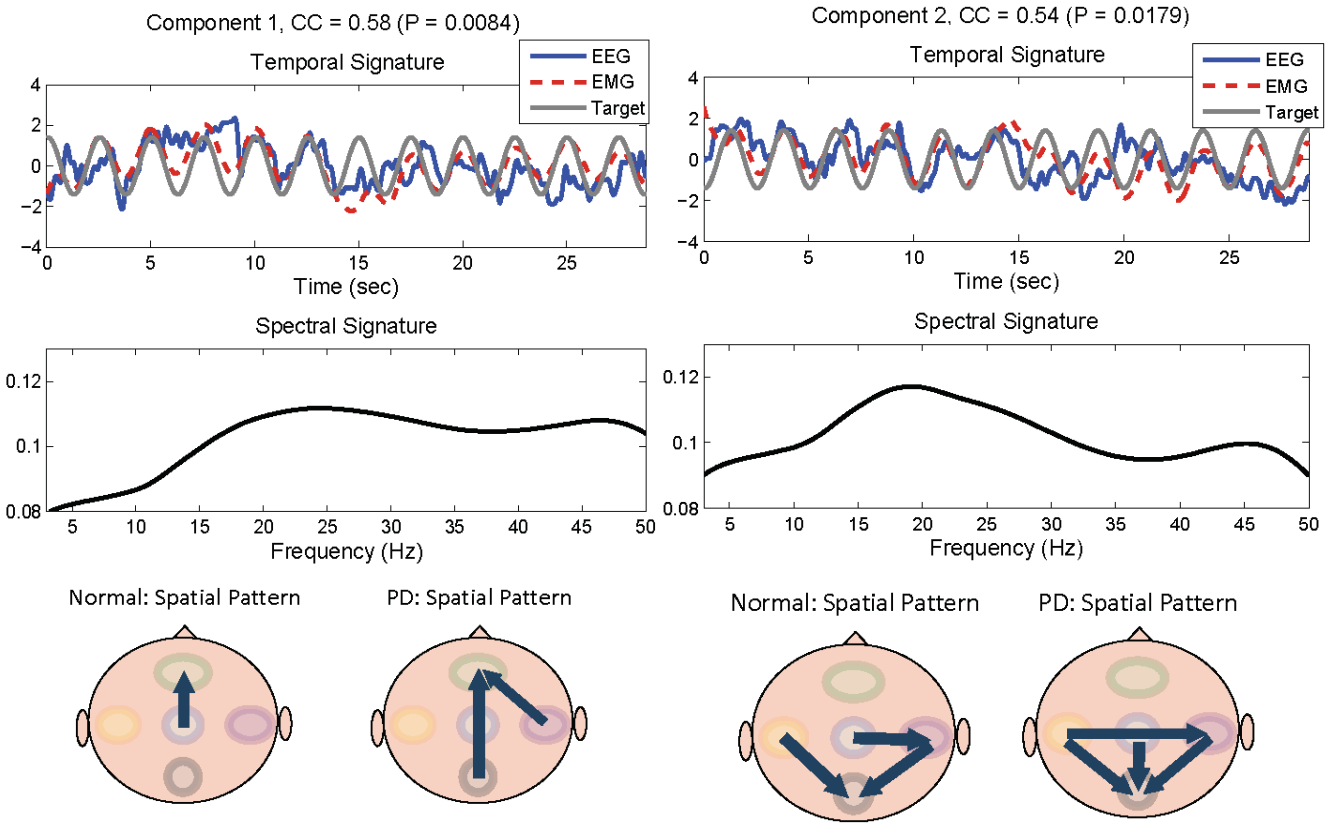
Multiblock PLS for EEG-EMG Fusion (3)



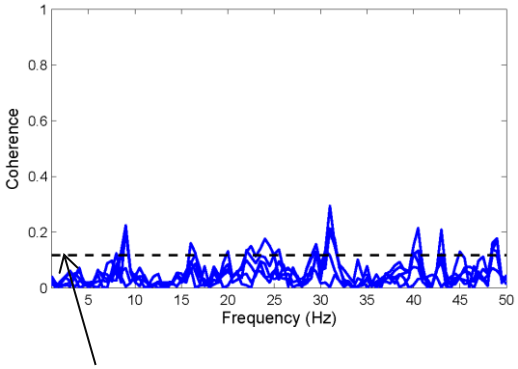
can be easily extended to model 3-dimensional data (e.g., EEG spectrogram or time-varying PDC)

Multi-subject EEG and EMG Coupling

EEG PDC as predictor and EMG amplitude as response



Coherence between raw EEG and EMG of a typical normal subject



95% confidence limit

- exact frequency of maximal EEG-EMG coupling vary across subjects
  ➔ combining coherence results across subject may be difficult
- mbPLS model provides a systematic method to infer common patterns across subjects ➔ allows robust group inference in the face of inter-subject variability

J Chiang, Z J Wang, M J McKeown (2012) A multiblock PLS model of cortico-cortical and corticomuscular interactions in Parkinson's disease ***Neuroimage*** 63: 3. 1498-509

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A Joint PLS-ICA framework

- **PLS provides components that maximally co-vary between predictor (x) and response (y) that are uncorrelated**
- **ICA provides components in EEG and EMG that may have no relation to one another.**

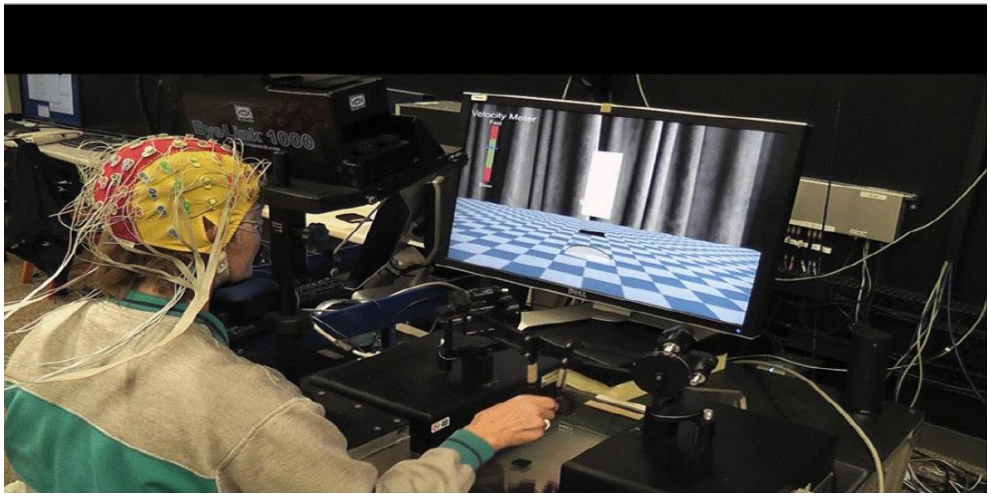
➢ **Propose: joint PLS-ICA framework**

$$\max_{w_1, w_2} \quad \alpha \left[\mathrm{E}((w_1{}^T x)(w_2{}^T y))\right]^2 + \beta \left[\mathrm{E}(\mathrm{G}(w_1{}^T x)) - \mathrm{E}(\mathrm{G}(u_1))\right]^2 + \theta \left[\mathrm{E}(\mathrm{G}(w_2{}^T y)) - \mathrm{E}(\mathrm{G}(u_2))\right]^2$$

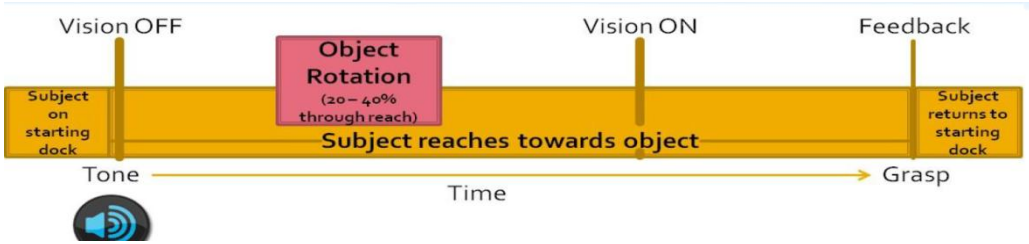
$$\text{s.t.} \quad w_i{}^T w_i = 1, \quad i = 1, 2. \qquad \propto + \beta + \theta = 1$$

Where G(.) is a non-linear function (e.g. log cosh (.))

Combining EEG and Behavioural Data



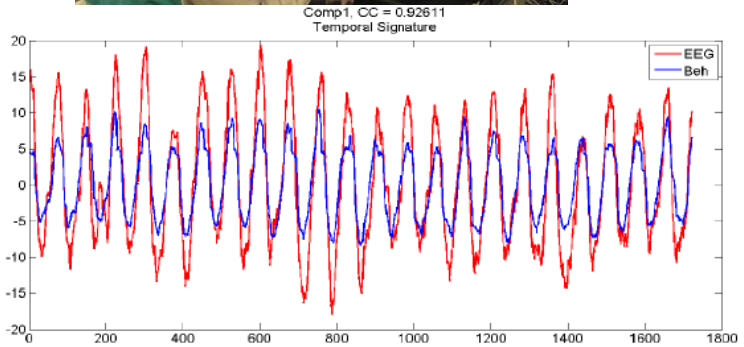
c/o Dr. Howard Poizner, UCSD



1. aperture	2. aperture velocity	3. Eye-Thumb X Dis.
4. Eye-Thumb Y Dis.	5. Eye-Index X Dis.	6. Eye-Index Y
7. hand position (X)	8. hand position (Y)	9. hand position (Z)
10.hand sagittal velocity	11.hand tangential velocity	12.hand acceleration
13.hand jerk	14.Thumb tangential velocity	15.Index tangential velocity

Combining EEG and Behavioural Data

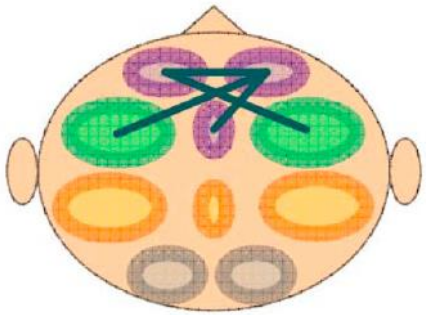
EEG features: short-window band-limited pair-wise coherences
Assume: time courses constant across subjects for a given task

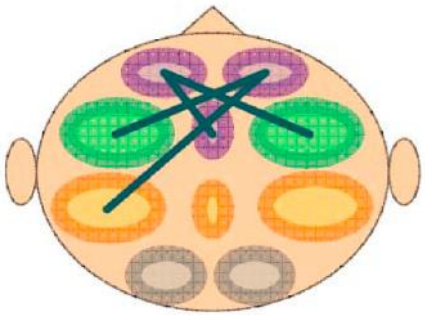


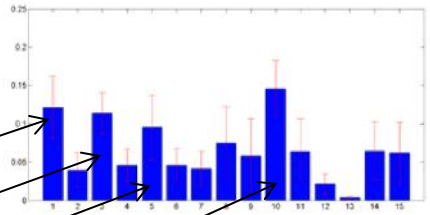
Perturbation

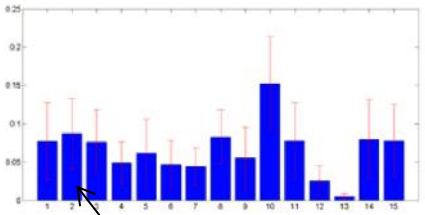
No

Yes





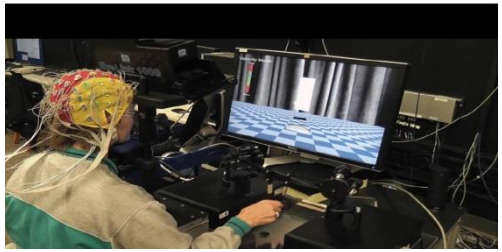


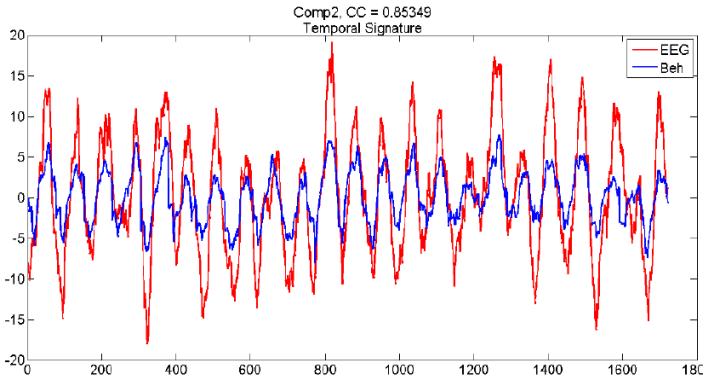


Aperture size
Eye-thumb X-distance
Eye-Index X distance
Hand saggital velocity

Aperture velocity

Combining EEG and Behavioural Data





Perturbation

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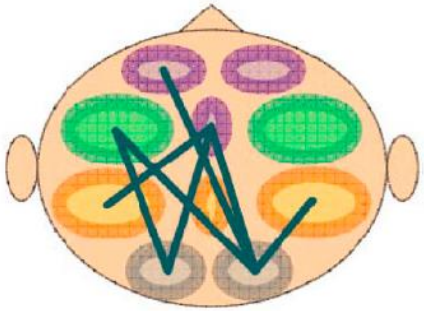

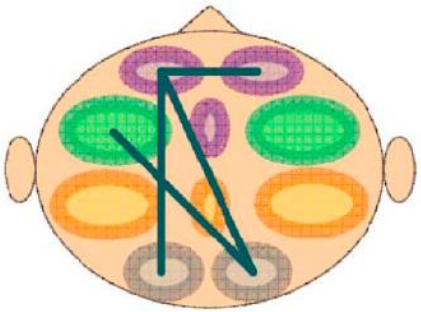

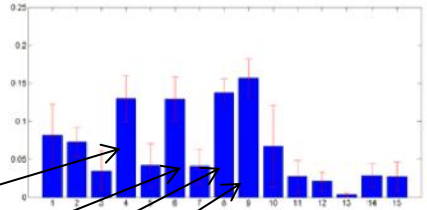

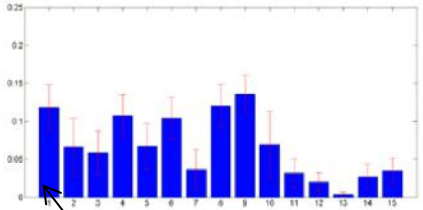

Eye-thumb Distance

Eye – index Y distance

Hand Position Y

Hand Position Z

Aperture

Summary

- 3D Moment Invariant descriptors of activation
- Replicator Dynamics for network assessment
- PCfdr method for Bayesian Network learning
- Robust, group LASSO for fMRI connectivity
- EEG source connectivity
- Multiblock PLS
- ICA-PLS method

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Société Parkinson Canada

NSERC CRSNG

Vancouver CoastalHealth
Promoting wellness. Ensuring care.

Canada Foundation for Innovation
Fondation canadienne pour l'innovation

Pacific Alzheimer Research Foundation

Questions????

PACIFIC PARKINSON'S Research Centre

UBC

The University of British Columbia

Vancouver, Canada

Brain Research Centre

3-way analysis

The proposed tridirectional method is actually a two-step modeling strategy:

(1)Tri-LV Extraction: One super latent variable (supLV) t_g is designed to relate the subLVs. The optimization problem is formulated as below

$$\begin{aligned} \max \quad & ((t_g{}^T X_1 w_1)^2 + (t_g{}^T X_2 w_2)^2 + (t_g{}^T X_3 w_3)^2) \\ \text{s.t.} \quad & t_g{}^T t_g = 1, \quad w_i{}^T w_i = 1, \quad \forall i = 1, 2, 3. \end{aligned}$$

The solution can be derived by the method of Lagrange multipliers as below

$$(X_1 X_1{}^T + X_2 X_2{}^T + X_3 X_3{}^T) t_g = \lambda_g t_g,$$

$$t_i = X_i w_i = \sqrt{\frac{1}{\lambda_i}} X_i X_i{}^T t_g,$$