脳のネットワーク構造を探る

MEG（脳磁界計測）を用いた脳活動の機能的結び付き（functional connectivity)の推定と可視化

株式会社　シグナルアナリシス

関原　謙介

本技術資料は，以下の方々との共同研究の成果に基づいています．

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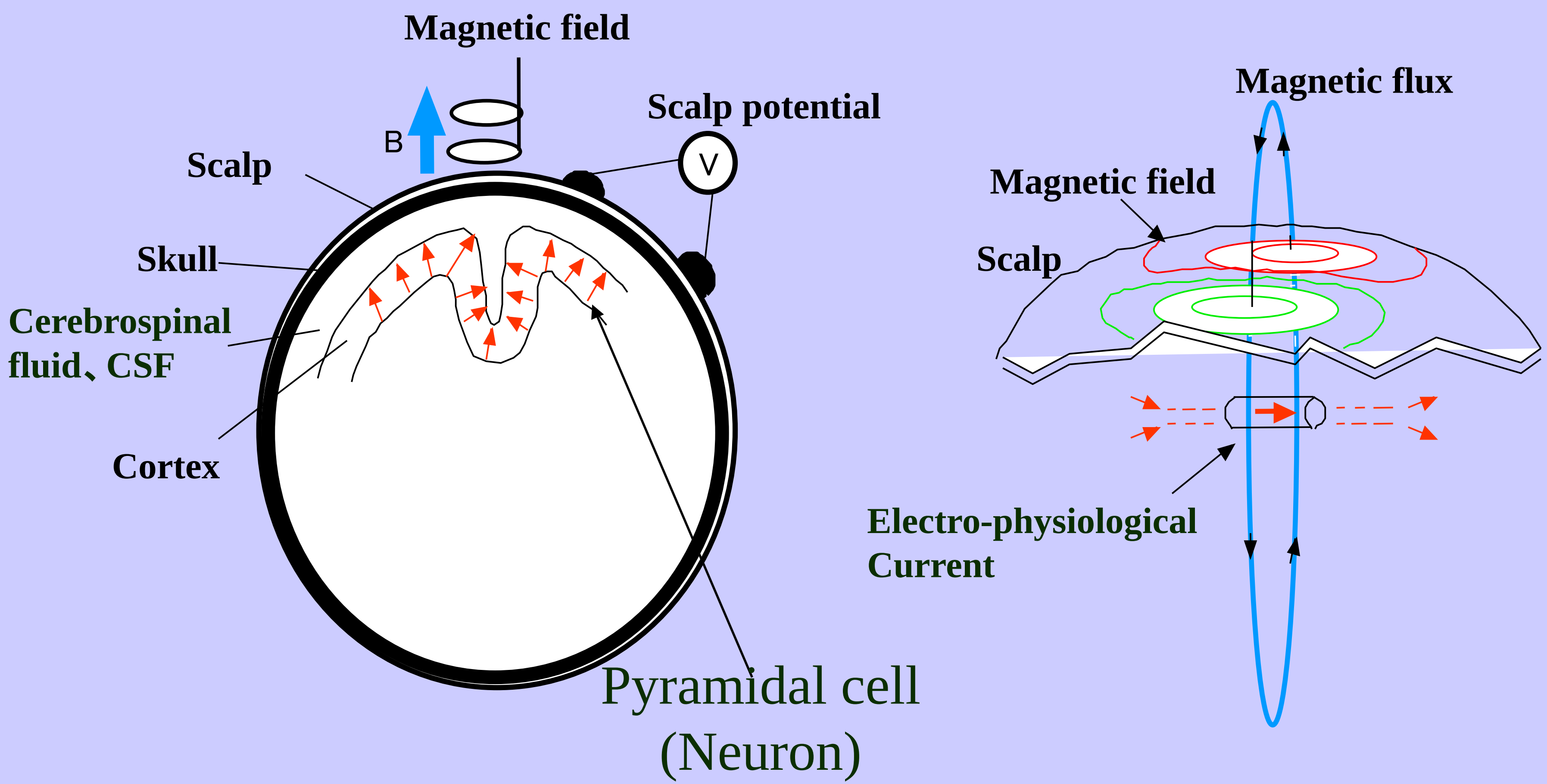
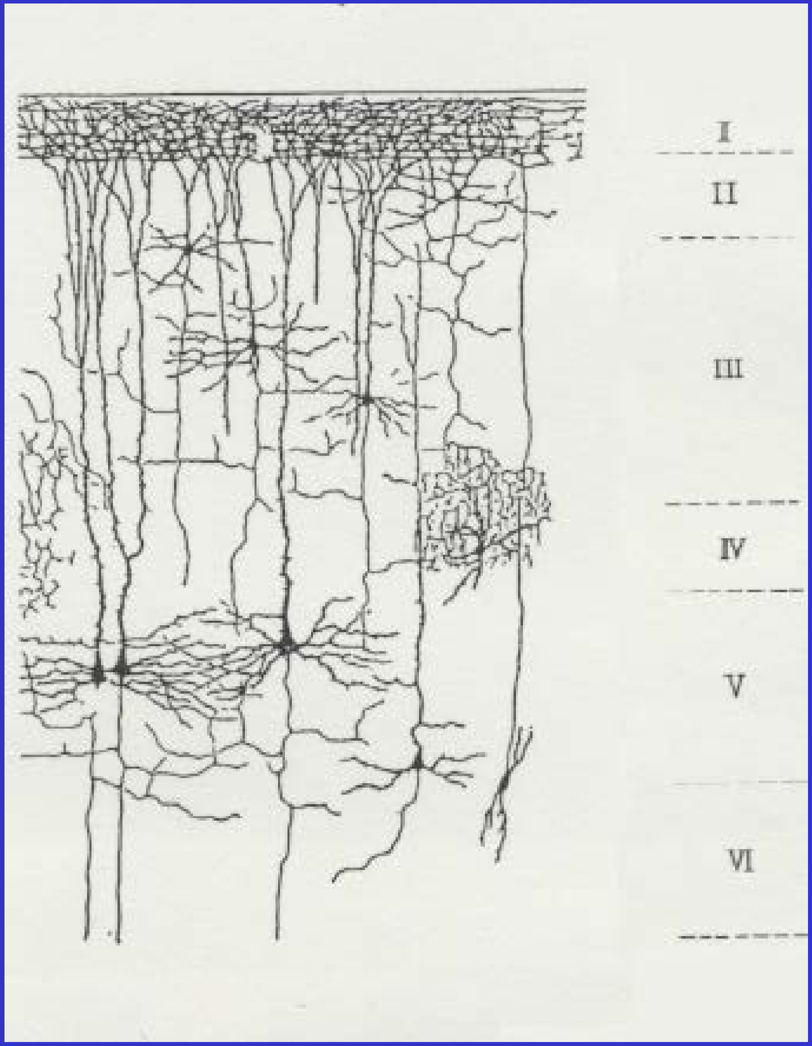
What is the generators of bio-electromagnetic field



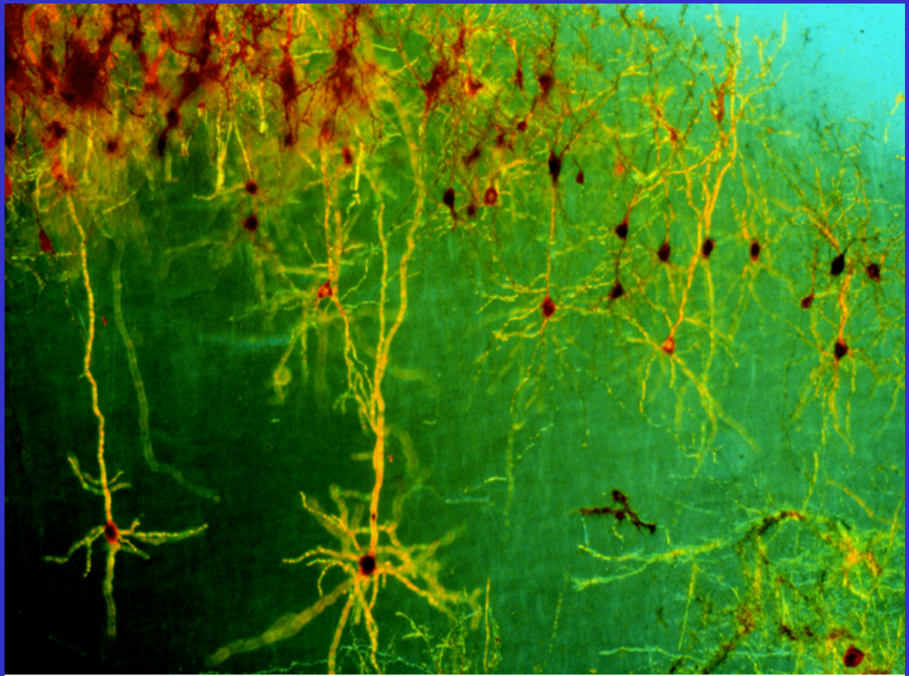
- 大脳皮質には多数の錐体細胞(neuron)がほぼ同じ向きで整列している.
- 錐体細胞が興奮するとその樹状突起(dendrite)に電流が流れる.
- 多数の整列した錐体細胞に電流が流れると頭部周囲で検出可能な磁場を発生する(pTの強度). これを高感度磁束計(SQUID)で検出する.

Neurons are tiny magnets

Cross-sectional sketch of human cortex



Microscope photograph of pyramidal neurons of mouse cortex



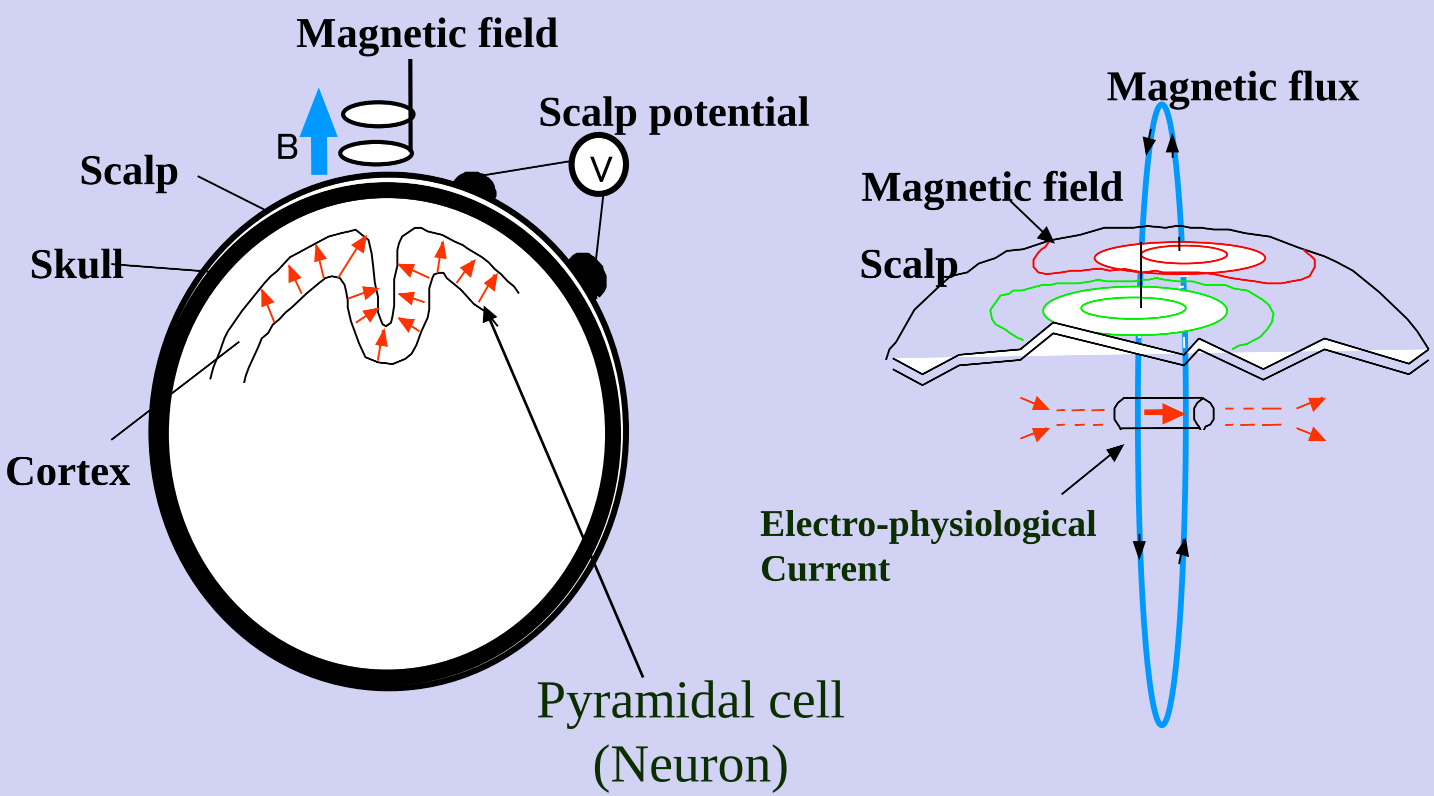
Pyramidal neurons of mouse cortex. Picture: Tobias Bonhoeffer, MPI of Neurobiology

頭部皮膚上で電位を計測する.

脳波計測(electroencephalography,EEG)

頭部周囲で磁場を計測する.

脳磁界計測(magnetoencephalography,MEG)

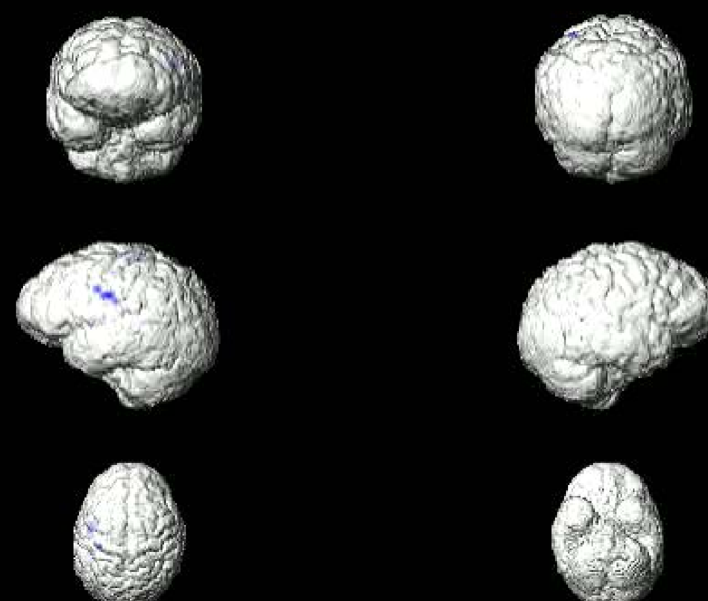


What is Electro-Magnetic Brain Imaging?

- *Neural activity is reconstructed and visualized.*
- *Non-invasive imaging of direct neural activity with high temporal resolution (millisecond).*

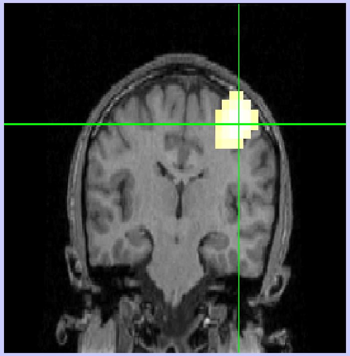
MEG/(EEG) Measurements

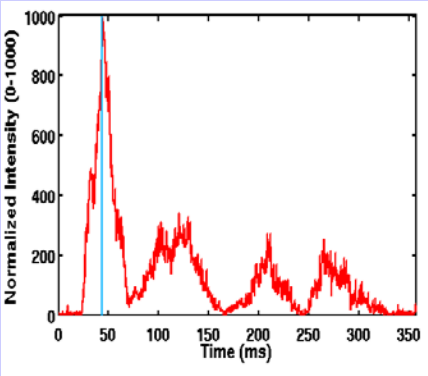
Spatio-Temporal Reconstruction of Brain Activation



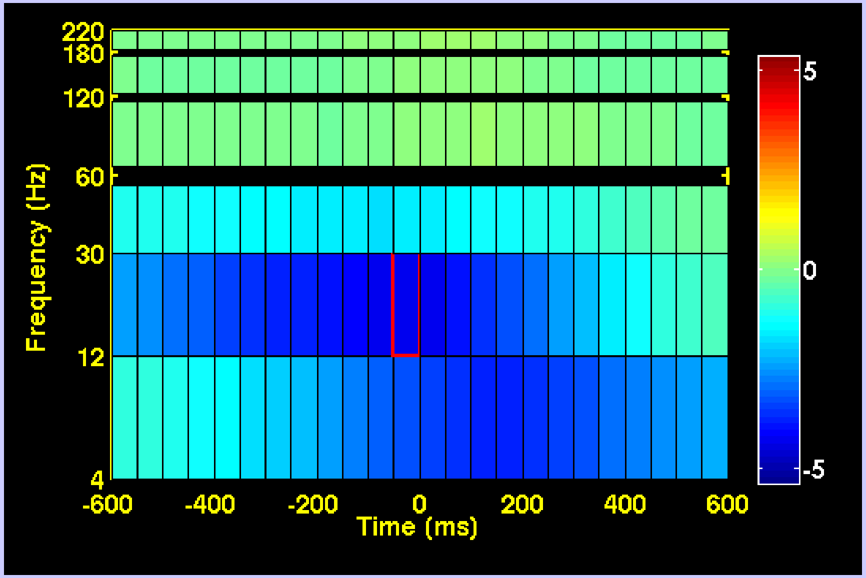
Electro-magnetic brain imaging is an essential tool for human neuroscience

4-D Imaging

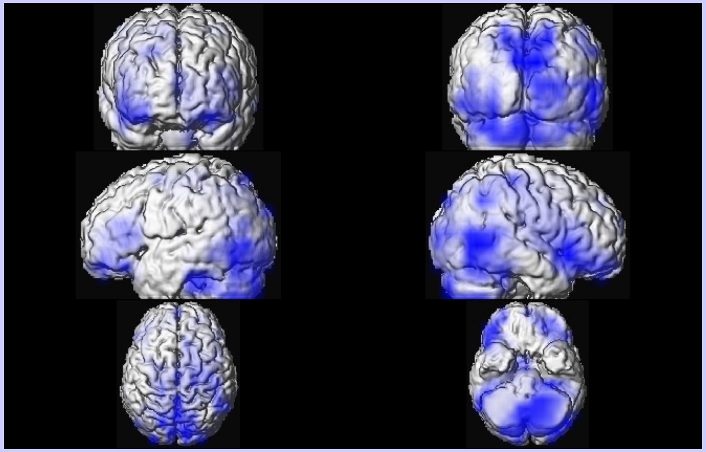




Time-frequency imaging



Imaging Brain Connectivity



Narrow-band adaptive beamformer

Frequency-specific weight

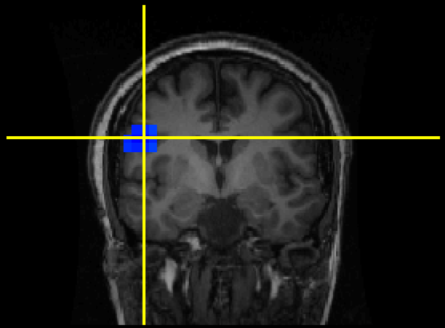
$\boldsymbol{R}(f)$: Covariance matrix calculated from the target frequency band of the signal.

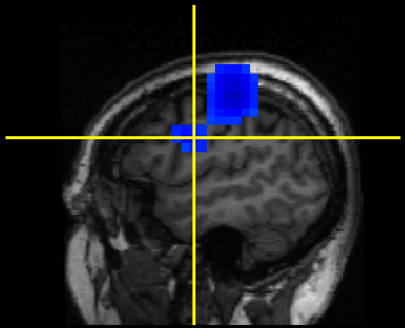
$$\boldsymbol{w}(f) = \boldsymbol{R}(f)\,\boldsymbol{l}(\boldsymbol{r}) \,/\, [\boldsymbol{l}^T(\boldsymbol{r})\boldsymbol{R}(f)\,\boldsymbol{l}(\boldsymbol{r})]$$

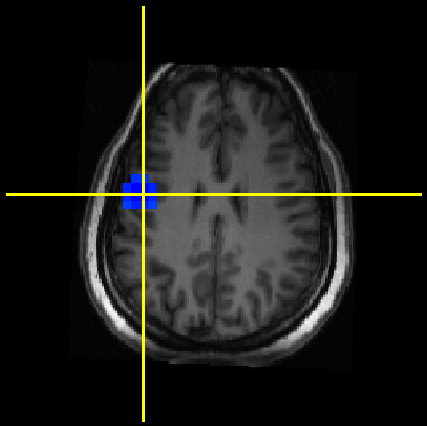
自発脳磁界のタスクによる変調(Event-related synchronization / desynchronization)や脳律動 を周波数選択的に解析し，それらに関連した脳領域を再構成できる.

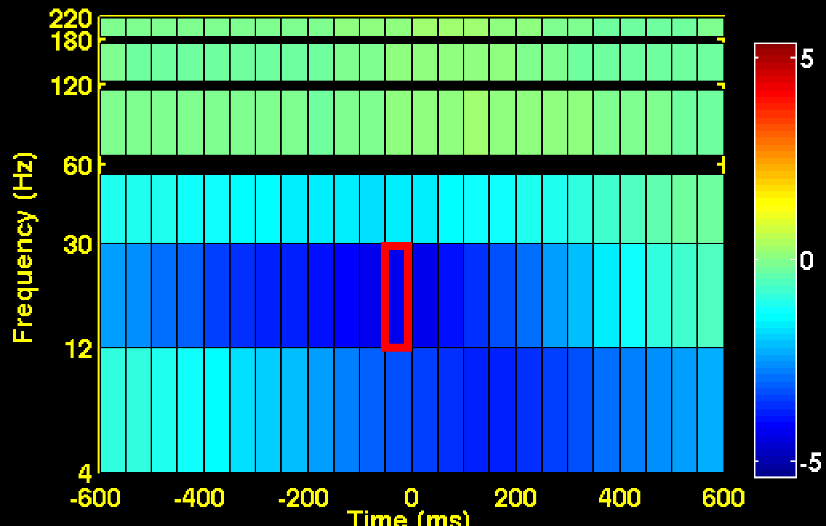
Five-dimensional imaging of brain activity caused by hand-motor movements

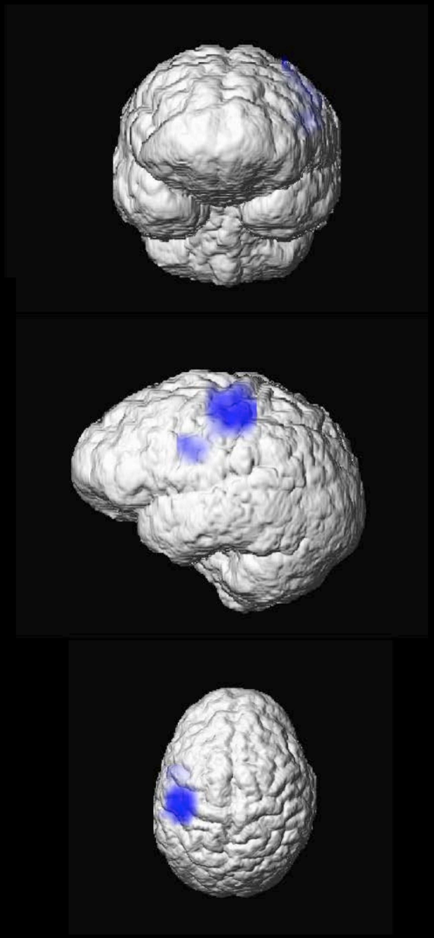
Voluntary right index finger movement.









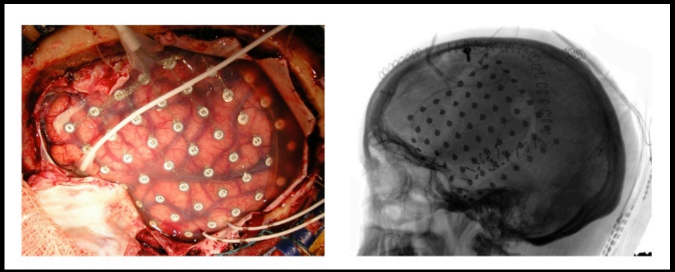


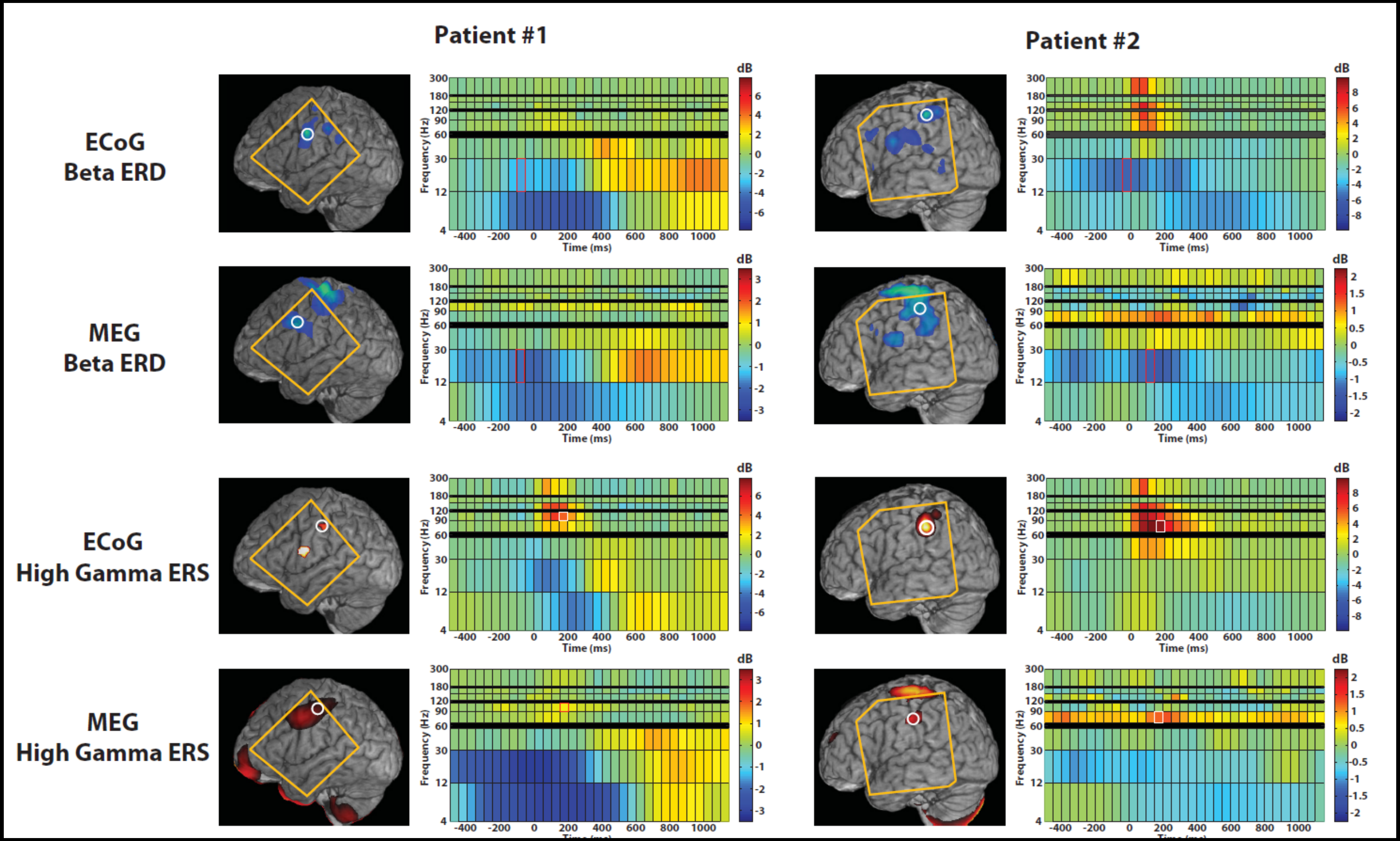
-25 ms
12-30 Hz

button press

Comparison with ECoG results

Right finger (RD2) movement





Dalal S.S., Guggisberg A.G., Edwards E., Sekihara K., et al., Neuroimage. 2008 May 1;40(4):1686-700.

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Adaptive Spatial Filters for Electromagnetic Brain Imaging

Neural activity in the human brain generates coherent synaptic and intracellular currents in cortical columns that create electromagnetic signals which can be measured outside the head using magnetoencephalography (MEG) and electroencephalography (EEG). Electromagnetic brain imaging refers to techniques that reconstruct neural activity from MEG and EEG signals. Electromagnetic brain imaging is unique among functional imaging techniques for its ability to provide spatio-temporal brain activation profiles that reflect not only where the activity occurs in the brain but also when this activity occurs in relation to external and internal cognitive events, as well as to activity in other brain regions. Adaptive spatial filters are powerful algorithms for electromagnetic brain imaging that enable high-fidelity reconstruction of neuronal activity. This book describes the technical advances of adaptive spatial filters for electromagnetic brain imaging by integrating and synthesizing available information and describes various factors that affect its performance. The intended audience include graduate students and researchers interested in the methodological aspects of electromagnetic brain imaging.

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Sekihara · Nagarajan

Adaptive Spatial Filters for Electromagnetic Brain Imaging

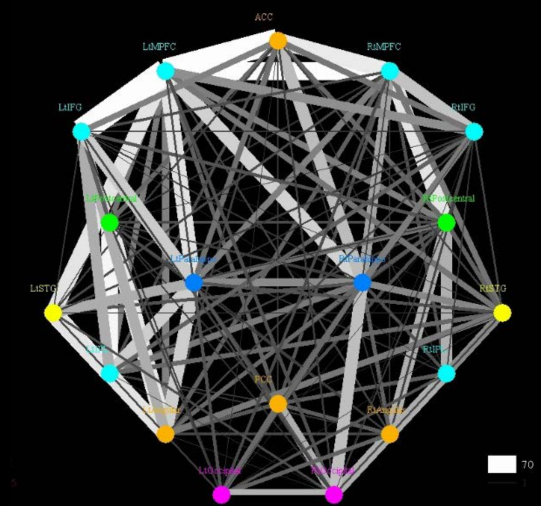
Series in Biomedical Engineering

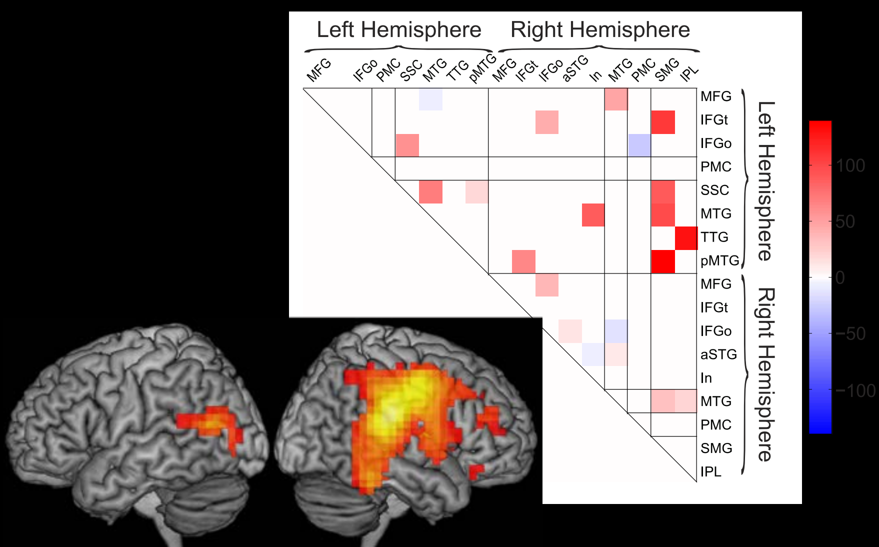
Kensuke Sekihara
Srikantan S. Nagarajan

Adaptive Spatial Filters for Electromagnetic Brain Imaging

Springer

Brain functional connectivity imaging





- Functional connectivity analysis estimates connections among brain activities. It eventually tries to estimate brain networks, and its dynamics.

- We are particularly interested in “resting-state brain network”, which is the brain (network) activity when a subject does nothing, i.e., when a subject is in a resting state.

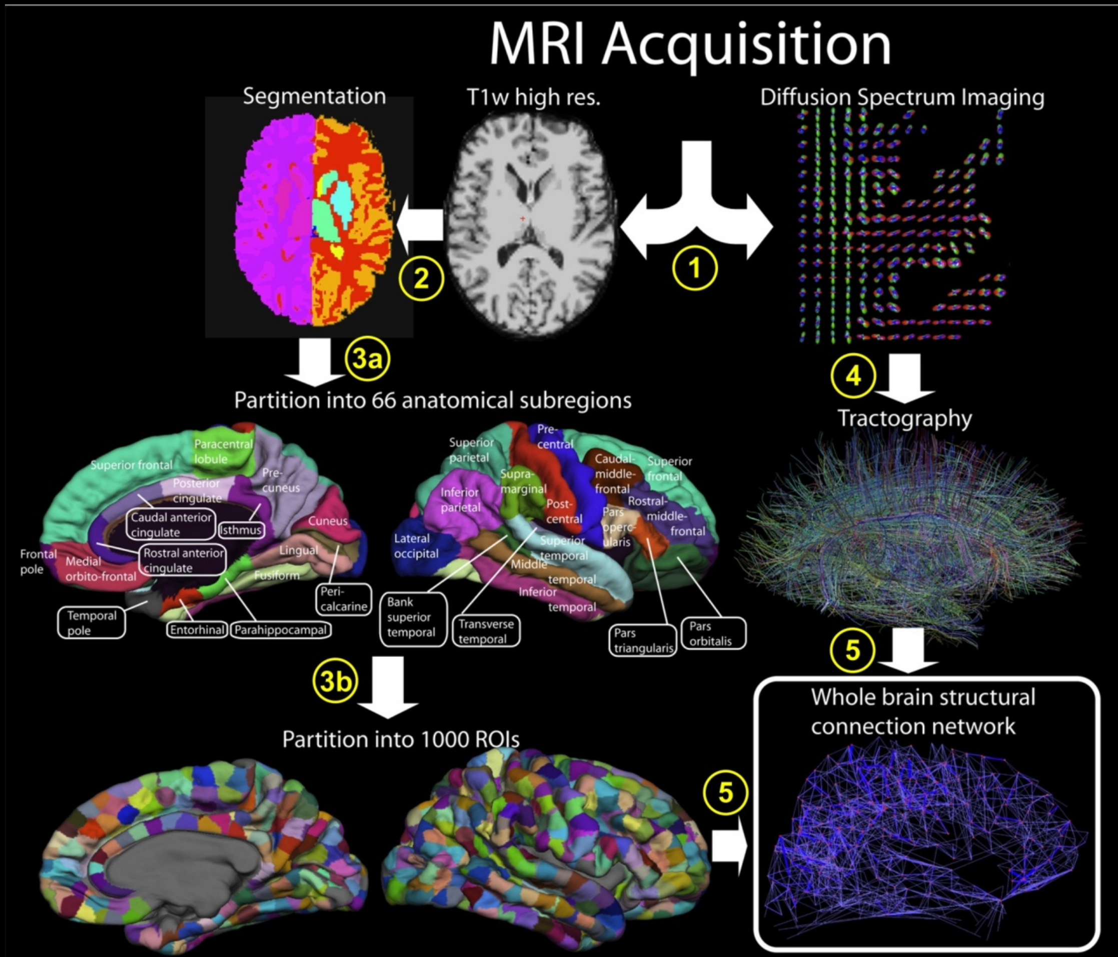
Resting-state brain network

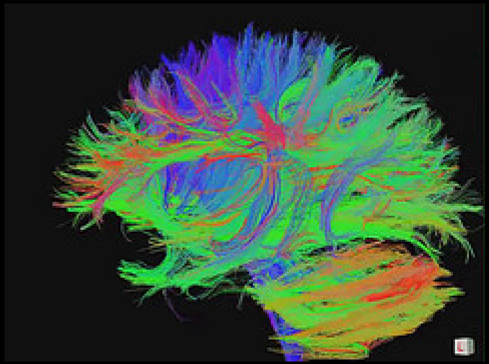
Subject is absent-minded, i.e., she is not concentrated on a particular task.

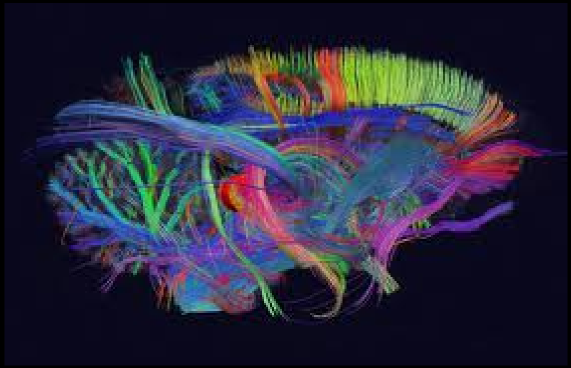
Subject is reading something, i.e., she is concentrated on a particular task.

- Recent investigation is reveling the fact that there are quite strong synchronous brain activities, even when a subject is not engaged in a particular task.
- Such synchronous brain activities are referred to as the resting-state brain network.
- The resting-state brain network is found to be different between a healthy subject and a patient suffering from depression, schizophrenia, or Alzheimer's disease.

Anatomical connectivity vs. Functional connectivity







Anatomical (structural) networkは脳の配線の様子を表し，Functional networkは実際に通信の様子を表す．

脳活動における (functional connectivity) の解析

sensor space vs. source space

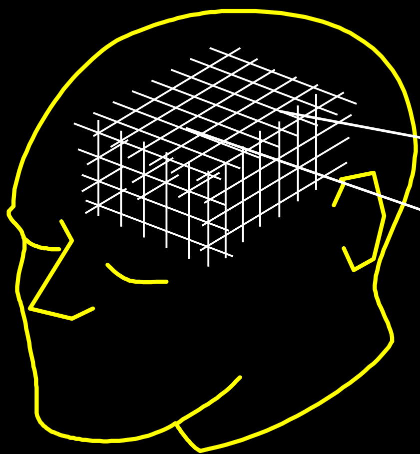
Sensor space analysis:

センサーデータを用いて脳活動のconnectivityを評価する.

Source space analysis:

センサーデータから信号源空間を再構成し，各ボクセルにおけるタイムコースを用いて脳活動のconnectivityを評価する.

Voxel pair-wise coherence measure



voxel time courses　　voxel spectra

$$s_k(t) \longrightarrow \sigma_k(f) = \int s_k(t) e^{-2\pi i f t} dt$$

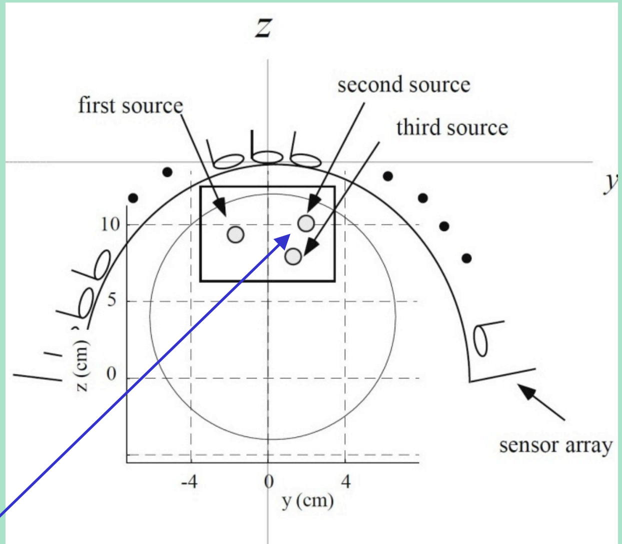
$$s_j(t) \longrightarrow \sigma_j(f) = \int s_j(t) e^{-2\pi i f t} dt$$

$$\eta_{k,j}(f) = \left| \frac{\left\langle \sigma_k(f) \sigma_j(f)^* \right\rangle}{\sqrt{\left\langle \left|\sigma_k(f)\right|^2 \right\rangle \left\langle \left|\sigma_j(f)\right|^2 \right\rangle}} \right|$$

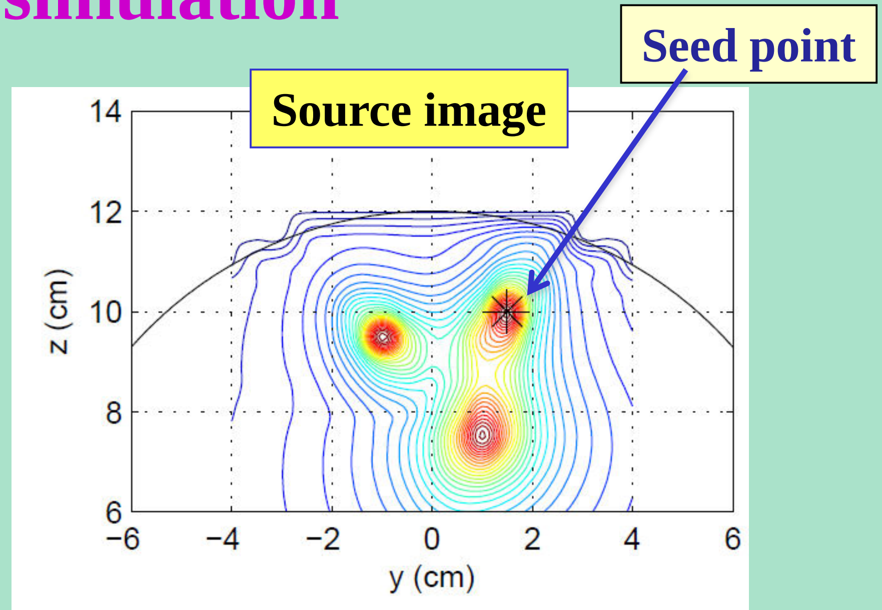
Seed coherence:

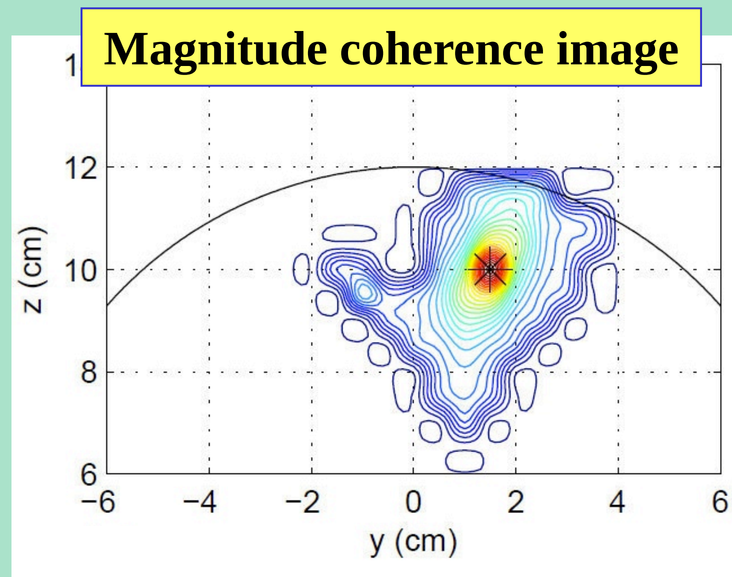
基準となるボクセルを決めて，そのボクセル活動に対するコヒーレンスを計算する．基準となるボクセルはseedと呼ばれる．

Seed blur – computer simulation



The second source interacts with the other two sources.





Seedボクセルを中心とした大きなピークを生じていて（Seed blurと呼ばれる）シードの活動に関連した活動が隠されてしまっている.

Coherenceの虚部(Imaginary part)を用いる必要性

Common interferenceの問題

$$s_k(t) \Rightarrow s_k(t) + \chi(t)$$
$$s_j(t) \Rightarrow s_j(t) + \chi(t)$$

両方のタイムコースに共通に重畳する妨害信号(interference)はゼロラグの相関$R(0)$を生じる.

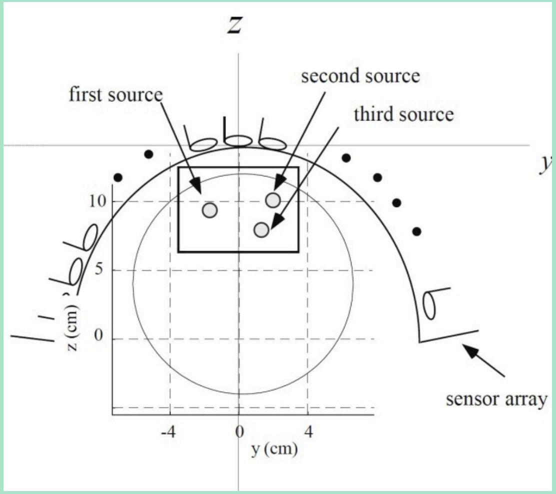
Coherence: $\eta_{j,k}(f) = \Re\left[\eta_{j,k}(f)\right] + i\Im\left[\eta_{j,k}(f)\right]$

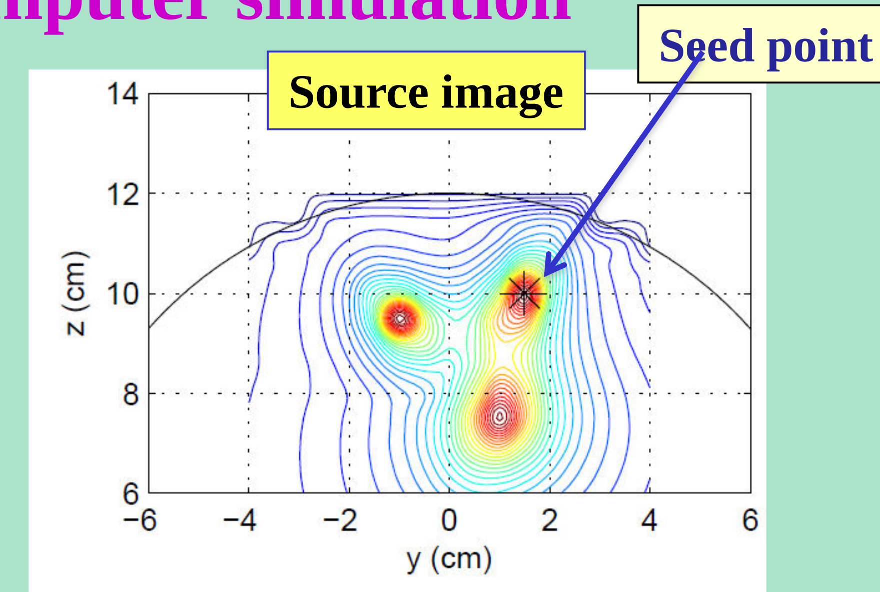
実部:　$R(0)$ に対応. Common interferenceの影響を受ける.

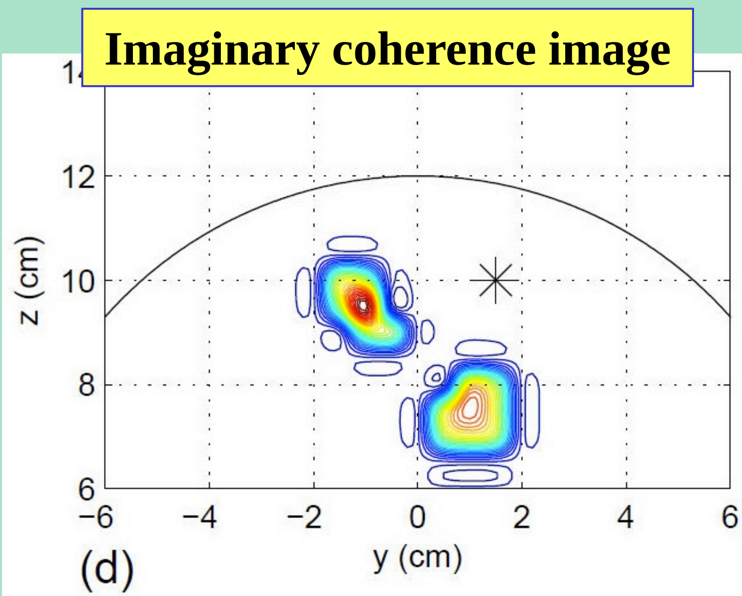
虚部: $R(\tau)$ $(\tau \neq 0)$ に対応. 脳活動の結びつきから生じると考えられる.

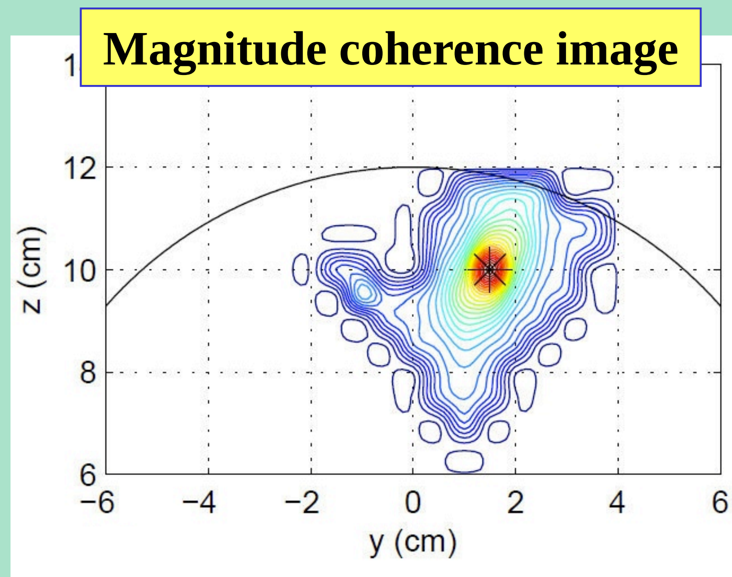
いろいろな妨害要因から生じる偽のコヒーレンスを除去するため, 実部を捨て去り, 虚部のみを用いる.

Imaginary coherence– computer simulation



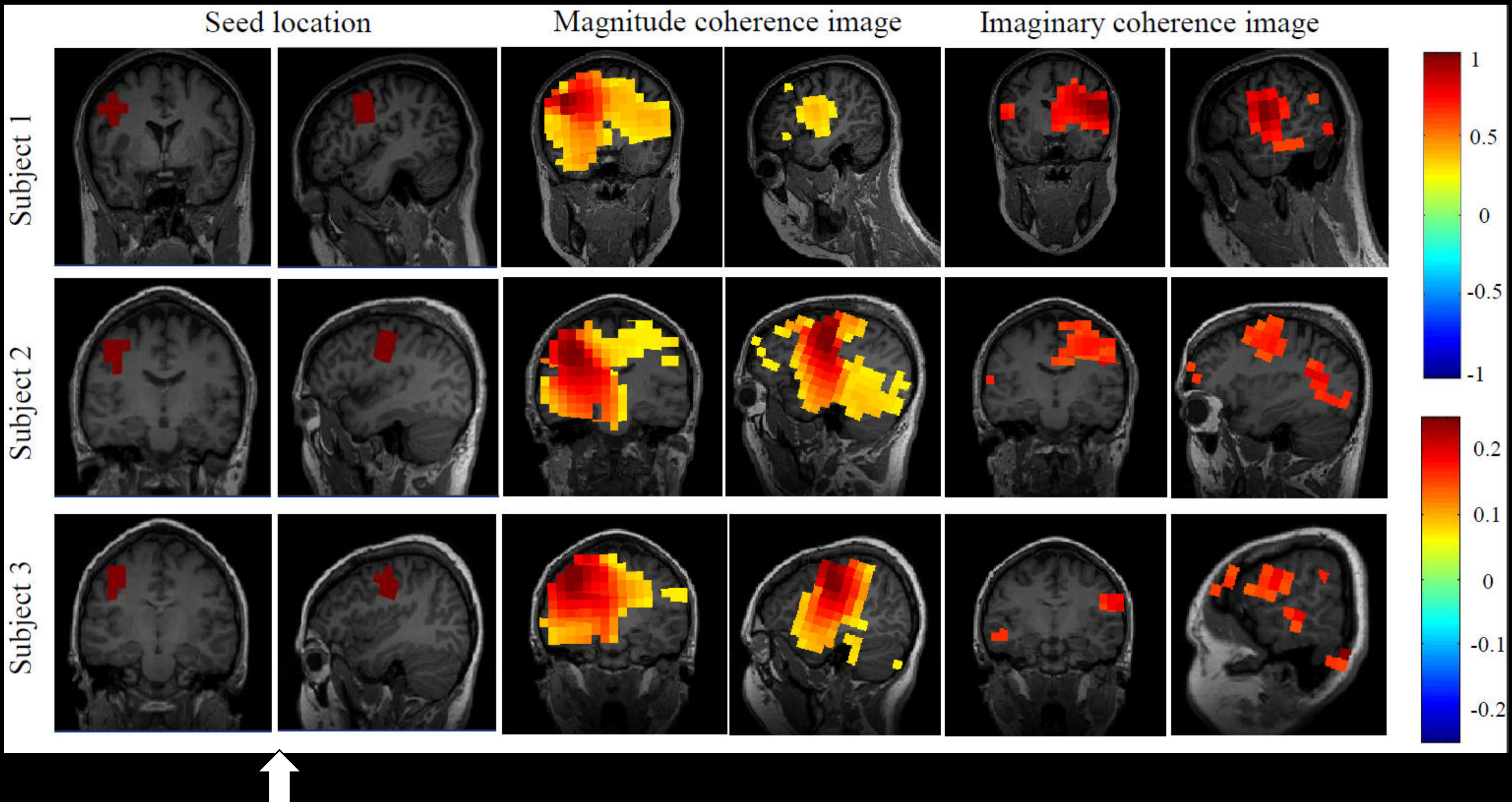






Seed blurが除かれ，Seedボクセルの活動に関連したボクセルが描出されている.

Seed blur:Resting-state MEG, beta-band coherence image



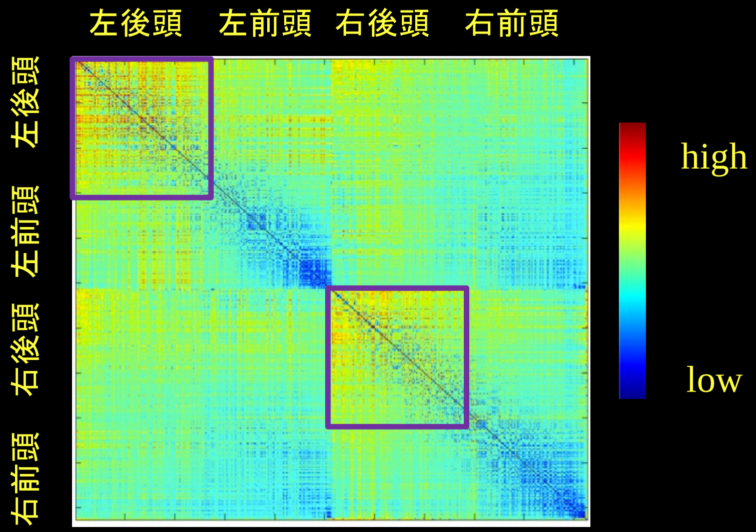
Voxels within the left pre-central gyrus (left primary motor area) were selected as seed voxels.

Connectivity analysis

Seed voxelをさらにscan

↓

All-voxel-to-all-voxel connectivity matrix

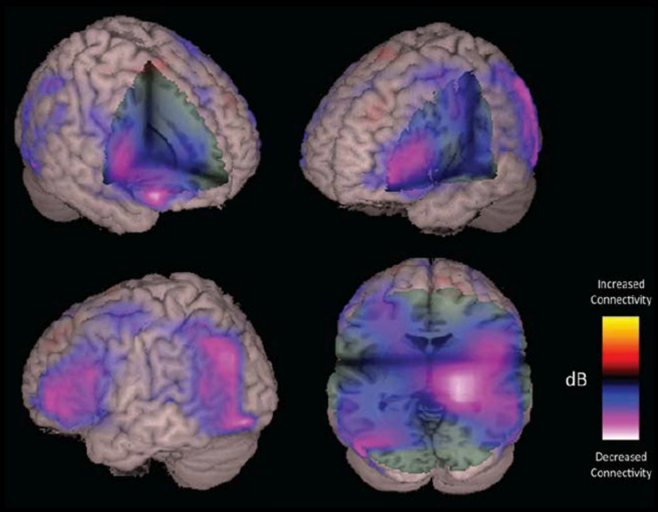


voxel × voxelの情報量を持つ分布

Connectivity matrixを行（列）方向にアベレージ

↓

Mean imaginary coherence (MIC) mapping



connectivityの平均値を濃度に持つ3次元画像

Mapping of mean imaginary coherence (MIC)

各ボクセルにおいて，そのボクセルと他の全てのボクセルとのコヒーレンスの総和を計算する.

Coherence between the jth and kth voxels:

$$\eta(f,\boldsymbol{r}_j,\boldsymbol{r}_k) = \alpha(f,\boldsymbol{r}_j,\boldsymbol{r}_k) + i\beta(f,\boldsymbol{r}_j,\boldsymbol{r}_k)$$

Mean imaginary coherence for the jth voxel:

$$\overline{\beta}(f,\boldsymbol{r}_j) = \frac{1}{K}\sum_{k=1}^{K} |\beta(f,\boldsymbol{r}_j,\boldsymbol{r}_k)|$$

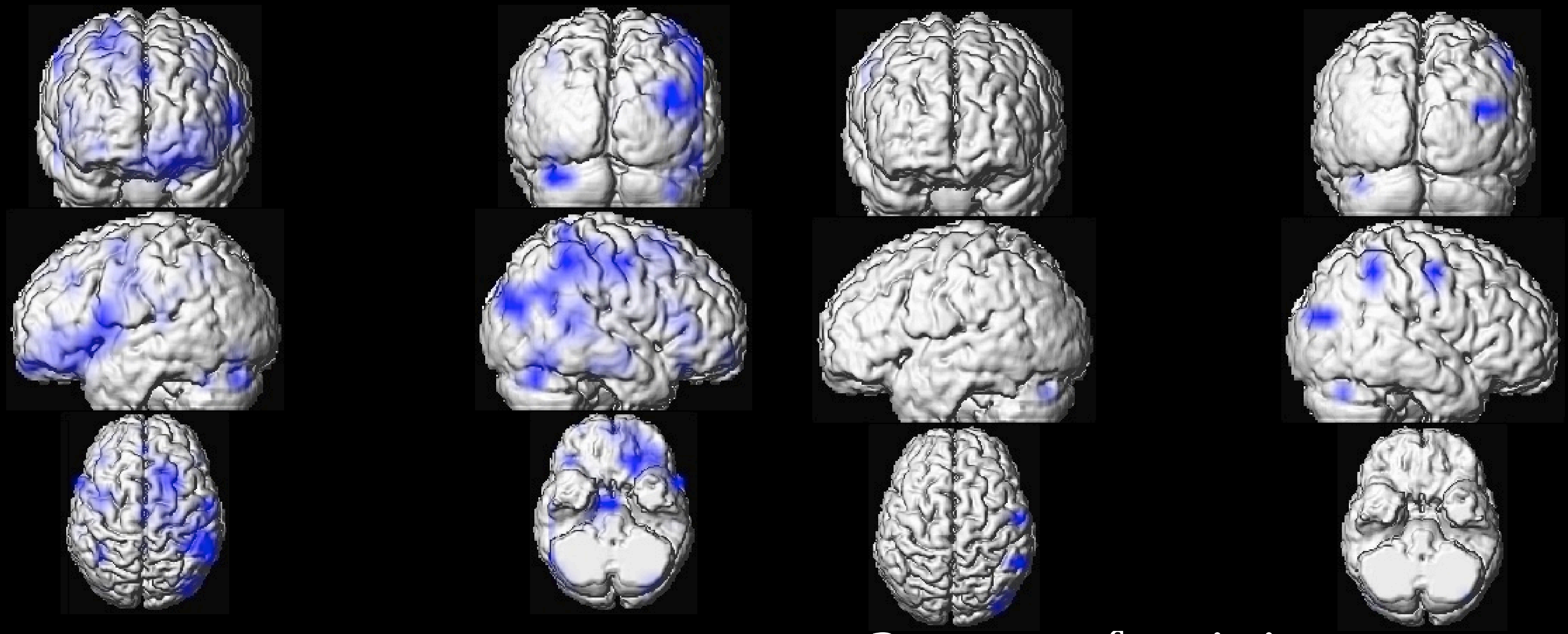
$\boldsymbol{r}_j$ 以外の全てのボクセルとの和を取る. Global connectivity と呼ぶ.

$\overline{\beta}(f,\boldsymbol{r}_j)$ は $\boldsymbol{r}_j$における脳組織の他の脳組織との「接続の活発さ」の指標になるはず!!(作業仮説)

A. G. Guggisberg *et al.*, Annals of Neurology, Sep 25, 2007

Mean imaginary coherence mapping for a patient with a traumatic brain damage

青い領域がMIC値の統計的に有意な低下を示す.



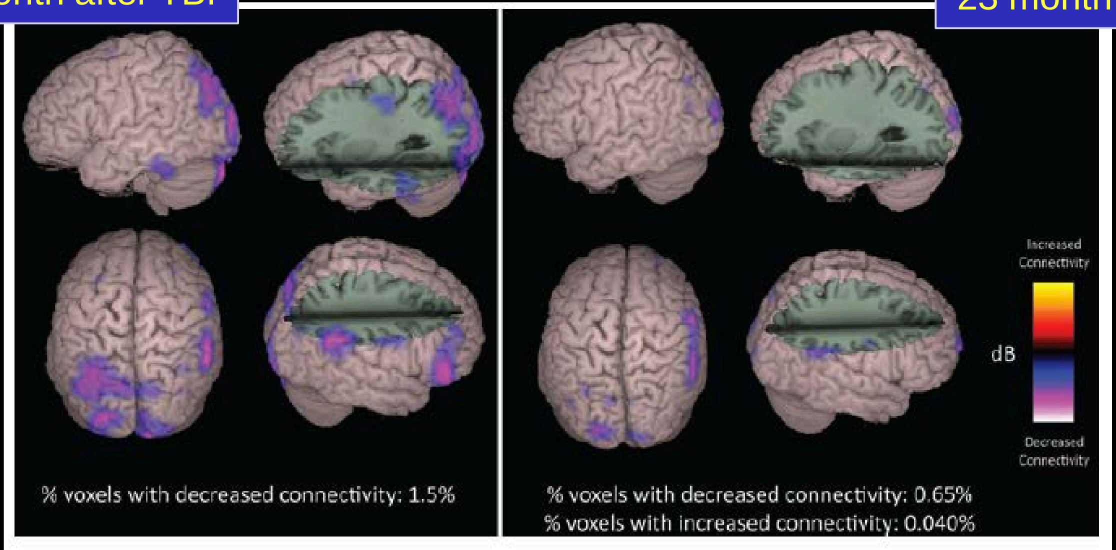
1 month after injury　　2 years after injury

2年後の結果はMIC値の低下を示す領域が減少し, 脳の各部位における機能の回復を示唆している.

Individual patient cases

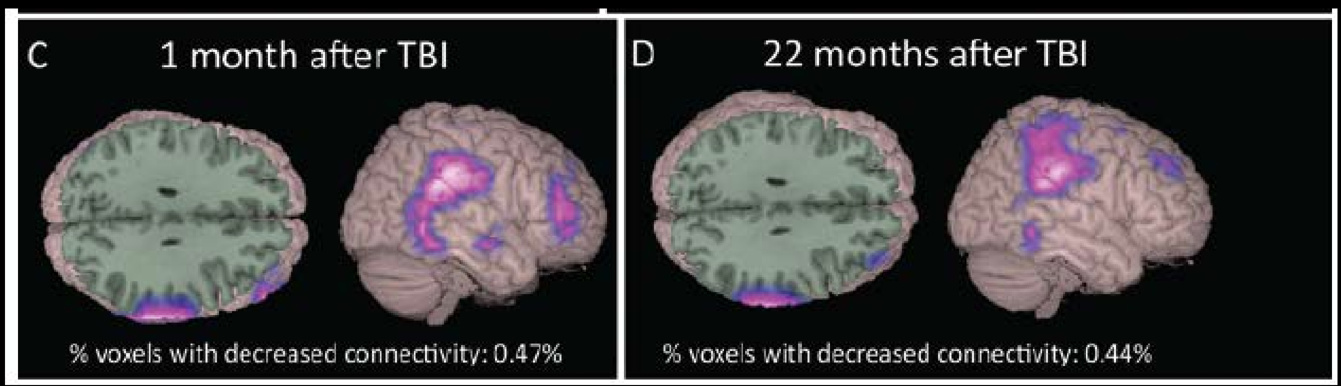
9 month after TBI

23 month after TBI



Results from a patient with a significant recovery

Significant decrease of under-connected voxels

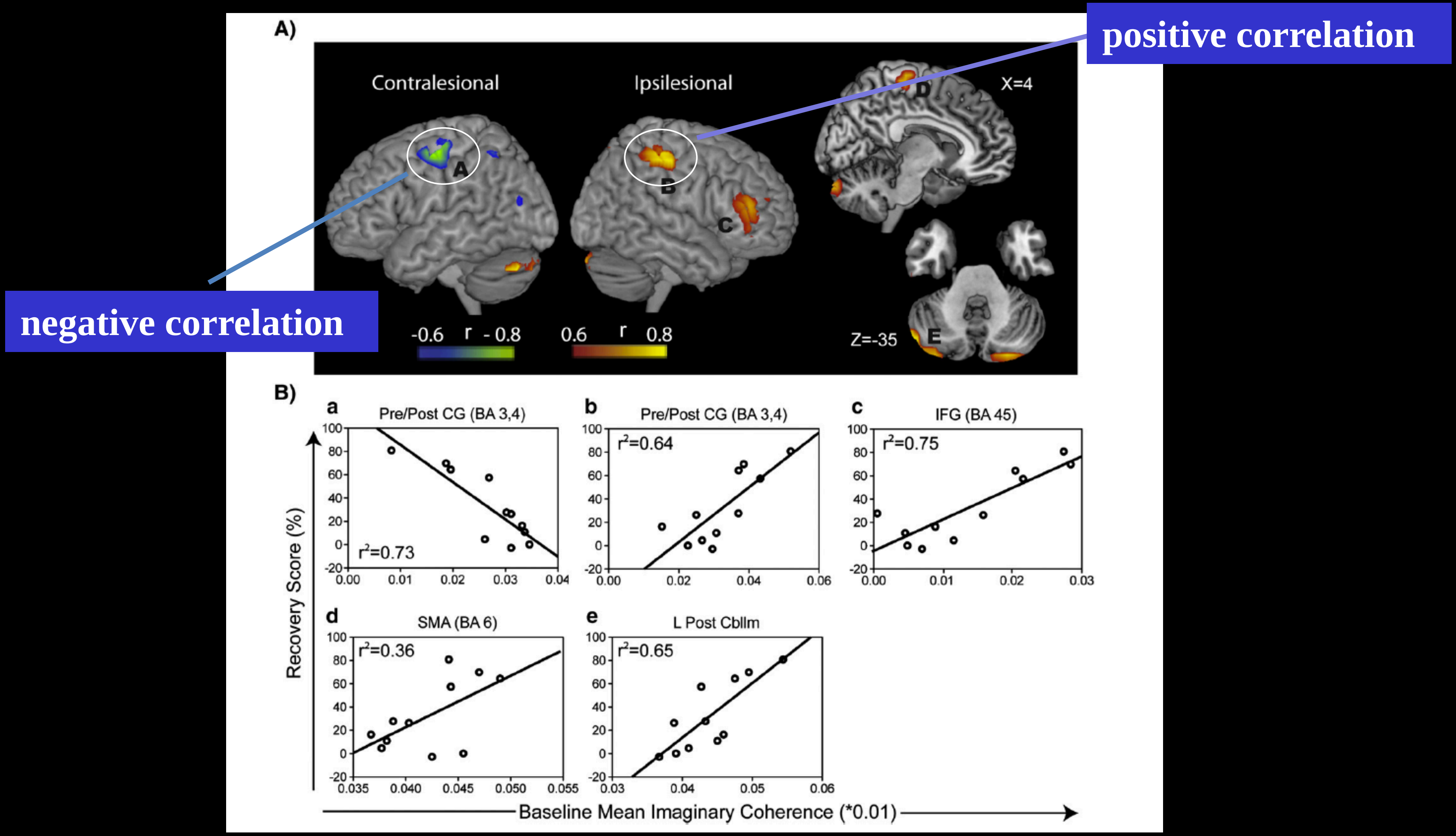


Results from a patient with a slow recovery

Slight decrease of under-connected voxels

Decrease of under-connected (decreased MIC) voxels is in accordance with the patient's recovery

Correlation with recovery score

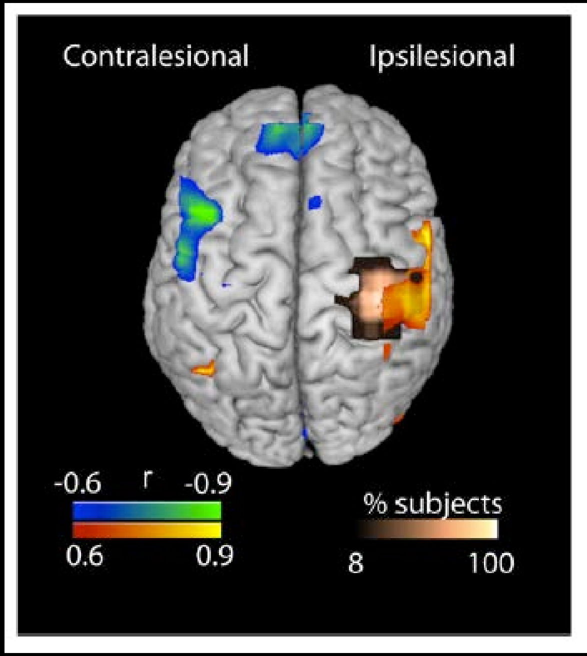


Correlation between mean imaginary coherence and recovery score.

(The correlation is corrected for nuisance parameters such as time post stroke.)

K. P. Westlake at al. Experimental Neurology 237 160-169, 2012

Summary: Correlation between mean imaginary coherence and recovery score:



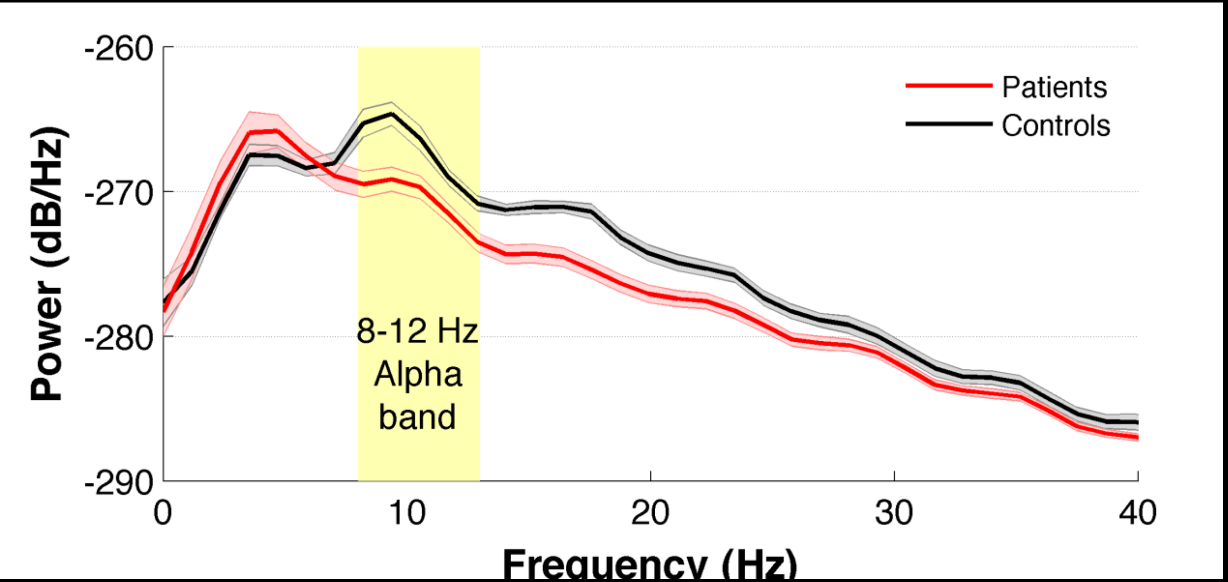
A positive correlation is found near the ipsi-lesional sensorimotor cortex, and significant negative correlation with the contra-lesional sensorimotor cortex.

Values of mean imaginary coherence from the initial MEG session may be able to predict each subject’s recovery performance.

If ipsi-lesional and contra-lesional motor areas respectively have high and low MIC values, that patient possibly has a large recovery score.

Figure 1

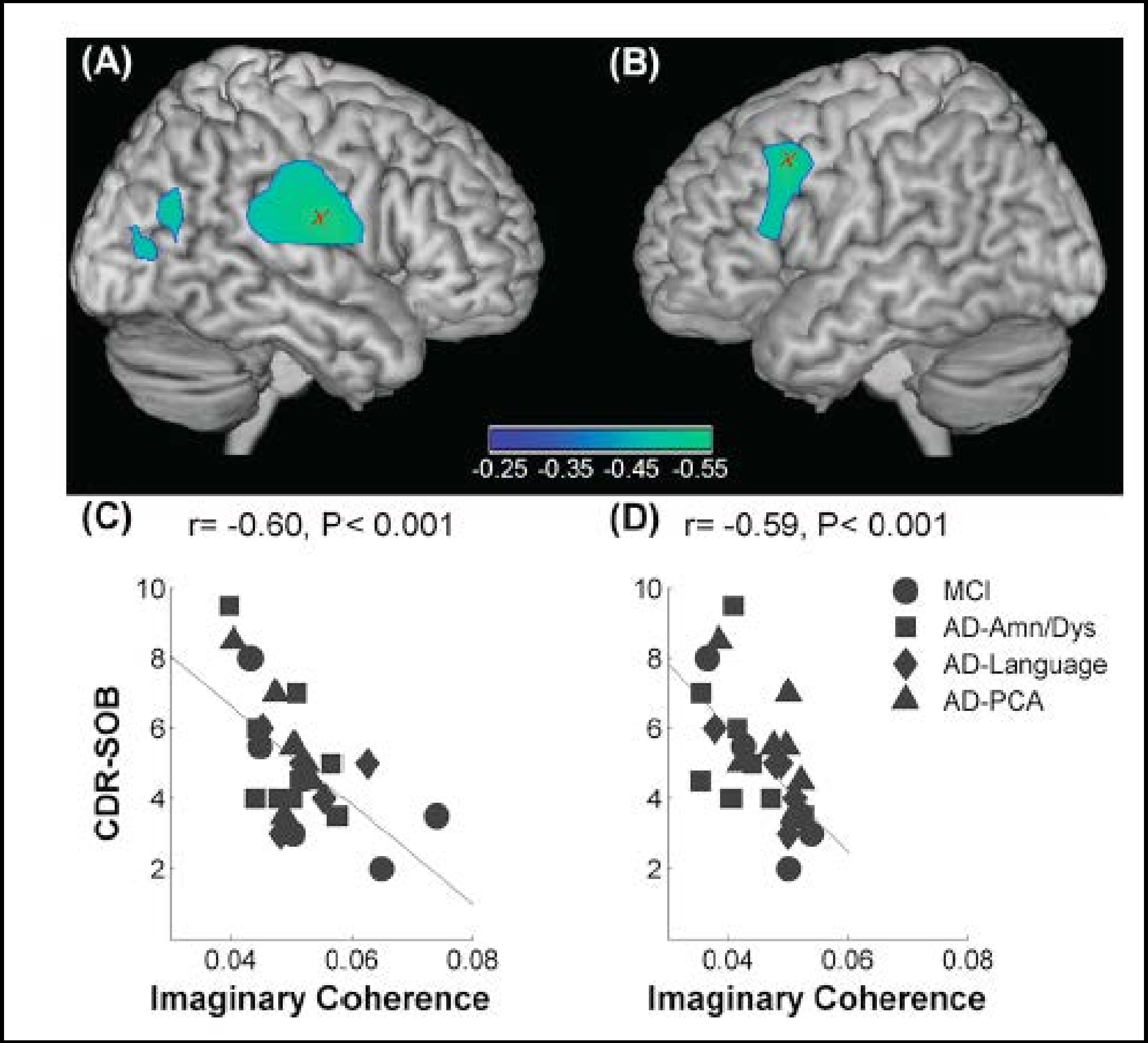
Resting-state MEGI in Alzheimer's spectrum



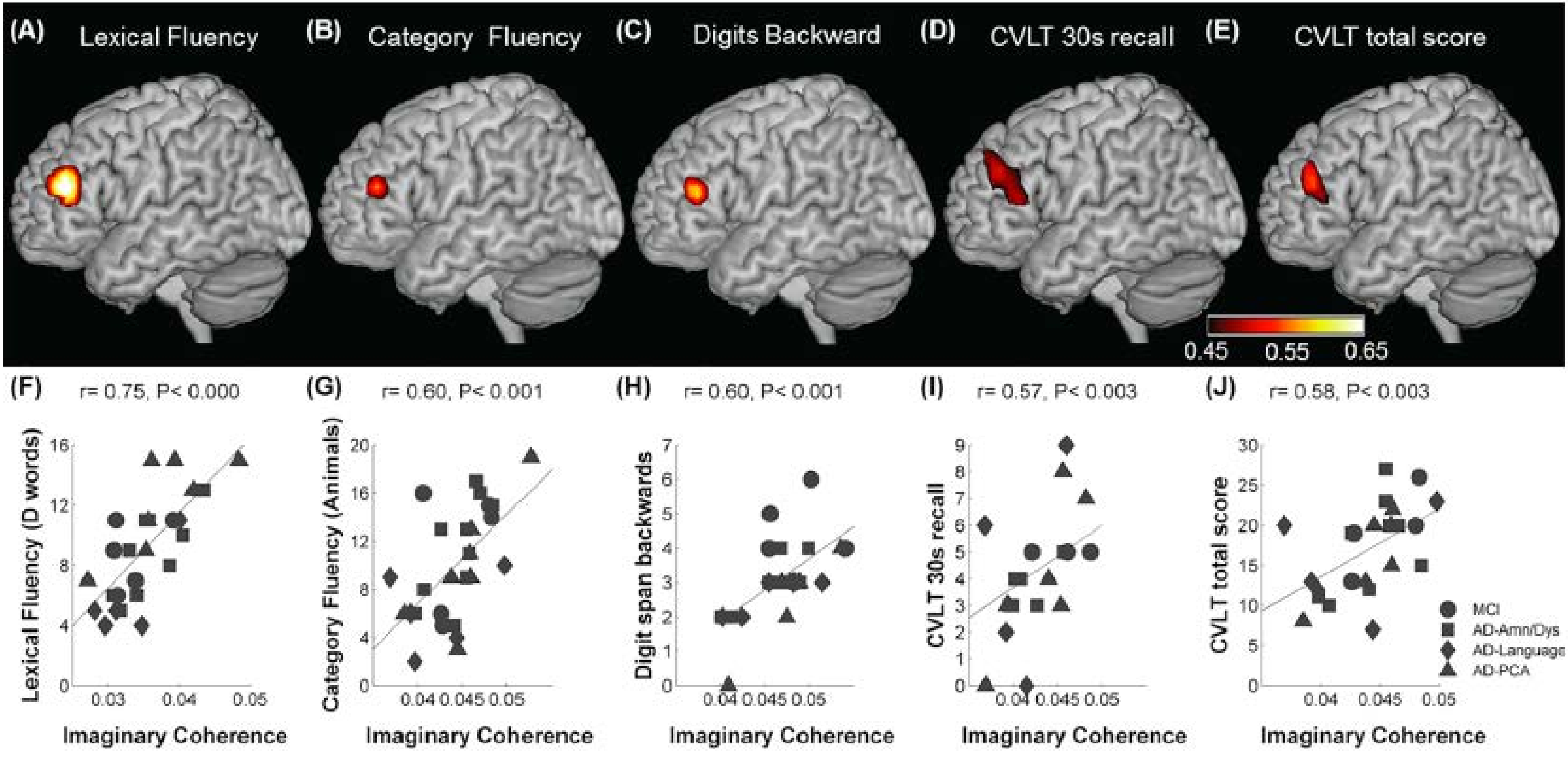
Age (years)	63.2 ± 7.1
MMSE (/30)	22.5 ± 4.2
Sex (% male)	41
Handedness (%right)	92
Education (years)	15.8 ± 2.2
CDR	0.84 ± 0.3#
CDR-SOB	5.1 ± 1.8#
Age at onset (years)	57.8 ± 7.1
Disease Duration	5.4 ± 3.3

7 PCA, 10 Amnesic/Dysexecutive,
5 LvPPA & 5 MCI

Regional resting MEGI FC is correlated with disease severity in AD spectrum

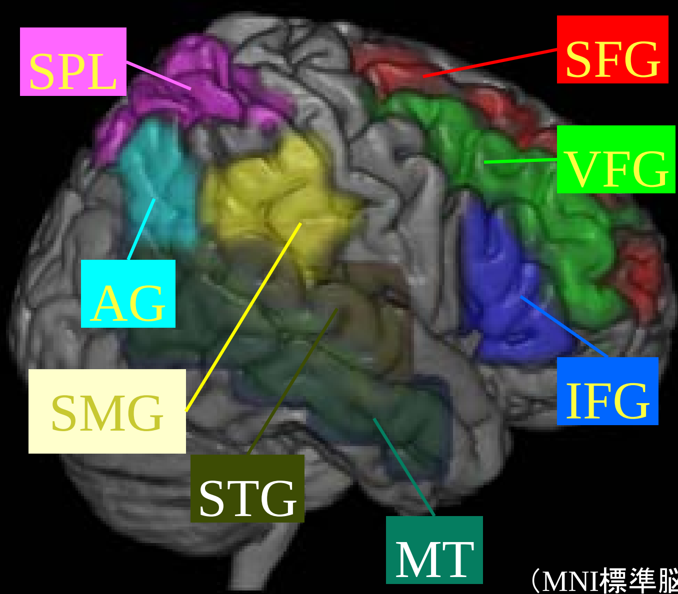


Left DLPFC resting MEGI FC is correlated with cognitive performance in AD spectrum



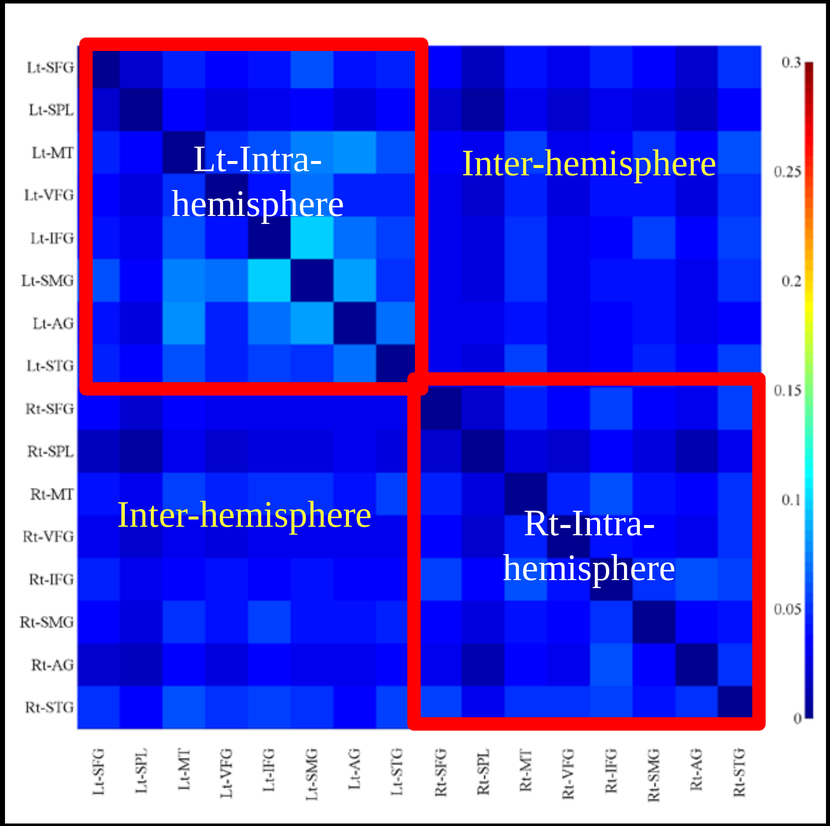
半側空間無視の患者におけるfunctional connectivityの推定

（大脳半球の障害のため半側からの刺激を認識できなくなる症候）



（MNI標準脳）

Coherence Matrix



右半球に障害を持つ患者８名に対して，resting-state MEGを計測し，アルファ帯域のimaginary coherenceによりfunctional connectivityを推定し，上図のノードにおけるcoherence matrixを作成.

All-voxel-to-all-voxel connectivity analysis

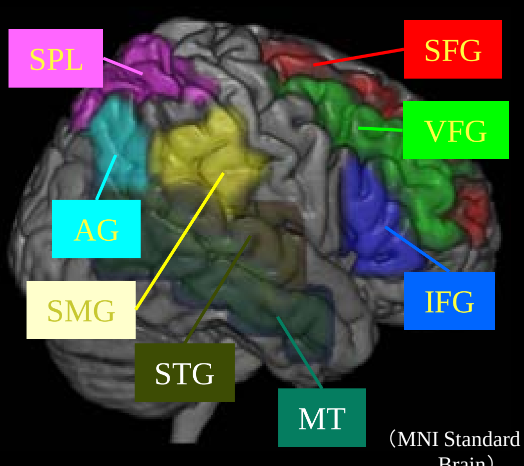
OPEN ACCESS Freely available online PLOS | ONE

Disturbed Resting Functional Inter-Hemispherical Connectivity of the Ventral Attentional Network in Alpha Band Is Associated with Unilateral Spatial Neglect

Tsutomu Sasaki[1*], Masayuki Abe[2], Eiichi Okumura[3], Toyoji Okada[4], Kimito Kondo[5], Kensuke Sekihara[6], Wataru Ide[7], Hajime Kamada[7]

- 13 patients with brain damage in their right hemispheres
- 8 patients show USN symptoms(USN+), and 5 patients has no USN symptoms(USN-).
- 5 healthy controls.
- 16 voxels are selected, corresponding to representative brain areas shown here.

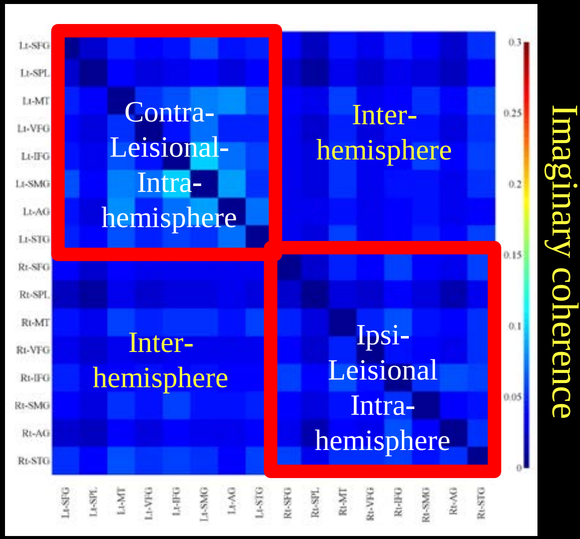
Selected voxels



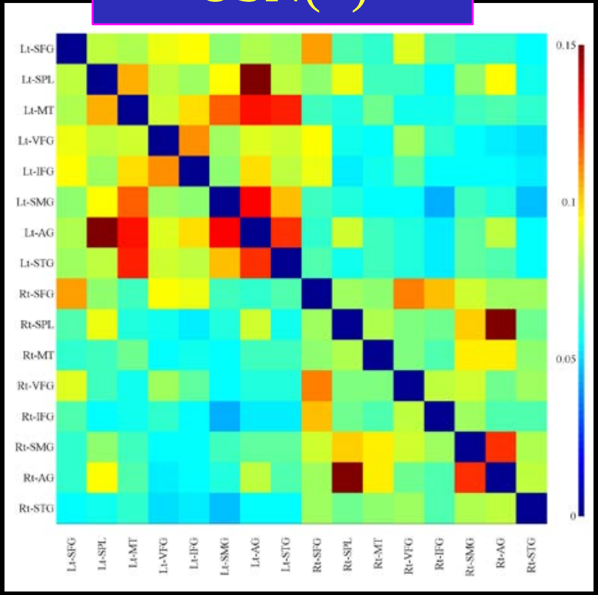
All-voxel-to-all-voxel imaginary coherence matrix is computed using resting state alpha-band MEG.

Resting-state alpha-band connectivity:

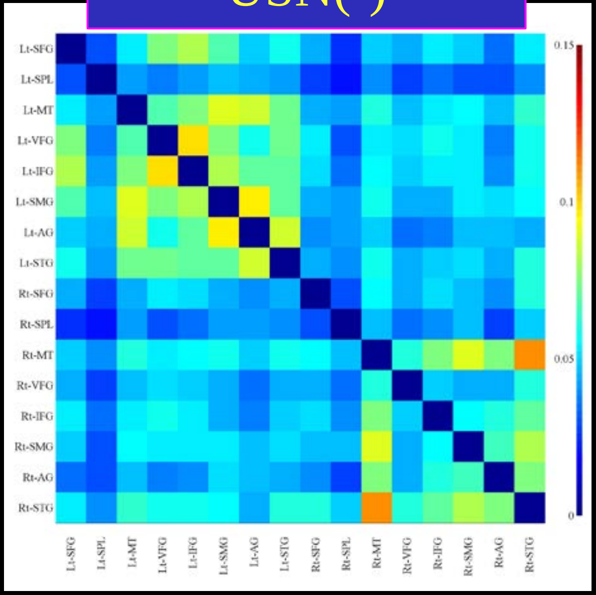
results of all-voxel to all voxel coherence matrix



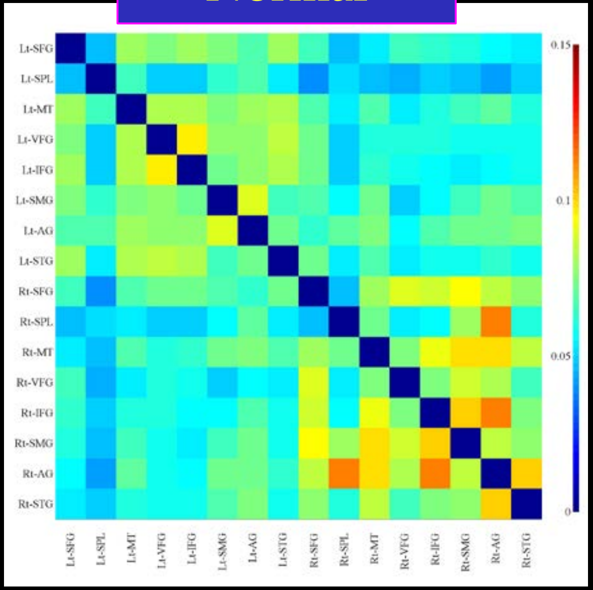
USN(+)



USN(-)



Normal

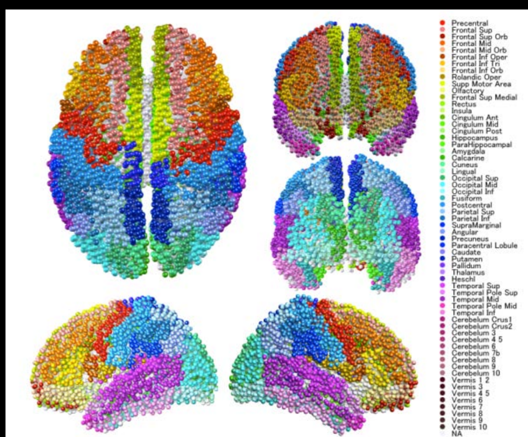


Patients with USN+ have excess intra-hemispheric connectivity, particularly in the contra-leisional hemisphere.

All-voxel-to-all-voxel connectivity analysis applied to schizophrenia patients:

Magnitude vs. imaginary

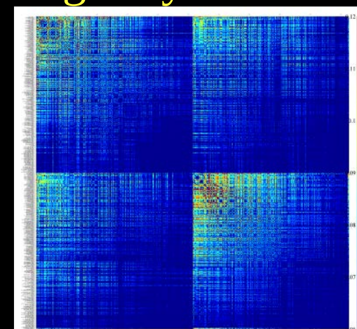
- Resting state.
- 8-13 Hz (alpha band).
- 12 patients, and 12 healthy controls.



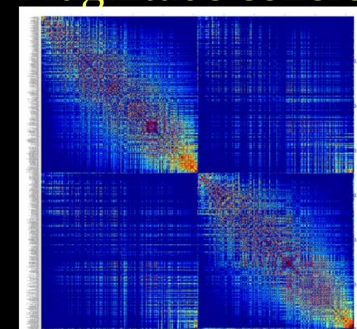
512 voxels assumed in subject's cortex

Patient (grand average)

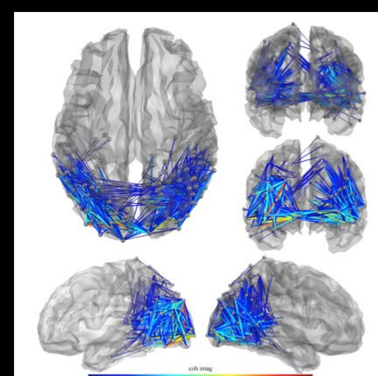
Imaginary coherence

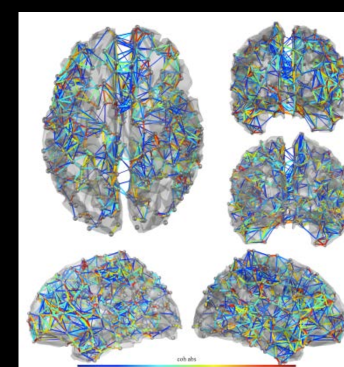


Magnitude coherence



Coherence matrix display

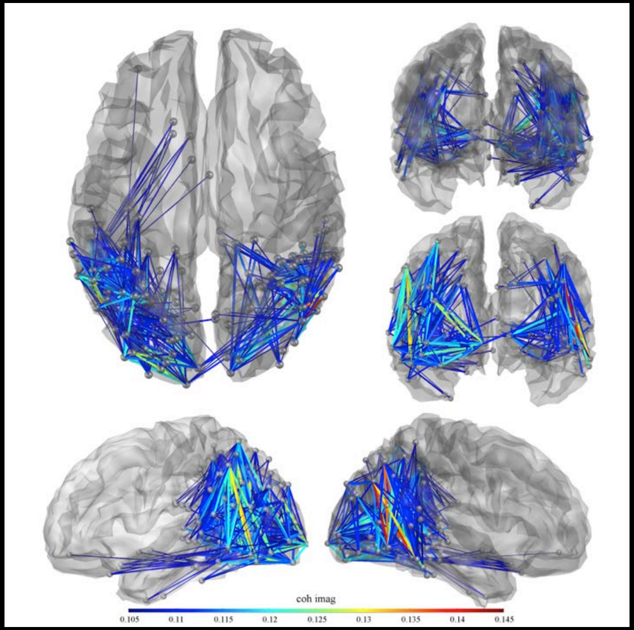




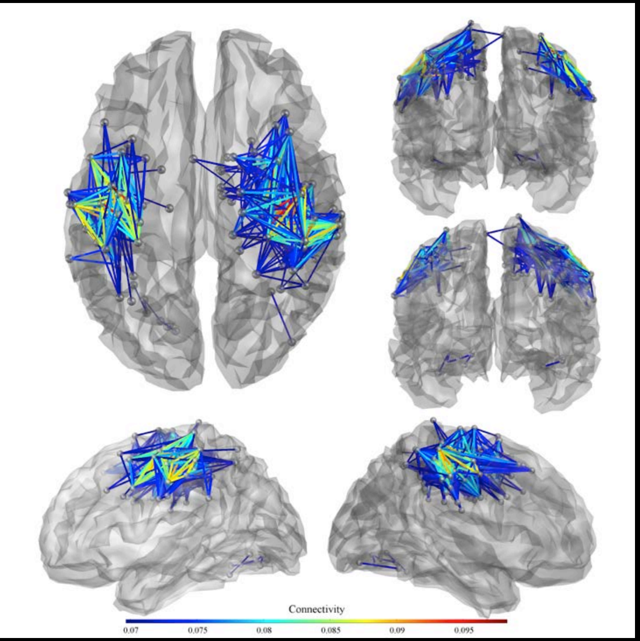
Connection plot display

Magnitude coherence matrix contains seed blur, which obscures true interaction. Connection plot for magnitude coherence is not interpretable.

connectivity mapの周波数依存性
正常コントロール群のアベレージ



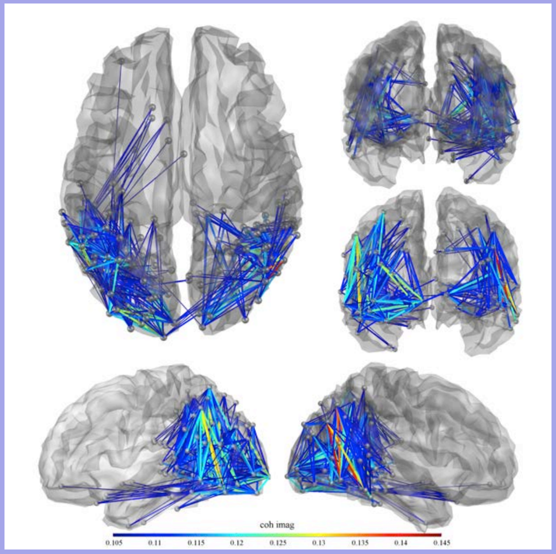
アルファ帯域



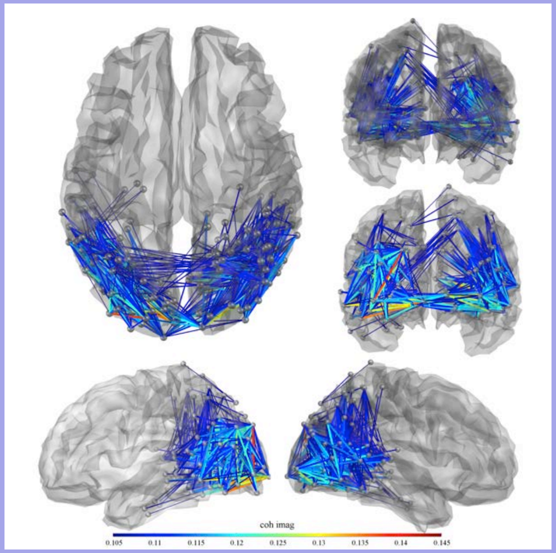
ベータ帯域

Imaginary Coherence　グループ比較

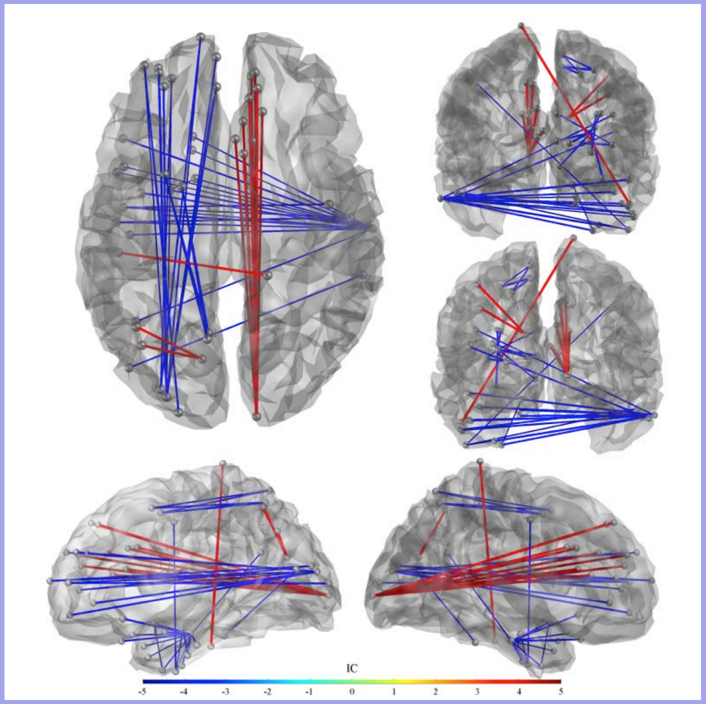
健常者平均



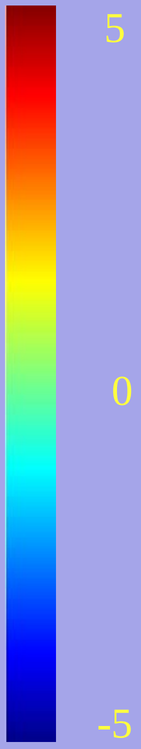
患者平均



2 sample t test $p<10^{-3}$



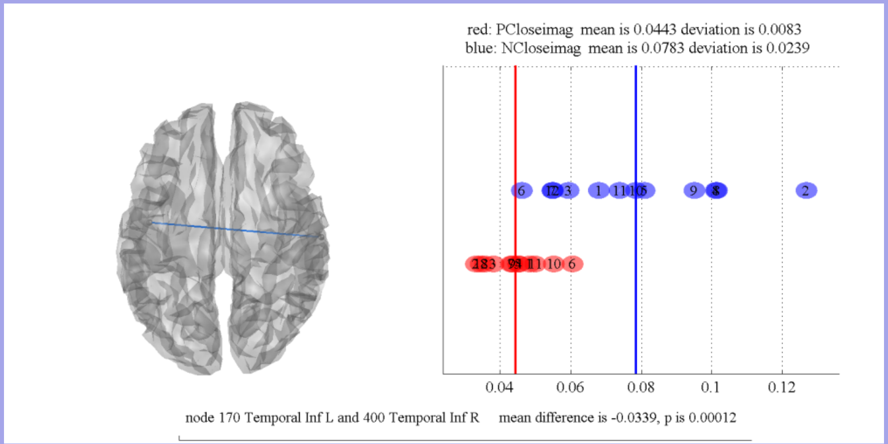
t value



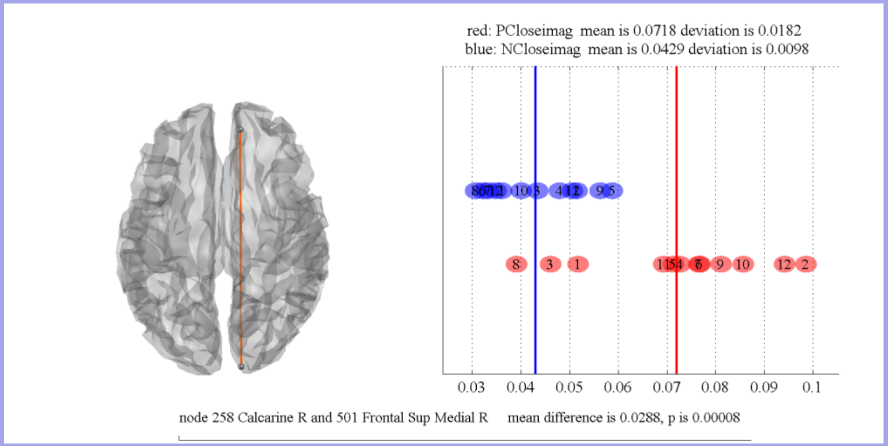
患者と健常者の判別

connectivity measure:
imaginary coherence

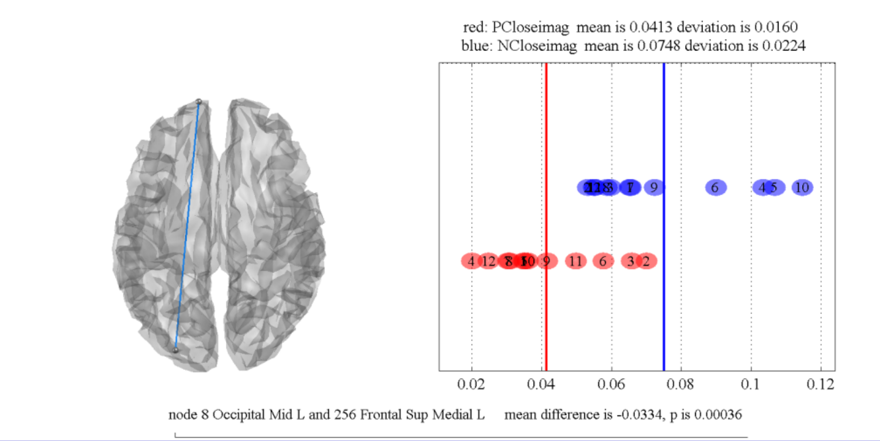
79%



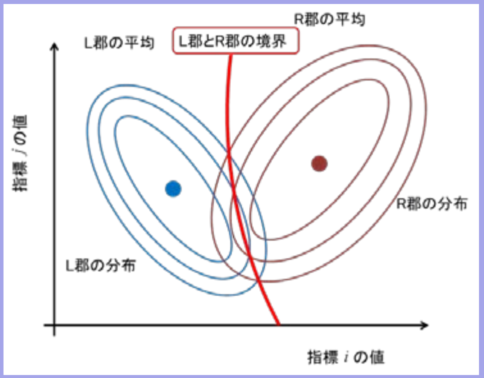
75%



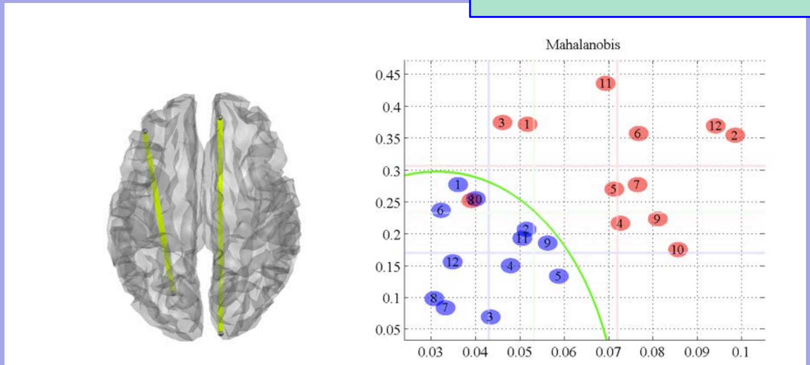
87%



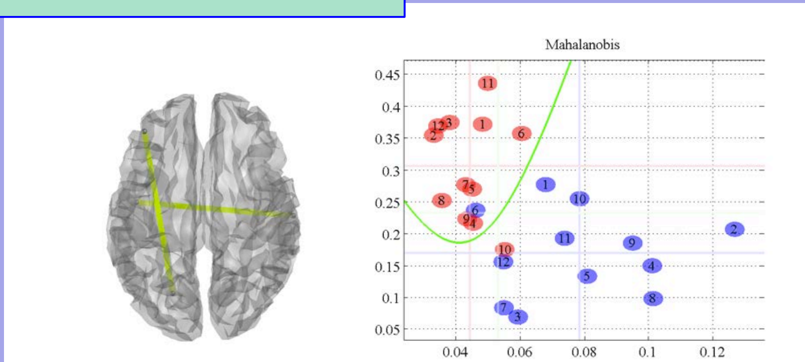
2つのコネクションを用いた患者と健常者の判別



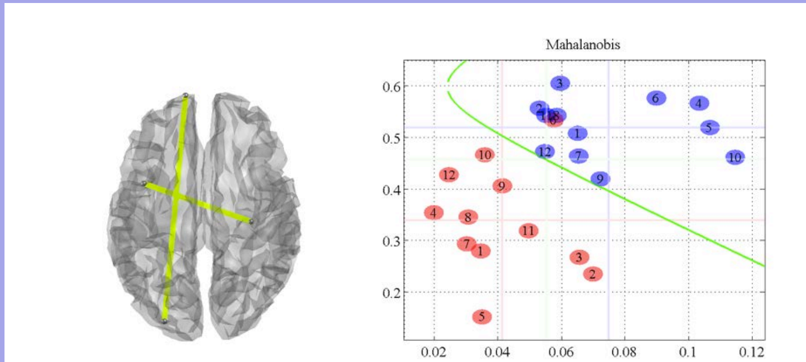
判別率95%以上を達成!!



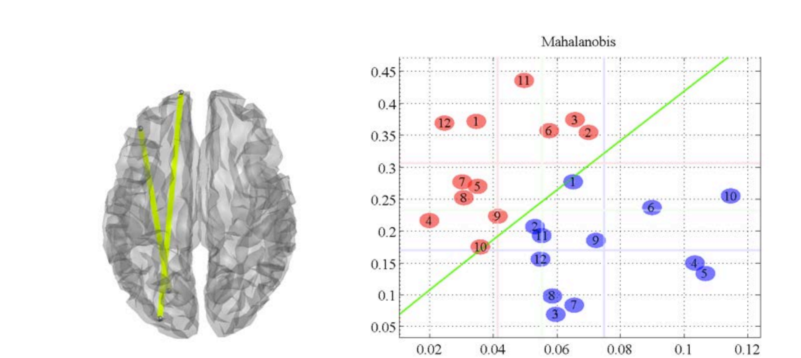
node 258 Calcarine R and 501 Frontal Sup Medial R(imaginary), 31 Lingual L and 239 Frontal Inf Orb L(magnitude)



node 170 Temporal Inf L and 400 Temporal Inf R(imaginary), 31 Lingual L and 239 Frontal Inf Orb L(magnitude)



node 8 Occipital Mid L and 256 Frontal Sup Medial L(imaginary), 196 Precentral L and 392 Insula R(magnitude)



node 8 Occipital Mid L and 256 Frontal Sup Medial L(imaginary), 31 Lingual L and 239 Frontal Inf Orb L(magnitude)

認知症に関連したコネクションを見つける事が出来れば，認知症のバイオマーカーとして使う事が出来，MEGが認知症初期診断の有効な診断手法となり得る.

まとめ

- 安静時脳活動のネットワークは健康な脳と，何かしら異常のある（病気の）脳とでは大きく異なることが明らかになりつつある．
- この知見はMEGの臨床応用に大きなインパクトを与えつつある．
- MEGを用いた安静時ネットワークの解析から認知症を早期に診断し，とその後の進行を予測できるバイオマーカーの発見が期待されている．

精神疾患や神経内科的疾患の多くは脳のネットワークの病気であると言われて久しいが，MEGにより脳ネットワークの異常を検出できるようになりつつあり，認知症など脳疾患の有力な早期診断手法になり得る．