Sep 27, 2020

国際脳MRIチュートリアル

Brain/Minds beyond MRI tutorial

国際脳プロトコルMRIデータでできるようになること
・
国際脳MRI解析パイプラインの現状と今後

Current status and future of Brain/Minds beyond MRI protocol and preprocessing

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脳コネクトミクスイメージング研究チーム

なぜ脳MRIの標準化が必要か?

1. 神経科学とヒト脳・脳病態の理解の橋渡し
2. MRIの再現性・病態予測能・診断能の向上
3. 大規模研究の必要性

Human Connectome Project (HCP)
- Cutting-edge & high quality 3T MRI techniques
- 1,200 subjects

Van Essesn 2016, Ugurbil 2016
Glasser et al Nature Neurosci 2016

UK biobank
- Cohort study with 100,000 healthy controls
- Biomarkers based on Brain 3T MRI data

Millar et al., Nat Neurosci 2016
Smith et al., Nat Neurosci 2016

ABCD
- a long-term monitoring of environmental, behavioral assessments, multimodal neuroimaging and biospecimen for 10 years at 21 sites.

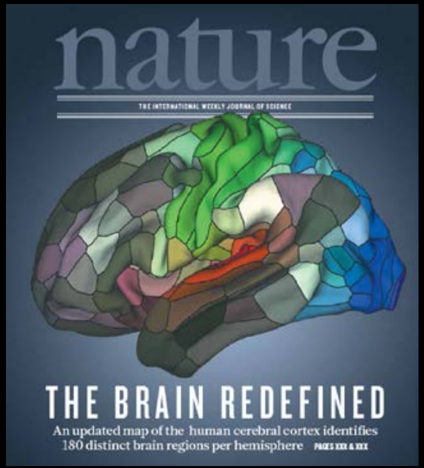
Casey et al., Dev Cogn Neurosci, 2018

Multi-site clinical neuroimaging project in Japan
- Lead by Dr. Kawato in SRPBS - 2409 participants
- Developed automated diagnosis of psychiatric diseases based on resting-state network

Yamada et al., 2017
Yahata et al., Nat Commun 2017
Yamashita et al., PLOS Biol 2019

~50 areas

Brodmann 1909



180 areas

Glasser et al Nature 2016

4. しかしまだデータの取得方法、解析手法の標準化は確立していない

ヒト脳分析の困難ーデータ取得と前処置

- 脳の構造の分析
  1. 同じ被験者・同じMRI装置で異なる時点で撮影
  2. 3次元的非線形位置合わせ

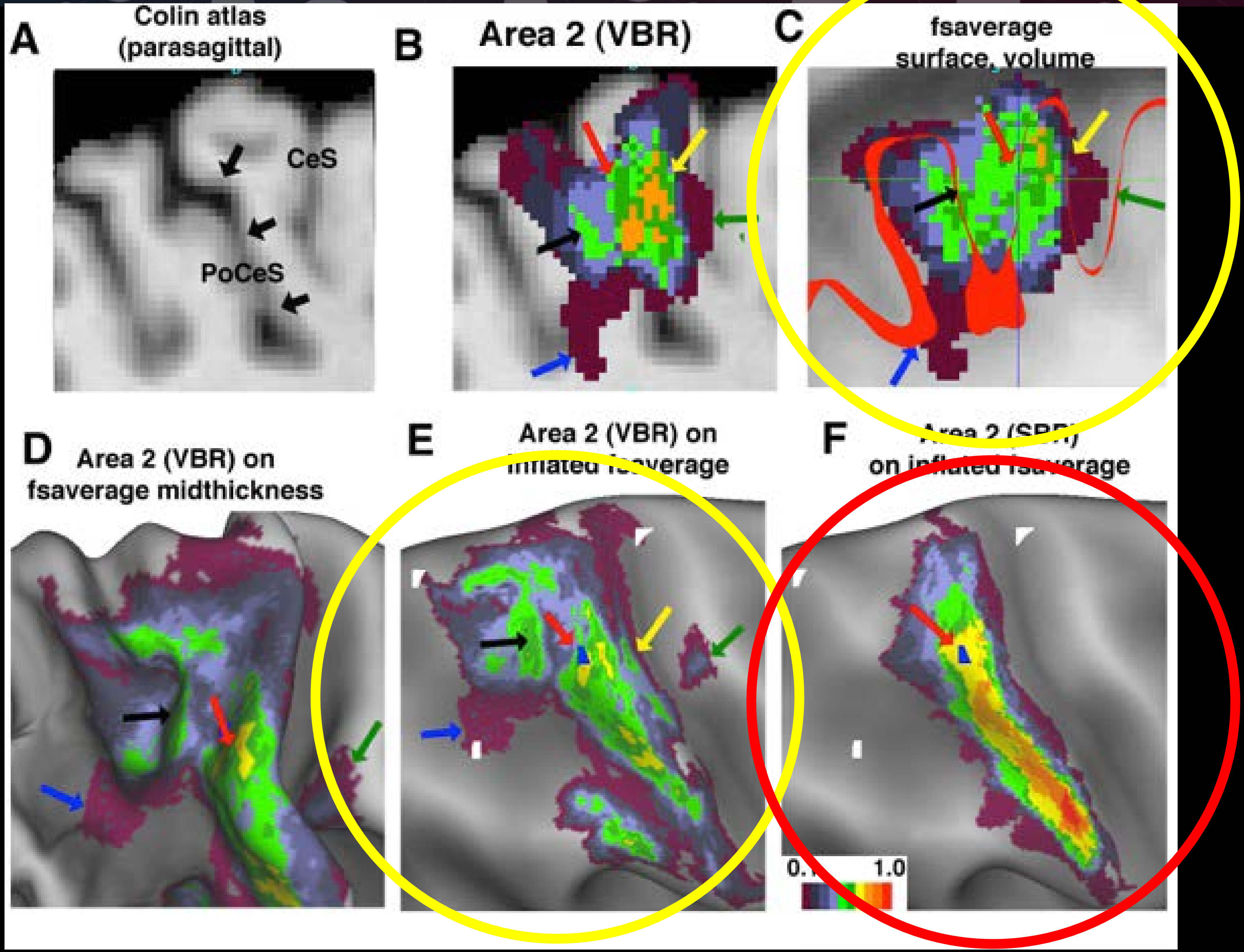
- 前頭頭頂連合野での再現性劣化

- 対策
  1. B1の均一性を考慮した撮像法と解析技術の適用

Verio_test/data/C?_VB_T1_MPR_SPC0

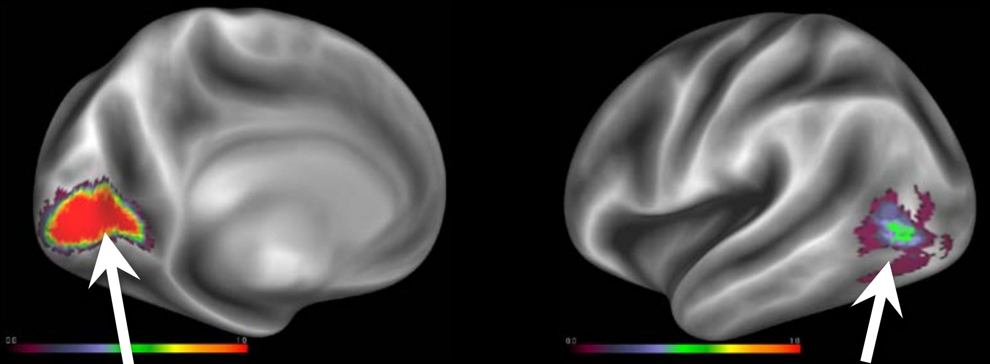
Volume- vs Surface-based Registration

- Cytoarchitectonic Area 2 (Grefkes et al., 2001)
- Surface-registered by FreeSurfer (Fischl et al 2008)
- Volume-registration can not well align over the cortical surface
- Surface-based registration showed more focal overlap across subjects



脳の何を標準化するか？
ー‘形’から’機能’情報の位置合わせ

- 脳回形状(folding)による位置合わせ (e.g. FreeSurfer)
  - うまくいくが完璧ではない
  - 「脳分画」の標準化には形状だけでは不十分?

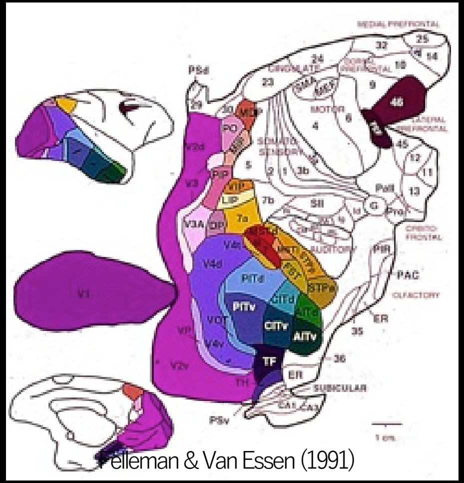


Glasser @ HCP Course 2016
From Fischl et al 2008

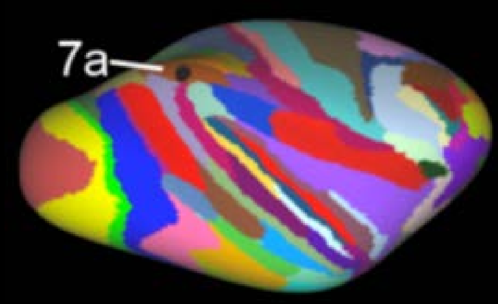
V1 Max Overlap 100%

MT+ (hOc5) Max Overlap 50%

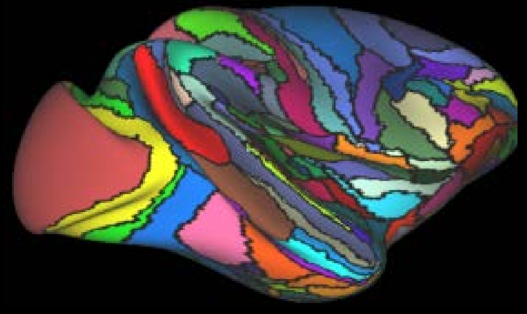
- “FACT” (Function, Architecture, Connectivity, and Topology)による位置合わせ・分画化?



91 architectonic areas
(Markov et al., 2014)

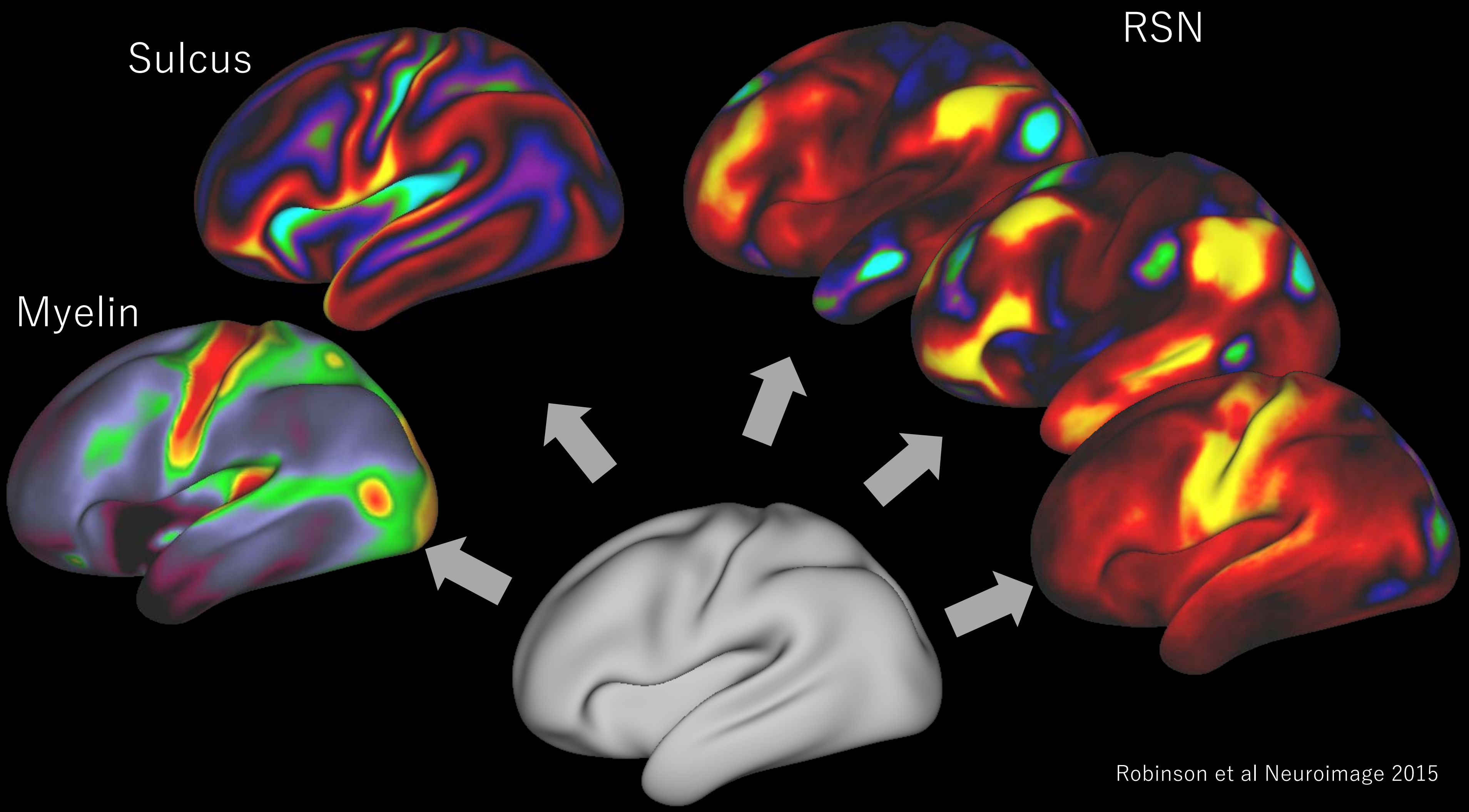


164 architectonic areas
(Paxinos et al., 2000)



マルチモーダル表面位置合わせ

- Multi-modal Surface Matching (MSM)



Robinson et al Neuroimage 2015

HARP (HARmonized Protocol in Brain/Minds-beyond)

1. Next-generation multi-site, standardized, high-spec 3T MRI* protocols in Japan

   *High-spec 3T - MRI scanner should have an ability of multi-band EPI sequence, and 32ch head coil. Started with five high-spec 3T MRI scanners (Siemens) but welcome other scanners/vendors in near future

2. The purpose is to harmonize across scanners and to allow cross-site studies of clinical brain imaging in neurology, psychiatry and neuroscience

3. Optimized preprocessing with surface-based analysis to harmonize across protocols (HARP, SRBP, HCP, UK biobank)

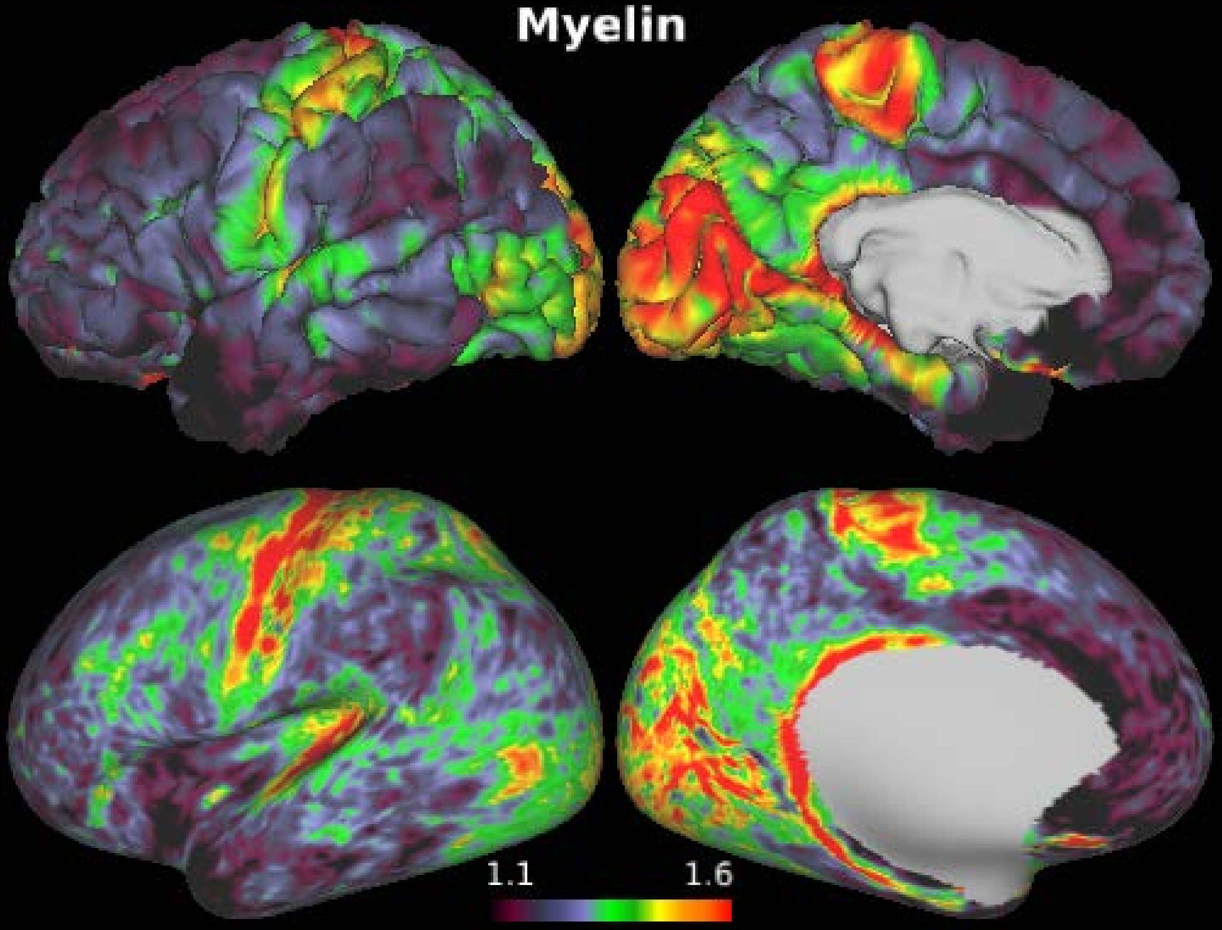
4. Higher-level harmonization with traveling subjects' study

Koike et al., BioRxiv

Structural MRI

- Spatial resolution
  - 0.8 mm in HARP & CRHD ~ a half of minimum cortical thickness
- Fat suppression (w/ water excitation pulse)
  - Reduce bone marrow signals in cranium
  - Works when estimating brain & cortical surface
  - HARP & CRHD: ON
  - Cf. HCP: ON, UK Biobank: OFF
- Apparent TE of T2w was adjusted across scanners

- Preprocessing includes
  - Registration to AP-PC space – 'FLIRT' and 'FNIRT'
    Smith et al., 2004, Jenkinson et al., 2012
  - Homogeneity correction – T1w/T2w-based etc.
    Glaseser et al. NeuroImage 2013
  - Cortical surface reconstruction – 'FreeSurfer'
    Fischl and Dale et al. 2001
  - Create myelin-like contrast with T1w/T2w - 'Connectome Workbench'
    Glaseser et al. J Neurosci 2011



Viewed by Connectome Workbench, 'wb_view'

B1不均一性の補正

- 従来の画像解析プログラムではソフトウェア的に信号値均一化補正を行ってきた（例：MNI N3, N4, SPM, FSL FAST ）
- 実際にはバイアスフィールドは撮像装置や個体の個性（コイル感度、RF照射の均一性、頭部形状や誘電率・撮像時位置等）によって異なる
- HCPでは’ミエリン信号補正法’を採用。T1wおよびT2w画像のデータ取得による実際的手法。

$$Brain\ tissue\ myelin\ contrast\ x \propto T1w \propto 1/T2w$$

$$T1w = x * F$$

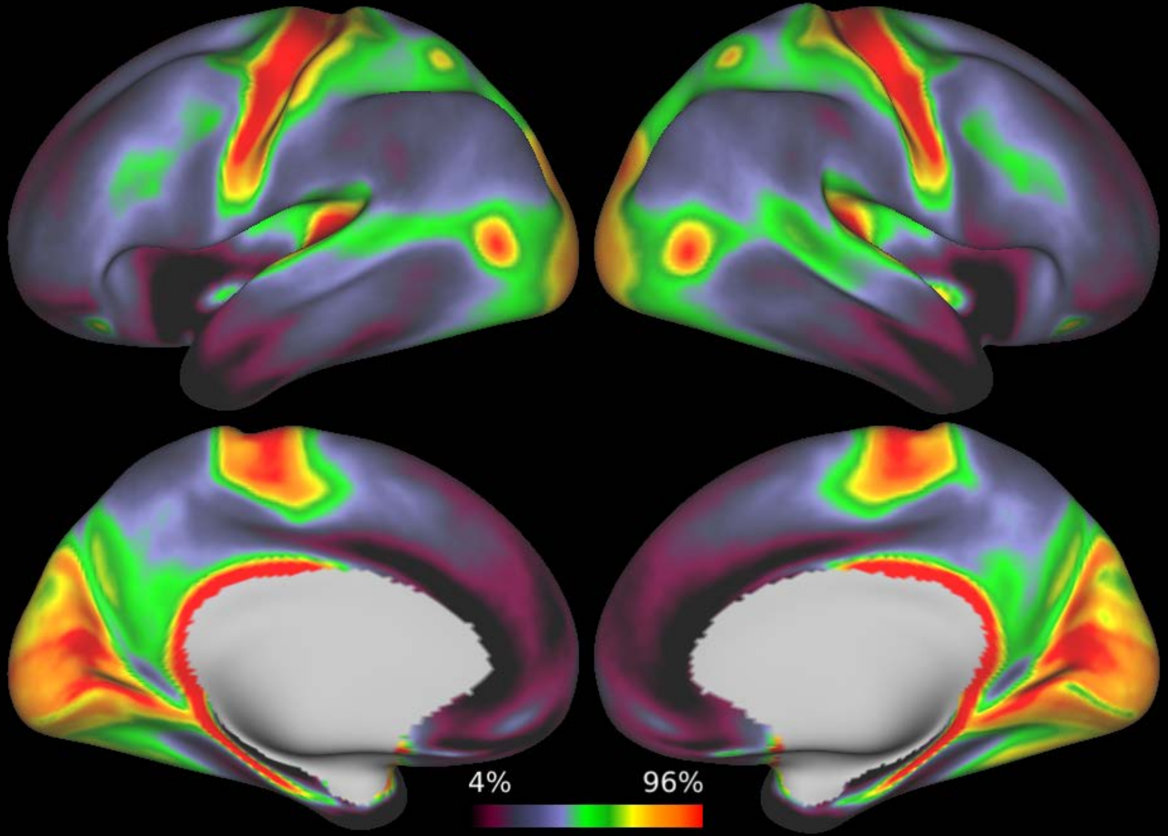
$$T2w = \frac{1}{x} * F$$

$$\therefore \sqrt{T1w * T2w} = \sqrt{(x * F) * \left(\frac{1}{x} * F\right)} = F$$

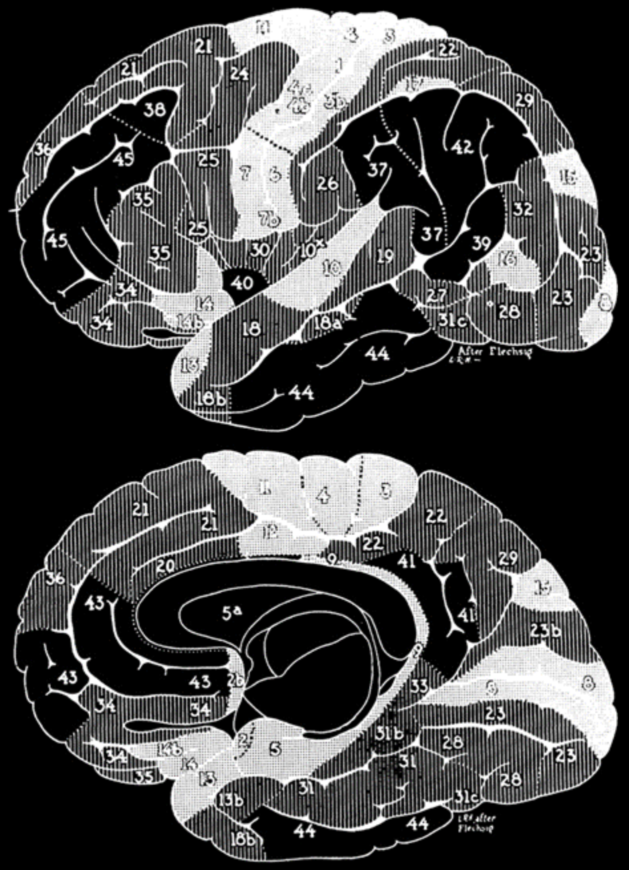
Glasser et al Neuroimage 2013

皮質表面解析ーミエリンマップ

- T1w/T2wのコントラストにより作成
- 一次運動感覚野、MTなどの特異的部位にコントラスト
- 既知のミエリンマップの表面マップとも酷似



Glasser & Van Essen 2011
Glasser et al., Nature 2016



Paul Flechsig (1847-1929)

fMRIは測定器か？

RIKEN Center for Biosystems Dynamics Research

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

ELSEVIER

Challenges in the reproducibility of clinical studies with resting state fMRI: An example in early Parkinson's disease

Ludovica Griffanti [a], Michal Rolinski [b,c], Konrad Szewczyk-Krolikowski [b,c], Ricarda A. Menke [a], Nicola Filippini [a,d], Giovanna Zamboni [a], Mark Jenkinson [a], Michele T.M. Hu [b,c], Clare E. Mackay [a,b,d,*]

ORIGINAL RESEARCH ARTICLE

Front. Neurosci., 05 October 2017 | https://doi.org/10.3389/fnins.2017.00546

The Effect of Low-Frequency Physiological Correction on the Reproducibility and Specificity of Resting-State fMRI Metrics: Functional Connectivity, ALFF, and ReHo

Ali M. Golestani[1*], Jonathan B. Kwinta[1,2], Yasha B. Khatamian[1] and J. Jean Chen[1,2]

Human Bra

Reproducibility of R-fMRI Metrics on t
of Different Strategies for Mult
Comparison Correction and Sampl

Xiao Chen,[1,2] Bin Lu,[1,2] and Chao-Gan Yan [1,2,3,4*]

[1]CAS Key Laboratory of Behavioral Science, Institute of Psychology, Beijing, China
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[3]Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[4]Department of Child and Adolescent Psychiatry, NYU Langone Medical Cen School of Medicine, New York, NY, USA

Reproducibility of functional brain alterations in major depressive disorder: evidence from a multisite resting-state functional MRI study with 1,434 individu

Mingrui Xia, Tianmei Si, Xiaoyi Sun, Qing Ma, Bangshan Liu, Li Wang, Jie Meng, Miao Chang, Xiaoqi Huang, Ziqi Chen, Yanqing Tang, Ke Xu, Qiyong Gong, Fei Wang, Jiang Qiu, Peng Xie, Lingjiang Li, Yong He, DIDA-Major Depressive Disorder Working Group

doi: https://doi.org/10.1101/524496

Now published in *NeuroImage* doi: 10.1016/j.neuroimage.2019.01.074

nature

Review Article | Published: 12 June 2008

What we can do and what we cannot do with fMRI

Nikos K. Logothetis

Nature 453, 869–878(2008) | Cite this article

6536 Accesses | 1630 Citations | 176 Altmetric | Metrics

nature

Variability in the analysis of a single neuroimaging dataset by many teams

https://doi.org/10.1038/s41586-020-2314-9

Received: 14 November 2019

Accepted: 7 April 2020

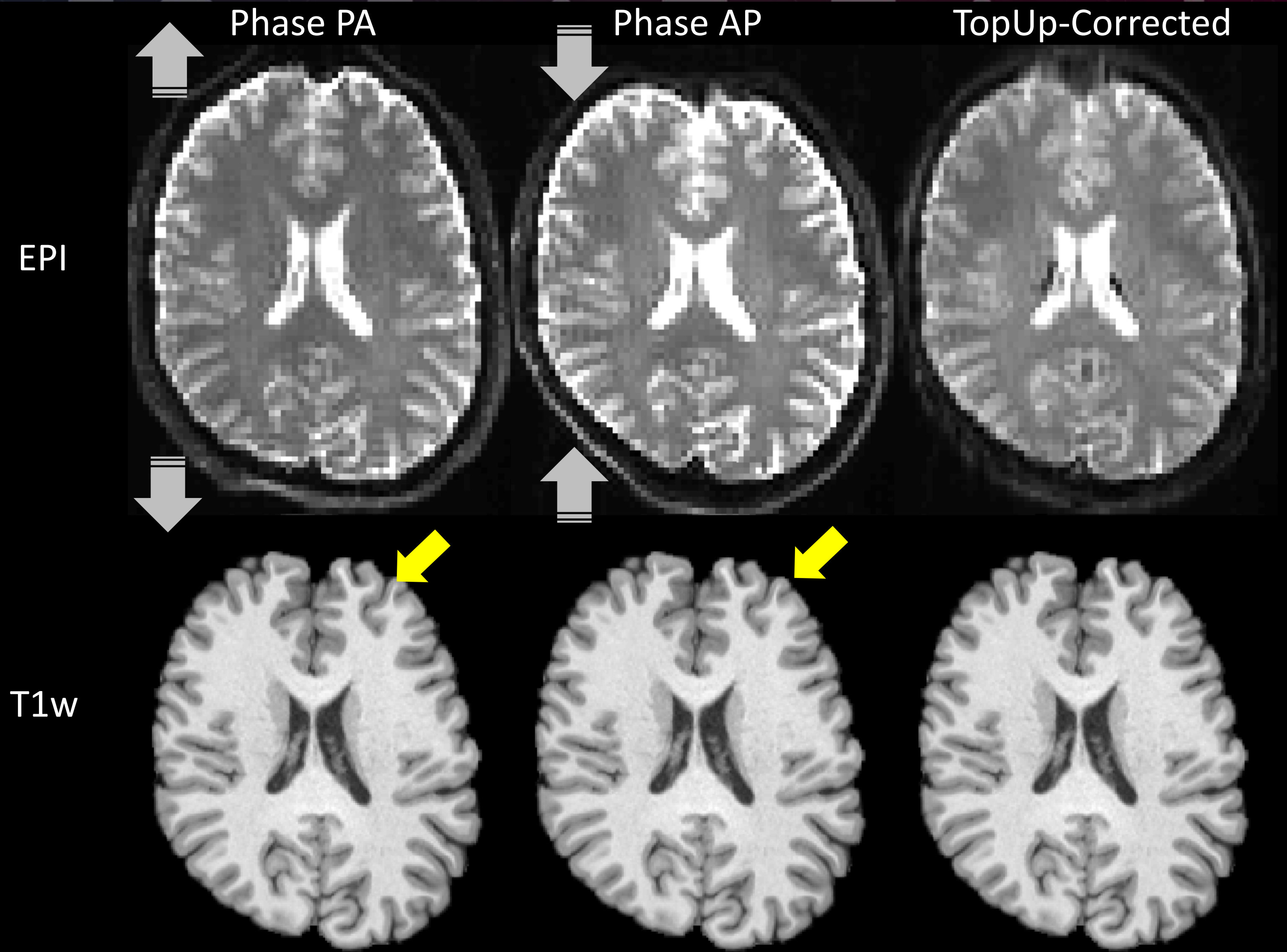
A list of authors and affiliations appears in the online version of the paper.

Data analysis workflows in many scientific domains have become increasingly complex and flexible. Here we assess the effect of this flexibility on the results of

fMRI scan

- Spatial resolution
  - 2.4mm in HARP
  - 2.0mm in CRHD
- Temporal resolution
  - 0.8 sec in HARP & CRHD
- Contrast equalized
  - TE=34.4 ms in HARP
- Fieldmap with opposing phase encoding spin-echo EPI
- Inhomogenity of static magnetic field (B0) causes distortion of EPI image in phase encoding direction
- B0-distortion corrected by 'TopUp'

Andersson et al., NeuroImage 2003



Data from RIKEN-BCIL:/mnt/pub/MRI/Human/HCP-RIKEN/H19022202

fMRIデータの性状

- fMRI信号*の分散 =

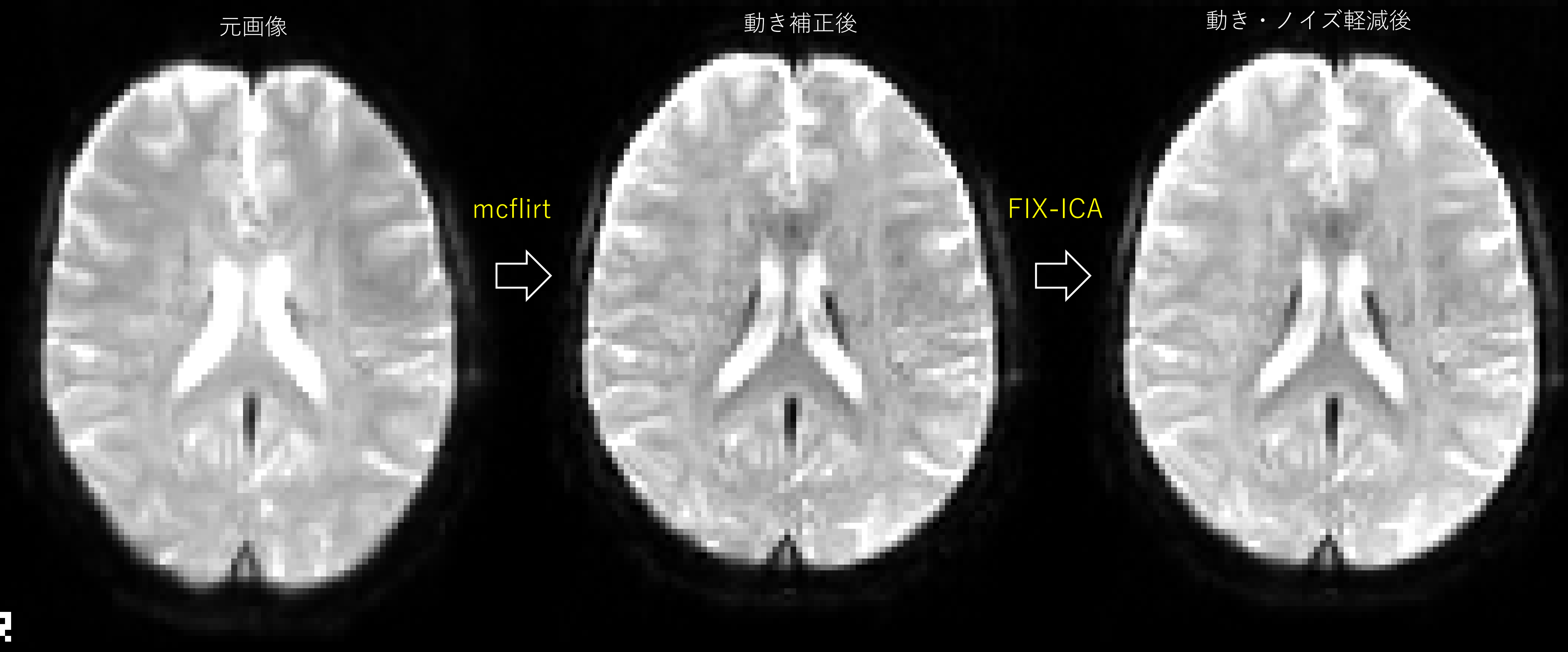
53 % : 非構造ノイズ
15 % : 被験者動き
13 % : 線形の信号ドリフト
12 % : 構造ノイズ
1 % : 生理学的BOLD信号ノイズ
6 % : 構造的BOLD信号

- 動き補正、歪み補正を行ったあとのfMRI信号についての統計結果
- 独立成分分析（ICA)により構造的特徴をもつ要素を抽出・分類しそれらの要素の時間変動から算出したもの

Glasser @ HCP course
Marcus et al., 2013

ノイズの無いfMRI

- 頭の動きにより画像内での頭部の位置がずれる。動きにより画像にも特有のノイズが発生する。
- 古典的には、数学的な位置合わせにより動き補正を行うのみであった。
- 最近の解析技術により機械学習を用いた画像ノイズ除去技術が確立してきた



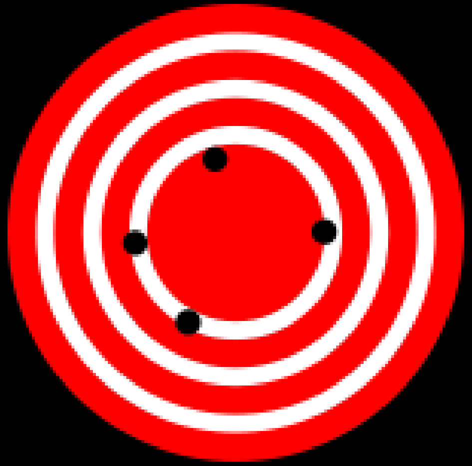
ノイズリダクション

1. ~~周波数カット~~
   - ~~課題fMRI：課題周期の２倍以上の周期~~
   - ~~安静時fMRI: 0.1Hz以上、0.01Hz以下~~
   - ~~Cons: BOLD信号情報の欠損~~
2. ~~空間的平滑化~~
   - ~~ガウシアンフィルター~~
   - ~~Cons: 空間情報の劣化~~
3. ICA-AROMA
   - ICA→体動に関連するアーチファクト分類→除去
   - CIFTIFY, fmriprepに導入
4. ICA-FIX
   - ICA→教師付け機械学習による画像アーチファクト・生理ノイズ(体動・拍動等）の分類→除去
   - FSL, HCP pipelineに導入
   - 課題fMRIも安静時fMRIも組み合わせたmulti-run ICA-FIX
   - プロトコールに合わせた教師付け必要⇒国際脳HARP用に作成中

呼吸、心拍、血管、脳室、CSF

測定器の精度・正確度

- 精度：複数回の値（複数回の測定または計算の結果）の間での互のばらつきの小ささの尺度である。偶然誤差の小ささを言う。再現性や反復性ともいう。
- 正確度：その値が「真値」に近い値であることを示す尺度である。系統誤差の小ささを言う。



高正確度だが低精度

低正確度だが高精度

Accuracy and Precision Wikipedia 2020

- 非侵襲神経画像法では真値はわからない。そのため、理屈にかなった測定法を使う必要あり
- 精度（再現性・反復性）がまずは重要！

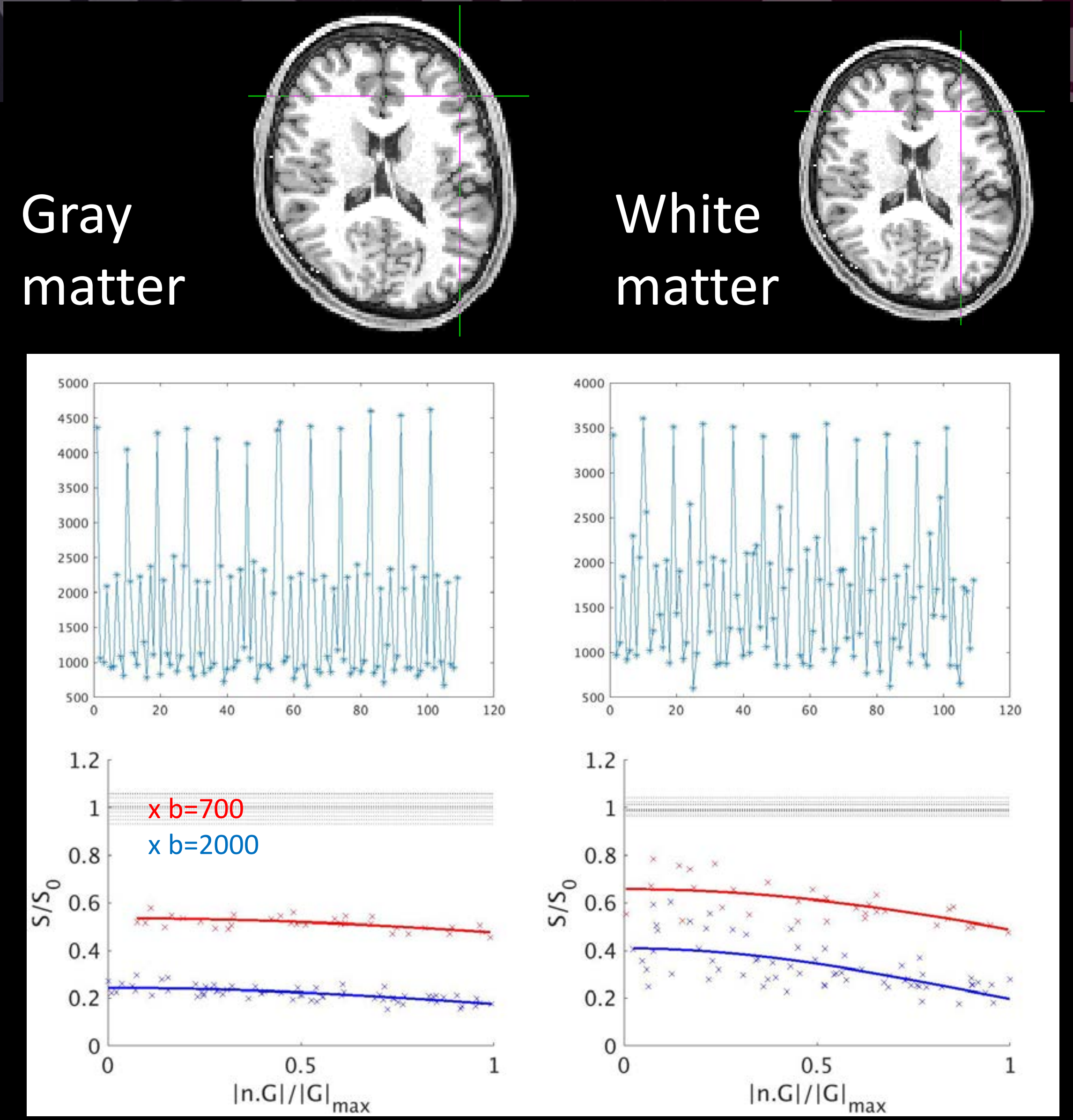
dMRI - Microstructure

- Microstructure modeling using dMRI
    - Diffusion Tensor Imaging (DTI)
    - Diffusion Kurtosis Imaging (DKI)
    - Neurite Orientation Dispersion Density Imaging (NODDI)

Zhang et al., NeuroImage 2012

- HARP is good for NODDI
    - 2-shell with b=700 and 2000 sec/mm^2 was chosen for NODDI

      Zhang et al., NeuroImage 2012
    - Spatial resolution (1.7mm) was chosen based on tSNR (same resolution as in HCP ABCD, higher resolution than in UK biobank)

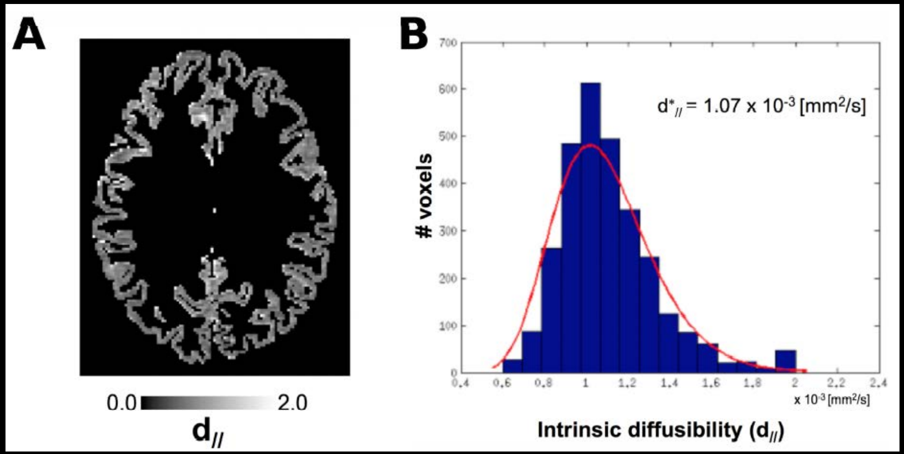


HARP dMRI data obtained at RIKEN, fitted with NODDI model

dMRI - Cortical Microarchitecture

- Optimized intrinsic parallel diffusibility ($d_{//}$)
  - Assumed parameter in NODDI
  - White matter: 1.7 mm^2/s
  - Gray matter: 1.1 mm^2/s

Alexander et al. NeuroImage 2010
Zhang et al. NeuroImage 2011
Fukutomi et al. NeuroImage 2018
Guerrero et al. BioRxiv 2019



Fukutomi et al., NeuroImage 2018

- Accurate NODDI fitting

  'CUDIMOT' – accelerated and precise calculation using GPU

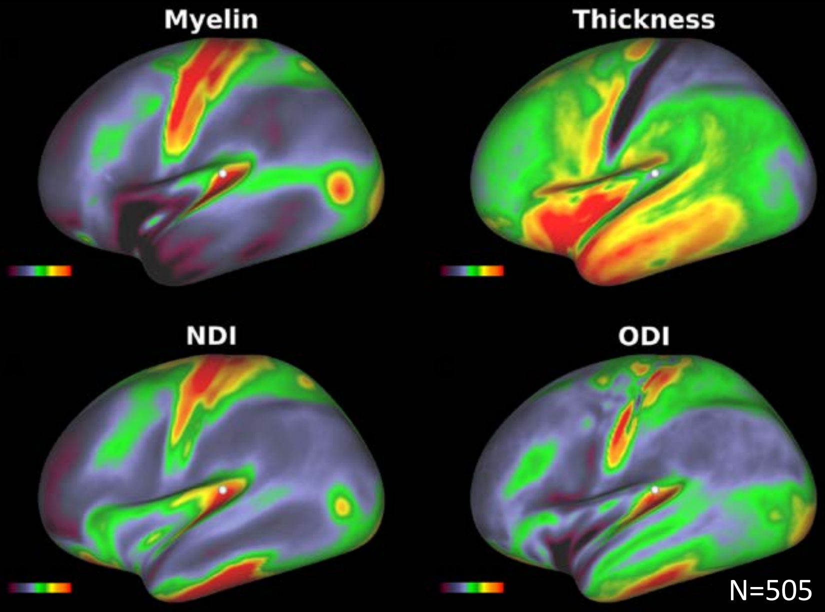
Hernandez-Fernandez et al. NeuroImage 2019

- Optimized cortical surface mapping

  'NoddiSurfaceMapping' – surface mapping of microarchitecture

Fukutomi et al. NeuroImage 2018

Fukutomi et al. Sci Rep 2019



Fukutomi et al., NeuroImage 2018, Fukutomi et al., Sci Rep 2019

dMRI – Tractography is Challenging

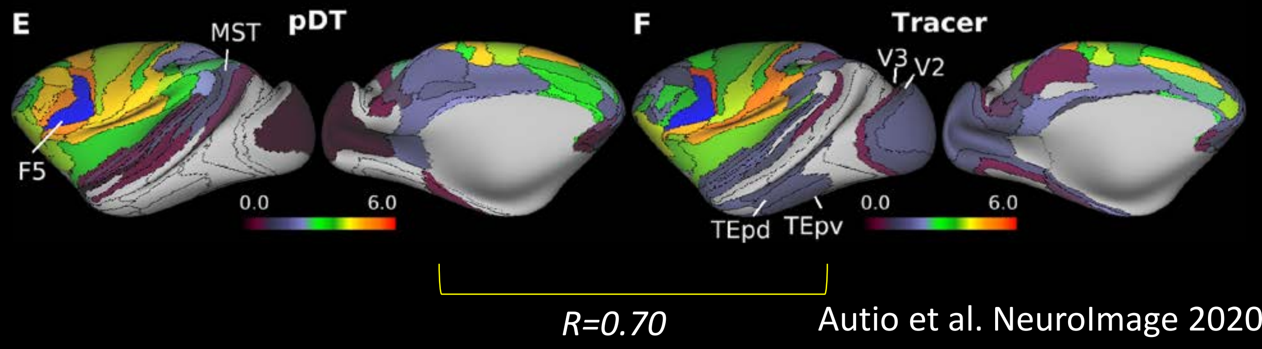
- What is the optimal number of diffusion-weighted direction in dMRI tractography?

- High-quality dMRI (#DIR >270) showed high sensitivity to 3rd crossing fibers (65%) in white matter and accurate tractography comparable with neural tracer (R=0.70)

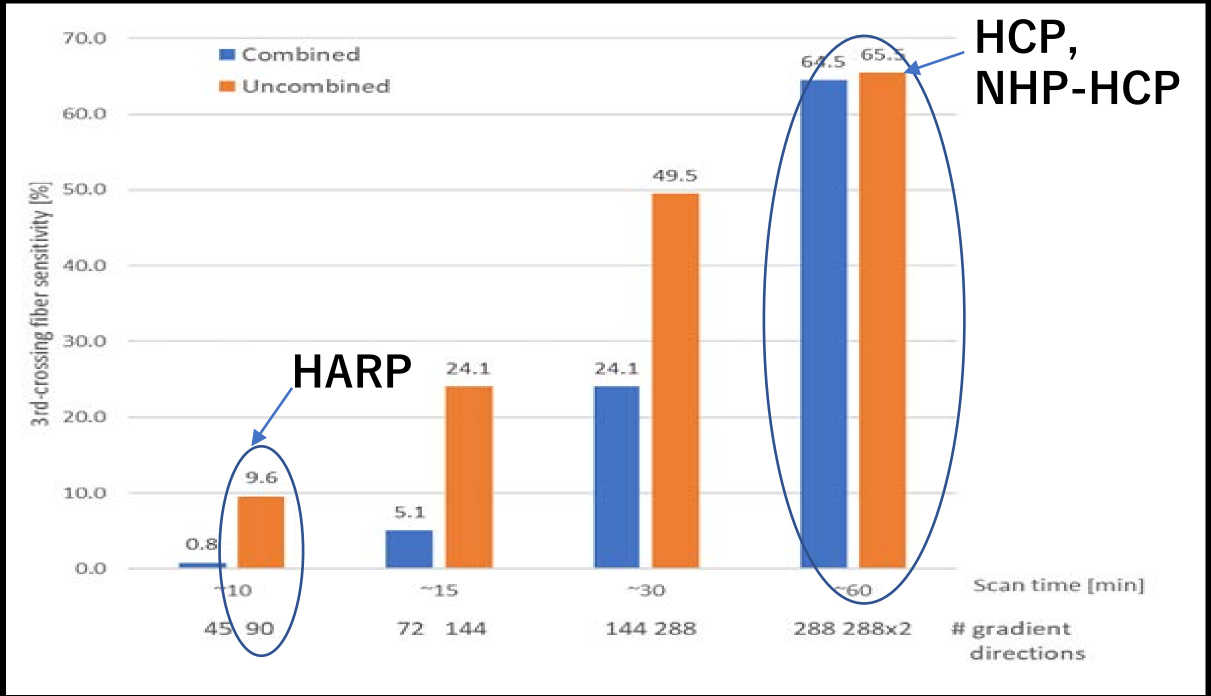
Autio et al. BioRxiv 2019

  - Using ‘Bedpostx_gpu’ and ‘Probtrackx_gpu’

- Simulation revealed that 3rd crossing fiber sensitivity highly depends on the number of diffusion gradient directions.
  - Simulated using HCP data
  - Sensitivity to 3rd fiber is only ~10 % when used 90-direction dMRI (like in HARP)



Autio et al. NeuroImage 2020



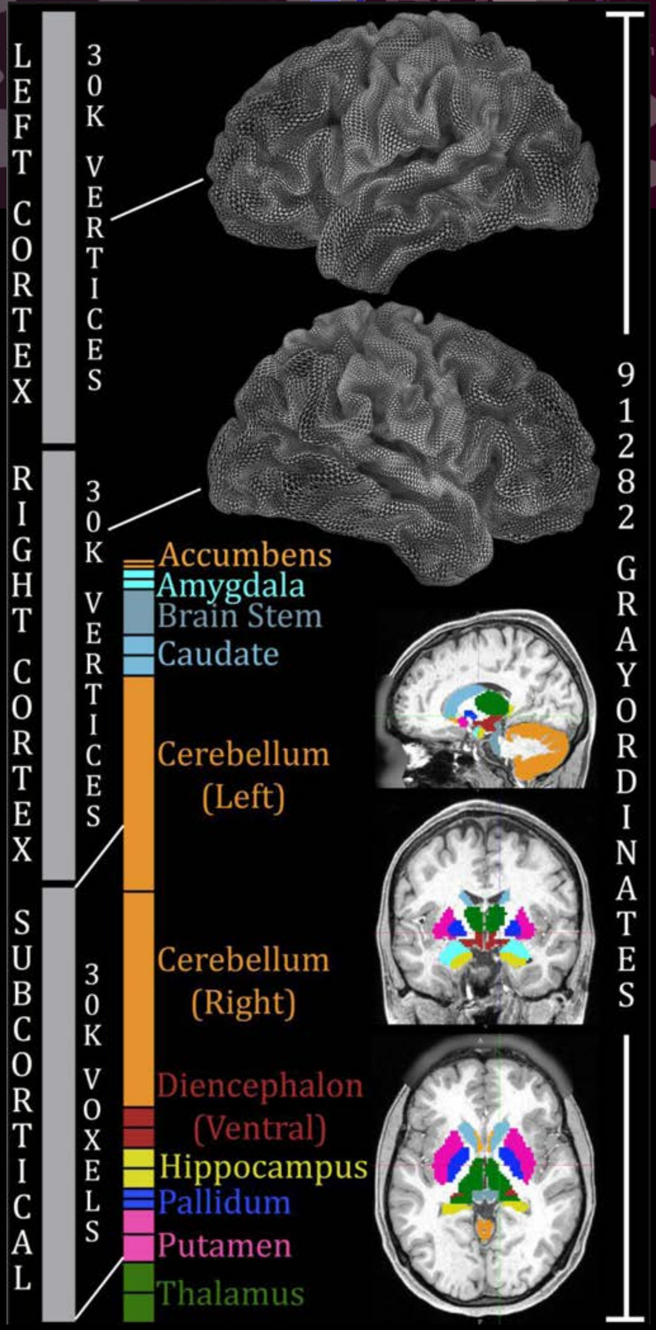
HCPスタイル神経画像法

- 7つの信条
- 大量のマルチモーダルデータを取得すること
- 解像度・画質の最大化（マルチバンドfMRI, dMRI）
- 歪み、ぼけを最小限にすること
- 正確な位置情報を重視（CIFTI grayordinates　灰白質座標）
- 正確な位置合わせ（個人間・実験間）
- 正確な分画化
- 生データの共有・出版物に関連するデータの共有

Glasser et al. Nat Neurosci 2016

標準脳画像フォーマットーCIFTI

- CIFTI : Connectivity Informatics Technology Initiative
- 大脳皮質表面の頂点(vertex)と皮質下構造物の画素（Voxel）-> 灰白質座標(grayordinates)
- 隣接する頂点・画素間の距離はほぼ同じで皮質厚に基づいて決定
  - 頂点・画素間距離
    ヒト2mm
    マカクサル1.25mm
    マーモセット1mm
  - 総数
    ヒト91,282個　(2 x 30k surface, 30k voxels)
    マカクサル26,020個 (2 x 10k surface,
    マーモセット3,086個
- データは2Dの行列のように並ぶ
  - 各灰白質座標を順番に縦方向(column方向）に並べる
  - 時間方向や複数の種類・個人の画像は横方向(row方向）に並ぶ
- MATLABでの扱いも容易。
- 拡張子: .dscalar.nii, dtseries.nii, dconn.niiなど

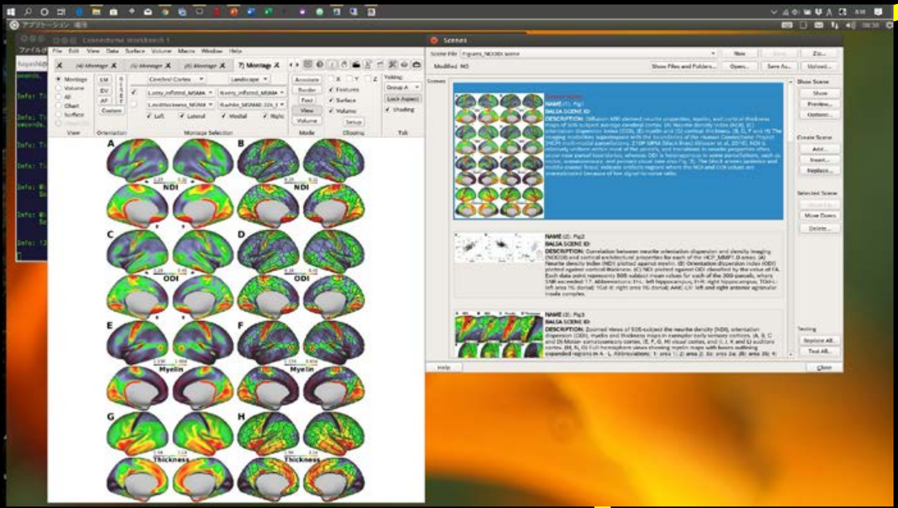


Glasser et al Neuroimage 2013

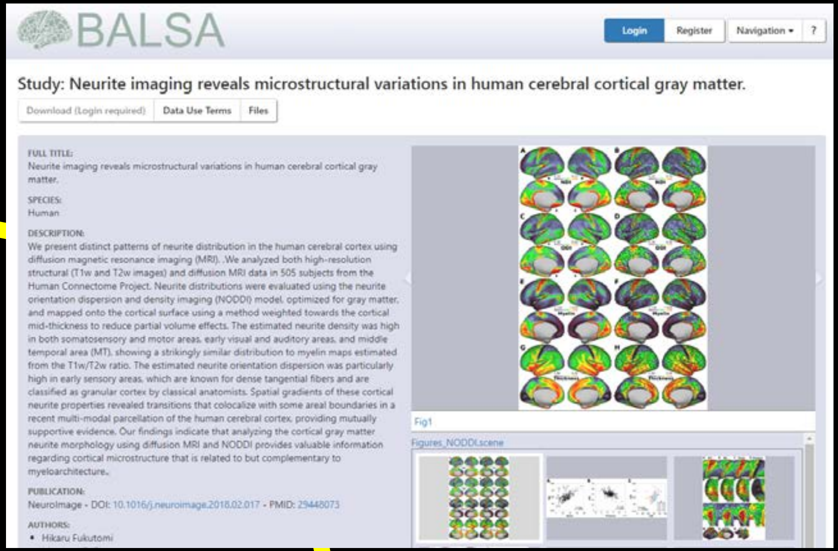
wb_view

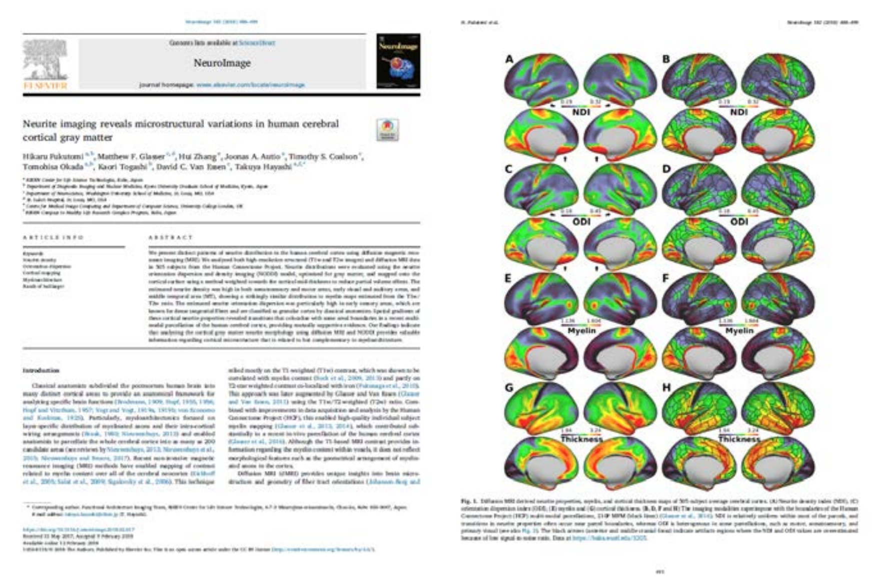
- 論文の図･データの共有

wb_view



BALSA https://balsa.wustl.edu/study/show/k77v

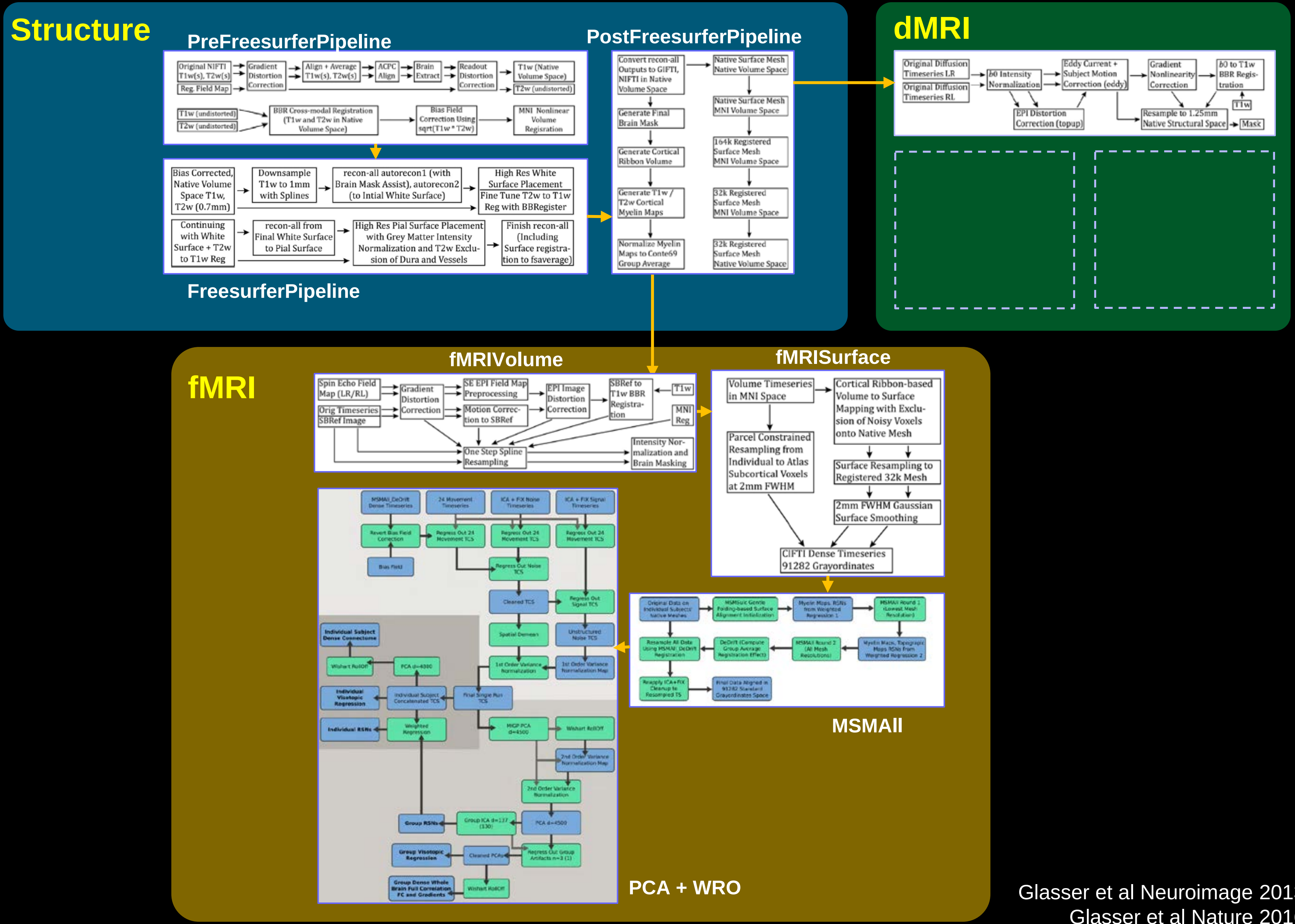




Publication

Fukutomi et al 2018

HCPパイプラン



Glasser et al Neuroimage 2013
Glasser et al Nature 2016

高次レベル解析ツール

- PALM https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM/
  - 画像データ(CIFTI, GIFTI, NIFTI)やテキストデータ等の統計を行えるプログラム
  - パーミューテーションテスト
  - 多変量推定統計：Non-Parametric Combination (NPC), MANOVA, MANCOVA, CCA, PLS
  - 多重比較補正（空間、モダリティ）
- Matlab
  - CIFTI I/O
  https://github.com/Washington-University/HCPpipelines/tree/master/global/matlab
- Python
  - NiBabel
  - Ciftify

HCPパイプラインーコマンド

```
# Set environments
$ export HCPPIPEDIR=<path to HCPPIPEDIR>/Pipelines
$ export HCPEXAMPLES= $HCPPIPEDIR/Example/Scripts
$ source $HCPEXAMPLES/SetUpHCPPipeline.sh
```

⇦ 環境設定

```
# Structural MRI
PreFreeSurferPipelineBatch.sh
FreeSurferPipelineBatch.sh
PostFreeSurferPipelineBatch.sh
```

⇦ 構造MRI画像の前処置

```
# Functional MRI
GenericfMRIVolumeProcessingPipelineBatch.sh
GenericfMRISurfaceProcessingPipelineBatch.sh
IcaFixProcessing.sh
$HCPPIPEDIR/ICAFIX/PostFix.sh
```

⇦ 機能的MRI画像の前処置

⇦ ICAコンポーネントのノイズ、信号を再分類し <subject>/MNINonLinear/Results/<fmminames>の中のReclassifyAsNoise.txtおよびReclassifyAsSignal.txtに記入する。

```
$HCPPIPEDIR/ICAFIX/ReApplyFixPipeline.sh
$HCPPIPEDIR/MSMAll/MSMAllPipeline.sh
$HCPPIPEDIR/DeDriftAndResample/DeDriftAndResamplePipeline.sh
$HCPPIPEDIR/ICAFIX/ReApplyFixPipeline.sh
```

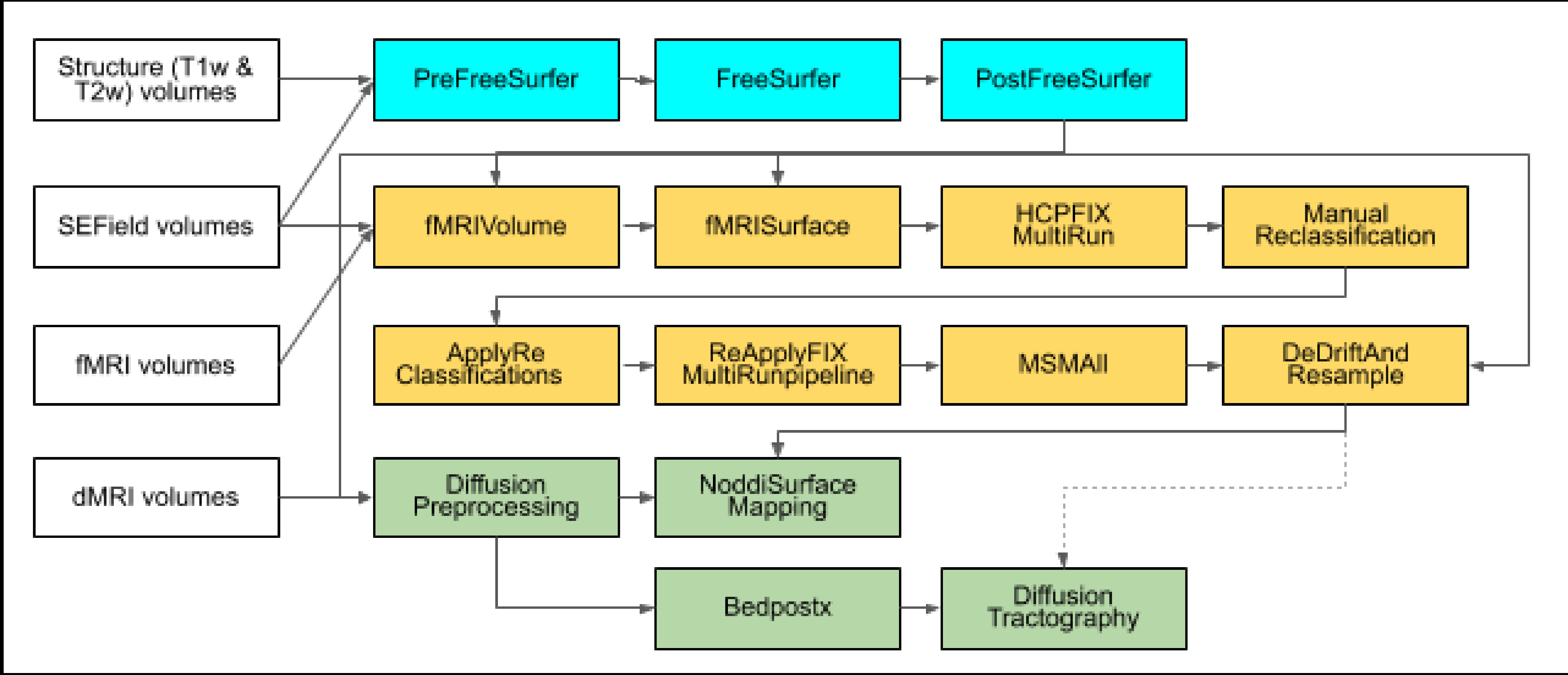
```
# Diffusion MRI
DiffusionPreprocessingBatch.sh
```

⇦ 拡散MRI画像の前処置

```
# Task fMRI
$HCPPIPEDIR/TaskfMRIAnalysis/TaskfMRIAnalysis.sh
```

⇦ タスクMRI画像の前処置

HCPパイプライン　依存関係



まとめ

- 大規模脳MRI研究が国際的にも加速している。高精度のデータ取得と標準化はこれから臨床神経学・精神科学の分野における診断技術の開発に重要な課題である。
- 国際脳では世界に類を見ない多機種のハイスペック3T-MRI装置に対応したハーモナイズドプロトコール（HARP)を策定し、研究を開始した。
- 高解像度、高画質、高均一性の画像を取得し、大脳皮質の複雑性を考慮した分析を行う。前検討結果により、従来よりも再現性が高いデータ取得・解析法であることが示唆される。
- 今後トラベリングサブジェクトの研究推進により統計学的ハーモナイゼーションを行う予定。

Brain/MINDS Beyond Human Brain MRI Project: A Protocol for Multi-Site Harmonization across Brain Disorders Throughout the Lifespan

Running Head: Brain/MINDS Beyond MRI study

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Koike et al., BioRxiv

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Brain/MINDS Beyond

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for HARP protocol/preprocessing and traveling subject study

Scanners

		Prisma	Skyra	Verio VD	Verio VB	Trio
Magnet	Field strength [T]	3				
	Bore size [cm]	60	70			60
	Max. FOV [cm]	~50				~40
	Zero helium boil-off	yes				no
Gradient	Max gradient [mT/m]	80	45			
	Max slew rate [T/m/sec]	200				
RF system	Max Rx channels	128		32		
	Parallel Tx	2		no		
	Head RF Coil	32ch	32ch	32ch	32ch	32ch
Sites		RIKEN, Tokyo U, ATR	Kyoto U, Hiroshima U, Showa U, Kyoto Pre U, Fukushima U	NCNP	NIPS ATR	Tamagawa U

Structure MRI – T1w

T1_MPR	Prisma	Skyra	Verio VD	Verio VB	Trio
FOV(RxPxS) [mm]	256x240x180				
orientation	sagittal (PE dir. : A >> P)				
matrix size	320x300x224				
resolution [mm]	0.8x0.8x0.8				
TR/TE [msec]	2500/2.18/1000				
scan time [min:sec]	5:22				
flip angle [deg]	8				
accelartion (PE)	pF : 6/8, PI : GRAPPA(factor:2, ref.line:32)				
bandwidth [Hz/Px]	220				
Fat sat	Water excite fast				
filter	Distortion Corr OFF, Prescan Normalize				

Structure MRI – T2w

RIKEN BDR RIKEN Center for Biosystems Dynamics Research

T2_SPC	Prisma	Skyra	Verio VD	Verio VB	Trio
FOV(RxPxS) [mm]	256x240x180				
orientation	sagittal (PE dir. : A >> P)				
matrix size	320x300x224				
resolution [mm]	0.8x0.8x0.8				
TR/TE [msec]	3200/564		3200/565	3200/564	3200/562
scan time [min:sec]	5:31	5:31	5:22	6:26	6:26
excitation	variable flip angles				
turbo factor	314	314	326	167	167
accelartion (PE)	PI : GRAPPA(factor:2, ref.line:32)				
bandwidth [Hz/Px]	744	679	679	679	781
filter	Distortion Corr OFF, Prescan Normalize, Image Filter(sharpening & smoothing)				

Functional MRI

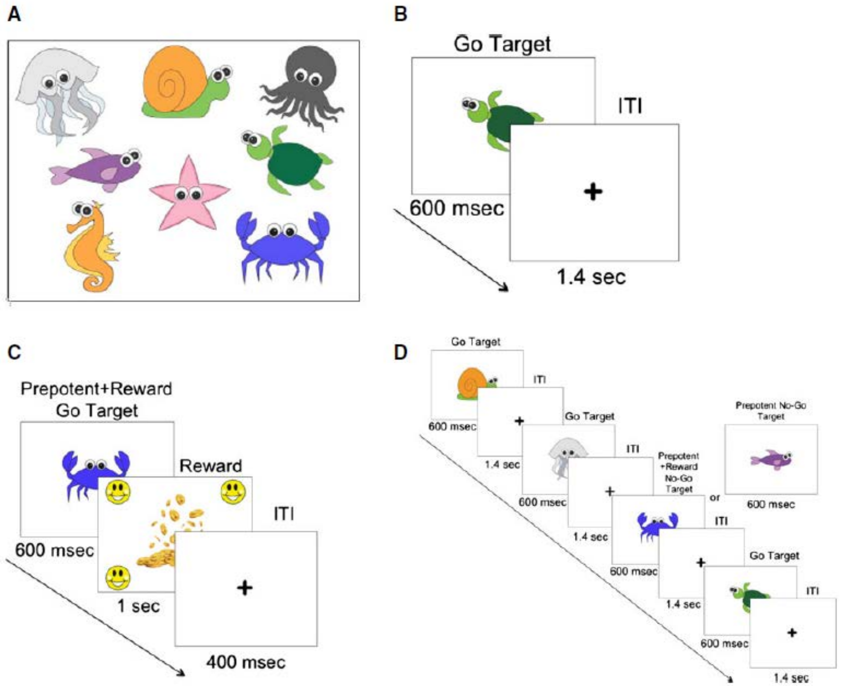
fMRI	Prisma	Skyra	Verio VD	Verio VB	Trio
FOV(RxPxS) [mm]	206x206x144				
orientation	transverse (PE dir. : swapped alternatively btw A >> P & P >> A)				
matrix size	86x86x60				
resolution [mm]	2.4x2.4x2.4				
TR/TE [msec]	800/34.4				
#measurements	375				
scan time [min:sec]	5:08				
flip angle [deg]	52				
accelartion (PE)	PI : Multi-band(factor:6)				
bandwidth [Hz/Px]	2076	2077	2079	2078	2326
Echo spacing	0.63				0.59
filter	Prescan Normalize ON				

Diffusion MRI

dMRI	Prisma	Skyra	Verio VD	Verio VB	Trio
FOV(RxPxS) [mm]	204x204x142.8				
orientation	transverse (PE dir. : swapped alternatively btw A >> P & P >> A)				
matrix size	120x120x84				
resolution [mm]	1.7x1.7x1.7				
TR/TE [msec]	3600/79	3600/89			3600/94
#diff. dirs. Label Phase encoding	53/54 AP/PA	67/68 AP/PA			
b-values [sec/mm^2] vols/dirs/dirs type of gradient	0 / 700/2000 13/32/64 monopolar	0 / 700/2000 17/40/80 monopolar			
scan time [min:sec]	3:32	4:54			
flip angle [deg]	90				
accelartion (PE)	pF:6/8, MB:3	pF:6/8, MB:3, GRAPPA:2(ref.scan:GRE)			
bandwidth [Hz/Px]	1984	1544	1436	1436	1736
filter	Prescan Normalize				

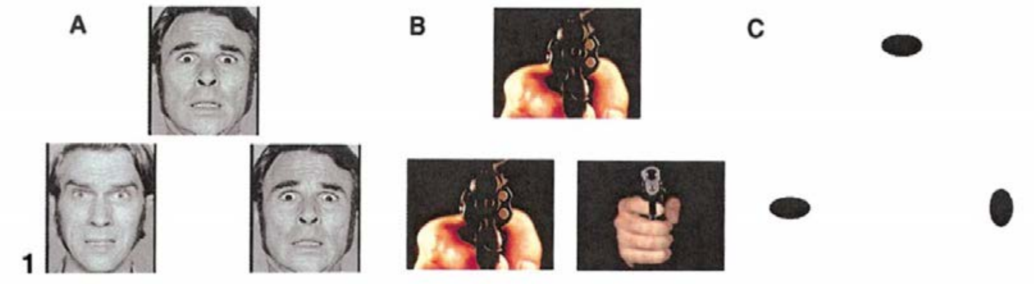
Task fMRI

CARIT



Winter & Sheridan et al. 2014

Emotion



Hariri et al. 2002