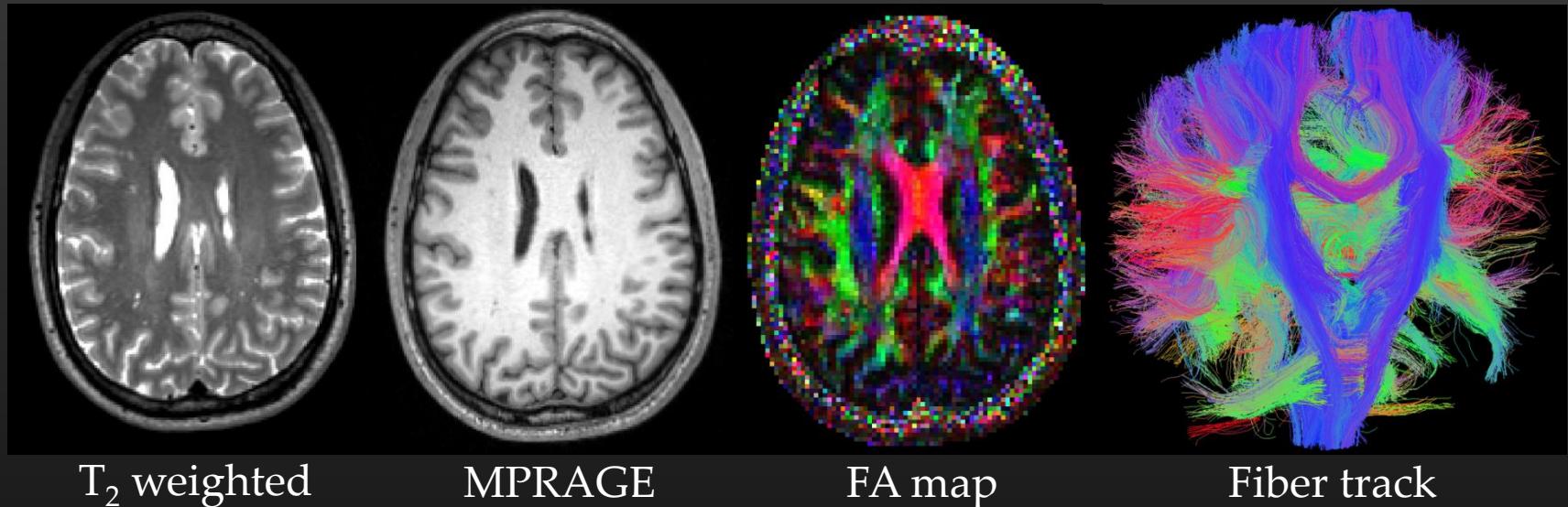


BDP: BrainSuite Diffusion Pipeline

Chitresh Bhushan

Why diffusion MRI?



T₂ weighted

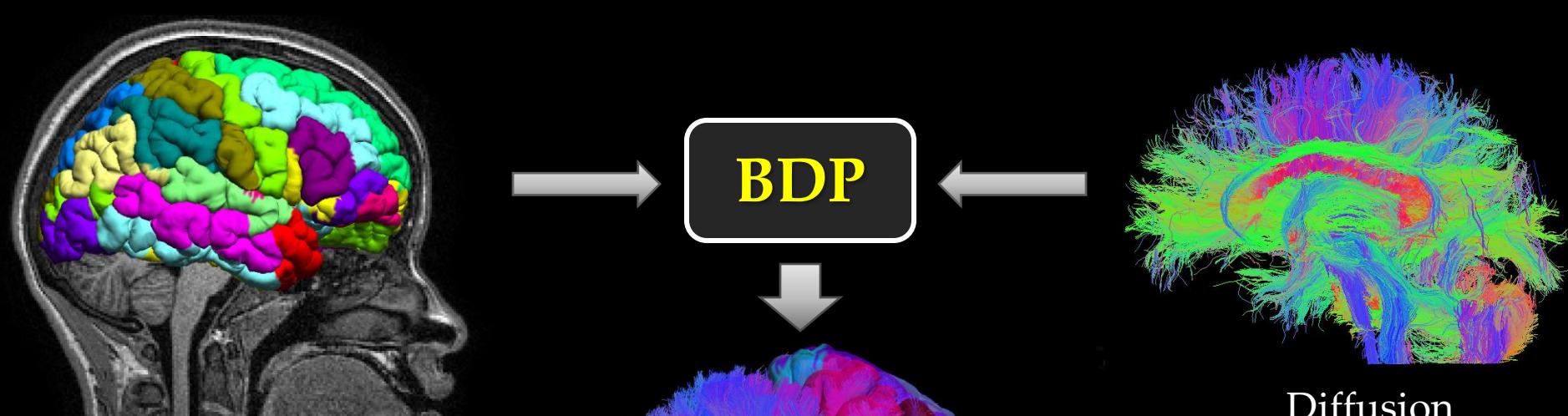
MPRAGE

FA map

Fiber track

- Quantify microstructural tissue characteristics
- Structural connectivity – ‘Connectome’
- Clinical – Abnormalities in white matter – stroke etc.
- Multimodal image analysis

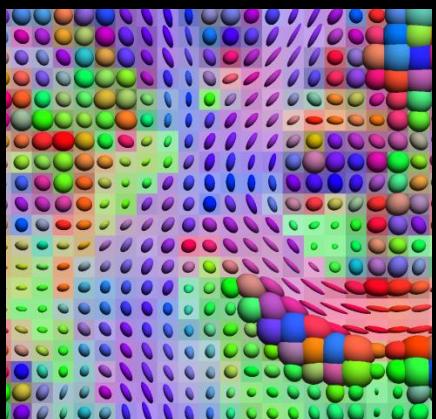
Sporns et al. 2005; Wedeen et al. 2008; Hagmann et al. 2007;
Jones et al. 2011; Johansen-Berg et al. 2009



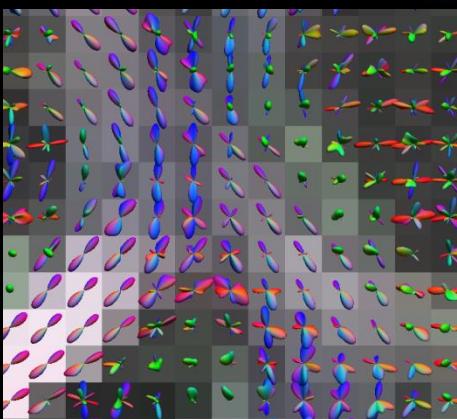
MPRAGE



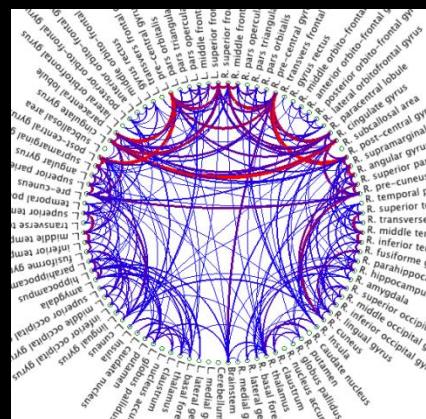
Diffusion



Tensor



ODF

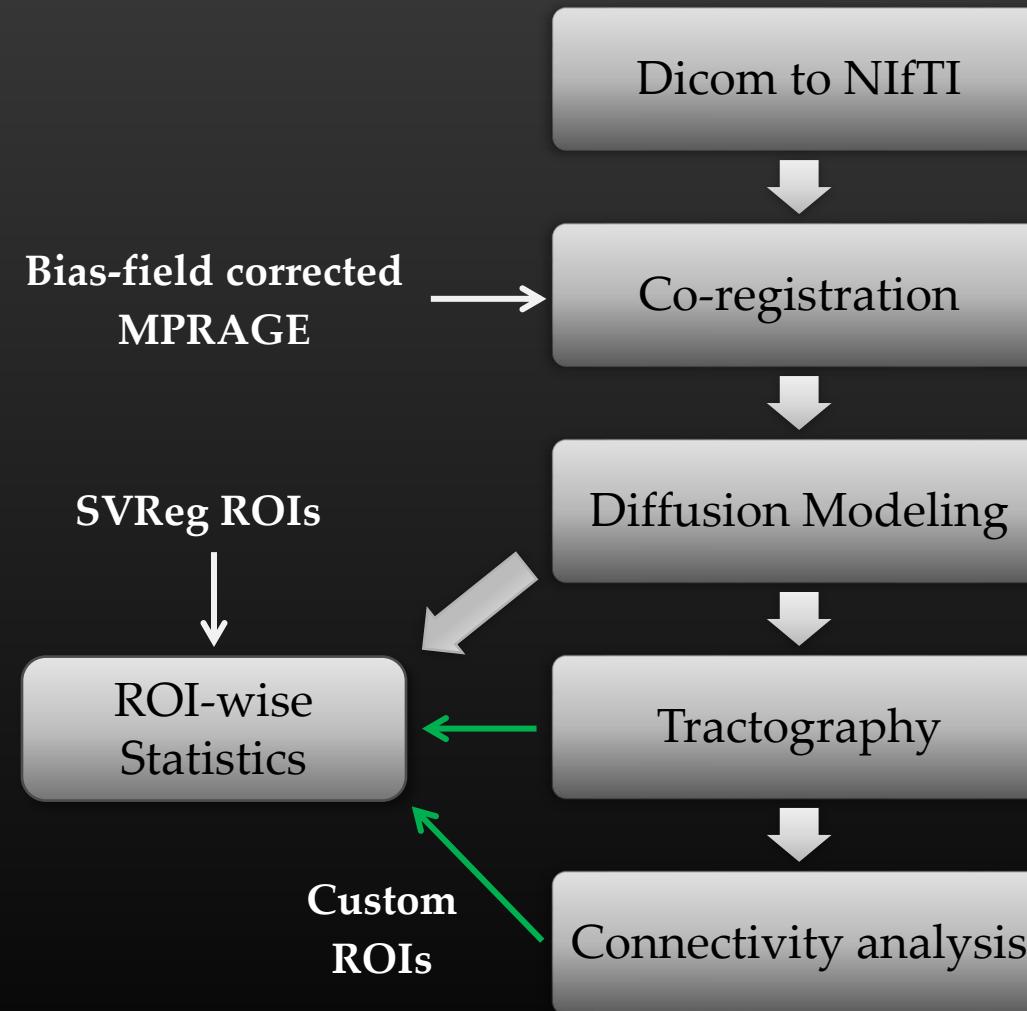


ROI Connectivity

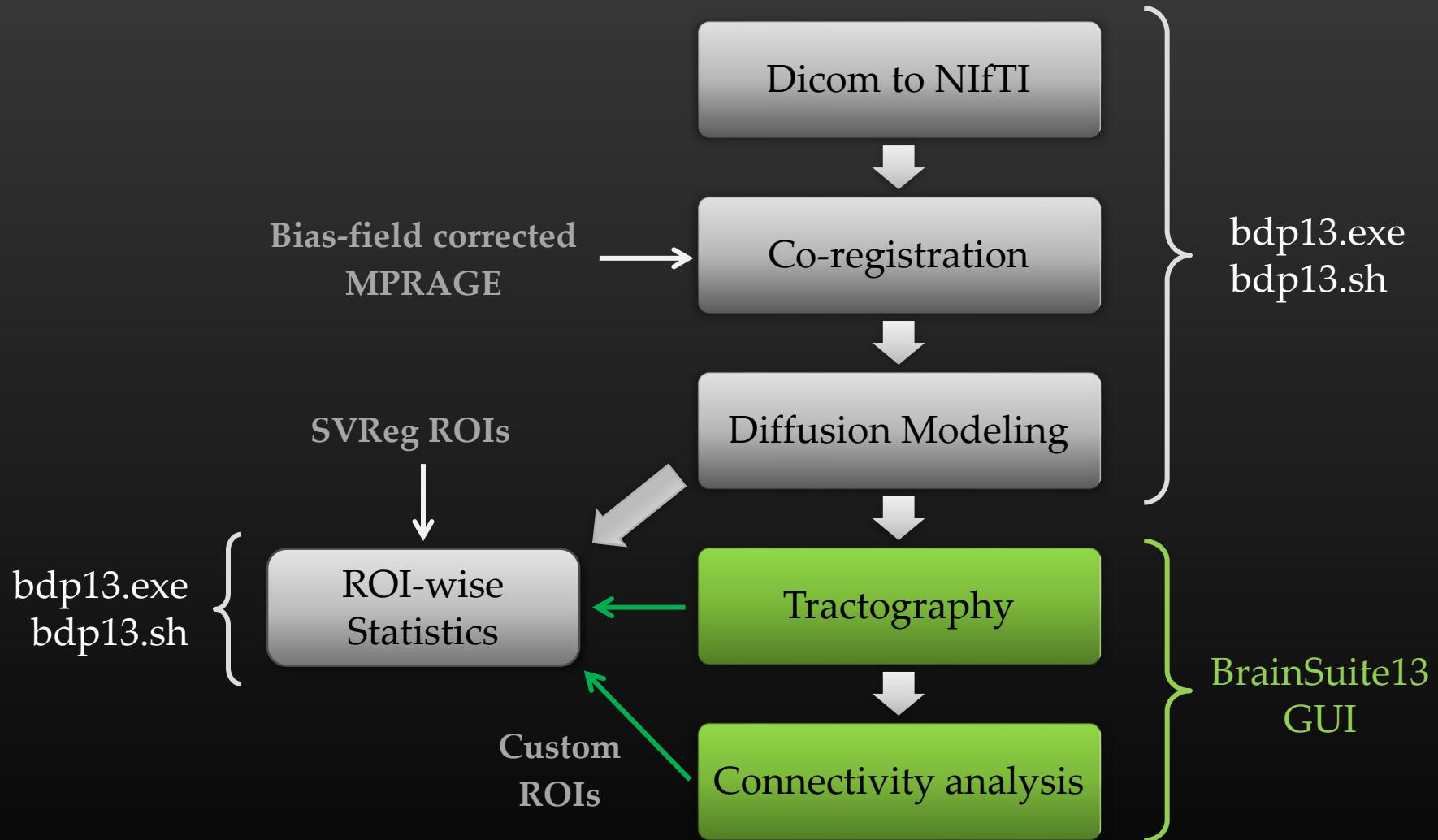
A	B	C	D
ROI_ID	Missing voxels	Mean (GM+WM)	Var (GM+WM)
120	2076	0.193647623	0.157876641
121	939	0.202837408	0.165470749
130	0	0.183879077	0.152853325
131	0	0.173550412	0.141550764
140	0	NaN	NaN
141	0	NaN	NaN
142	0	0.193445236	0.157581672
143	0	0.212929964	0.172584817
144	0	0.178581178	0.141114518
145	0	0.180468515	0.149058774
146	0	0.19012776	0.151103929
147	0	0.190880433	0.143366888
150	805	0.228198722	0.184615031
151	1173	0.223954752	0.184945568

ROI Statistics

Diffusion Pipeline

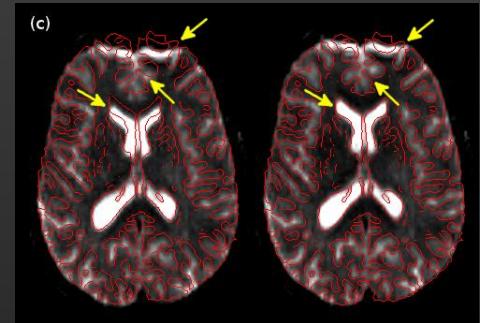


Diffusion Pipeline

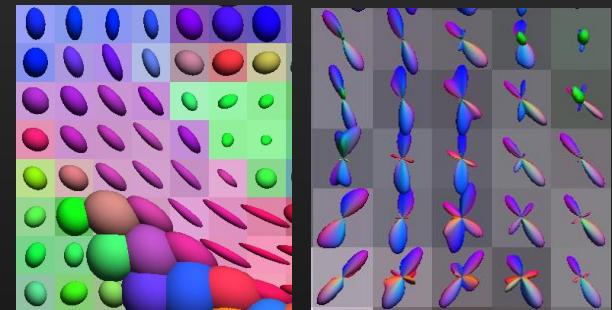


bdp.exe – overview

- Co-register diffusion and MPRAGE scan
 - Distortion correction – multiple methods



- Fit diffusion model
 - Multiple models – Tensor, ODFs
- Compute *basic* ROI-wise statistics
 - Custom ROIs, track based ROIs etc.



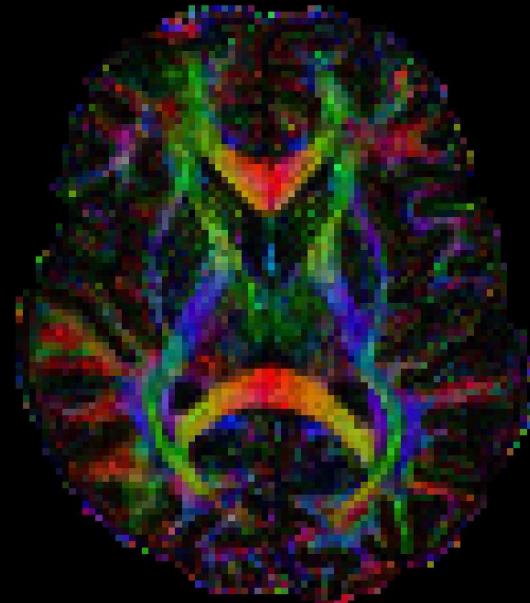
A	B	C	D	E	F	G
ROI_ID	Missing voxels	Mean (GM+WM)	Var (GM+WM)	Used voxels (GM+WM)	Mean (WM)	Var (WM)
120	2076	0.193647623	0.157876641	49453	0.367816687	0.158458
121	939	0.202837408	0.165470749	49200	0.384492725	0.163745
130	0	0.183879077	0.152855325	17984	0.371815881	0.152749
131	0	0.173550412	0.141550764	22918	0.347554863	0.142177
140	0	NaN	NaN	0	NaN	NaN
141	0	NaN	NaN	0	NaN	NaN
142	0	0.193445236	0.157581672	6447	0.394196153	0.124804
143	0	0.212929964	0.172584817	7183	0.414764017	0.14748
144	0	0.178581178	0.141114518	9902	0.345779568	0.12801
145	0	0.180468515	0.149058774	8167	0.353723109	0.141367
146	0	0.19012776	0.151103929	3030	0.36529085	0.157643
147	0	0.190880433	0.143366888	2865	0.348852992	0.136231
150	805	0.228198722	0.184615031	23130	0.397928327	0.16902
151	1173	0.223954752	0.184945568	21000	0.423291534	0.159717

Co-registration { & distortion correction

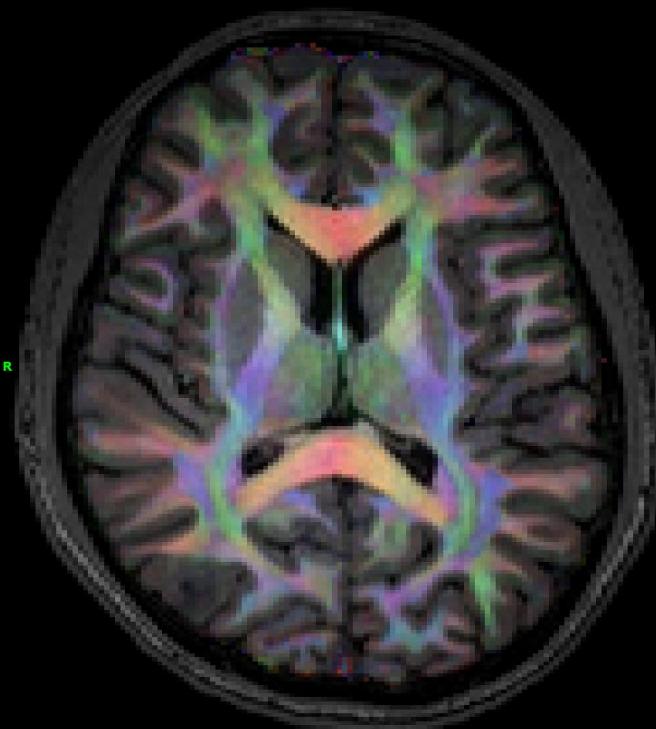


MPRAGE Coord
(Surfaces, Labels)

Co-register



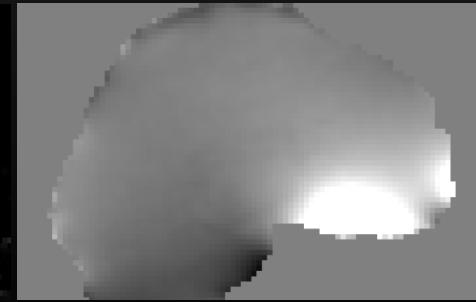
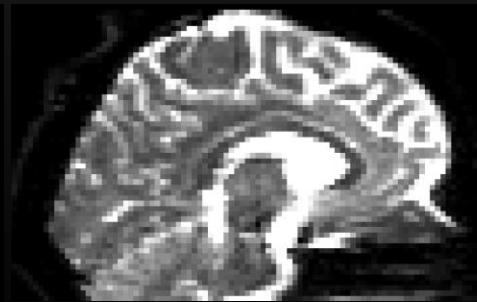
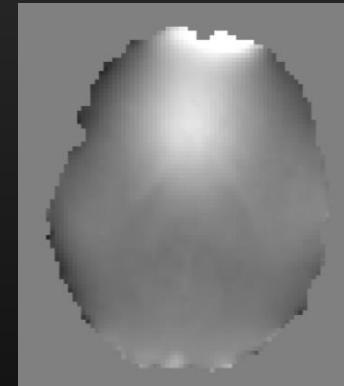
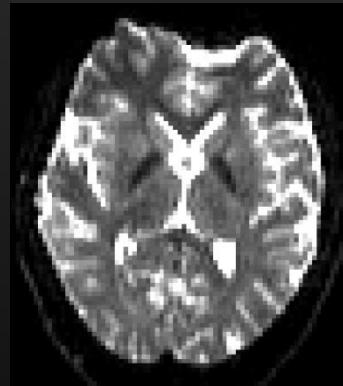
Diffusion Coord



Diffusion MRI -
Rigid registration
is not enough!

EPI distortion

- Diffusion MRI uses fast acquisition – Echo planar Imaging (EPI)
- Susceptibility differences \Rightarrow Magnetic field (B_0) inhomogeneity
- EPI is sensitive to B_0 inhomogeneity \Rightarrow Localized geometric distortion



MPRAGE image

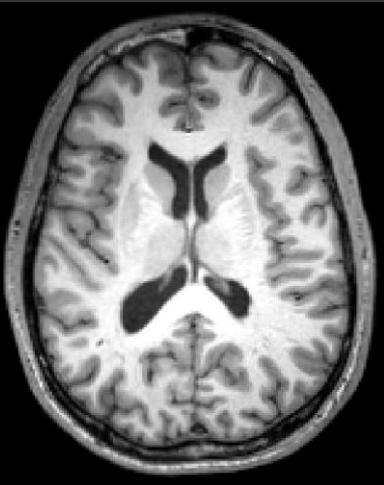
b=0 image (EPI)

Field inhomogeneity map

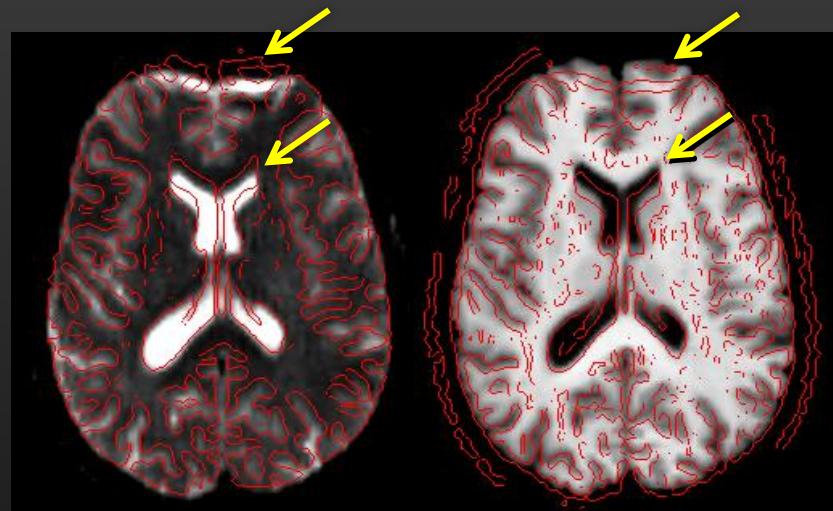
EPI distortion



b=0 image (EPI)



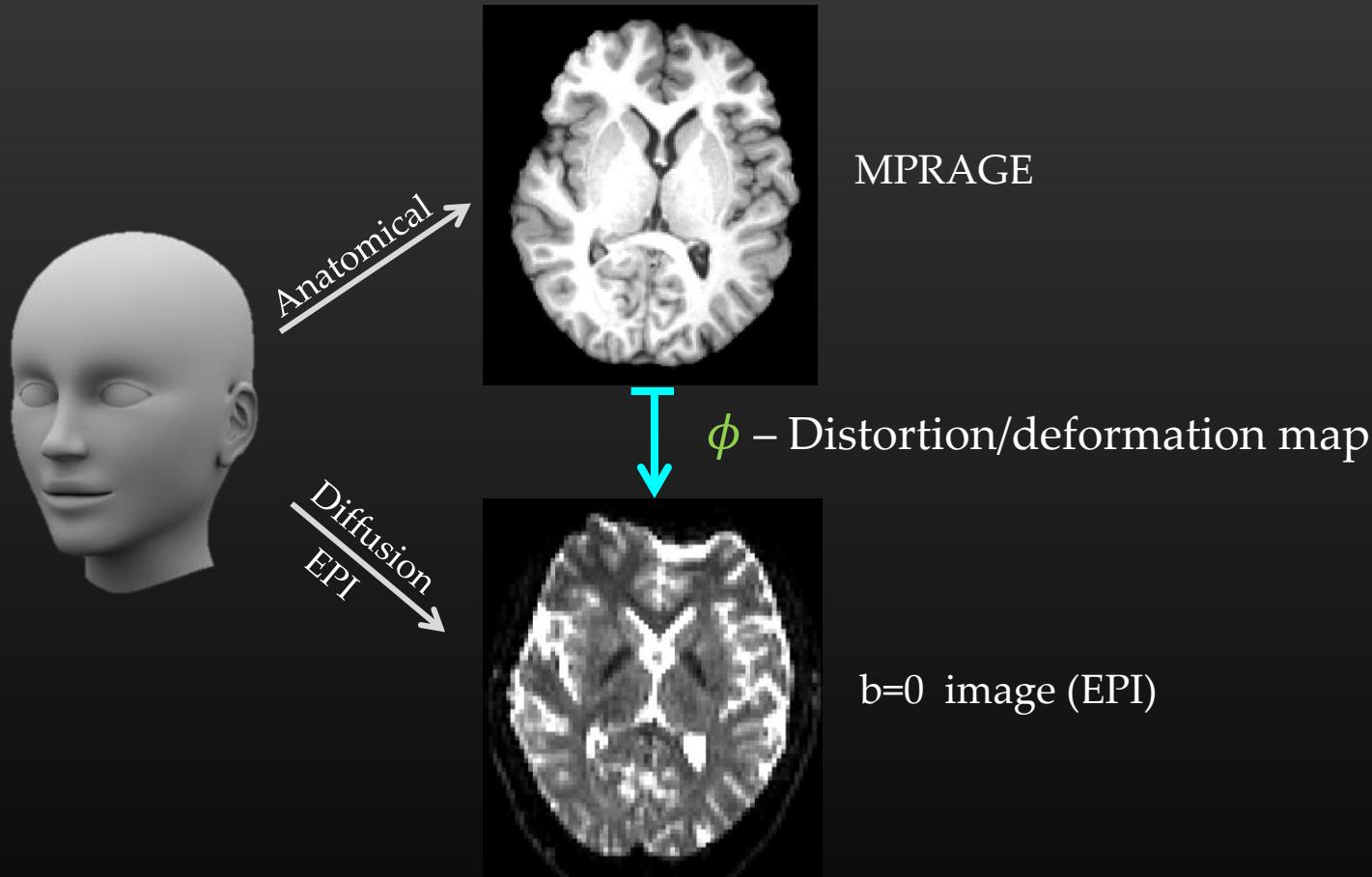
MPRAGE



Overlay with edges

- Misalignment with structural scans by several millimeters
- Limits the accuracy of multi-modal analysis

Distortion correction framework



- Somehow estimate/find the deformation map ϕ

Distortion correction in BDP

1. Registration based distortion correction

- Uses structural image to estimate distortion field
- Does *not* require any field inhomogeneity map

2. Fieldmap based distortion correction

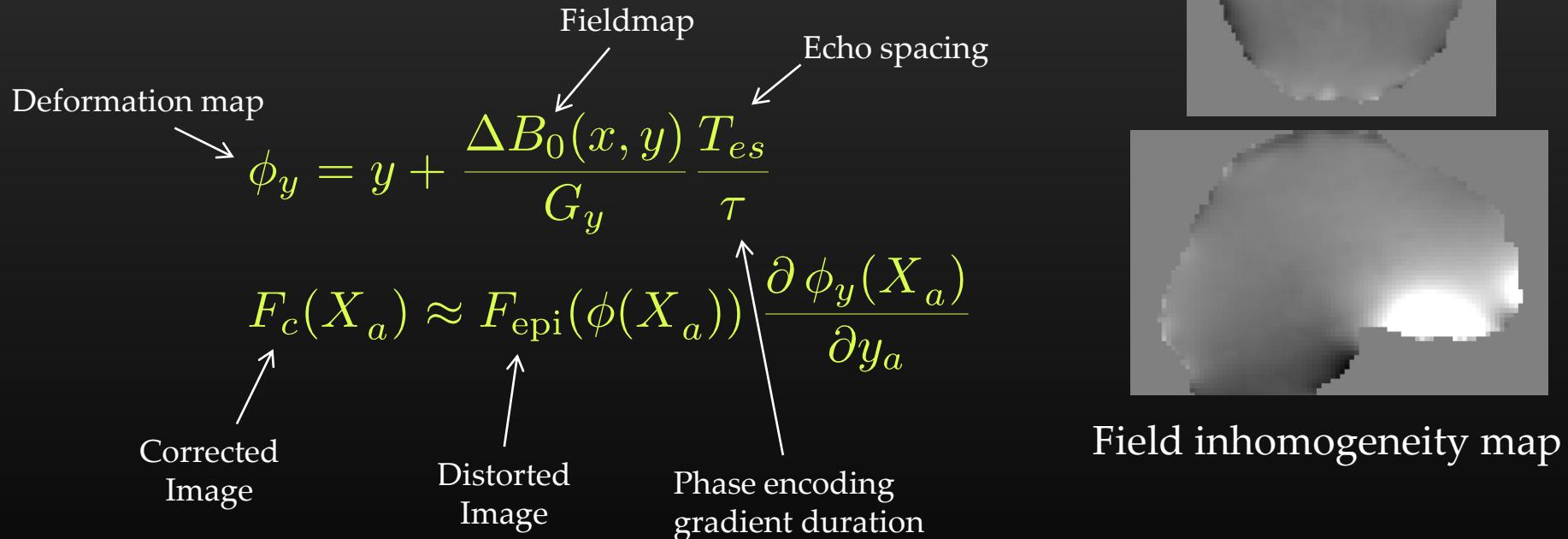
- Requires field inhomogeneity map
- Lower computational requirement

3. No distortion correction

- Only Rigid registration to MPRAGE

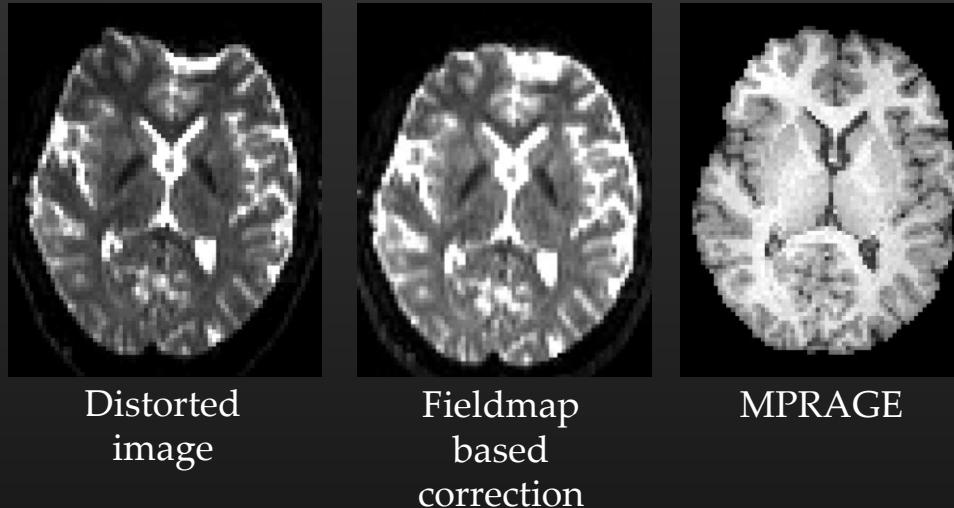
Fieldmap based correction

- › (Indirectly) Acquire the deformation map ϕ
- › Computed from field inhomogeneity map (fieldmap) $\Delta B_0(x, y)$



Fieldmap based correction

- Accurate correction in “most” regions

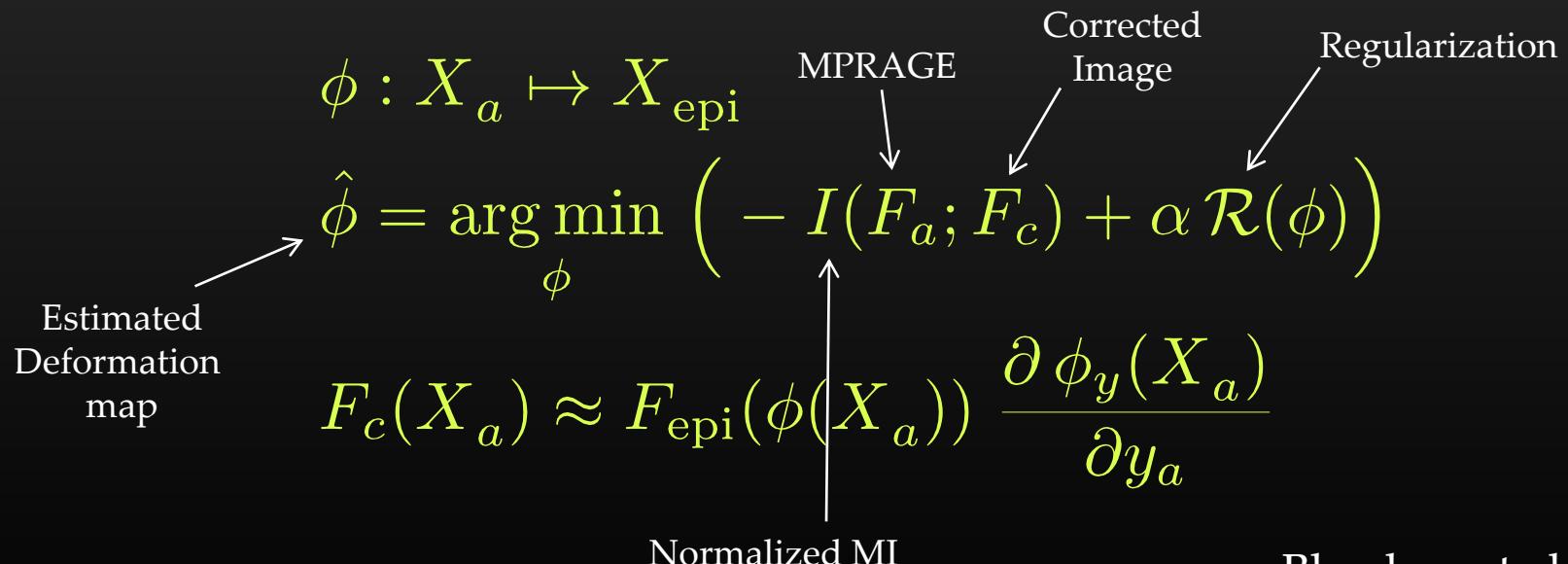


Drawbacks:

- Additional Data acquisition (fieldmap)
- Can not be used on data already acquired without field map
- Sensitive to errors in fieldmap acquisition/estimation

Registration based correction

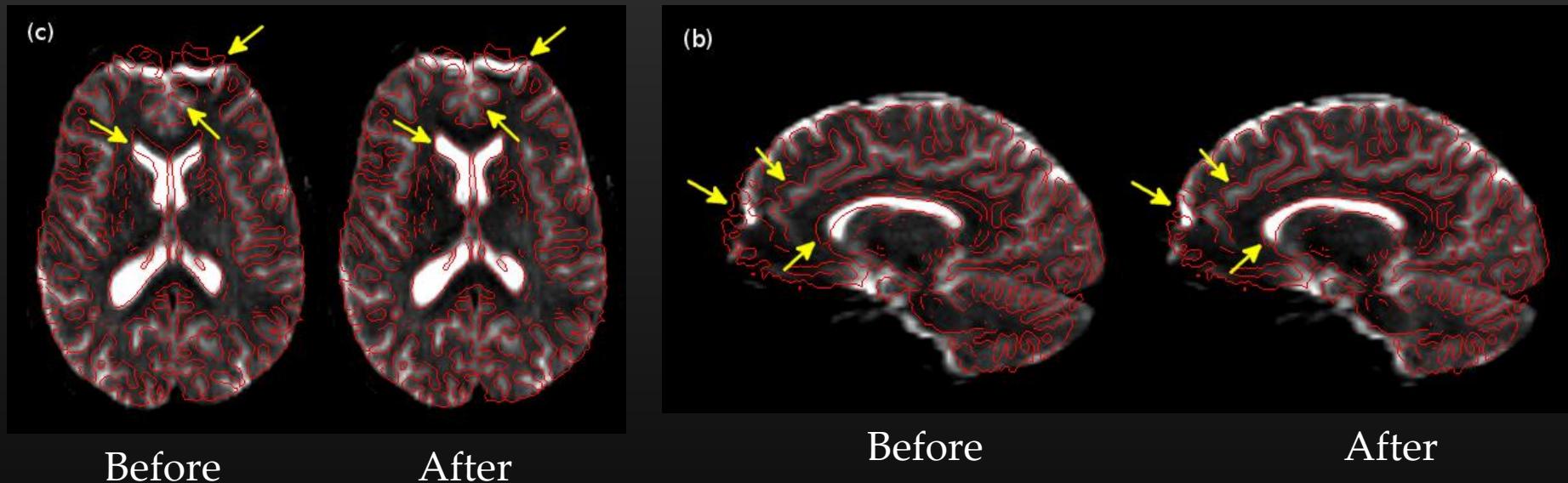
- No extra data (fieldmap) is required
- Estimate a deformation map ϕ which best aligns MPRAGE and b=0 image
 - Uses anatomical information
- Mutual-information based non-rigid registration



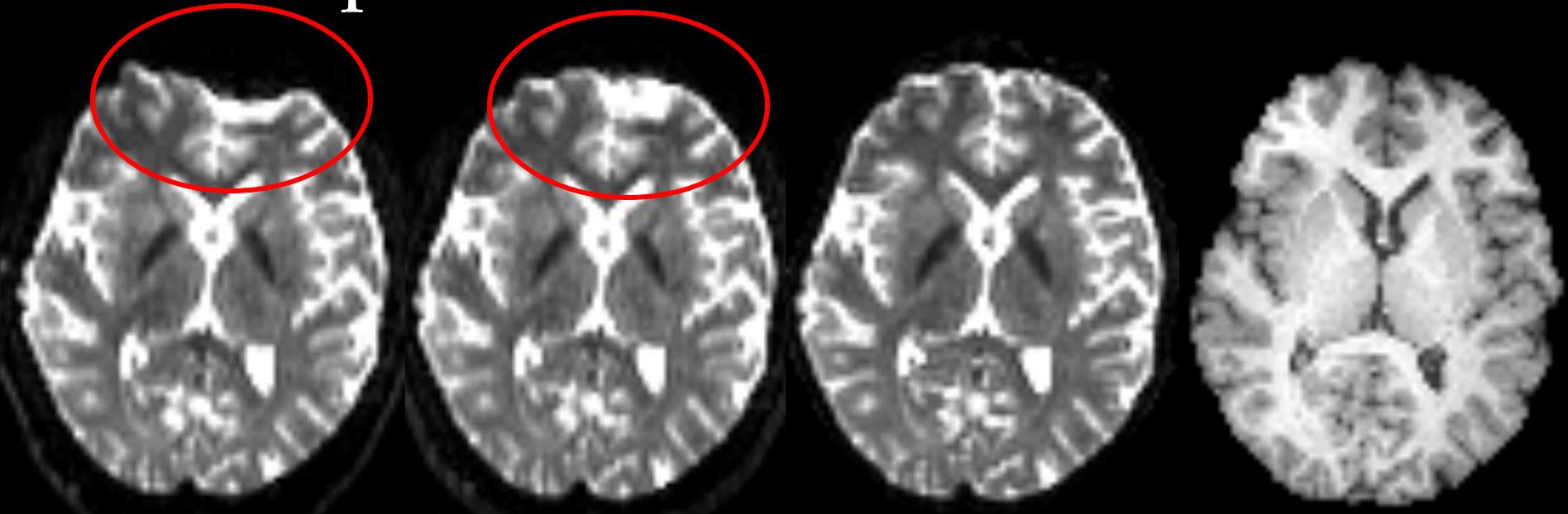
Bhushan et al. 2012

Registration based correction

- Similar performance to fieldmap method



Comparison



Registration
based correction

Fieldmap based
correction

Reversed Gradient /
Interlaced sampling*

MPRAGE

- Be aware of limitation of your dataset and/or correction method

* To be included in future version of BDP.
Bhushan et al., ISMRM 2013, p55

Summary: Distortion correction

1. Registration based distortion correction

- Uses structural image to estimate distortion field
- Does *not* require any field inhomogeneity map

2. Fieldmap based distortion correction

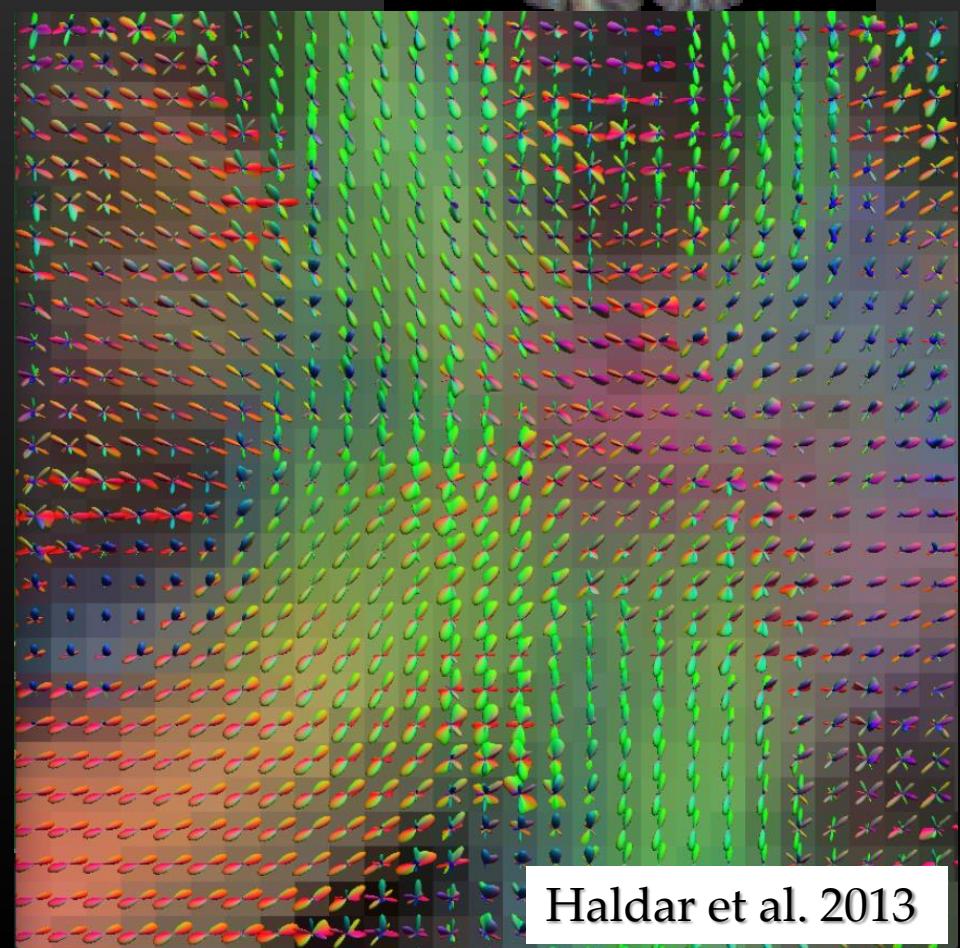
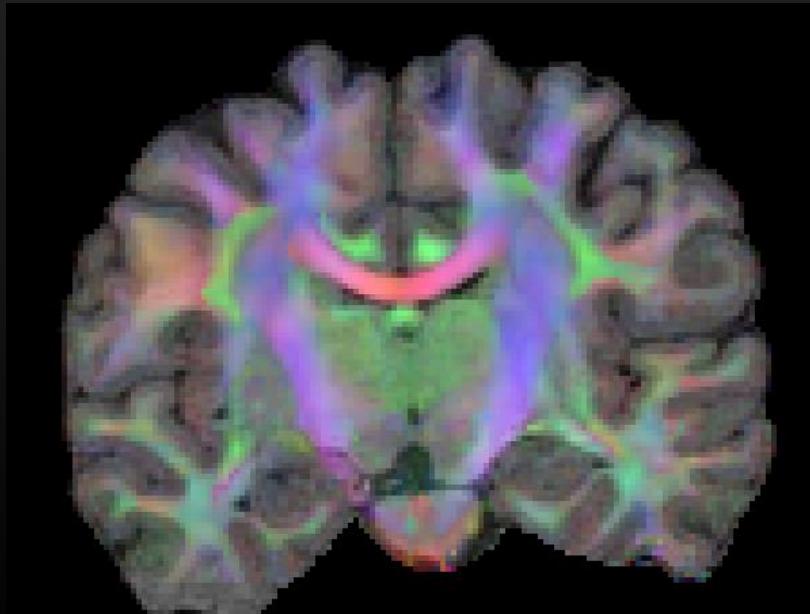
- Requires field inhomogeneity map
- Lower computational requirement

3. No distortion correction

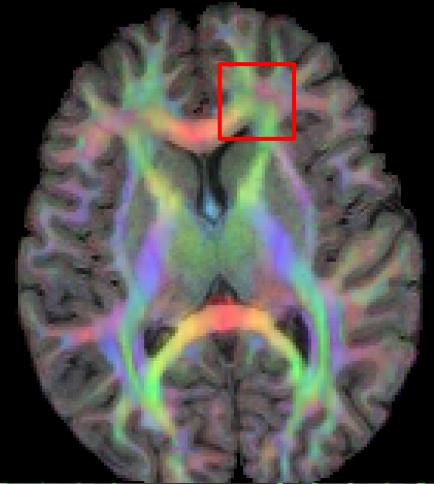
- Only Rigid registration to MPRAGE
- --no-distortion-correction

Diffusion models

- Estimates diffusion tensors
 - FA, MD, color-FA
 - Axial, Radial diffusivity
- ODFs using FRT and FRACT

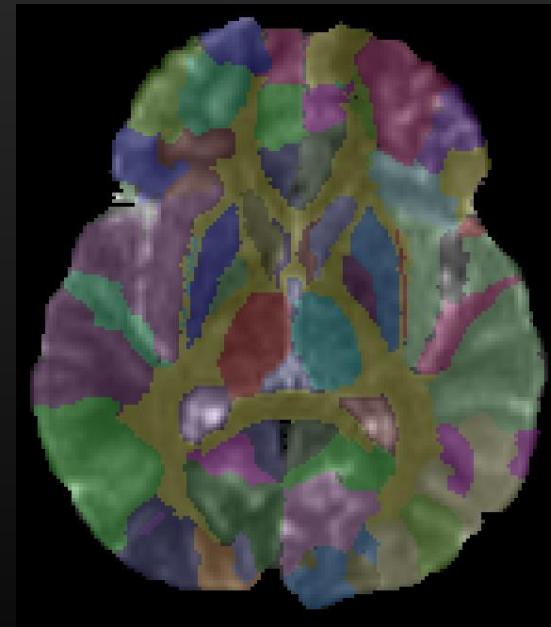
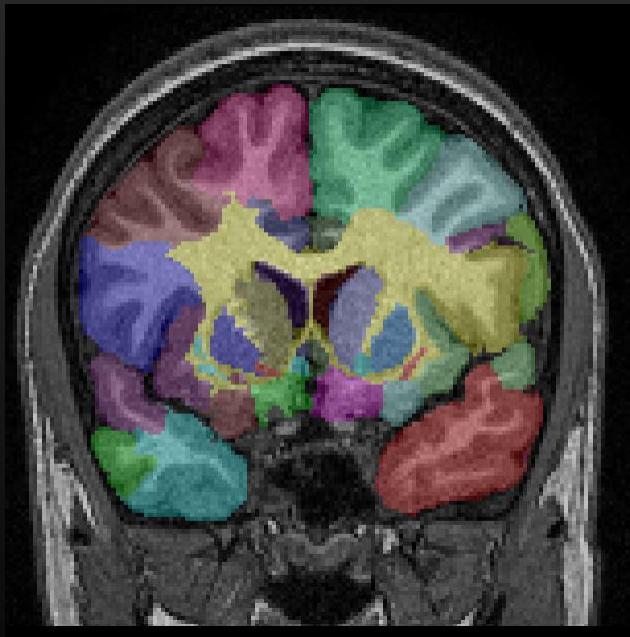


Haldar et al. 2013



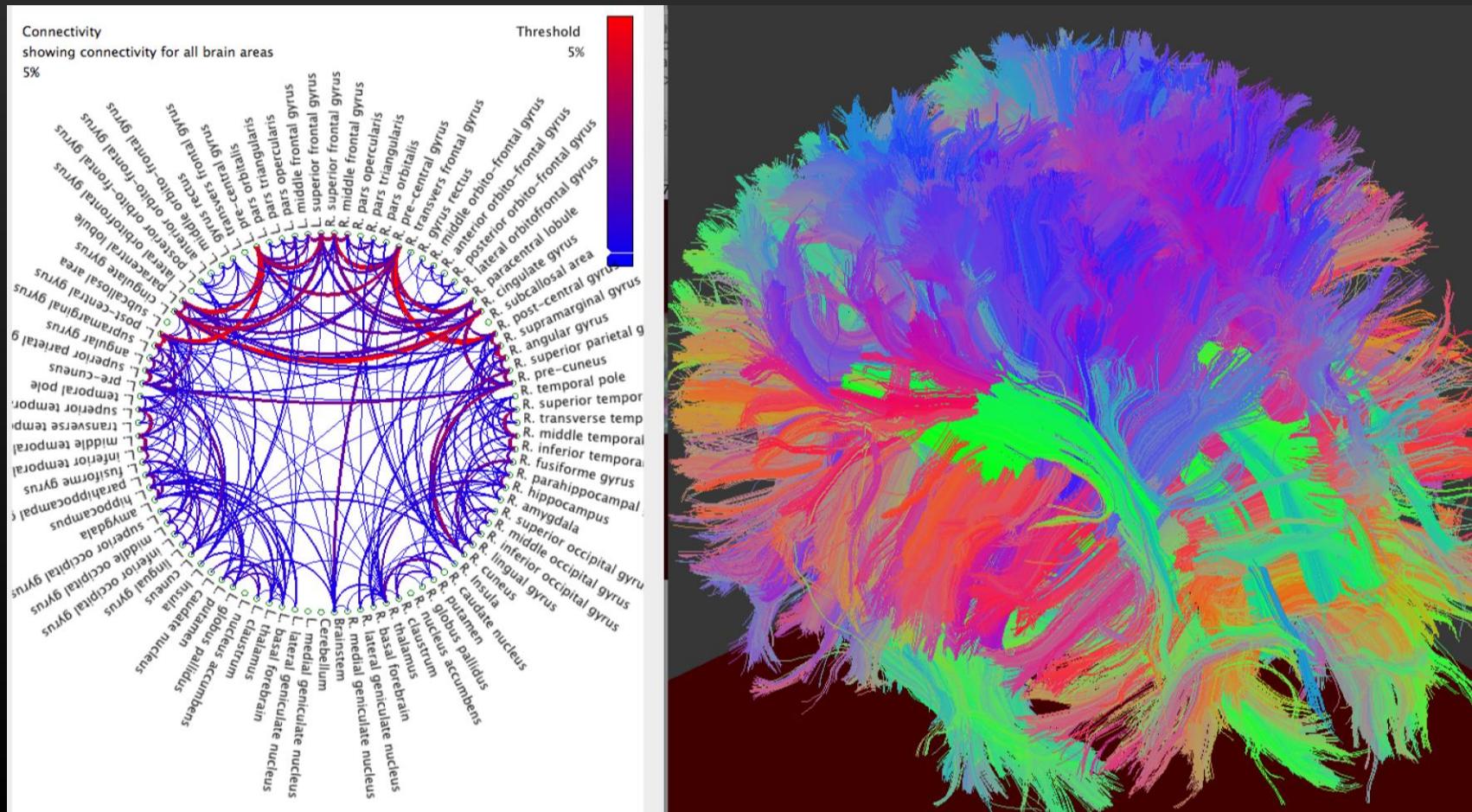
Tractography & connectivity

- Combine labels (from MPRAGE space) and diffusion information



Tractography & connectivity

- › Fiber tracking in MPRAGE and diffusion space
- › ROI-wise connectivity analysis

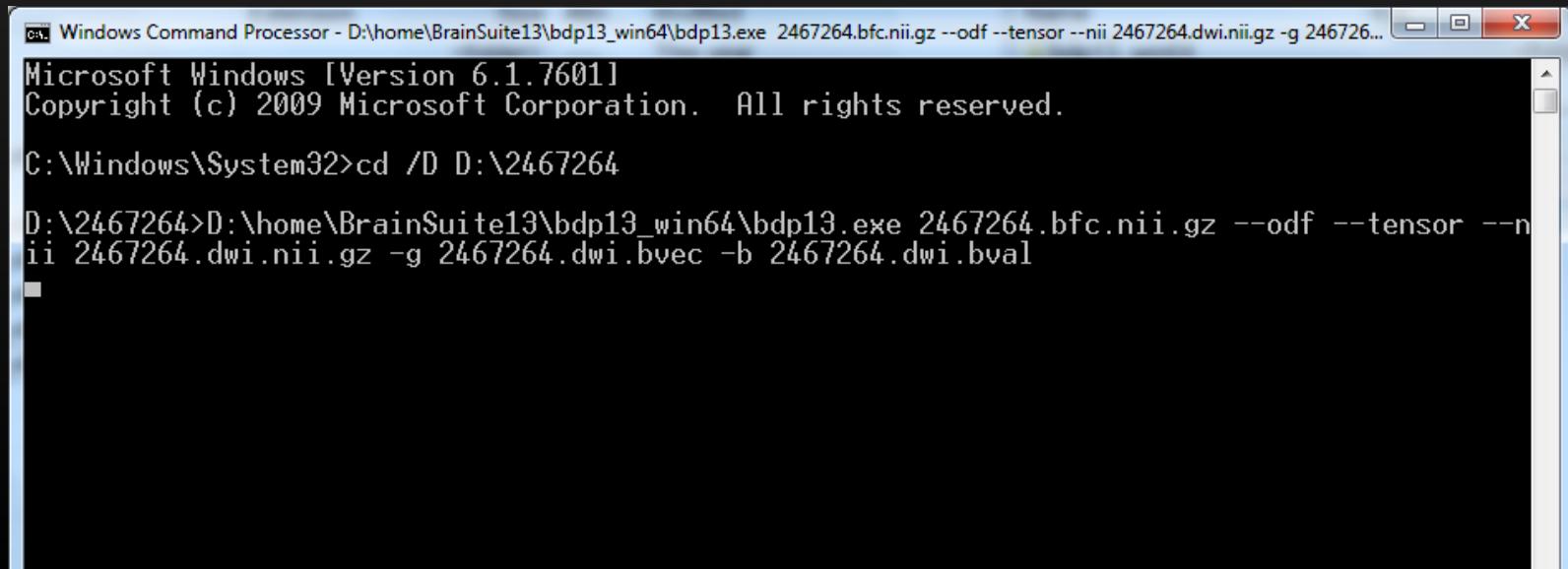


Syntax

NIfTI input (.nii or .nii.gz)

```
bdp13.exe <BFC File> [Optional Flags] --nii <4D DWI  
NIfTI> --bvec <Gradient file> --bval <b-value file>
```

- BDP expects diffusion gradient direction in voxel coordinates
- BDP uses NIfTI header matrix extensively for registration



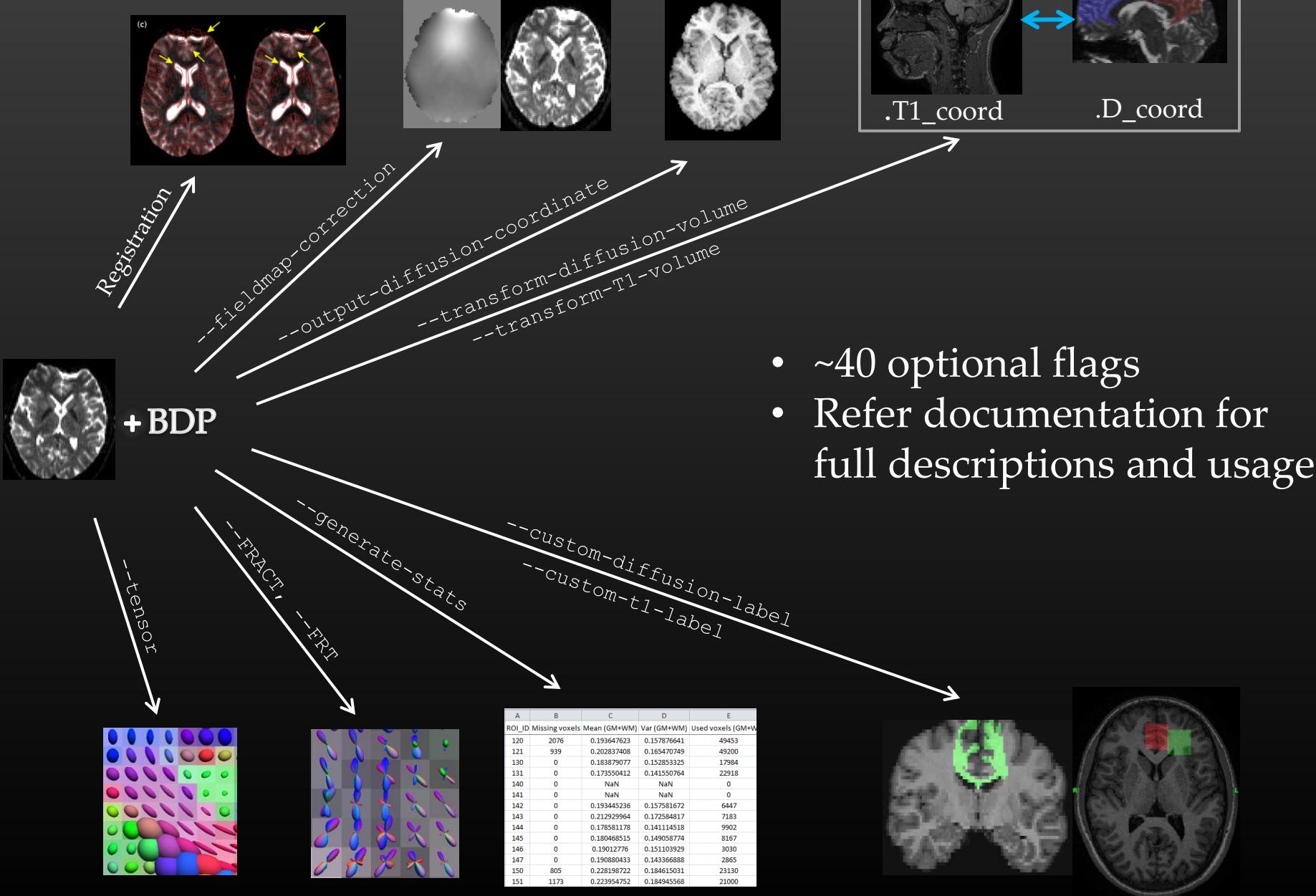
A screenshot of a Windows Command Processor window titled "Windows Command Processor - D:\home\BrainSuite13\bdp13_win64\bdp13.exe 2467264.bfc.nii.gz --odf --tensor --nii 2467264.dwi.nii.gz -g 2467264.dwi.bvec -b 2467264.dwi.bval". The window shows the command being run and its output.

```
Microsoft Windows [Version 6.1.7601]
Copyright (c) 2009 Microsoft Corporation. All rights reserved.

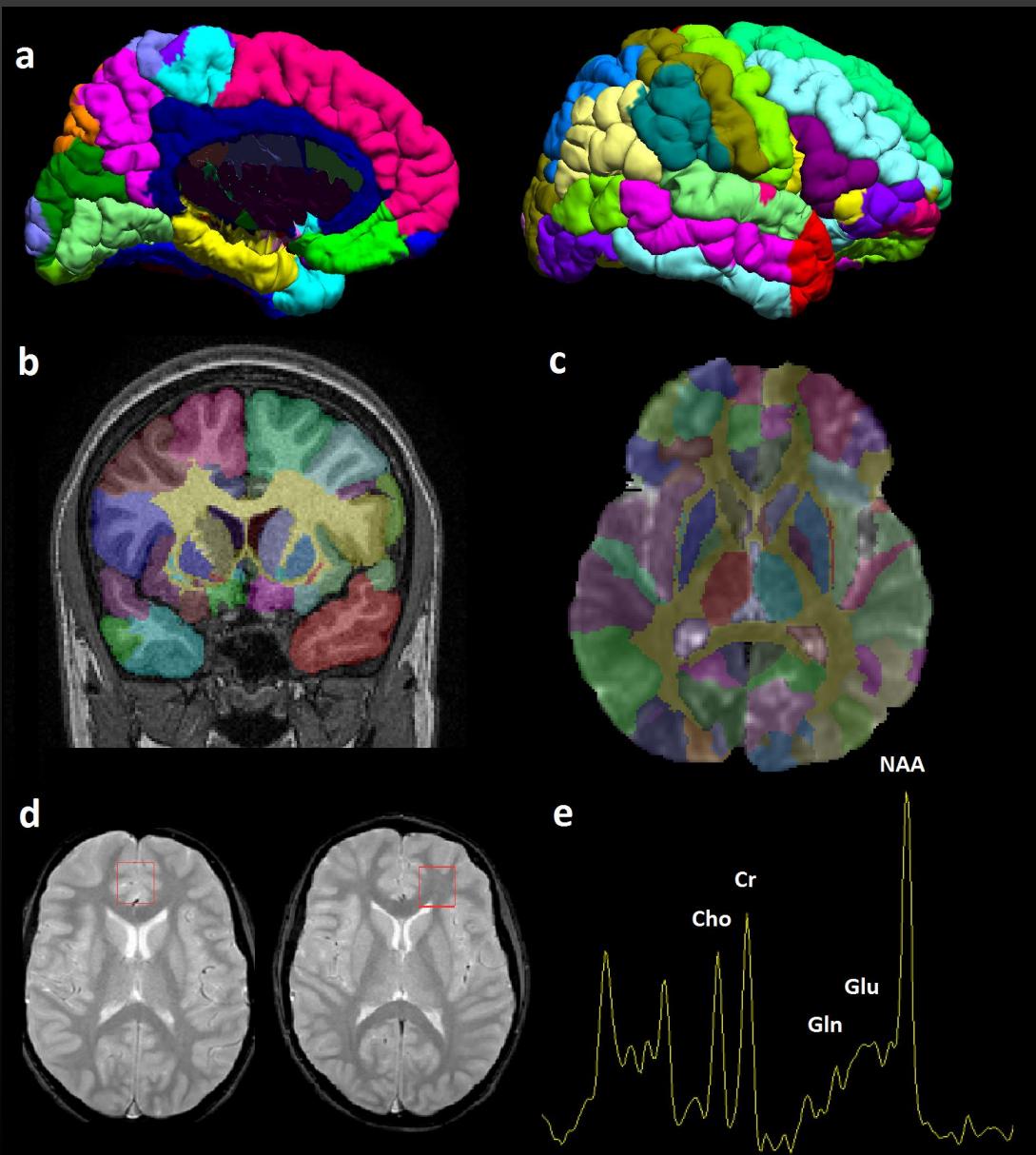
C:\Windows\System32>cd /D D:\2467264

D:\2467264>D:\home\BrainSuite13\bdp13_win64\bdp13.exe 2467264.bfc.nii.gz --odf --tensor --nii 2467264.dwi.nii.gz -g 2467264.dwi.bvec -b 2467264.dwi.bval
```

BDP: Flexible flags



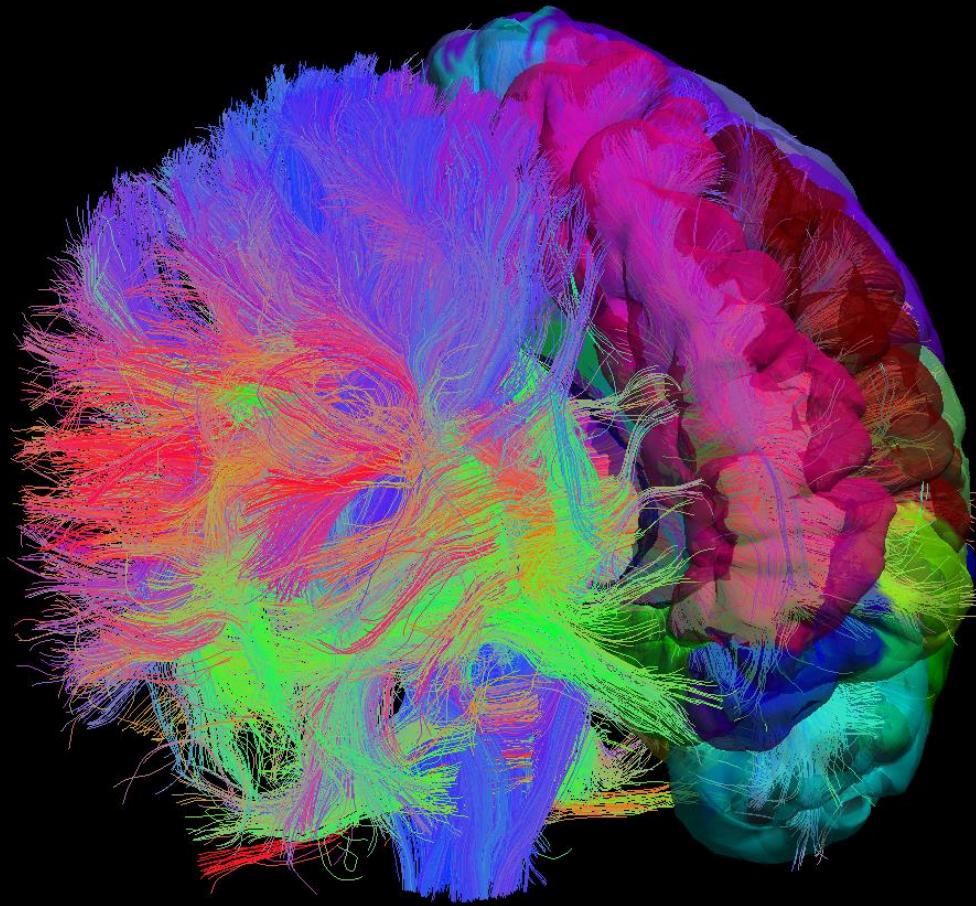
Example multimodal study



Choi et al., "A Multimodal Investigation of Neuronal/Axonal Integrity Using Structural T1-weighted Imaging, Diffusion Tensor Imaging, and H1 MR Spectroscopy", ISMRM 2013, Salt Lake City, p. 1951

References

- C Bhushan, JP Haldar, AA Joshi, RM Leahy , *Correcting susceptibility-induced distortion in diffusion-weighted MRI using constrained nonrigid registration*, APSIPA ASC, Hollywood, 3-6 Dec 2012
- DW Shattuck, AA Joshi, JP Haldar, C Bhushan, S Choi, AC Krause, JL Wisnowski, H Damasio, AW Toga, RM Leahy, *New BrainSuite13 Tools for Image Segmentation, Registration , Connectivity Analysis and Visualization*, OHBM, Seattle, 2013, p. 1688
- DW Shattuck, AA Joshi, JP Haldar, C Bhushan, S Choi, AC Krause, JL Wisnowski, AW Toga and RM Leahy, *Tools for Brain Image Segmentation, Registration, and Connectivity*, ISMRM, Salt Lake City, 2013, p. 2691
- C Bhushan, AA Joshi, RM Leahy, JP Haldar, *Accelerating Data Acquisition for Reversed-Gradient Distortion Correction in Diffusion MRI: A Constrained Reconstruction Approach*, ISMRM, Salt Lake City, 2013, p. 55



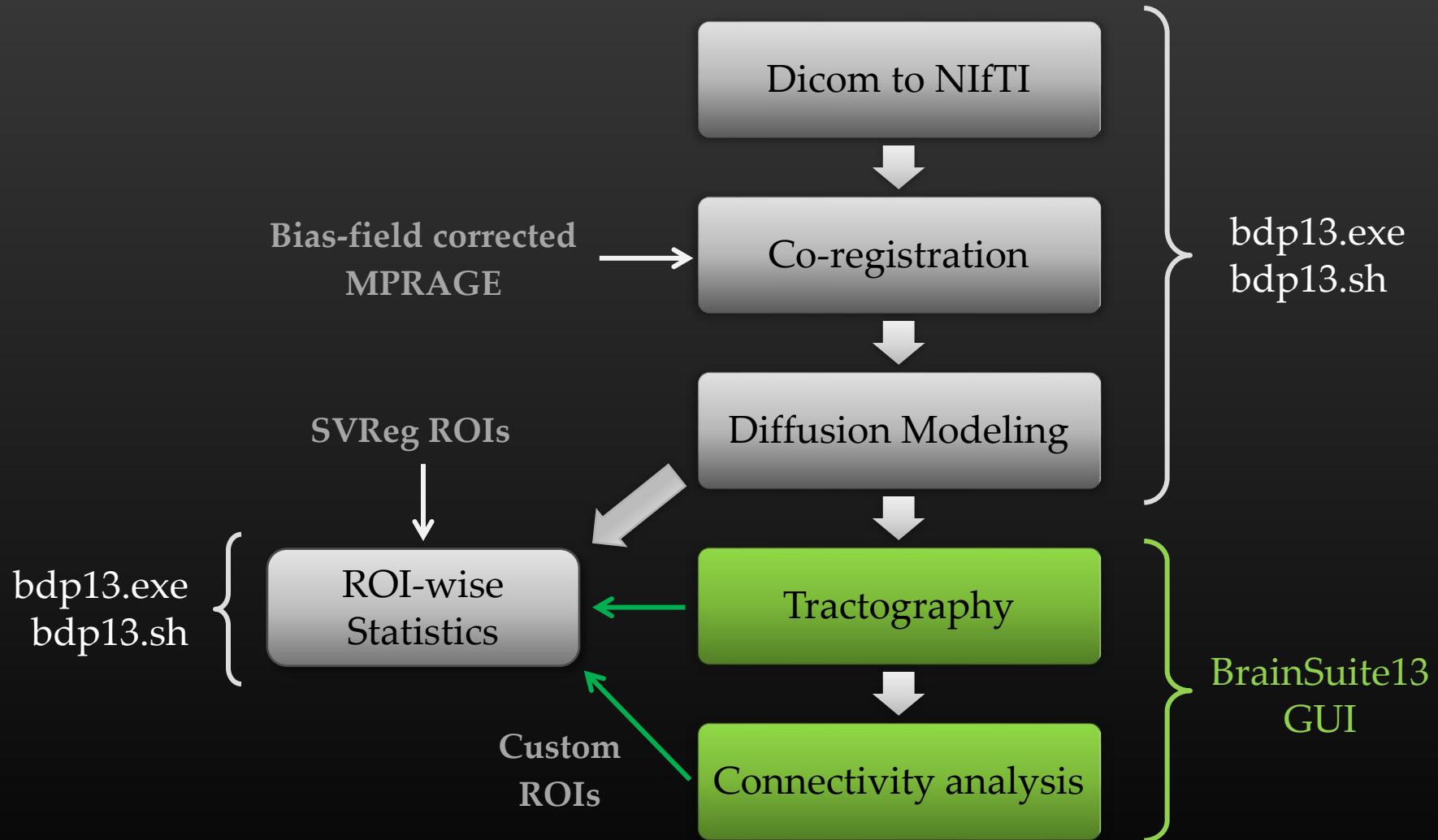
Download hands-on dataset

<http://is.gd/brainsuite>

Running BDP

{ or bdp13.exe

Diffusion Pipeline



bdp13.exe / bdp13.sh

- Command line tool
 - Highly extensible using your batch/shell scripts
- Flexible – numerous flags for custom processing
- Requires
 - Matlab 2012a MCR
 - Visual C++ runtime package (windows only)
- Documentation

<http://brainsuite.bmap.ucla.edu/processing/diffusion/>

- Detailed flag description
- <http://brainsuite.bmap.ucla.edu/processing/diffusion/flags/>

Syntax

DICOM

```
bdp13.exe <BFC File> [Optional Flags] -d <DICOM path> [DICOM path ...]
```

- Limited support
- BDP extracts (most) relevant diffusion scan parameters

NIfTI (.nii or .nii.gz)

```
bdp13.exe <BFC File> [Optional Flags] --nii <4D DWI NIfTI> --bvec <Gradient file> --bval <b-value file>
```

- BDP expects diffusion gradient direction in voxel coordinates
- BDP uses NIfTI header matrix extensively for registration

Linux and Macintosh

Replace `bdp13.exe` by `bdp13.sh`

Example

- C:\bdp13p17_win64\bdp13.exe C:\5934\5934.bfc.nii.gz
--nii C:\5934\5934.dwi.nii.gz --bvec
C:\5934\5934.dwi.bvec --bval C:\5934\5934.dwi.bval
- Flags are separated by space
- If required file are not in current working directory, then specify full path to files
- Any number of flags can be added
- Output files:
 - Many many files.... (see documentation for all details)
 - <fileprefix>.BDPSummary.txt
 - Summary of all the processing with references
 - The command used for future reference

<fileprefix>.BDPSummary.txt

BrainSuite Diffusion Pipeline: Processing Summary

BDP Version: 13p17

Processing finished: 19-Sep-2013 12:03:26

Scan: D:\BrainReg_Git\data\BDP_test_data\6067JH\5934JH

Diffusion MRI data was co-registered to the anatomical T1-weighted image and corrected for susceptibility-induced distortions using an acquired B0 fieldmap [Bhushan 2012].

Diffusion tensors were estimated using a weighted linear least squares method, and scalar diffusion parameters such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity, and axial diffusivity were computed based on an eigendecomposition of the tensors as described in [Kim 2009].

Orientation distribution functions (ODFs) were computed using the Funk-Radon Transform and the Funk-Radon Transform [Haldar 2013].

COMMAND USED:

```
bdp13.exe D:\BrainReg_Git\data\BDP_test_data\6067JH\5934JH.bfc.nii.gz
  --threads=4
  --dir=y-
  --odf
  --tensor
  --output-subdir windows_complied_v13p17_fieldmap
  --output-diffusion-coordinate
  --nii D:\BrainReg_Git\data\BDP_test_data\6067JH\6067JH.DWI.00.nii.gz
  --bvec D:\BrainReg_Git\data\BDP_test_data\6067JH\6067JH.DWI.00.bvec
  --bval D:\BrainReg_Git\data\BDP_test_data\6067JH\6067JH.DWI.00.bval
  --fieldmap-correction D:\BrainReg_Git\data\BDP_test_data\6067JH\6067JH.fieldmap.rad
  --echo-spacing=0.00036
```

Approximate processing time: 18.07 minutes

REFERENCES:

[Bhushan 2012] C. Bhushan, J. P. Haldar, "A nonrigid registration framework for susceptibility-induced distortion correction in diffusion MRI", Asia-Pacific Annual Summit and Conference

[Haldar 2013] J. P. Haldar, R. S. Giedd, "Diffusion MRI beyond the sphere: Application to hippocampal segmentation", NeuroImage, Volume 71, Pages 1-10

[Kim 2009] J. H. Kim, J. H. Cho, "Diffusion tensor imaging of mouse brain stem and cerebellum", Journal of Magnetic Resonance Imaging, Volume 29, Issue 2, Pages 342-347

Command line output

```
Reading input flags...

Output sub-directory already exists:
D:\BrainReg_Git\data\BDP_test_data\6067JH\windows_compiled_v13p17_fieldmap
The files in the output folder can be overwritten.
Checking input files...
Successfully generated b-matrices file.

BDP could not find any .mask.nii.gz file. BDP will use input bfc file itself as
brain mask. You can specify a custom head mask by using flag --t1-mask
<maskfile_name>. The custom mask must overlay correctly with input BFC image in
BrainSuite.

Reading the input parameters for co-registration...
Checking orientation information...Done
Extracting 0-diffusion (b=0) image from input DWIs...Done

DWI mask is not defined in input flags. BDP will generate (pseudo) mask from
0-diffusion (b=0) image. Automatic mask generation may not be accurate in some
situations and can affect overall quality of co-registration. In case
co-registration is not accurate, you can define a DWI mask by using flag
--dwi-mask <mask_filename>. The mask can be generated and hand edited in
BrainSuite interface. This mask would be used only for registration purposes
(and not for statistics computation).
Saved (pseudo) mask: D:\BrainReg_Git\data\BDP_test_data\6067JH\windows_compiled_v13p17_fieldmap\5934JH.dwi.RAS.mask.nii.gz

Distortion correction using fieldmap started...
Field of view (FOV) of Fieldmap and EPI (diffusion) scan seems to be different.
PNG images showing overlay will be generated with name:
D:\BrainReg_Git\data\BDP_test_data\6067JH\windows_compiled_v13p17_fieldmap\5934JH.dwi.RAS.correct.fieldmap_overlay

WARNING: Fieldmap and EPI (diffusion) data do not share same field of view
(FOV), but it seems that EPI data is totally included in fieldmap FOV. BDP will
only use information from overlapping FOV. It is *highly* recommended to check
the overlay images to make sure fieldmap and EPI data overlap correctly.
Fieldmaps should be pre-registered to EPI image in order to work correctly.

[=====>] 21/21 volumes done

Saving file...Done
Correcting DWI mask...
Field of view (FOV) of Fieldmap and EPI (diffusion) scan seems to be different.
PNG images showing overlay will be generated with name:
D:\BrainReg_Git\data\BDP_test_data\6067JH\windows_compiled_v13p17_fieldmap\5934JH.dwi.RAS.correct.mask.fieldmap_overlay
```

Command line
output – Always
verbose with
relevant important
information

Default flags

When no optional flag is defined:

- --tensor
- --dir=y
- Registration based distortion correction
- Only T1-coordinate outputs
- Outputs are saved in same directory as bfc file
- --threads=4

```
C:\bdp13p17_win64\bdp13.exe C:\5934\5934.bfc.nii.gz  
--nii C:\5934\5934.dwi.nii.gz --bvec  
C:\5934\5934.dwi.bvec --bval C:\5934\5934.dwi.bval
```

Help!

--help or -h

- Prints out description of all BDP flags
- Also reports the version of BDP executable being run

--check-for-updates

- Connects to BrainSuite server to check if a new version of BDP is available

All other flags and options are ignored and BDP terminates after printing help or checking for updates.

Of course online documentation:

<http://brainsuite.bmap.ucla.edu/processing/diffusion/>

Diffusion models

Multiple ‘model’ flags can be used at once:

- Diffusion Tensor
 - --tensor
 - <name>.eig.nii.gz – saves all eigen value/vectors
 - FA, colorFA, axial, radial, L2, L3, MD
- ODFs
 - --FRT
 - --FRACt
 - <name>.odf – Load saved Spherical harmonic coefficients
- Coordinate filename suffix
 - .T1_coord : In T1/MPRAGE coordinates
 - .D_coord : In diffusion coordinates

Distortion direction

--dir=<direction>

Define phase encoding direction

x : increases along the Right side of the subject

x- : increases along the left side of the subject.

y : increases along the Anterior direction of the subject

y- : increases along the posterior direction of the subject

z : increases along the Superior direction

z- : increases along the inferior direction

Example

--dir=y-

- -ve sign is important only for fieldmap based correction

Fieldmap based correction

Required

```
--fieldmap-correction <fname.nii.gz> (in rad/sec)  
--echo-spacing=<t> (in sec)
```

Example

```
--fieldmap-correction fieldmap.radians.nii.gz  
--echo-spacing=0.00036
```

Optional

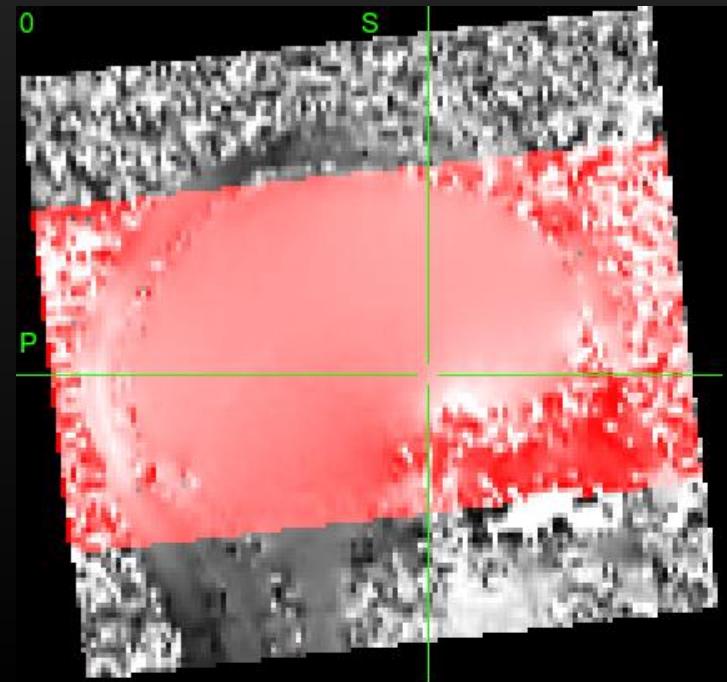
```
--fieldmap-smooth3=<S> (in mm)
```

```
--ignore-fieldmap-fov
```

- BDP checks for overlap of field of view (FOV) of diffusion scan and fieldmap scan
- Overrides FOV check

Example:

```
--fieldmap-smooth3=0.75
```



Some (more) useful flags

--output-subdir <directory_name>

- allows to specify a sub-directory name in which output files would be written
- Example:

```
--output-subdir BDPv17
```

--output-diffusion-coordinate

- Enables estimation of diffusion tensors and/or ODFs in the native diffusion coordinate
- All native diffusion coordinate files are saved in a separate folder named “diffusion_coord_outputs”
- Outputs in MPRAGE coordinates are always saved

Statistics flags

--generate-stats

- Requires extraction (& SVReg) output files
- Writes statistics for white matter(WM), grey matter(GM), and both WM and GM combined
- Outputs in .csv format

A	B	C	D	E	F	G	H	I	J	K
ROI_ID	Missing voxels	Mean (GM+WM)	Var (GM+WM)	Used voxels (GM+WM)	Mean (WM)	Var (WM)	Used Voxels (WM)	Mean (GM)	Var (GM)	Used voxels (GM)
120	2076	0.193647623	0.157876641	49453	0.367816687	0.158458	13550	0.12791613	0.095325	35903
121	939	0.202837408	0.165470749	49200	0.384492725	0.163745	14200	0.12913822	0.093767	35000
130	0	0.183879077	0.152853325	17984	0.371818811	0.152749	4789	0.11566798	0.076836	13195
131	0	0.173550412	0.141550764	22918	0.347554863	0.142177	5907	0.1131282	0.076227	17011
140	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0
141	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0
142	0	0.193445236	0.157581672	6447	0.394196153	0.124804	1873	0.11123998	0.073218	4574
143	0	0.212929964	0.172584817	7183	0.414764017	0.14748	2233	0.12188043	0.082116	4950
144	0	0.178581178	0.1411114518	9902	0.345779568	0.12801	2914	0.1088594	0.069754	6988
145	0	0.180468515	0.149058774	8167	0.353723109	0.141367	2412	0.10785522	0.072814	5755
146	0	0.19012776	0.151103929	3030	0.36529085	0.157643	764	0.13106996	0.091235	2266
147	0	0.190880433	0.143366888	2865	0.348852992	0.136231	768	0.13302445	0.093814	2097
150	805	0.228198722	0.184615031	23130	0.397928327	0.16902	8681	0.12622583	0.098437	14449
151	1173	0.223954752	0.184945568	21000	0.423291534	0.159717	7044	0.12334342	0.091737	13956
160	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0
161	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0

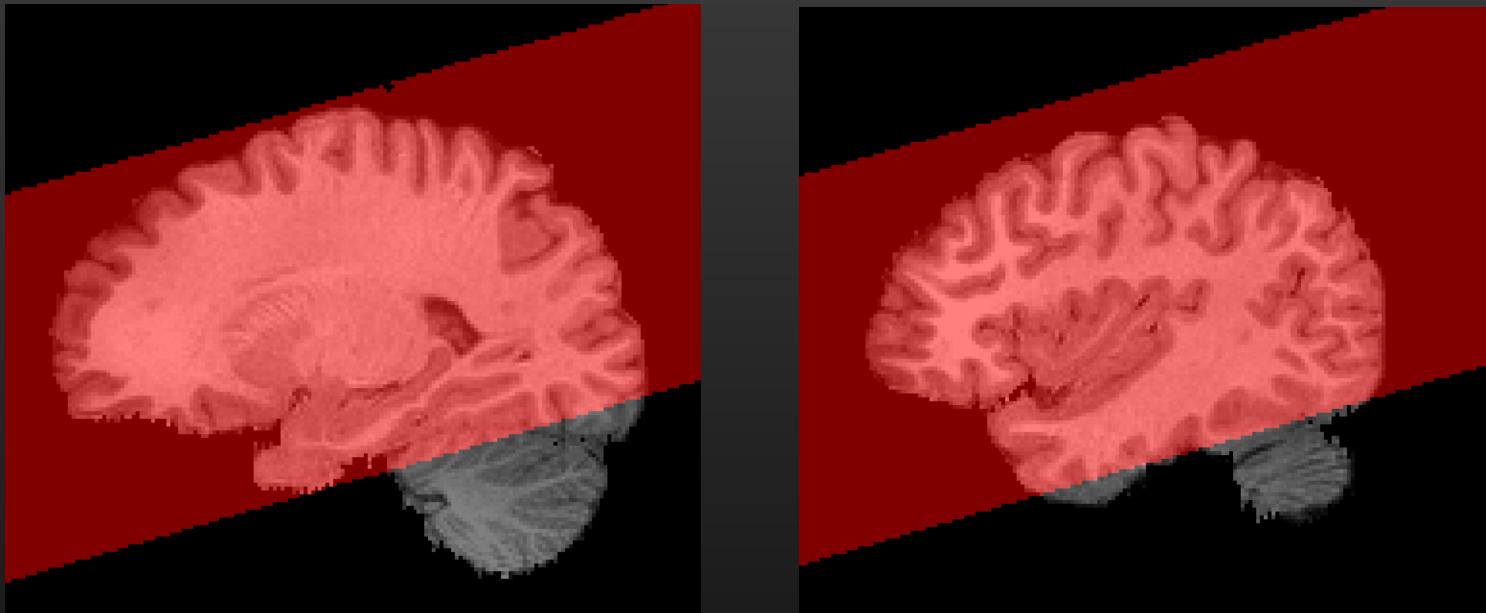
Statistics flags

A	B	C	D	E	F	G	H	I	J	K
ROI_ID	Missing voxels	Mean (GM+WM)	Var (GM+WM)	Used voxels (GM+WM)	Mean (WM)	Var (WM)	Used Voxels (WM)	Mean (GM)	Var (GM)	Used voxels (GM)
120	2076	0.193647623	0.157876641	49453	0.367816687	0.158458	13550	0.12791613	0.095325	35903
121	939	0.202837408	0.165470749	49200	0.384492725	0.163745	14200	0.12913822	0.093767	35000
130	0	0.183879077	0.152853325	17984	0.371818811	0.152749	4789	0.11566798	0.076836	13195
131	0	0.173550412	0.141550764	22918	0.347554863	0.142177	5907	0.1131282	0.076227	17011
140	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0
141	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0
142	0	0.193445236	0.157581672	6447	0.394196153	0.124804	1873	0.11123998	0.073218	4574
143	0	0.212929964	0.172584817	7183	0.414764017	0.14748	2233	0.12188043	0.082116	4950
144	0	0.178581178	0.1411114518	9902	0.345779568	0.12801	2914	0.1088594	0.069754	6988
145	0	0.180468515	0.149058774	8167	0.353723109	0.141367	2412	0.10785522	0.072814	5755
146	0	0.19012776	0.151103929	3030	0.36529085	0.157643	764	0.13106996	0.091235	2266
147	0	0.190880433	0.143366888	2865	0.348852992	0.136231	768	0.13302445	0.093814	2097
150	805	0.228198722	0.184615031	23130	0.397928327	0.16902	8681	0.12622583	0.098437	14449
151	1173	0.223954752	0.184945568	21000	0.423291534	0.159717	7044	0.12334342	0.091737	13956
160	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0
161	0	NaN	NaN	0	NaN	NaN	0	NaN	NaN	0

Default information:

- WM/GM from <name>.cortex.dewisp.mask.nii.gz
- SVReg labels from <name>.svreg.corr.label.nii.gz
- ROI_ID from brainsuite_labeldescription.xml
 - --custom-label-xml <filename.xml>

Statistics – FOV issues



- BDP detects overlap of field of view (FOV) of MPRAGE and diffusion scan
- Computes missing voxels in each ROI
- By default does *not* compute stats for ROI missing *any* voxel
- --force-partial-roi-stats
 - Force stats computation in all ROIs

Custom labels

```
--custom-diffusion-label <name>
```

```
--custom-t1-label <name>
```

- Define custom labels in either coordinates
- <name> can be either NIfTI filename or directory name
- Custom labels can be painted in BrainSuite13

```
--custom-label-xml <filename.xml>
```

- Example:

```
--custom-diffusion-label ROI26.nii.gz
```

```
--custom-t1-label T1_labels
```

- When --custom-label-xml is not used:
 - BDP generates 5-digit ROI IDs for each label found
 - Saves ROI ID maps (to labels found) in an .xml file
`<fileprefix>.BDP_ROI_MAP.xml`

Re-compute statistics

--only-generate-stats

--generate-stats-only

- Refined/manually corrected labels – re-run BDP to only compute statistics
- Skip all of the processing (co-registration, distortion correction and tensor/ODF estimation)
- All of the other flags MUST be used in the same way as they were in the initial BDP run

(<fileprefix>.BDPSummary.txt)

Transform image volumes

--transform-diffusion-volume <name>

--transform-t1-volume <name>

- To-and-fro from diffusion and T1-coordinates
- <name> can be either NIfTI filename or directory name
- This does *not* perform any distortion correction

--transform-interpolation <method>

- Define interpolation method
- linear, nearest, cubic or spline

--transform-data-only

- Skip all of the processing (co-registration, distortion correction and tensor/ODF estimation)
- All of the other flags MUST be used in the same way as they were in the initial BDP run (<fileprefix>.BDPSummary.txt)

Error!

```
C:\Windows\System32>D:\bdp13p17_win64\bdp13.exe zxdfasd.nii.gz
```

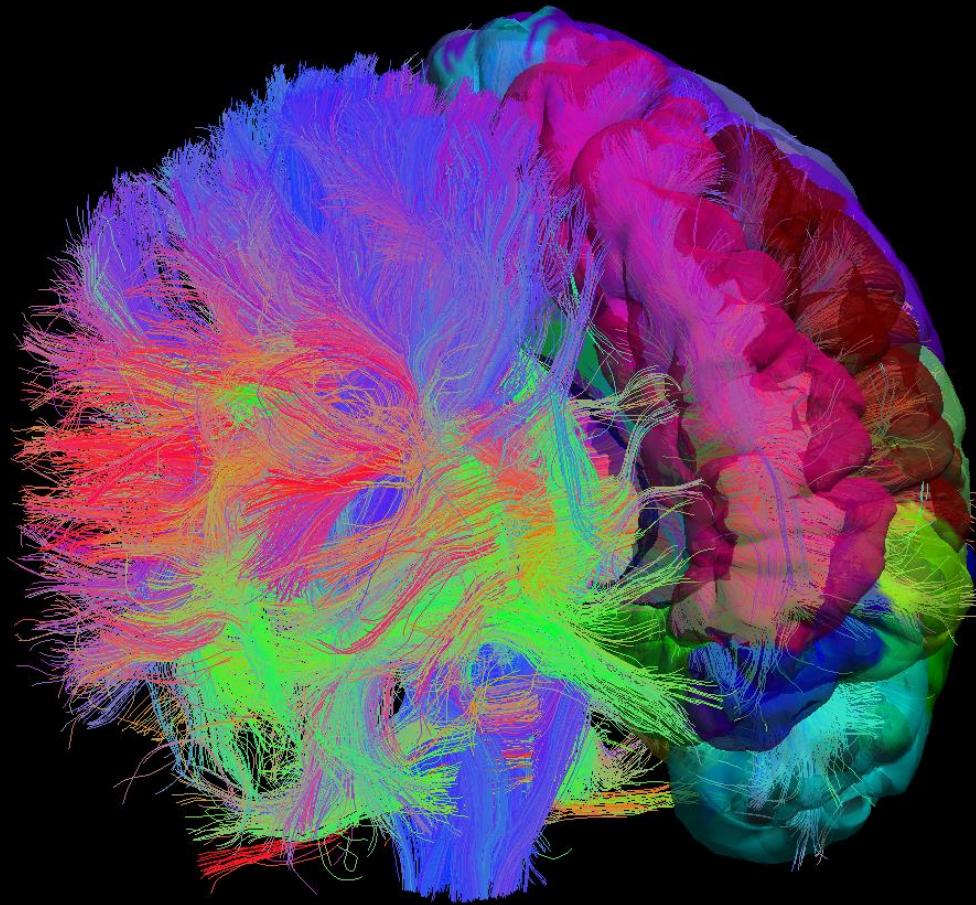
```
Reading input flags...
```

```
*****  
*                                              *  
*          Error running BDP                  *  
*                                              *  
*          FILE DOES NOT EXIST               *  
*                                              *  
*****
```

```
BDP could not find the file:  
zxdfasd.nii.gz
```

```
Check to make sure that the file exists and that you spelled  
its filename and path correctly
```

```
*****
```



BDP Documentation:

<http://brainsuite.bmap.ucla.edu/processing/diffusion/>

Detailed flag description:

<http://brainsuite.bmap.ucla.edu/processing/diffusion/flags/>