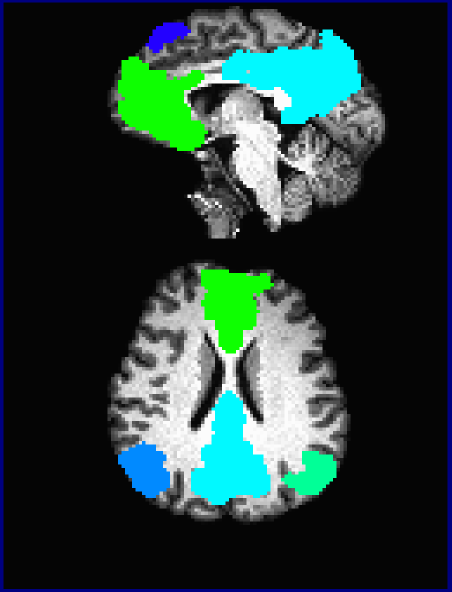
Introduction to AFNI+SUMA+FATCAT, Part II

DTI+tractography for data exploration and complementing functional connectivity

Terminology for tracking in FATCAT



Target: set of voxels with the same integer value, for which we want to find connections (e.g., GM ROI).

Network of targets: set of targets among which we want to find pairwise (AND-logic) or individual (OR-logic) connections (e.g., functional network).

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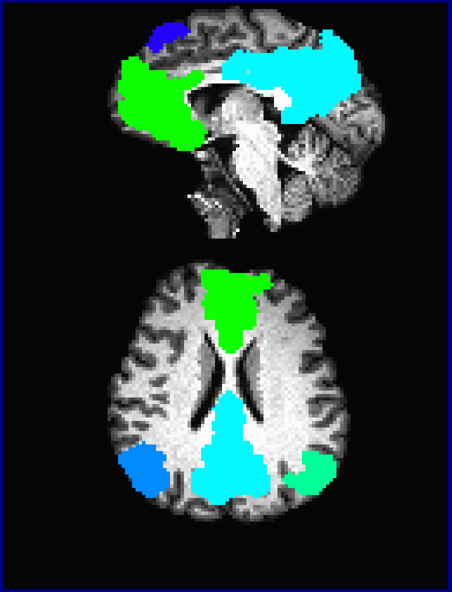

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Tract: set of ordered points in space related to estimated WM trajectory.

Bundle: set of one or more tracts through a single target (OR) or through any pair of targets (AND).

WM ROI: set of voxels through which a bundle passes (possibly after thresholding), useful for quantitative comparisons of average voxel vals.

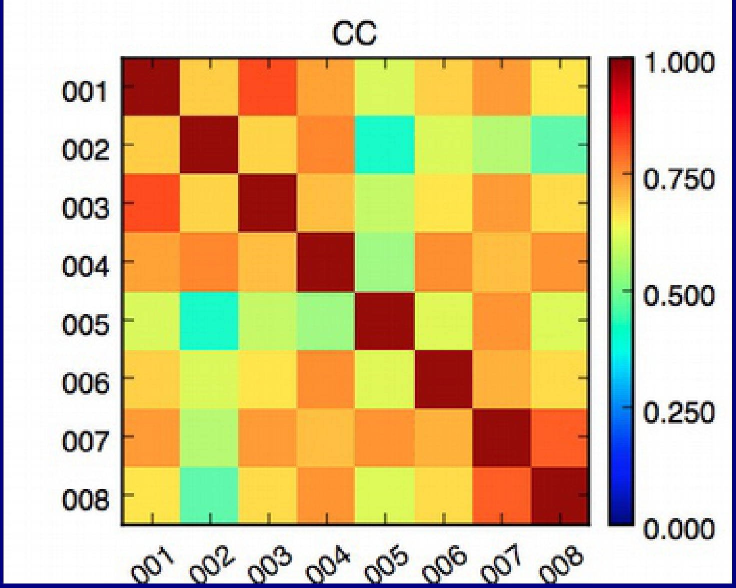
WM network: set of WM ROIs, likely complementing a given target network

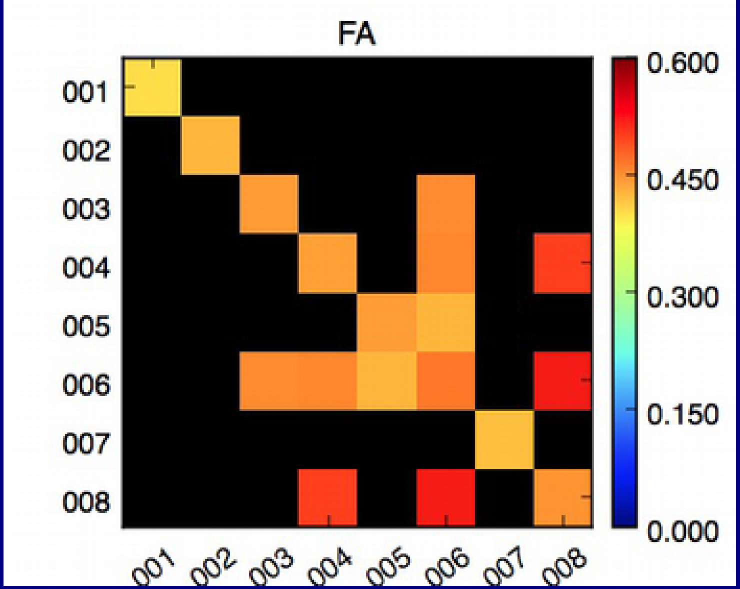
Terminology for tracking in FATCAT

"*N x N*" connectivity matrices for a network of *N* targets:

FC matrix: matrix of *functional* properties, such as average correlation between each pair of targets (→ value stored in each off-diagonal element)

SC matrix: matrix of *structural* properties, such as average FA in a WM ROI connecting two targets (off-diagonal) or WM ROI through single target (on-diagonal





Question for doing tractography:

where does one go to get the ROIs to try to connect?

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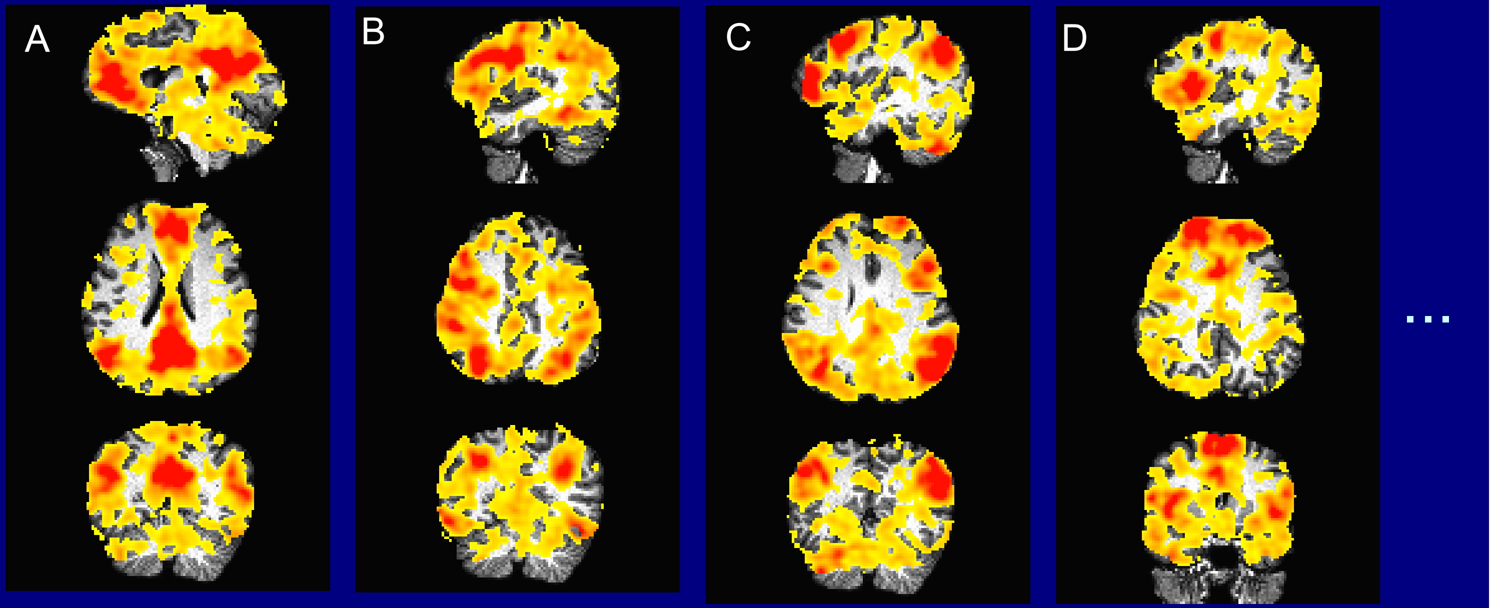
where does one go to get the ROIs to try to connect?

-> could go to atlases and standard maps,
or to exploratory spheres dotted around,

FMRI → networks of target ROIs

+ For example, one can perform seedbased correlation/ICA/etc. on a resting state study, resulting in several functional networks:

(each map of Z-scores; here, shown for Z>0)



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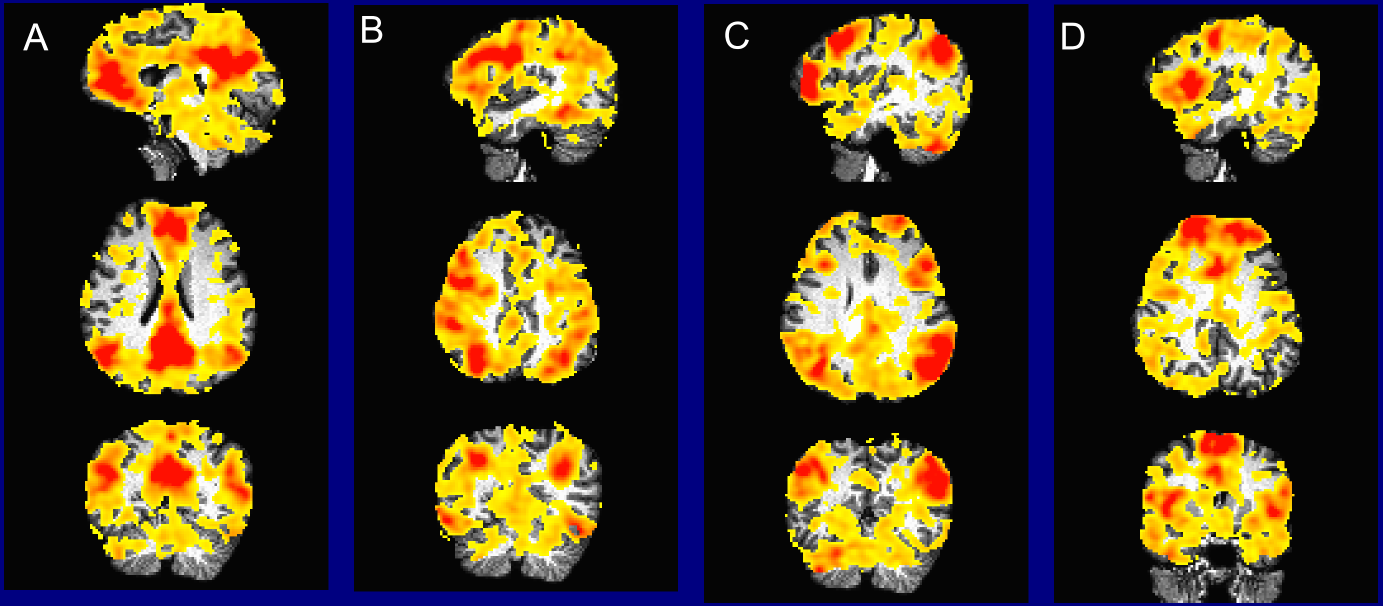

...

+ want to isolate GM ROIs, and then to expand each to make sure that they are at least touching nearby (*associated?*) WM voxels to have any hope to connect tracts

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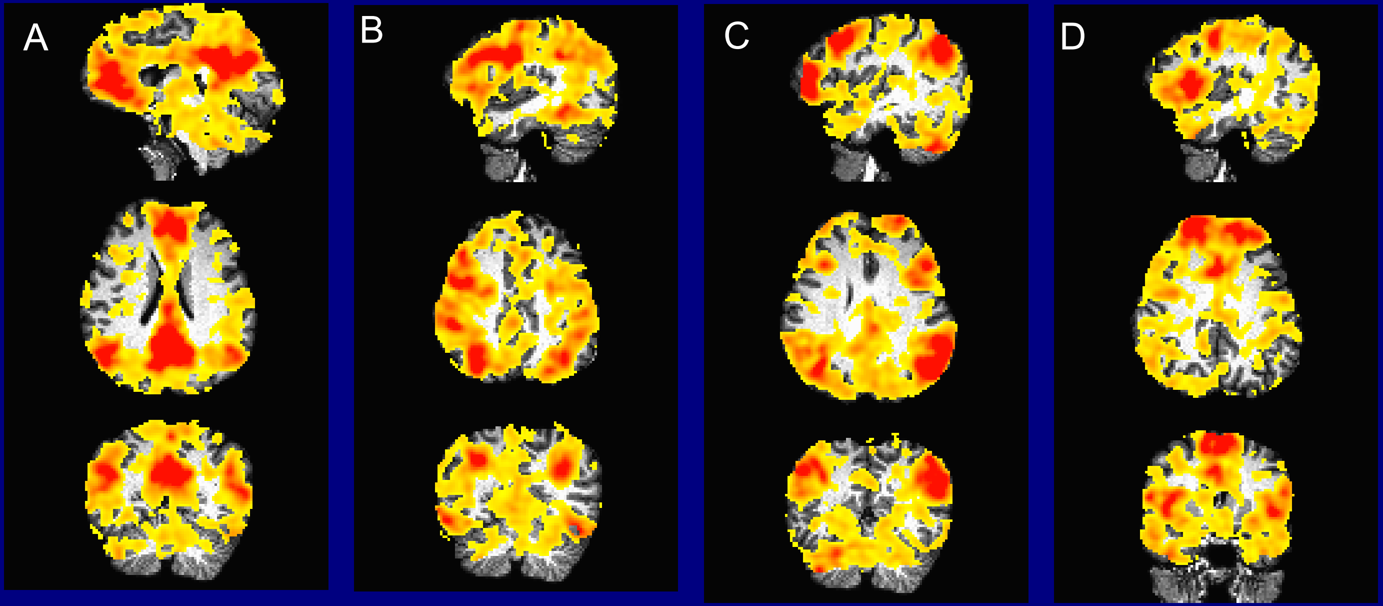
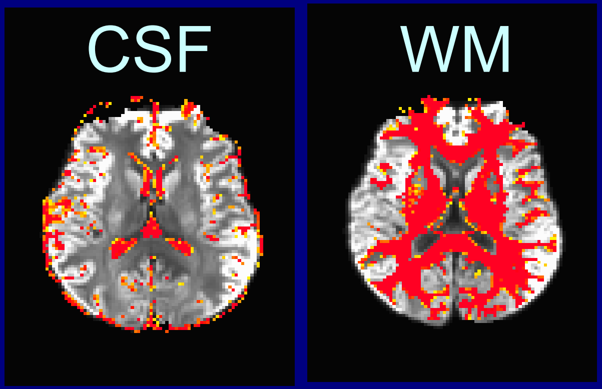


...

+ **3dROIMaker** can parcellate into GM ROIs based on:
    - thresholding voxel values
    - thresholding cluster size
    - subtract away CSF and WM voxels from segmentation maps
    - expand each GM ROI to location of WM (don't want to *overexpand* unphysically)

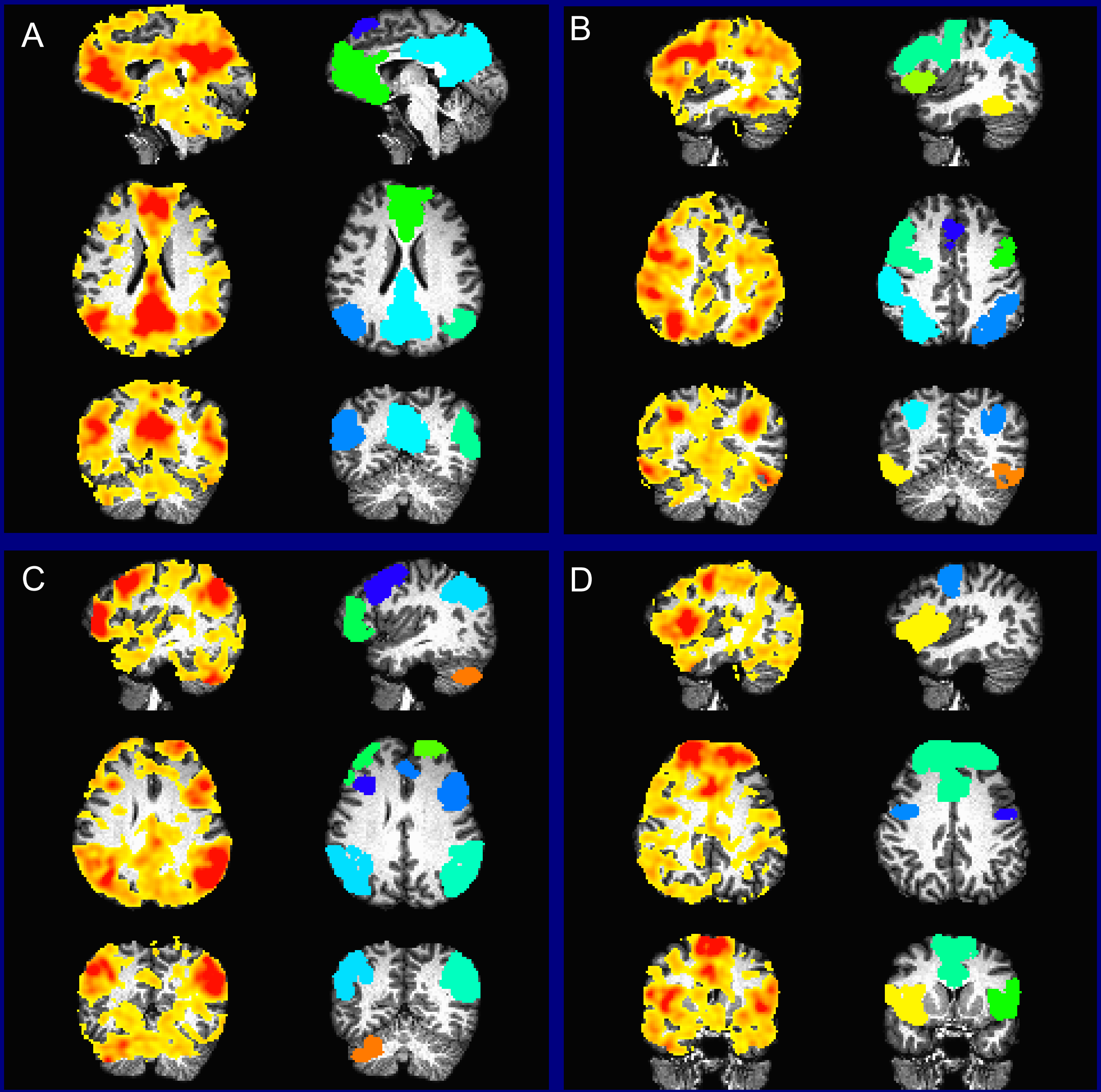


FMRI → networks of target ROIs

Example case for 4 group-level networks:

thresholded Z>3.0
cluster volume > 130 voxels
expand clusters +2 voxels
limit expansion with WM map

(NB: this involved mapping FMRI data and T1 tissue segmentation results into DWI space; used 3dAllineate)



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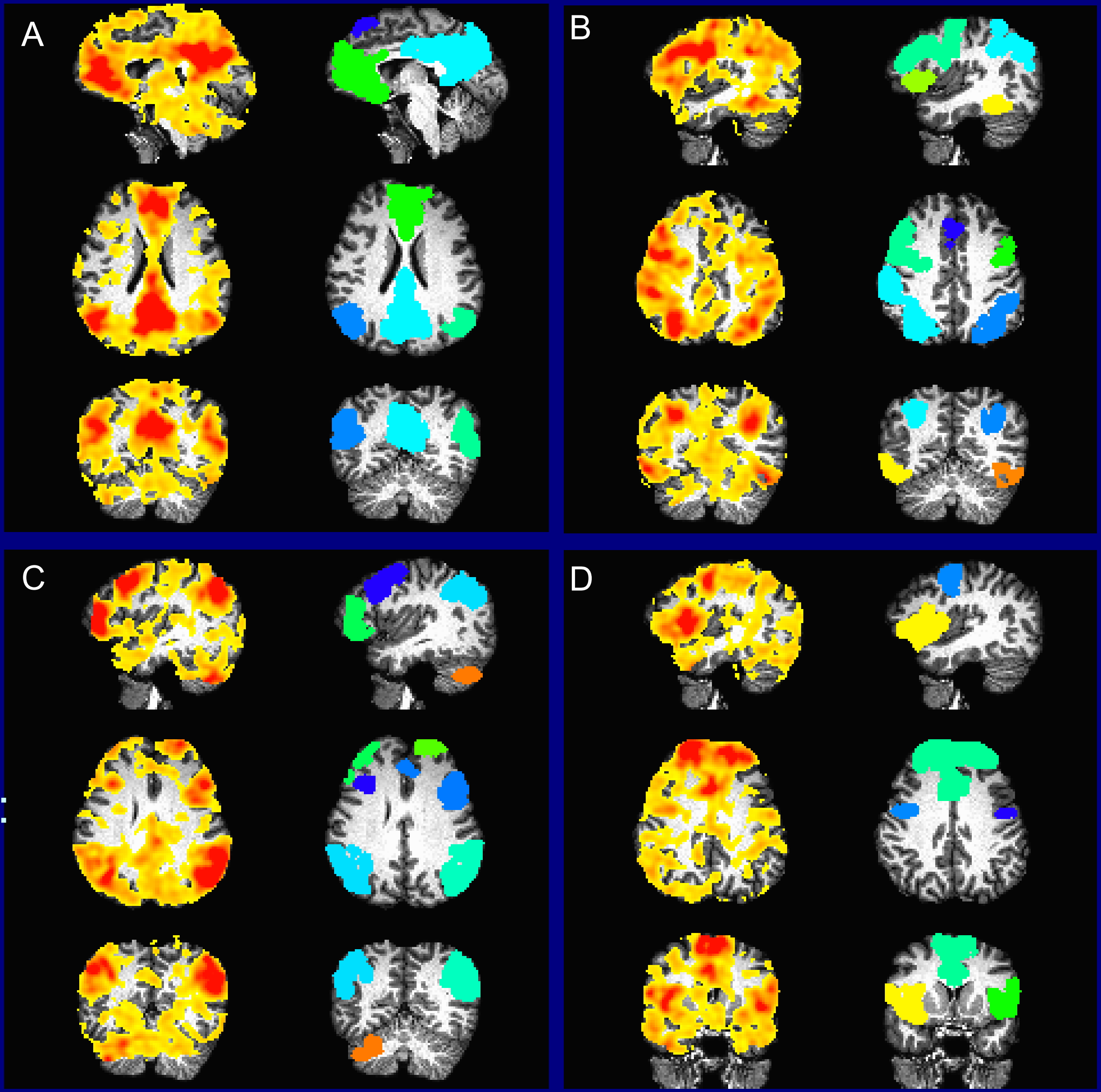
Also, for efficiency, can process multiple networks simultaneously: use a multibrick file, with each network processed separately in each brick



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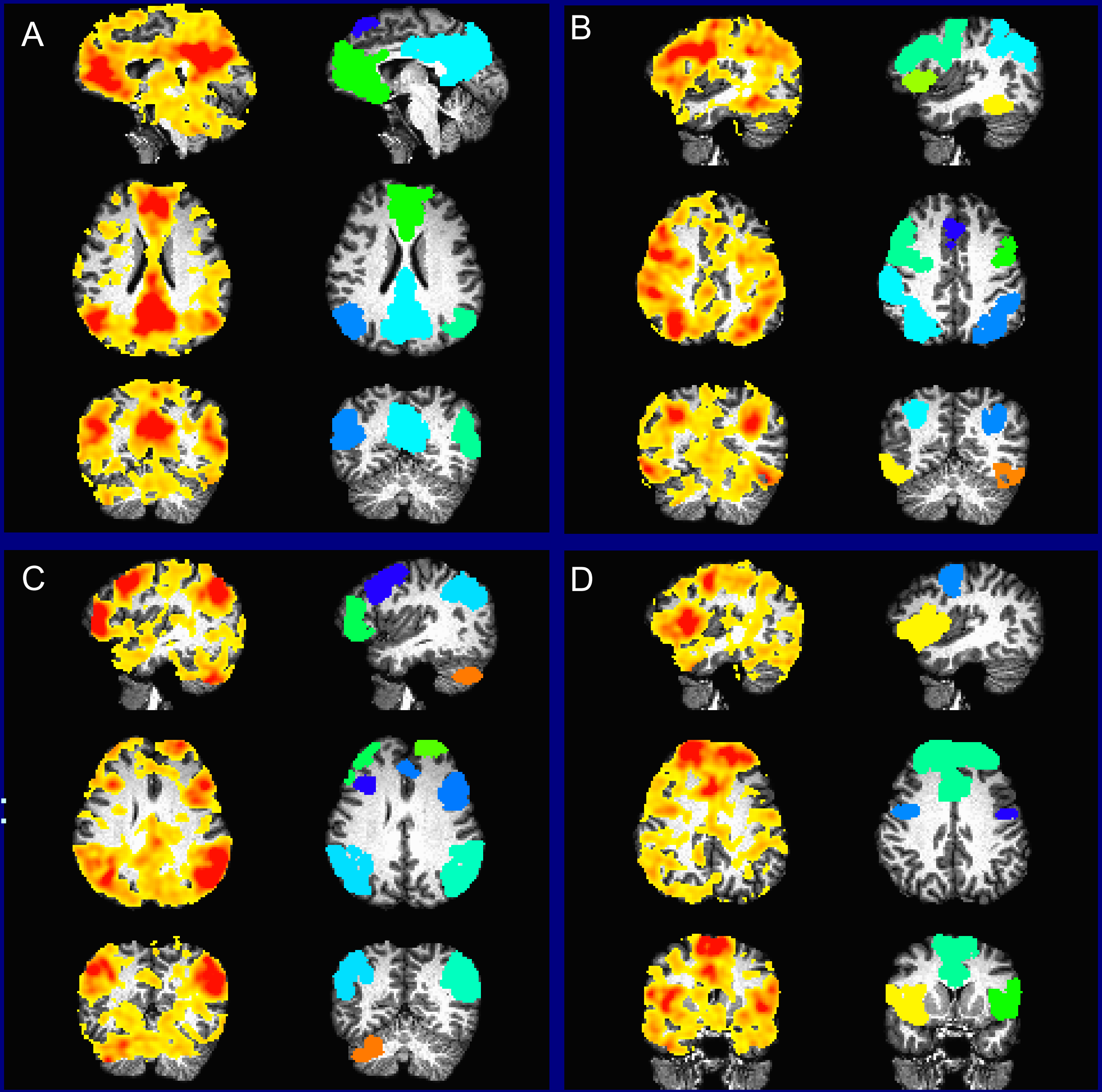

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Also, for efficiency, can process multiple networks simultaneously: use a multibrick file, with each network processed separately in each brick

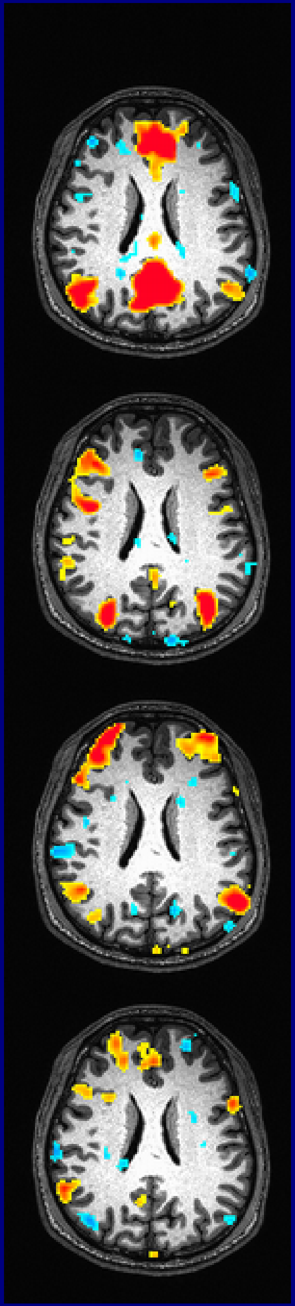
And, can use a single reference data set to have same labels across group.

Sidenote:

How to identify network maps, or match them with reference/group set?

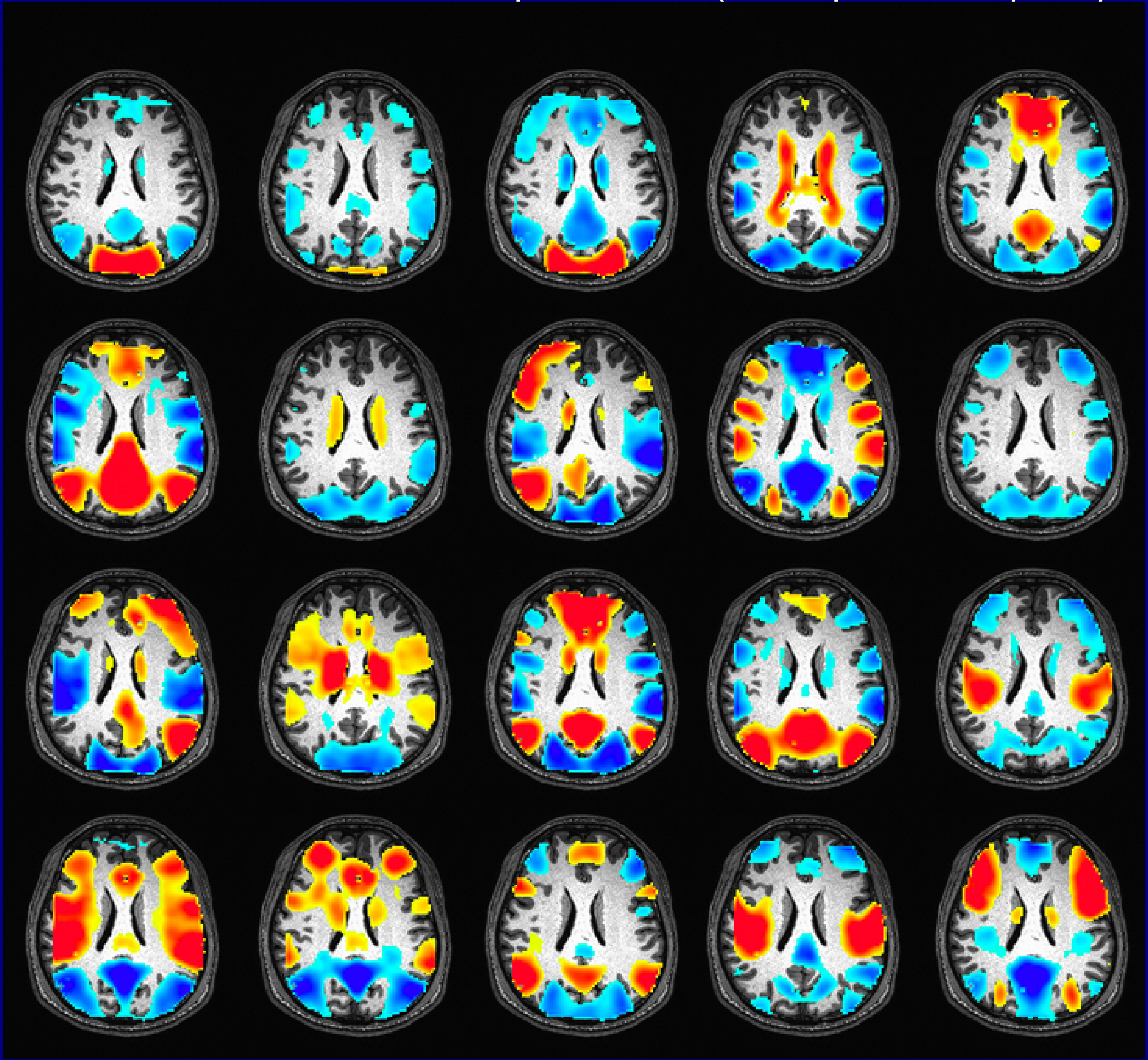
Matching Network maps

Some Z-score



?

Functional Connectome Project ref. set (in subject DWI space)



Matching Network maps

Some Z-score ICA results

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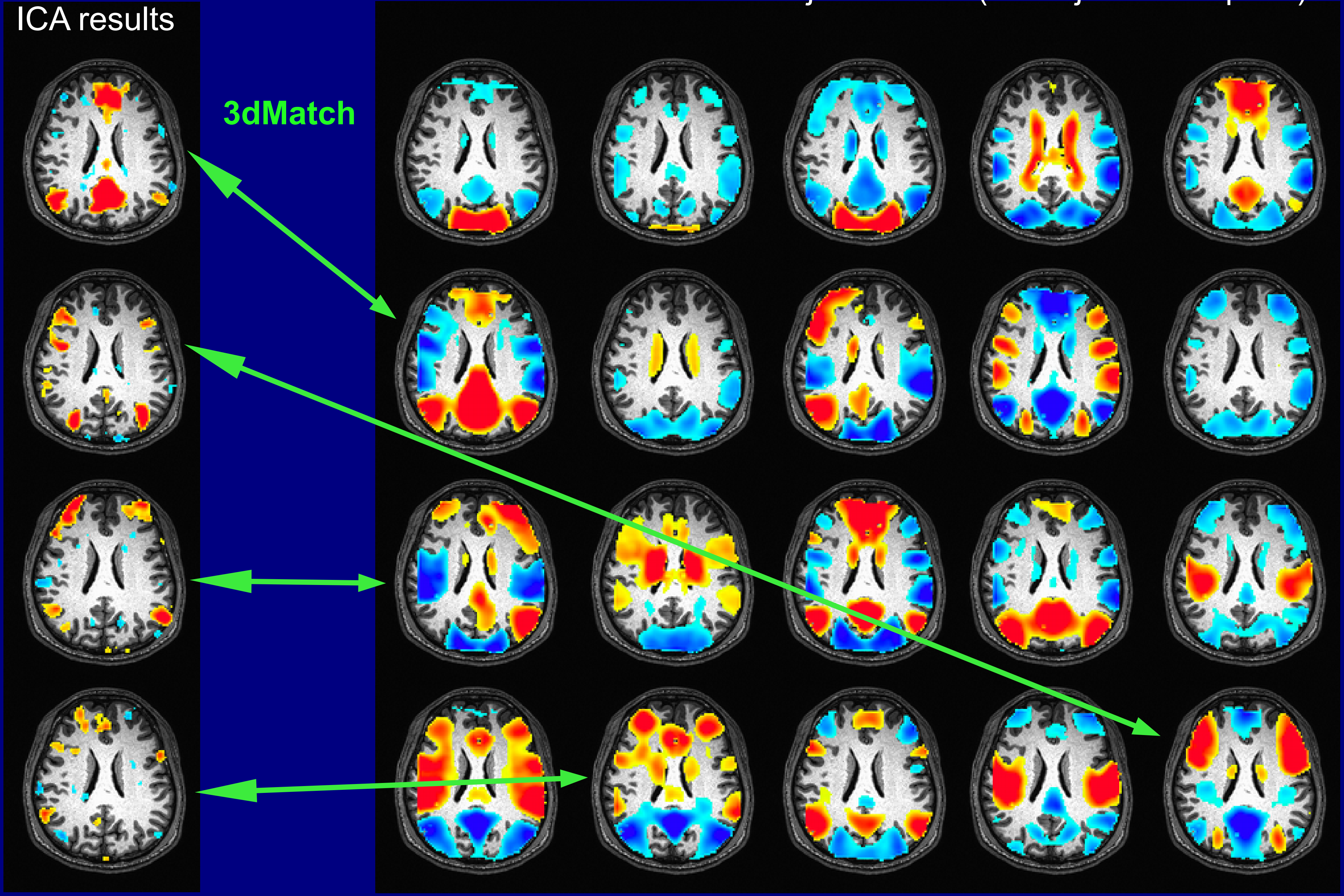
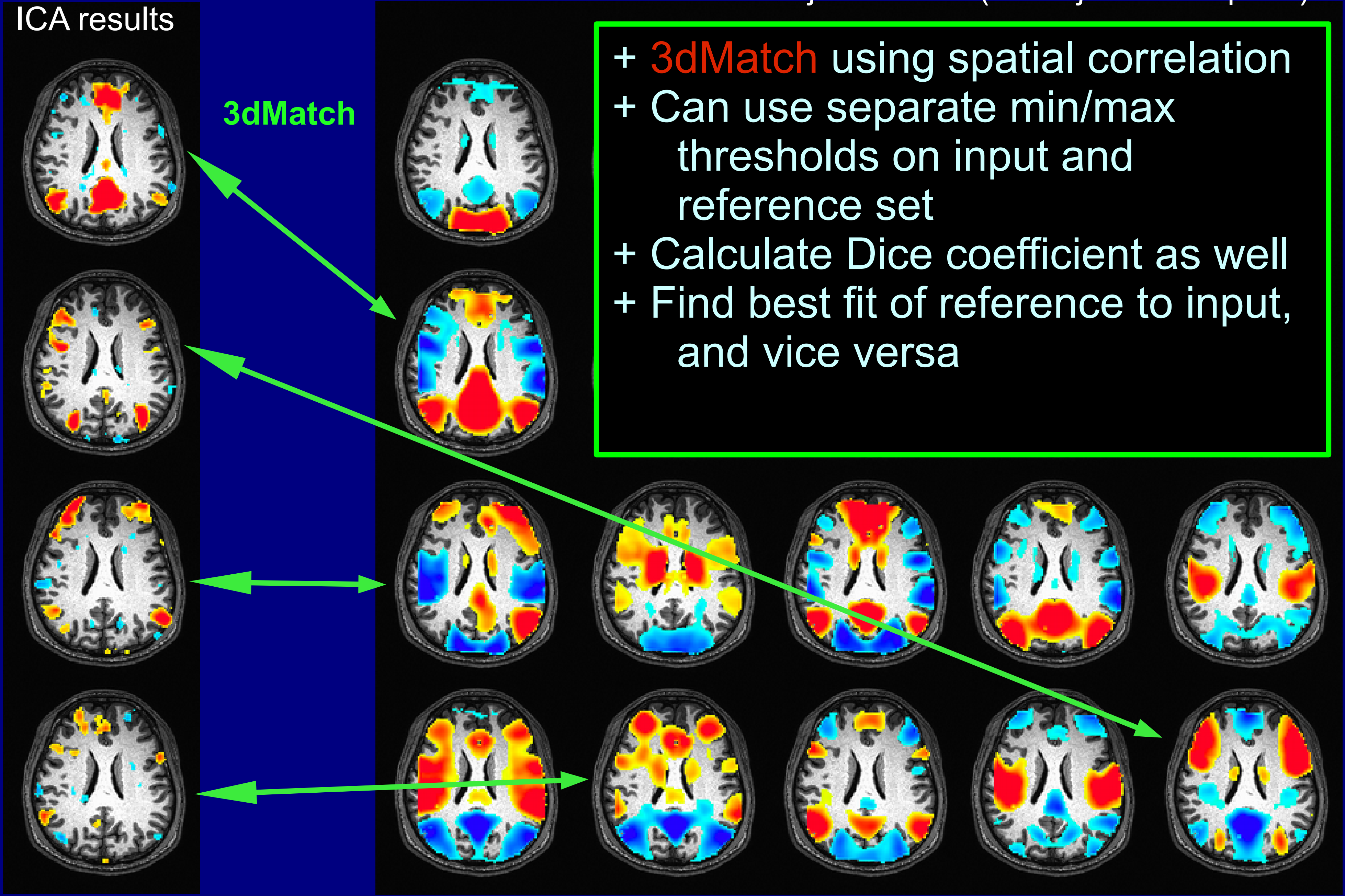


Matching Network maps



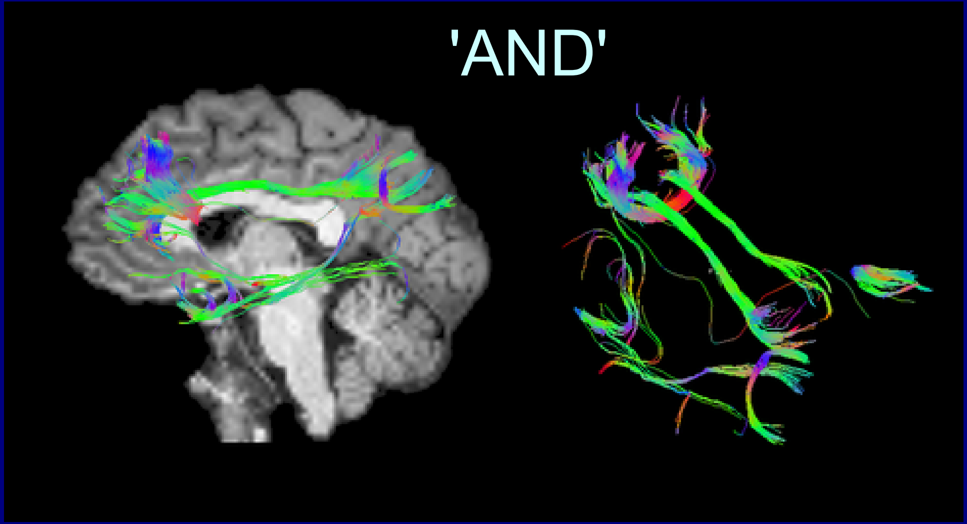
Some Z-score ICA results

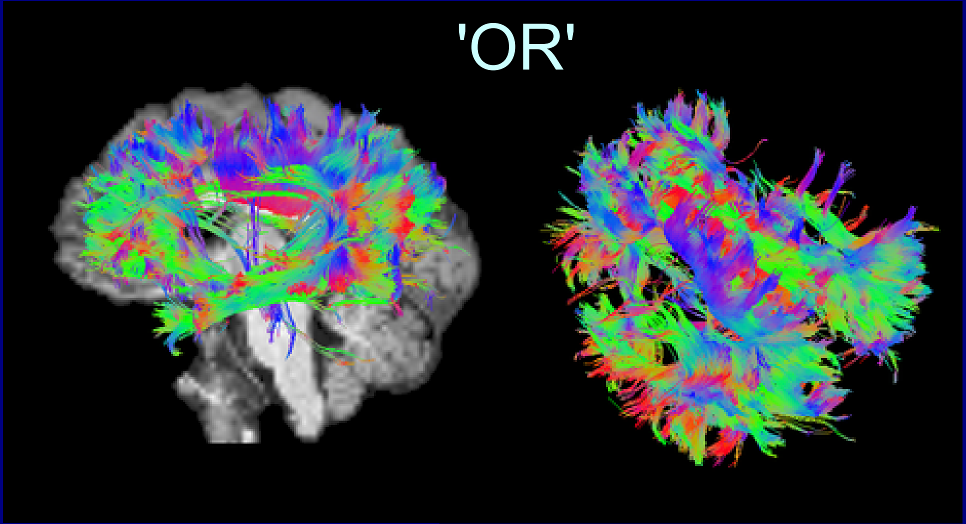
Functional Connectome Project ref. set (in subject DWI space)

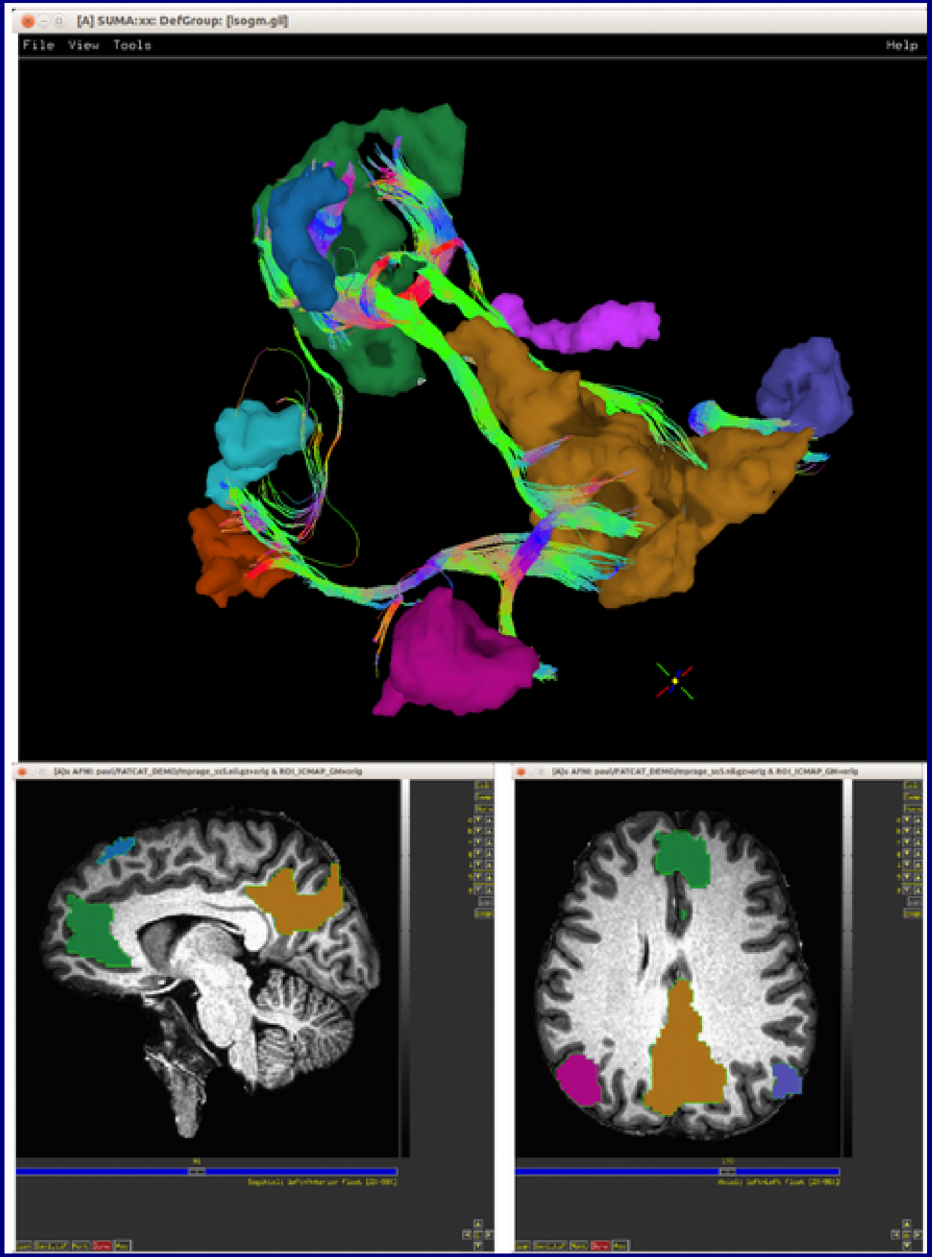
- + 3dMatch using spatial correlation
- + Can use separate min/max thresholds on input and reference set
- + Calculate Dice coefficient as well
- + Find best fit of reference to input, and vice versa

Example: Tractographic selections of WM

2) Use DTI-tractography to find likely location of WM associated with these 'targets'


'AND'


'OR'

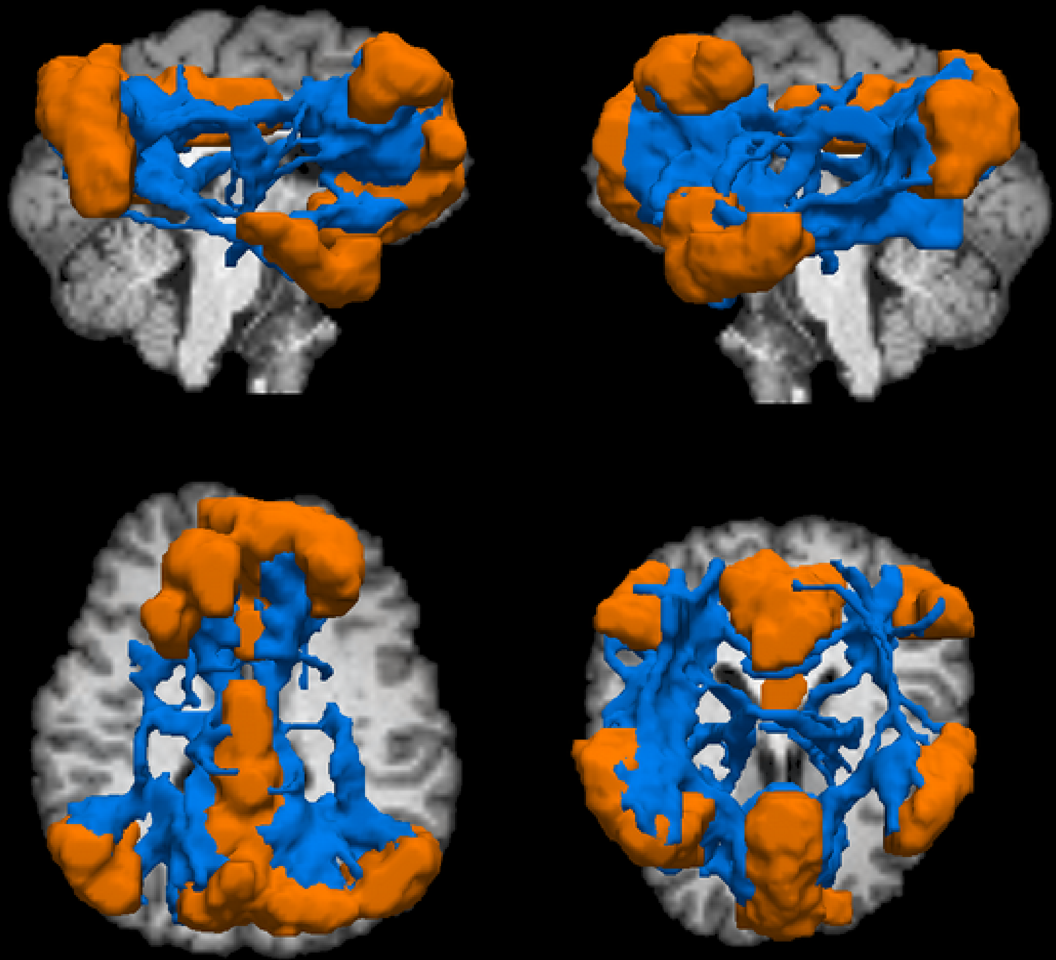


(Deterministic tracking using '3dTrackID -mode DET ...'*)*

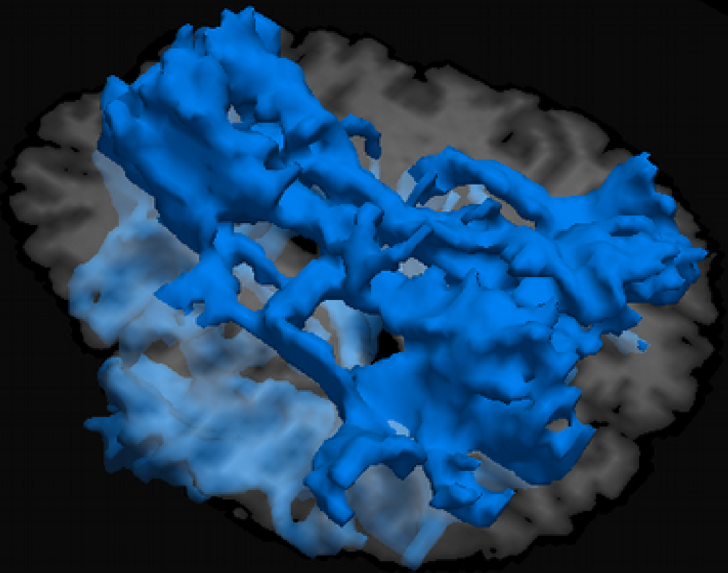
Example: Probabilistic tractography

More robust tracking method (many Monte Carlo iterations)

→ '***most likely***' locations of WM



orange = GM ROIs
blue = WM estimates
(via AFNI-FATCAT)



(Fully probabilistic tracking using '3dTrackID -mode PROB ...'*)*

Tractography: overview of flavors

All tracking done via 3dTrackID (name change from original FATCAT paper).

Modes of tracking:

DET (deterministic):
→ tract/bundle files
→ WM ROI files
→ SC (*.grid) files

+ fast estimates
+ view tracts in 3D (AND or OR logic)

PROB (probabilistic)
→ WM ROI files
→ SC (*.grid) files

+ slow(er)
+ uses DT uncertainty info for robustness
+ no tract viewing

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MINIP (mini-probabilistic)

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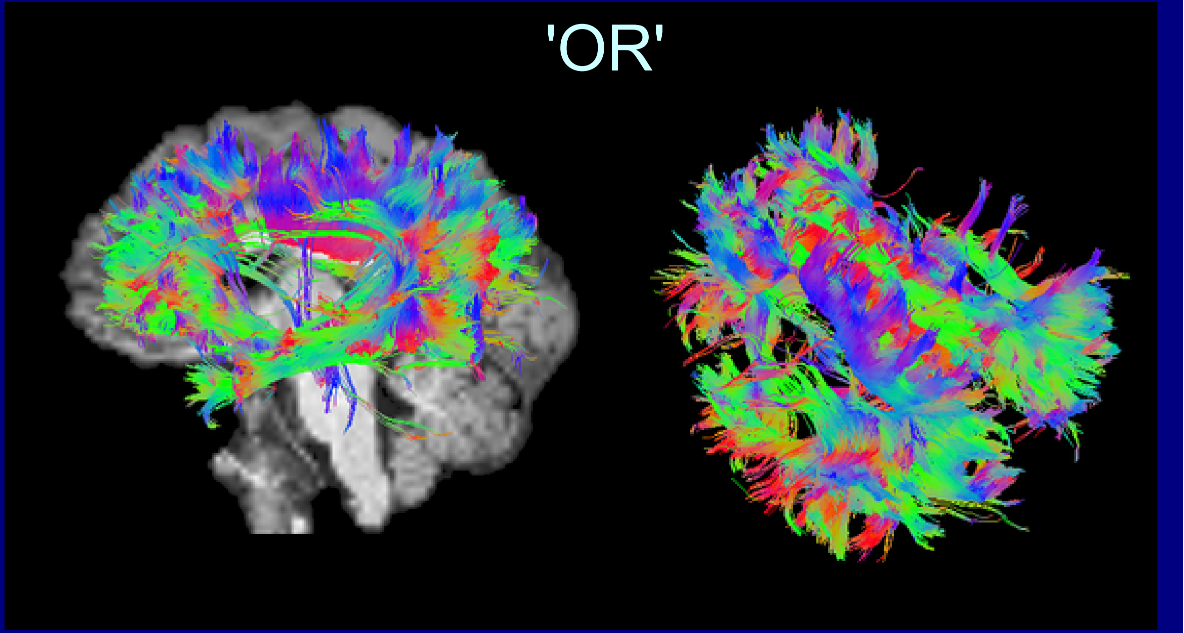
  (AND or OR logic)

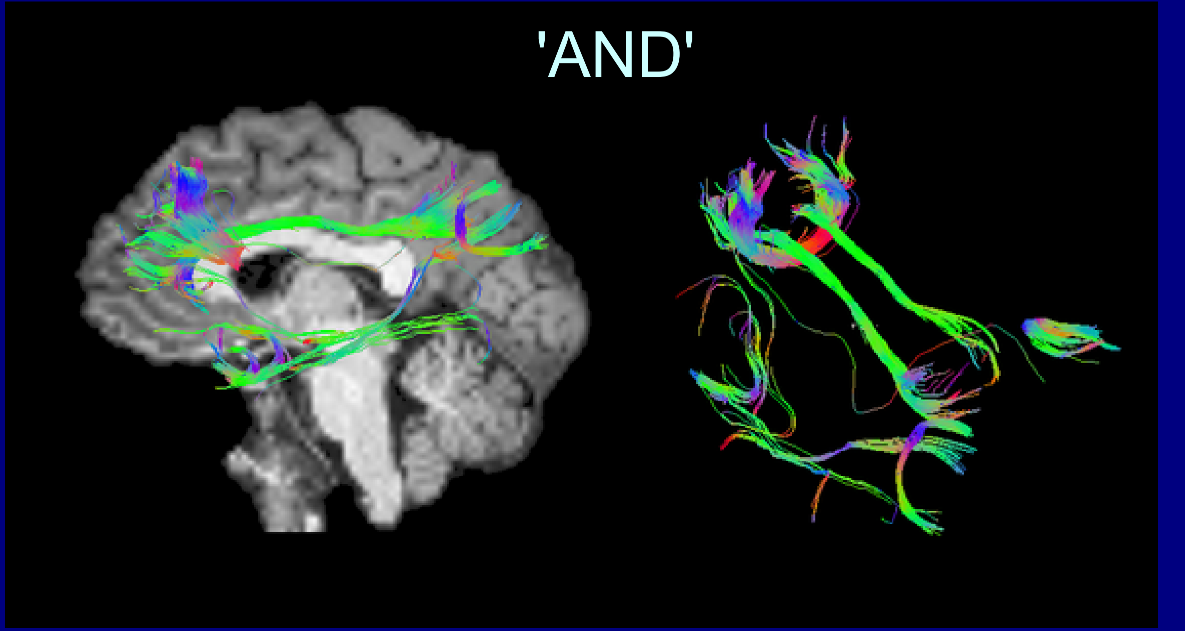
In each case, multiple target networks can be tracked simultaneously for greater efficiency, using a multibrick '-netrois' file, one network per brick.

Deterministic tractography

+ 3dTrackID -mode DET -logic { OR | AND }
+ uses FACTID
+ good for exploratory analysis and visualization of results


'OR'

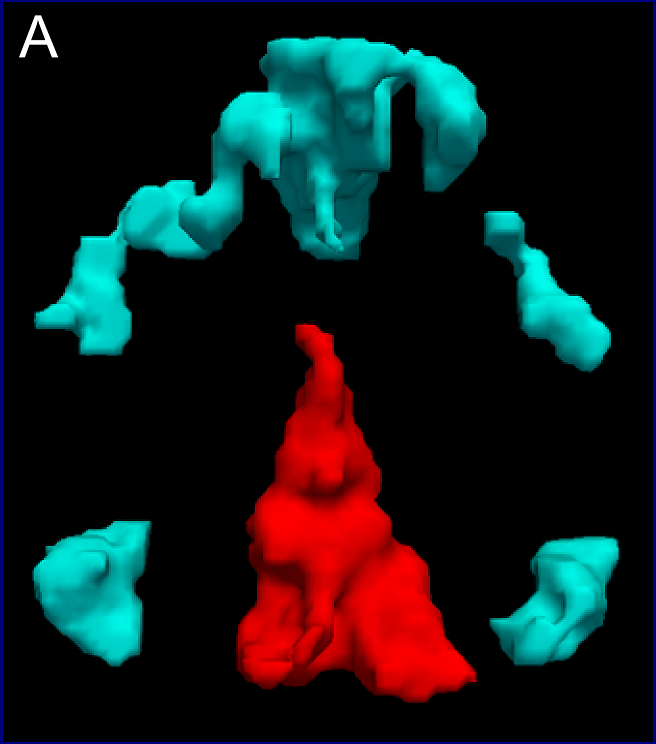
ex.: DMN network tractography results using ROIs from 3dROIMaker
(FA>0.2; max angle 60deg; 8 seeds/voxel)


'AND'

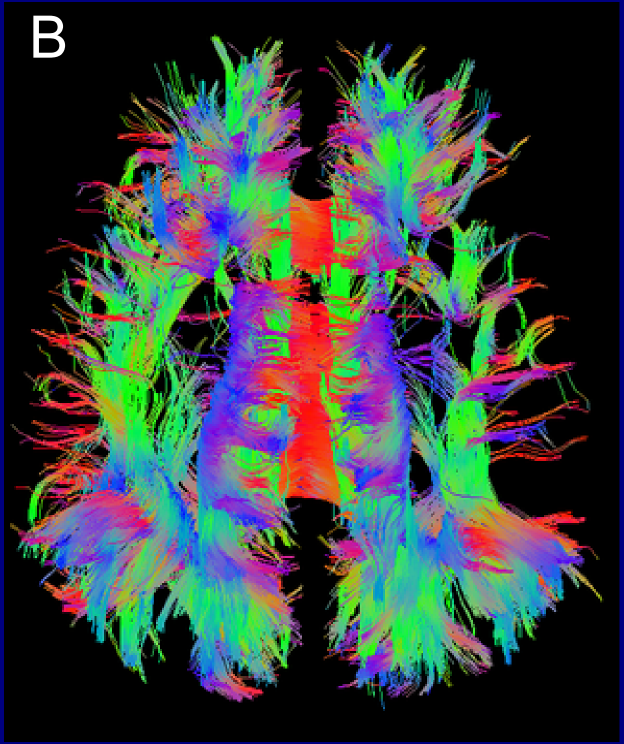
Deterministic tractography

```
+ 3dTrackID  -mode DET  -logic { OR | AND }
```

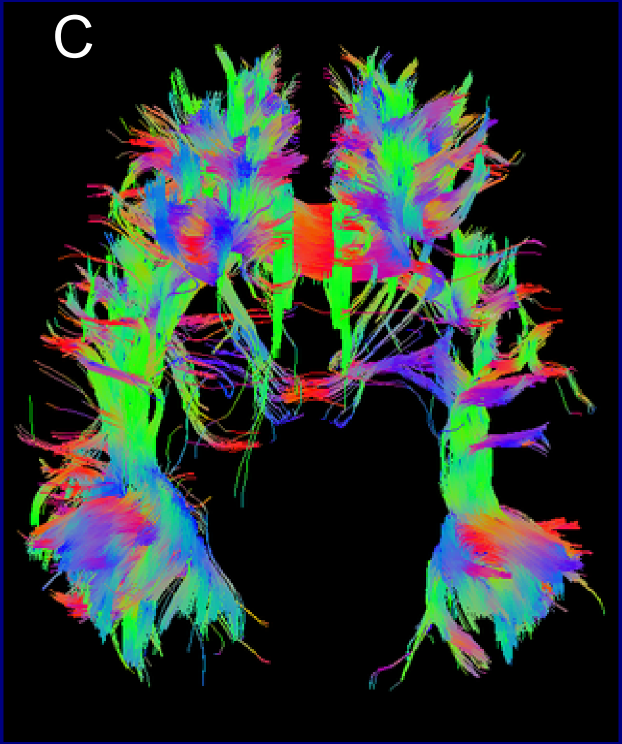
Control track propagation with `anti-mask' regions, simply defined by voxels =-1:



ROIs: blue>0, red<0



results when:
all ROIs>0
(no anti-mask)



results when:
blue>0, red<0
(using anti-masks)

Deterministic tractography

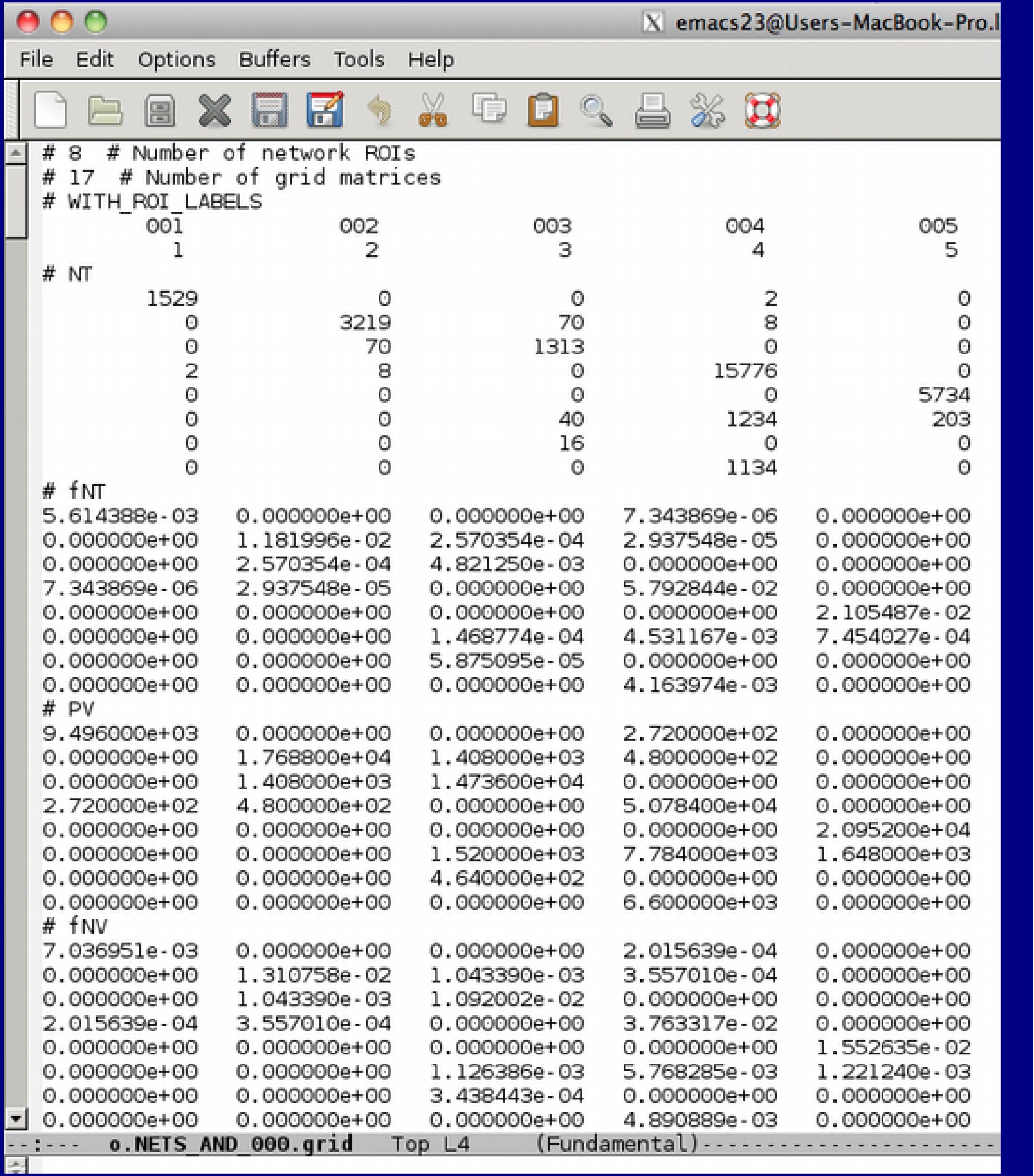
+ 3dTrackID -mode DET -logic { OR | AND }

+ Automatic quantification per network in produced PREFIX.grid files.

SC matrices of WM ROI parameters such as:
mean/std of FA, MD, RD, L1,
numbers of tracts,
volume of tracts
(and options for scaling tract-stats by ROI volumes)

+ possible to load in other files
for automatic statistics, also.

→ Will use in group stats later...



```
# 8  # Number of network ROIs
# 17  # Number of grid matrices
# WITH_ROI_LABELS
        001              002              003              004              005
          1                2                3                4                5
# NT
       1529                0                0                2                0
          0             3219               70                8                0
          0               70             1313                0                0
          2                8                0            15776                0
          0                0                0                0             5734
          0                0               40             1234              203
          0                0               16                0                0
          0                0                0             1134                0
# fNT
5.614388e-03   0.000000e+00   0.000000e+00   7.343869e-06   0.000000e+00
0.000000e+00   1.181996e-02   2.570354e-04   2.937548e-05   0.000000e+00
0.000000e+00   2.570354e-04   4.821250e-03   0.000000e+00   0.000000e+00
7.343869e-06   2.937548e-05   0.000000e+00   5.792844e-02   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   0.000000e+00   2.105487e-02
0.000000e+00   0.000000e+00   1.468774e-04   4.531167e-03   7.454027e-04
0.000000e+00   0.000000e+00   5.875095e-05   0.000000e+00   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   4.163974e-03   0.000000e+00
# PV
9.496000e+03   0.000000e+00   0.000000e+00   2.720000e+02   0.000000e+00
0.000000e+00   1.768800e+04   1.408000e+03   4.800000e+02   0.000000e+00
0.000000e+00   1.408000e+03   1.473600e+04   0.000000e+00   0.000000e+00
2.720000e+02   4.800000e+02   0.000000e+00   5.078400e+04   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   0.000000e+00   2.095200e+04
0.000000e+00   0.000000e+00   1.520000e+03   7.784000e+03   1.648000e+03
0.000000e+00   0.000000e+00   4.640000e+02   0.000000e+00   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   6.600000e+03   0.000000e+00
# fNV
7.036951e-03   0.000000e+00   0.000000e+00   2.015639e-04   0.000000e+00
0.000000e+00   1.310758e-02   1.043390e-03   3.557010e-04   0.000000e+00
0.000000e+00   1.043390e-03   1.092002e-02   0.000000e+00   0.000000e+00
2.015639e-04   3.557010e-04   0.000000e+00   3.763317e-02   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   0.000000e+00   1.552635e-02
0.000000e+00   0.000000e+00   1.126386e-03   5.768285e-03   1.221240e-03
0.000000e+00   0.000000e+00   3.438443e-04   0.000000e+00   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   4.890889e-03   0.000000e+00
--:---   o.NETS_AND_000.grid   Top L4     (Fundamental)----------------------
```

Deterministic tractography

+ 3dTrackID -mode DET -logic { OR | AND }

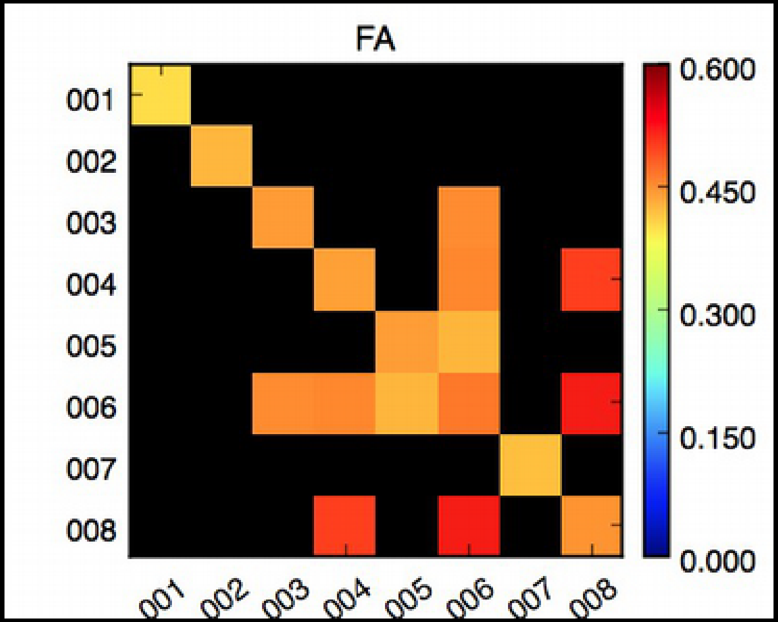
+ Automatic quantification per network in produced PREFIX.grid files.

SC matrices of WM ROI parameters such as:
mean/std of FA, MD, RD, L1,
numbers of tracts,
volume of tracts
(and options for scaling tract-stats by ROI volumes)

+ possible to load in other files for automatic statistics, also.

→ Will use in group stats later...

+ fat_mat_plot.py: command line tool to visualize each SC matrix:



+ can control font, colors, ranges, DPI, etc.

```
0.000000e+00   0.000000e+00   3.438443e-04   0.000000e+00   0.000000e+00
0.000000e+00   0.000000e+00   0.000000e+00   4.890889e-03   0.000000e+00
--:---  o.NETS_AND_000.grid   Top L4     (Fundamental)---------------------
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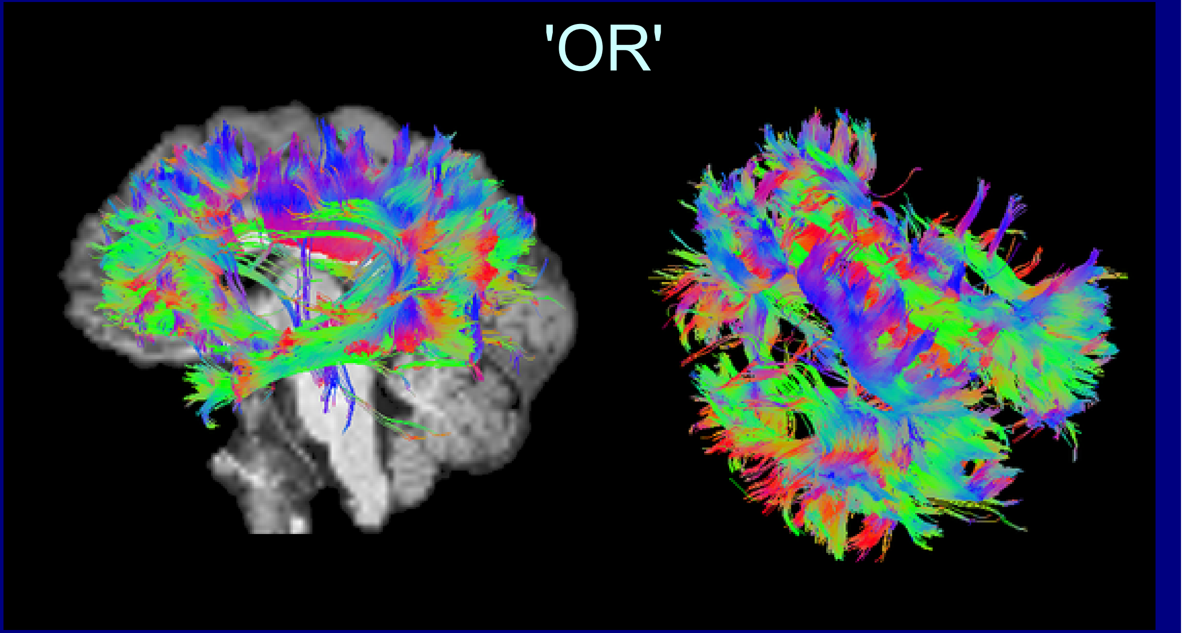

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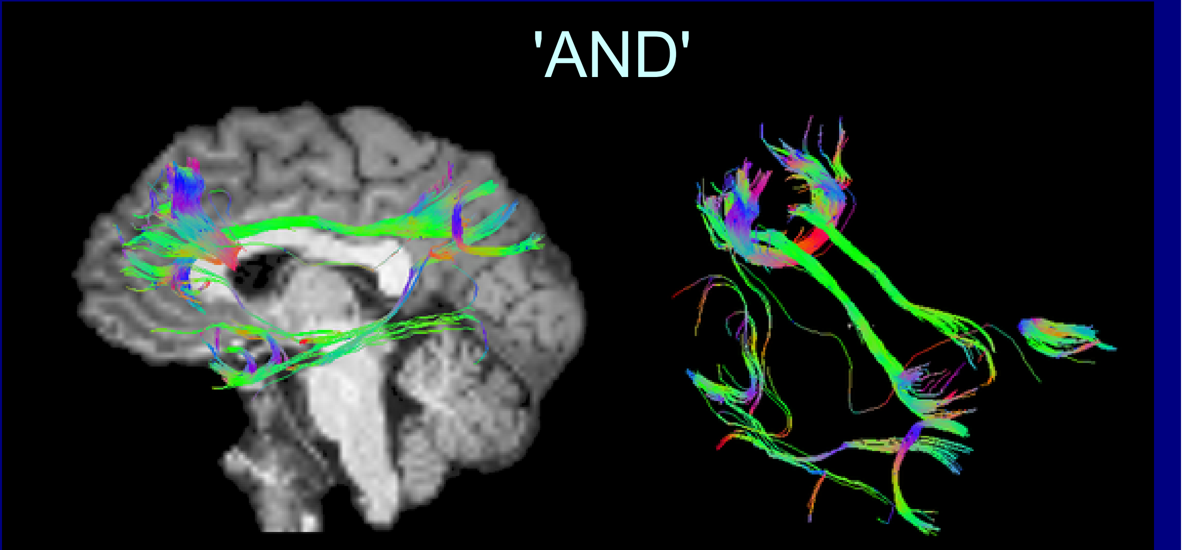


*Tract results may seem 'fine', but is **noise** affecting them? Are these the **most likely/robust** regions where tracts go?*

Brings up next question for doing tractography:

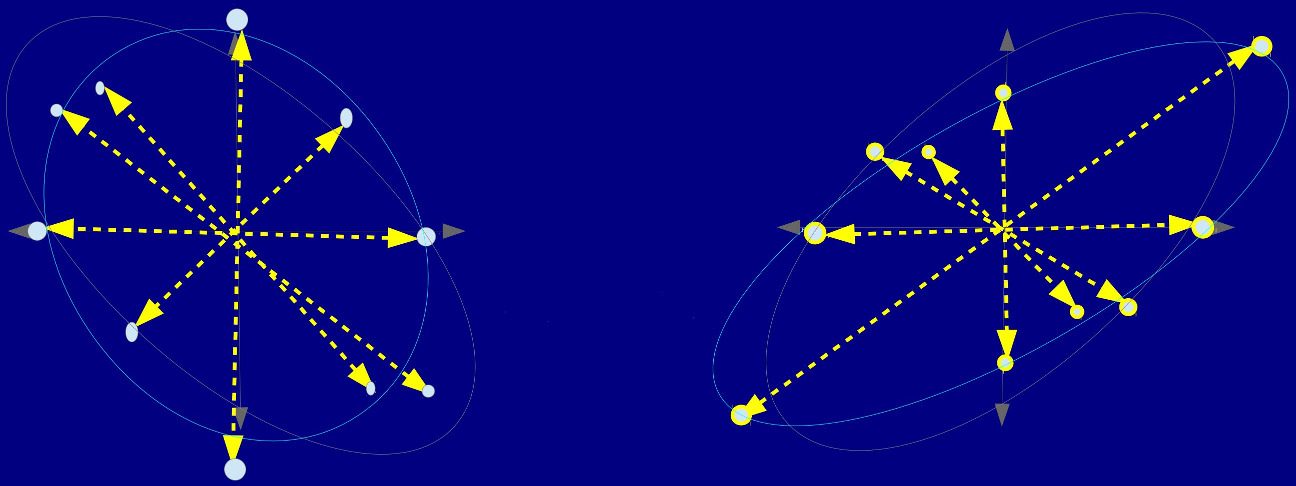
How do we estimate tensor parameter noise/uncertainty?

Noise in DW signals

MRI signals have additive noise

$$S_i = S_0 \, e^{-b \, \mathbf{g}_i^T \mathbf{D} \, \mathbf{g}_i} + \varepsilon,$$

where ε is (Rician) noise, with the effect of leading to errors in surface fit, equivalent to *rotations* and *rescalings* of ellipsoids:



'Un-noisy' vs perturbed/noisy fit

EPI distortions, subject motion, et al. also warp ellipsoids.

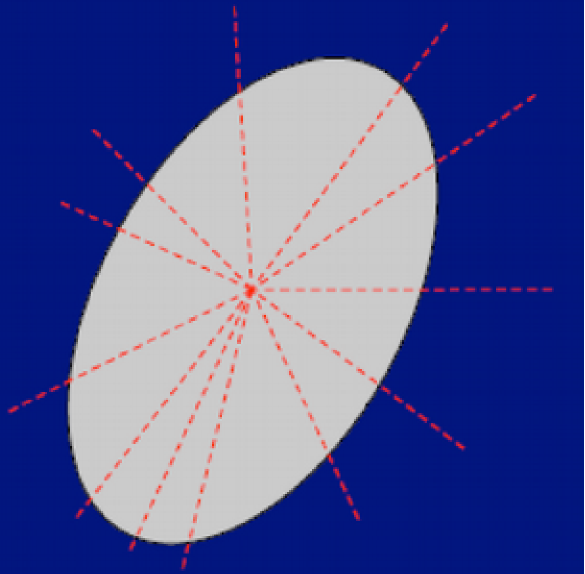
DTI Uncertainty

- We use jackknife resampling (e.g., Efron 1982)
  - Other studies have used bootstrapping (e.g., Jones 2003), or theoretical estimates (Jeong & Anderson 2008)
  - Jackknifing is efficient (just need one data set unlike bootstrap), simpler than theory, since, e.g., SNR is likely not constant across voxels

Jackknifing

- Basically, take M acquisitions

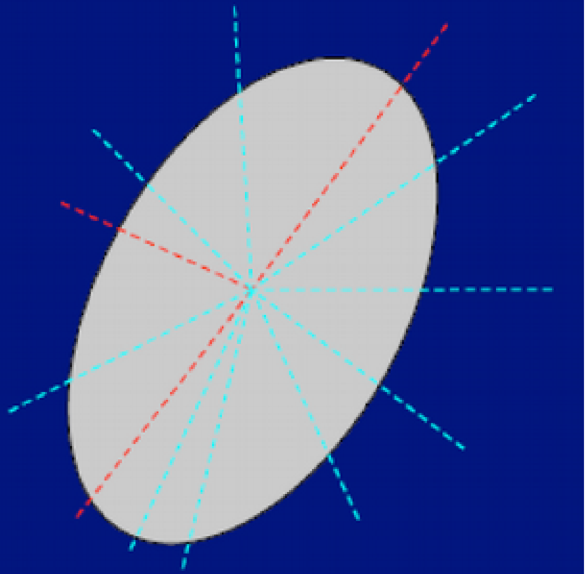
e.g., M=12



Jackknifing

- Basically, take M acquisitions
- Randomly select $M_J < M$ to use to calculate quantity of interest
  - standard nonlinear fits

e.g., $M=12$
$M_J=9$



$$[D_{11} \;\; D_{22} \;\; D_{33} \;\; D_{12} \;\; D_{13} \;\; D_{23}] = \ldots.$$

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- Repeatedly subsample large number (~10^3-10^4 times)

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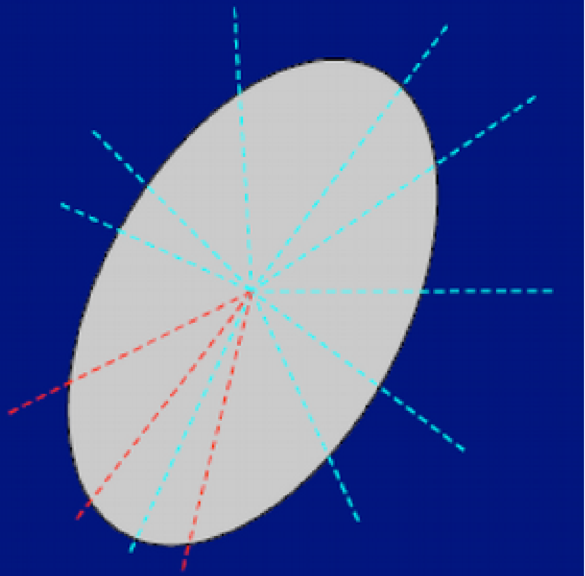

$$[D_{11}\ \ D_{22}\ \ D_{33}\ \ D_{12}\ \ D_{13}\ \ D_{23}] = \ldots.$$
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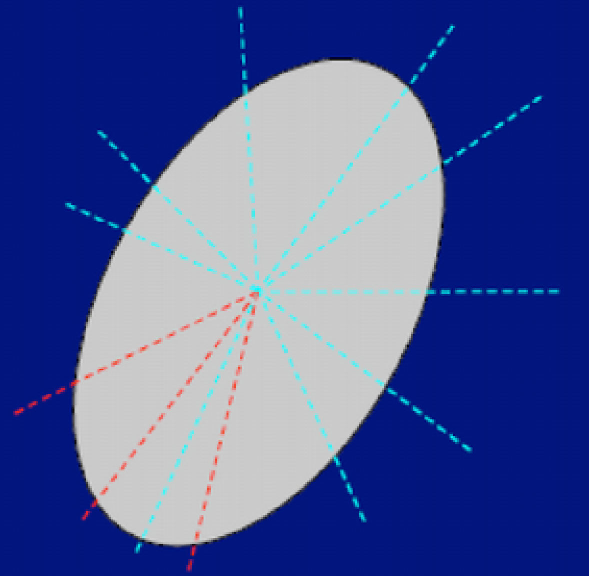
....

Jackknifing

- Basically, take M acquisitions
- Randomly select $M_J < M$ to use to calculate quantity of interest
  - standard nonlinear fits
- Repeatedly subsample large number (~10^3-10^4 times)
- Analyze distribution of values for estimator (mean) and confidence interval
  - sort/%iles
    - (not so efficient)
  - if Gaussian, e.g. $\mu \pm 2\sigma$
    - simple

e.g., $M=12$

$M_J=9$

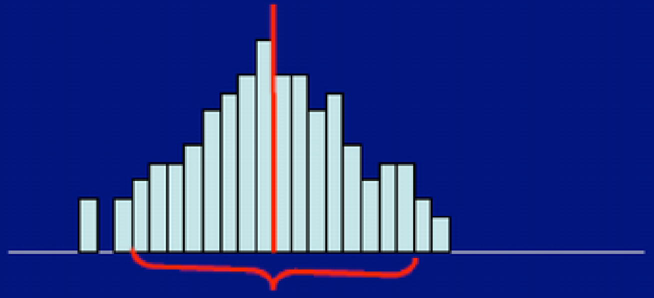


$[D_{11}\ \ D_{22}\ \ D_{33}\ \ D_{12}\ \ D_{13}\ \ D_{23}] = ...$

$[D_{11}\ \ D_{22}\ \ D_{33}\ \ D_{12}\ \ D_{13}\ \ D_{23}] = ...$

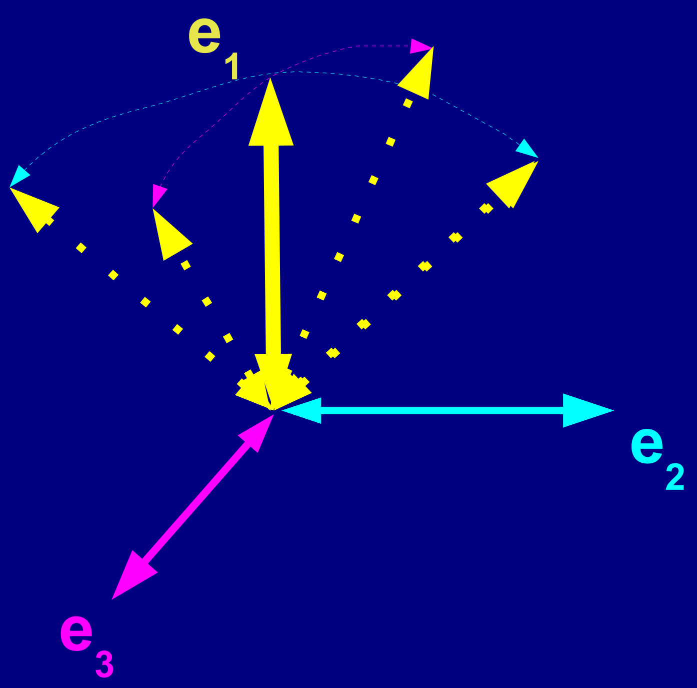
$[D_{11}\ \ D_{22}\ \ D_{33}\ \ D_{12}\ \ D_{13}\ \ D_{23}] = ...$

....

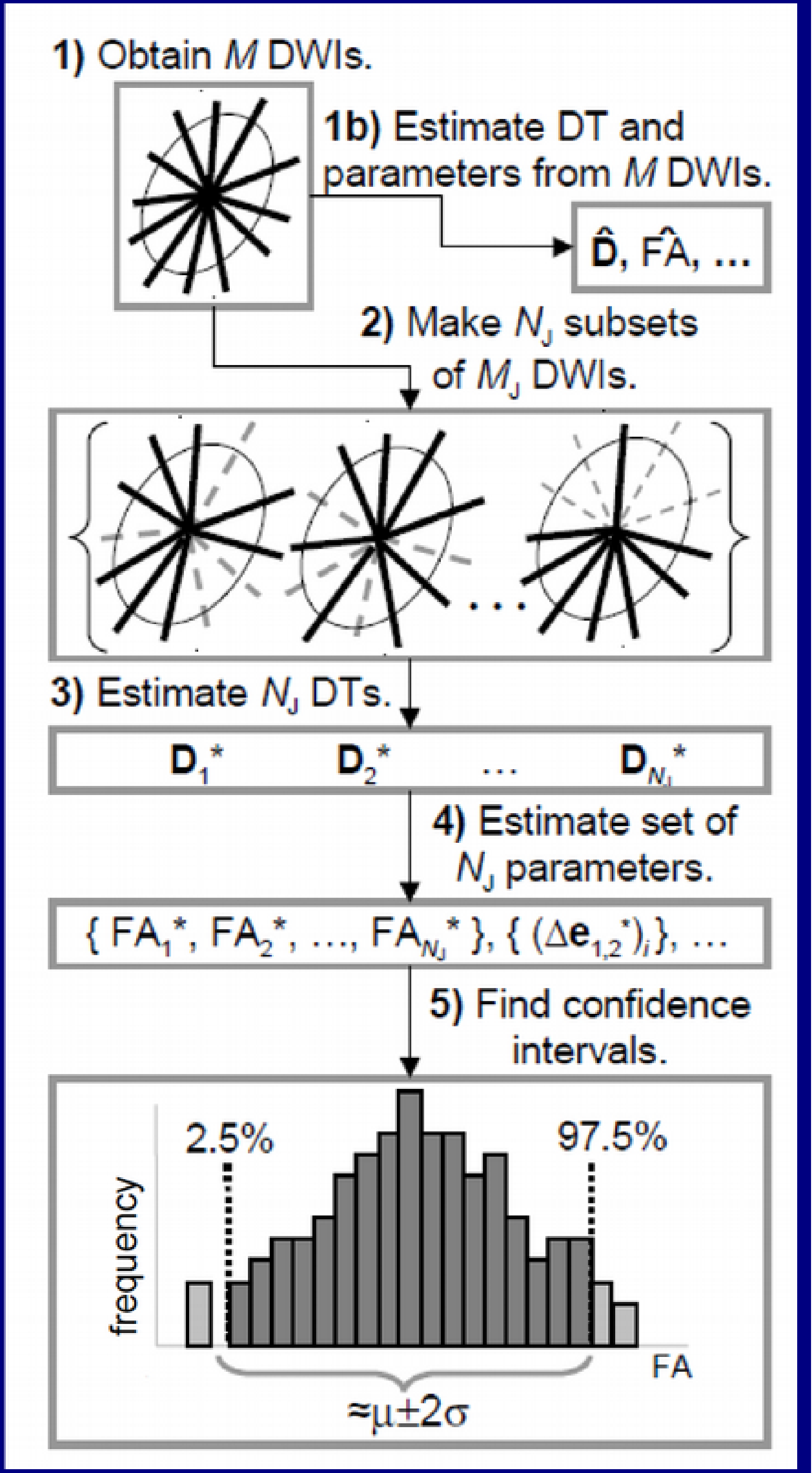


Uncertainty estimation

+ 3dDWUncert estimates bias and σ of first eigenvector $\mathbf{e}_1$ (main direction of diffusion), based on how much it could tip toward either $\mathbf{e}_2$ or $\mathbf{e}_3$:



.... and the bias and σ of FA


1) Obtain M DWIs.

1b) Estimate DT and parameters from M DWIs.

$\hat{D}$, $\hat{FA}$, ...

2) Make N_J subsets of M_J DWIs.

3) Estimate N_J DTs.

D_1^* D_2^* ... $D_{N_J}^*$

4) Estimate set of N_J parameters.

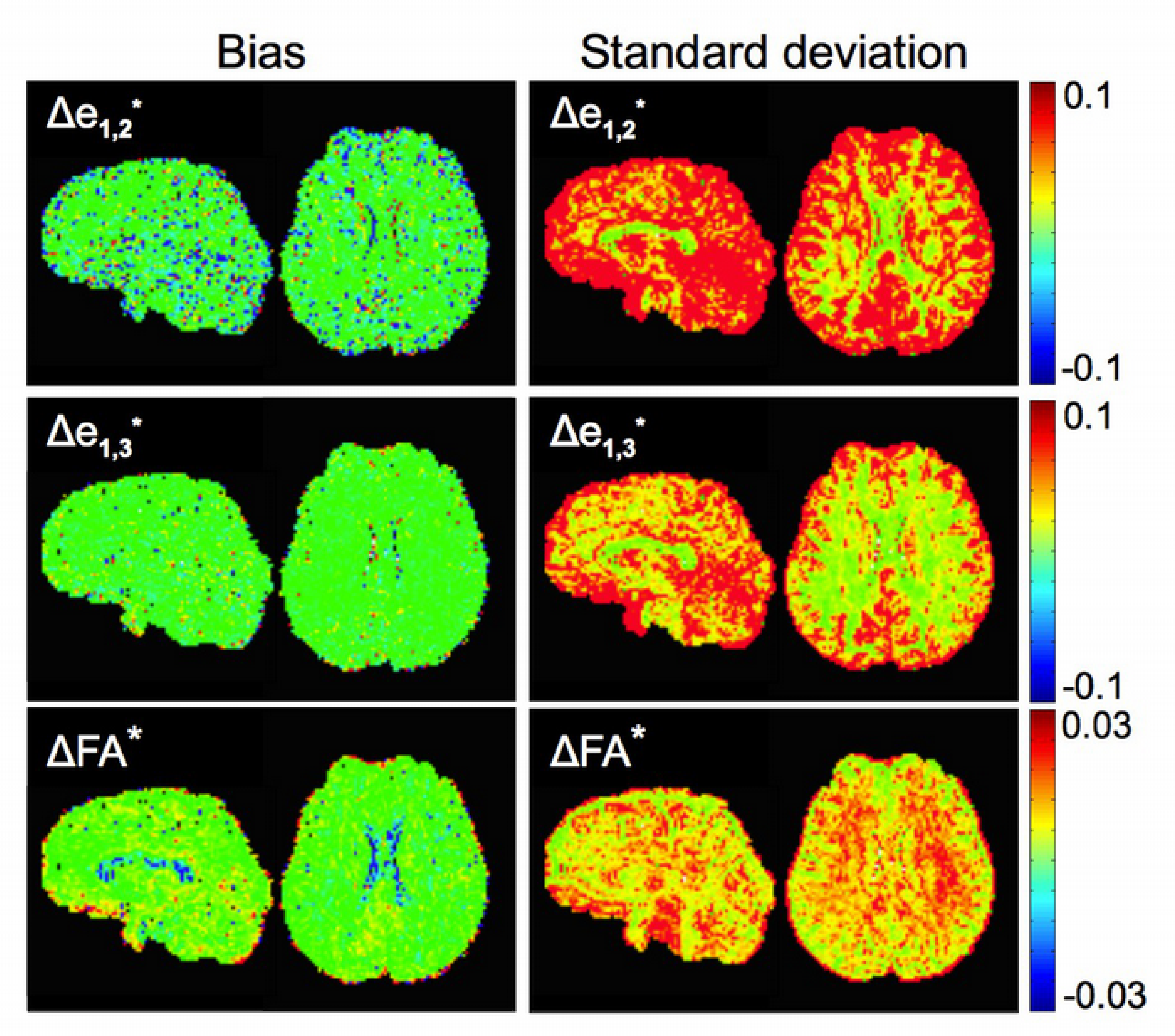
$\{ FA_1^*, FA_2^*, \ldots, FA_{N_J}^* \}, \{ (\Delta \mathbf{e}_{1,2}^*)_i \}, \ldots$

5) Find confidence intervals.

Uncertainty example

- + Can see difference in e1 uncertainty along e2 and e3

- + Tissue-dependent differences in FA uncertainty



Next question for doing tractography:

How do we take into account noise/uncertainty during tracking?

Probabilistic Tractography

- We know that estimates of DTI ellipsoids are not exactly representing tracts/bundles
  - Size scale differences between voxel/tracts, multiple tracts, complex structure, signal noise, eddy currents, nonlinear fits, etc.
- How to include errors/uncertainty in interpretation and usage?

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- *Probabilistic tractography*: use uncertainty in ellipsoid measures with Monte Carlo-esque simulations and build up large ~population of possible trajectories
  - E.g., Parker et al. (2003); Behrens et al. (2003)
  - Do DTI estimates; do whole brain tractography; keep track of number of tracks through relevant voxels; perturb DTI voxel estimates based on uncertainty values; do whole brain tract… [repeat many ~1000 times] … find voxels which had lots of traffic, define relative 'connectivity' based on traffic

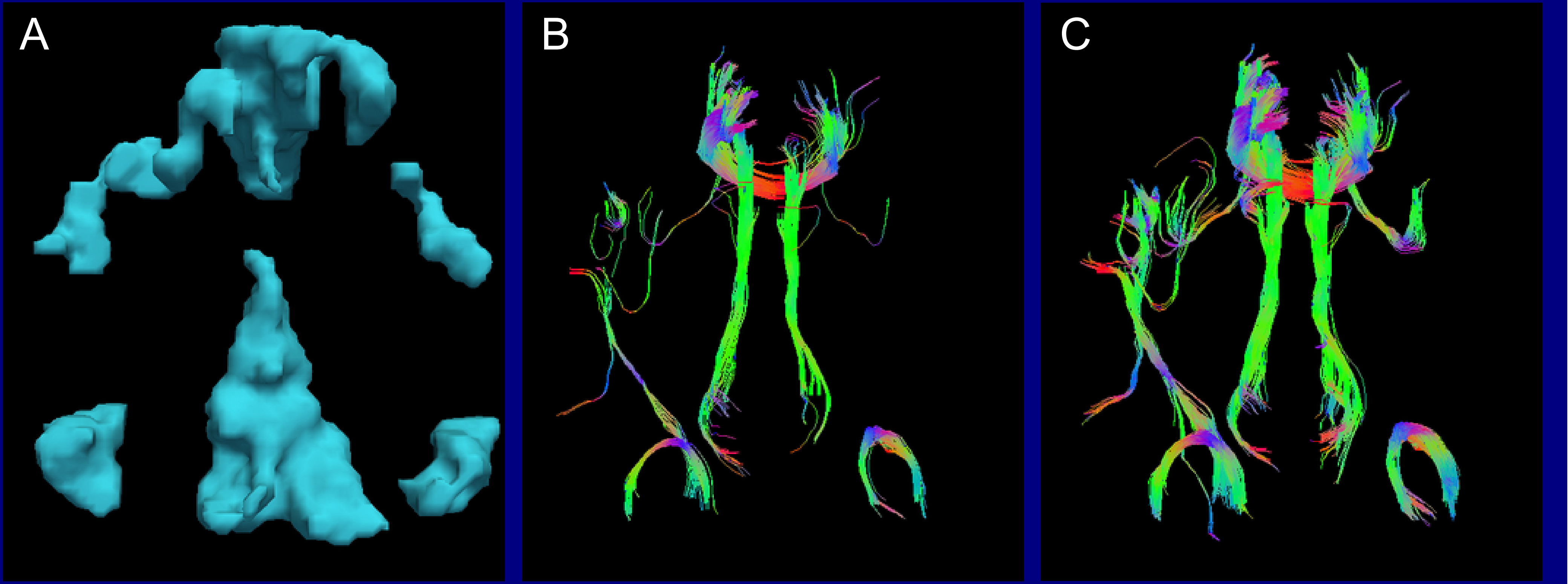
(Side note before continuing with
'full' probabilistic tracking)

Mini-Probabilistic Tracking

\+ Full probabilistic methods generate voxelwise brain maps without linear track structure

\+ 'Mini-probabilistic' tracking performs a few extra iterations of' deterministic' tracking on uncertainty-perturbed data sets

- track structure is retained,
- results generally exhibit more robust tracks and fewer false negatives than deterministic tracking alone
- false positives tend to be isolated and visually apparent.



Deterministic (AND)

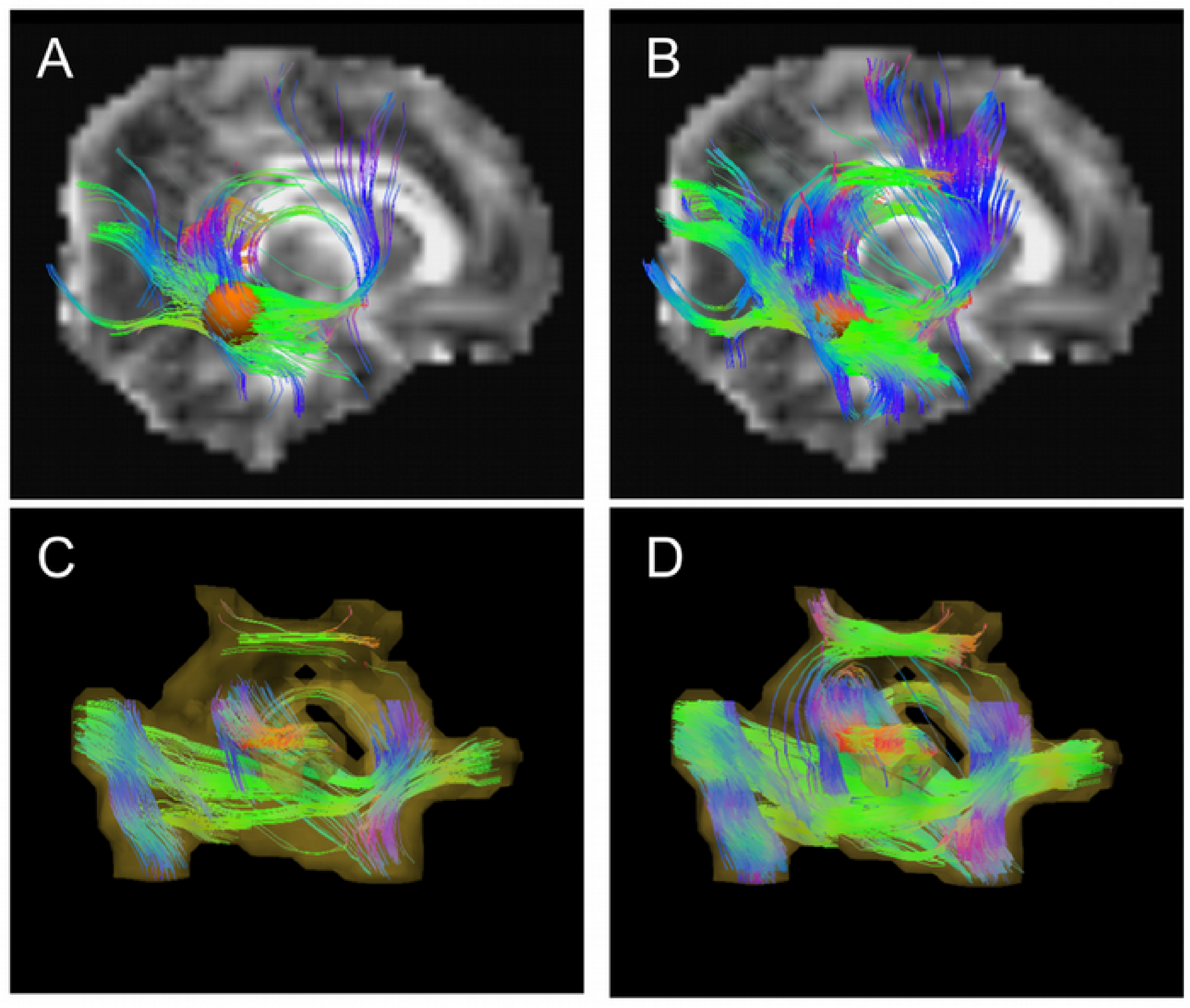
with `-mini_prob 7'

Mini-Probabilistic Tracking

Deterministic vs mini-Probabilistic

Through single ROI

AND logic through network, cf with full-prob results



(Taylor et al., 2014)

Probabilistic Tractography

- Note on interpretation: most reports define a parameter to be the probability of connection between voxels A and X:

  $\Psi(X,A)=\mu(X,A)/N$

  - N: number of iterations
  - μ: number of tracts through voxel X which either start from or pass through A

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-> for example, how literally can one equate a numerically-constructed tract through a ~2x2x2mm voxel with a fiber bundle with orders-of-magnitude smaller diameter?

-> or how can one compare this 'connectivity' between ROIs of different sizes on equal footing?

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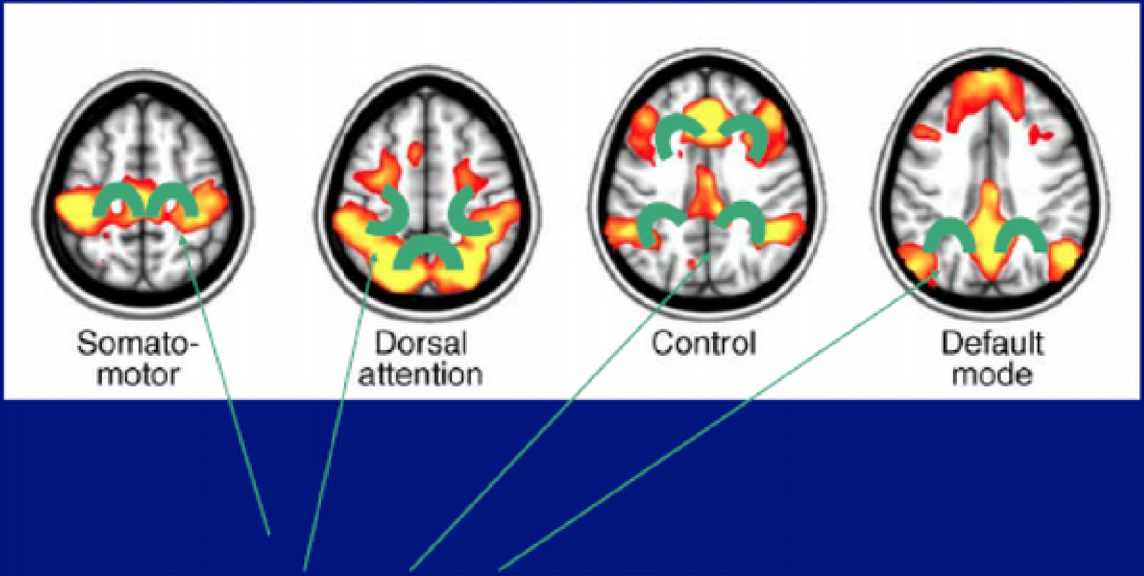
- While this quantity is somehow relevant in representing what relative ‘connectivity’ which can be estimated, exact interpretation as ‘probability of connectivity’ is tricky
- Prefer to think of Ψ more loosely as a probability of that voxel being a part of WM volume related to the two ROI-voxels.
  - Not probability of *connectivity* of A and X, but more *likelihood of a voxel being part of associated WM*

Probabilistic Tractography

- This interpretation more useful for working with GM networks. Recall interest:



GM ROIs network:

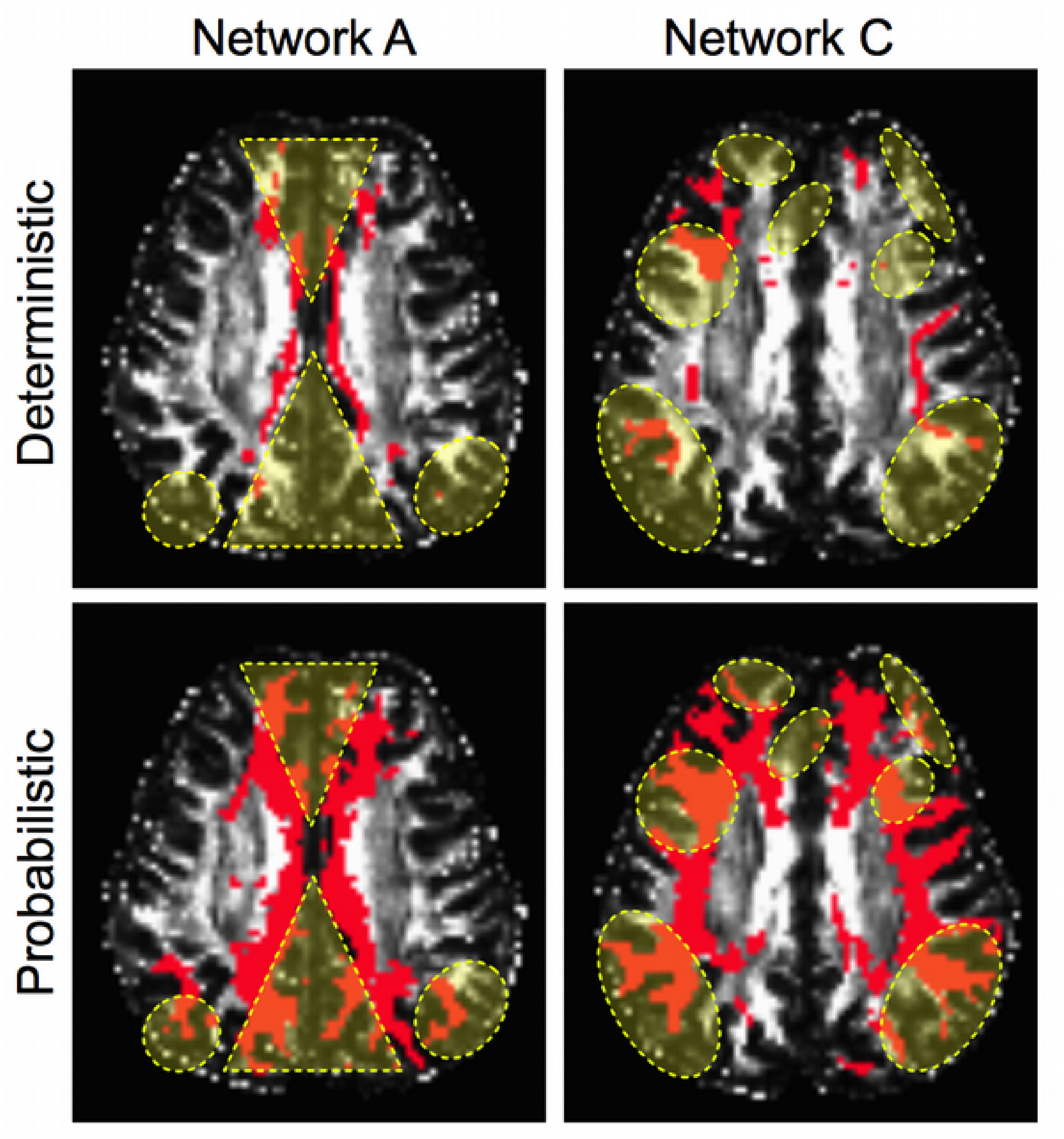
Associated WM ROIs

- Threshold Ψ per voxel after probabilistic tracking, use to define WM ROI between GM ROIs

Deterministic vs Probabilistic

- NB: coverage and connectivity differences between tractography types

- Deterministic can be useful for initial investigations, but is more susceptible to noise/errors and truncation



Probabilistic tractography

+ with networks of ROIs from 3dROIMaker and uncertainty from 3dDWUncert (as well as tensor estimates from, e.g., 3dDWItoDT), can finally do probabilistic tractography

+ 3dTrackID -mode PROB
  - does lots of Monte Carlo simulations: wholebrain tractography -> perturb FA & e1 based on uncertainty -> wholebrain tracking -> perturb -> wholebrain tracking -> etc.

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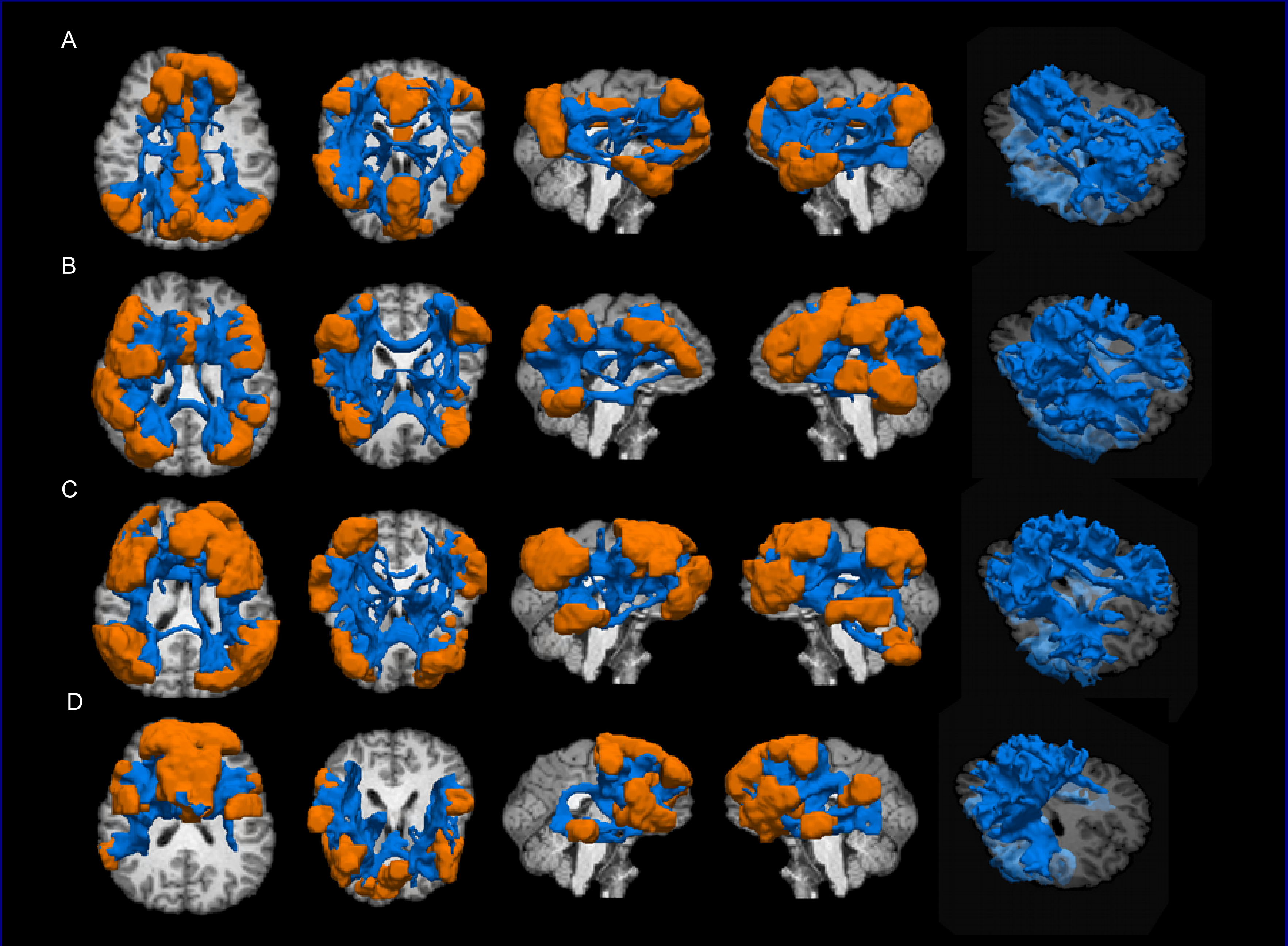
  - calculate stats on final WM ROIs found
  - analyze multiple networks **simultaneously** for efficiency (i.e., very little extra cost)

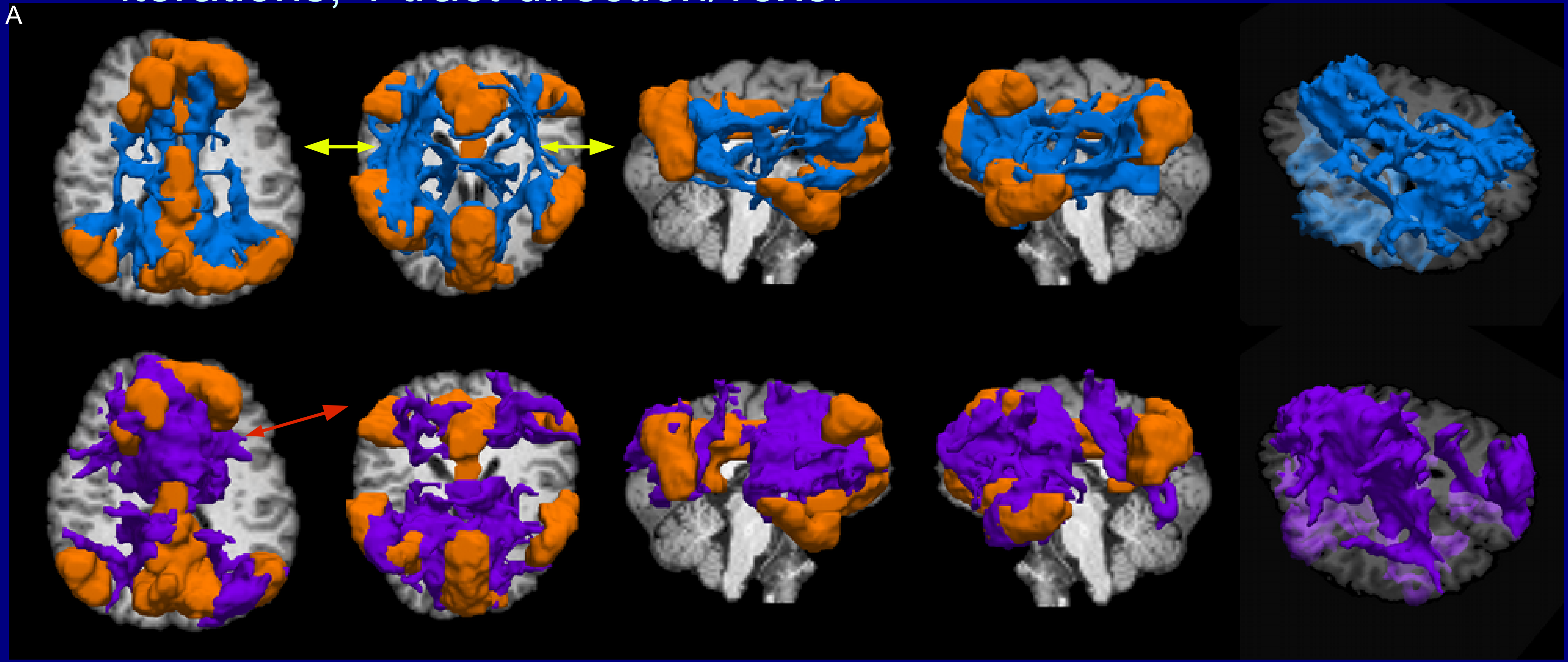
3dTrackID: Probabilistic tractography



(orange is ROI; blue is set of WM regions with tracts connecting)

3dTrackID: Probabilistic tractography

+ compare with existing algorithms:
    - purple: FSL-probtrackX (and FSL-bedpostX for uncertainty)
    - same parameters: FA>0.2, max angle 60deg, 5000 Monte Carlo iterations; 1 tract direction/voxel



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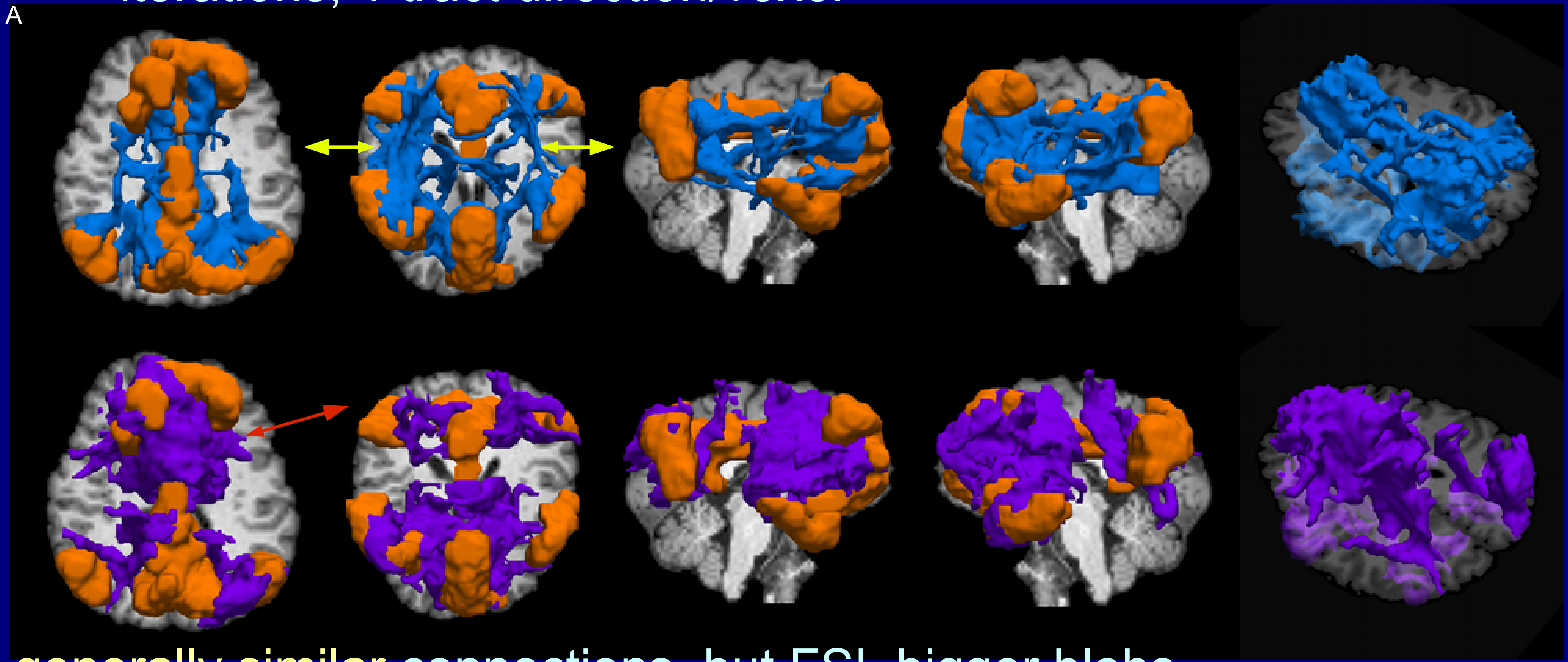

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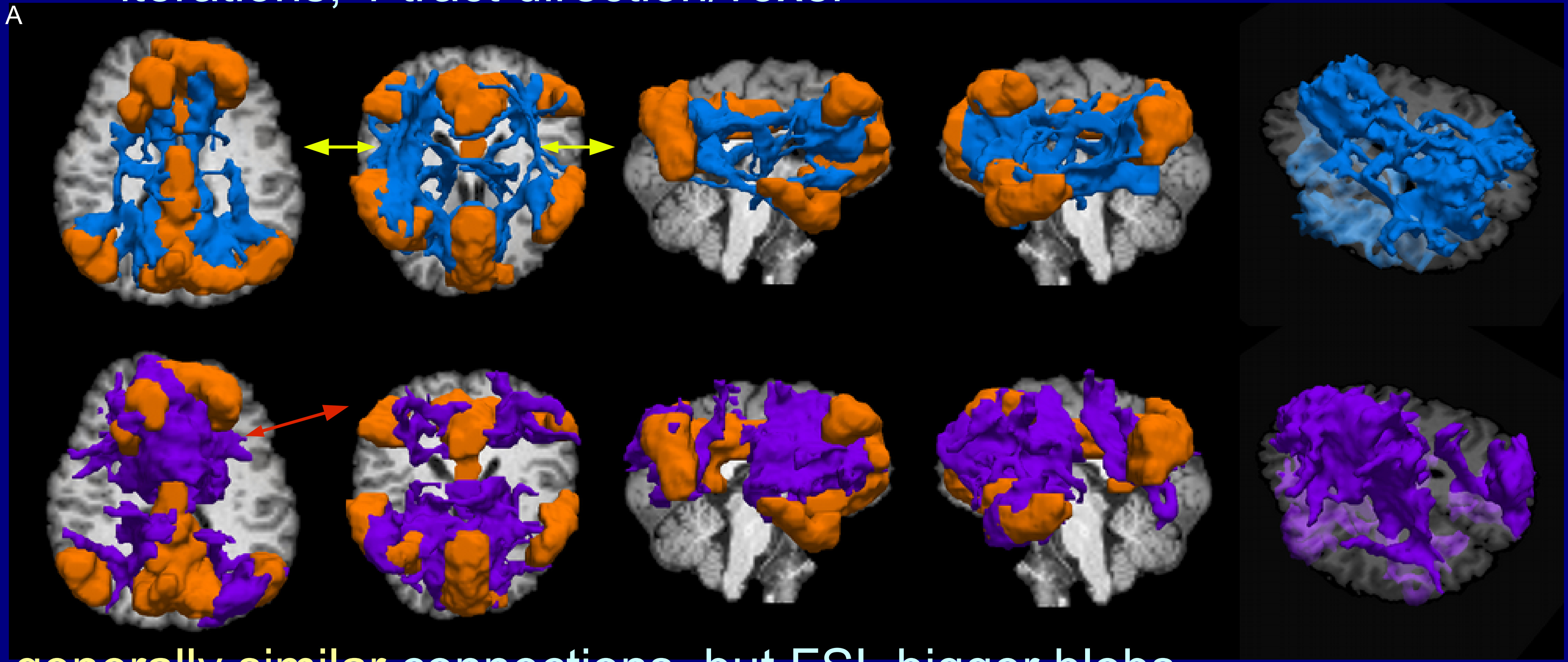

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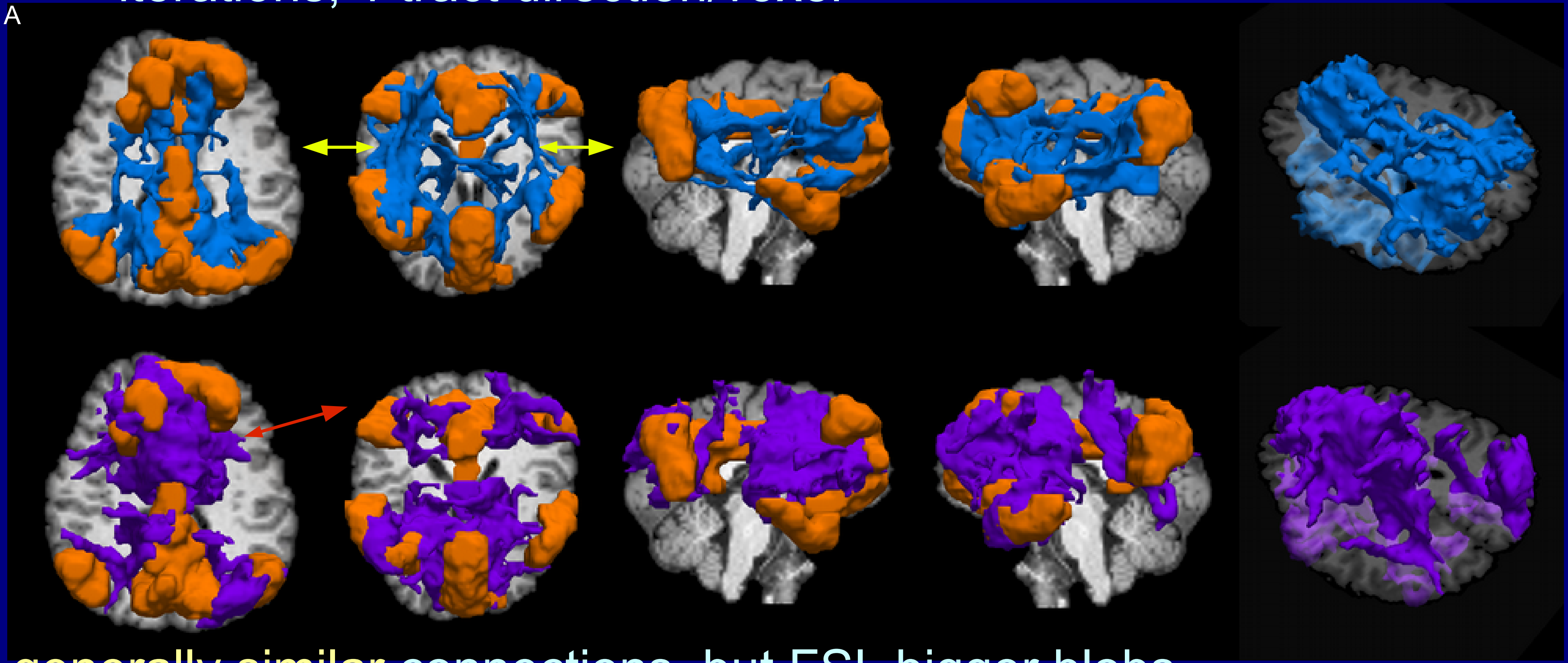

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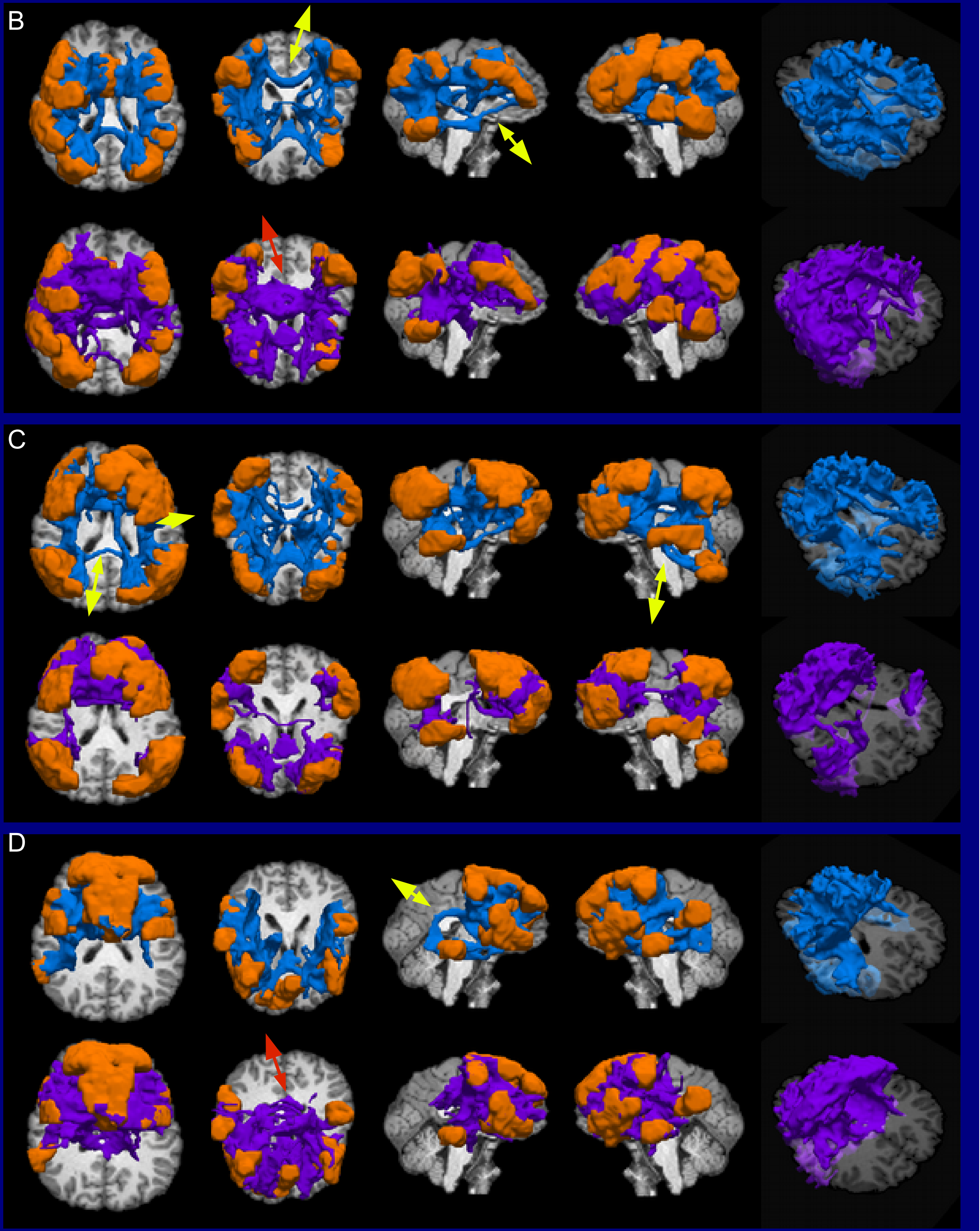
+ 3dDWUncert took *7min*; 3dTrackID took *25mins* total for 4 netw.

3dTrackID:

(other networks show similar results in terms of:

- narrow/wide regions of tracts;
- broadly similar locations;
- each program shows some tracks which the other doesn't)



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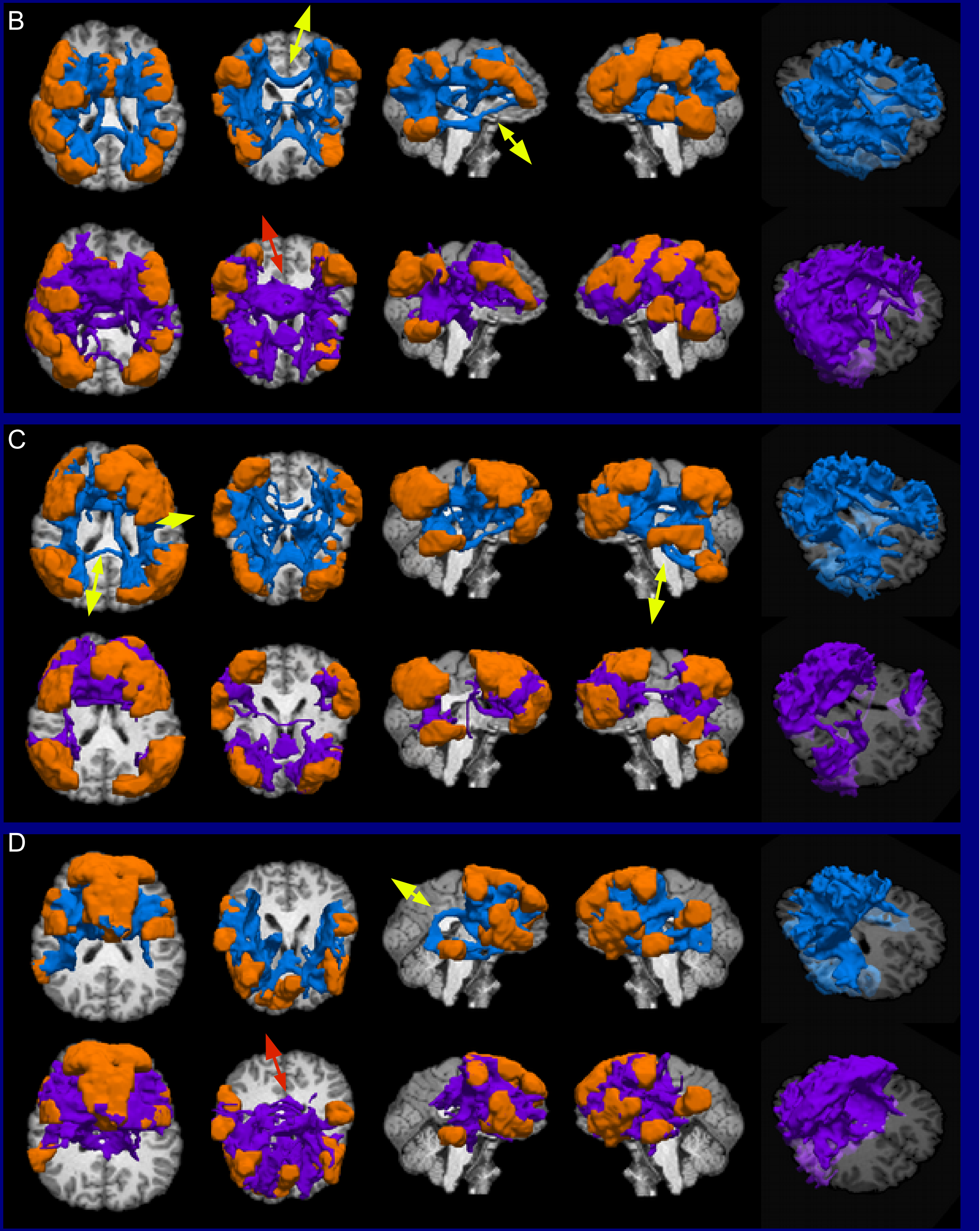
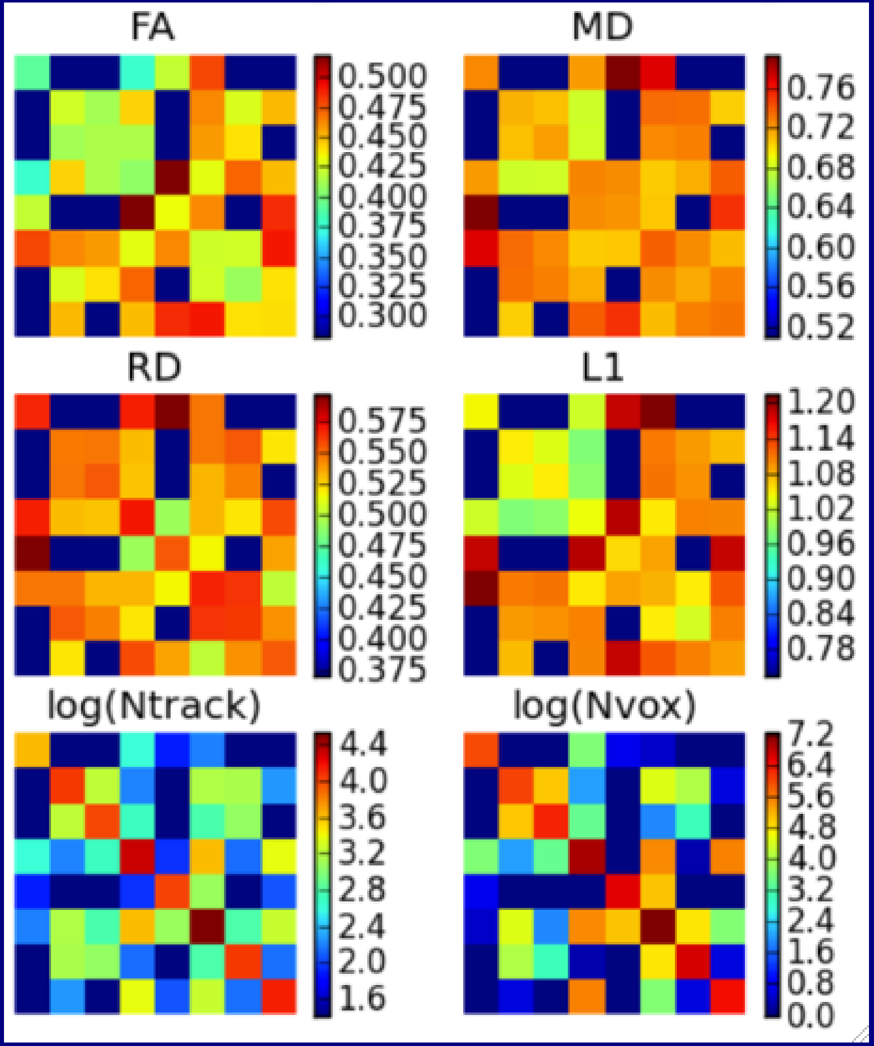


(3dTrackID automatically creates *.grid files for probabilistic files, as well.)

WM (ROI) Quantities

For connected pairs of GM ROIs in a network, have an average WM property (or can map to T1, PD...) →



Have produced sets of localized structural/anatomical quantities for comparison with functional values or behavioral scores, genetics, etc.

Can use for group or individual comparisons/regressions.

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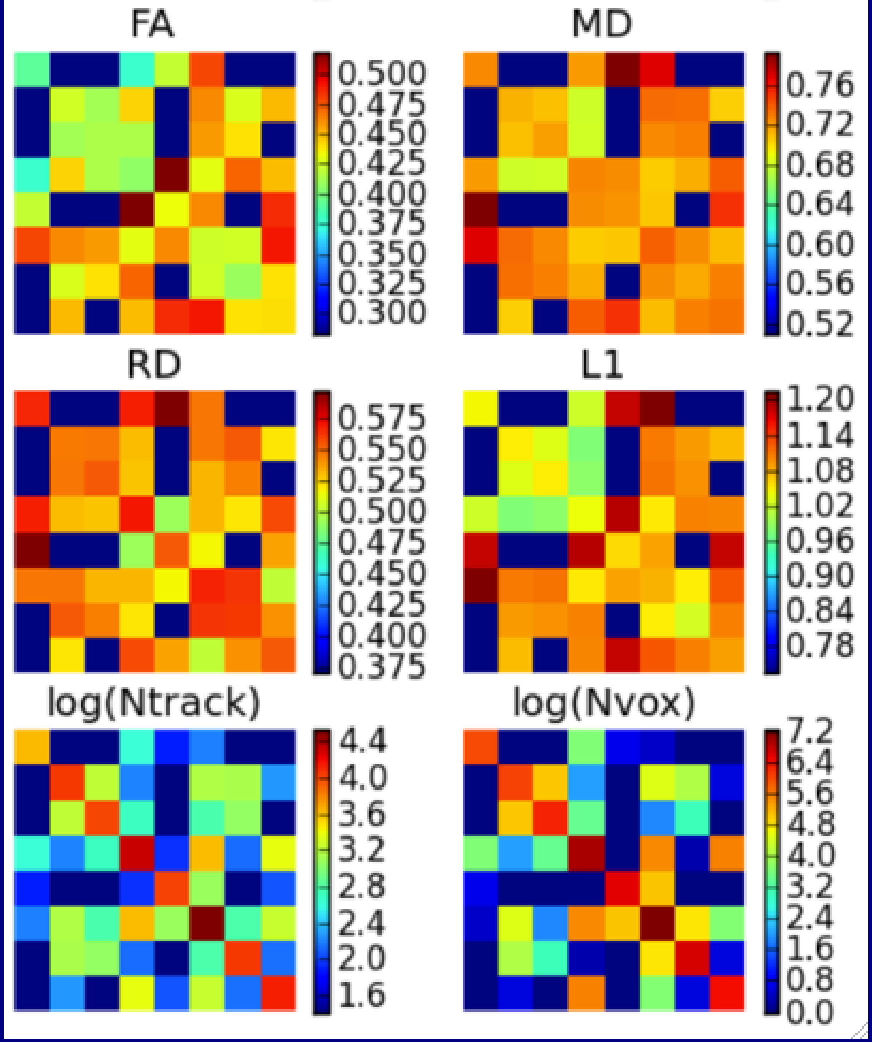

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3dNetCorr: correlation matrices Of average time series in ROIs (e.g., uninflated GM ROIs from 3dROIMaker)