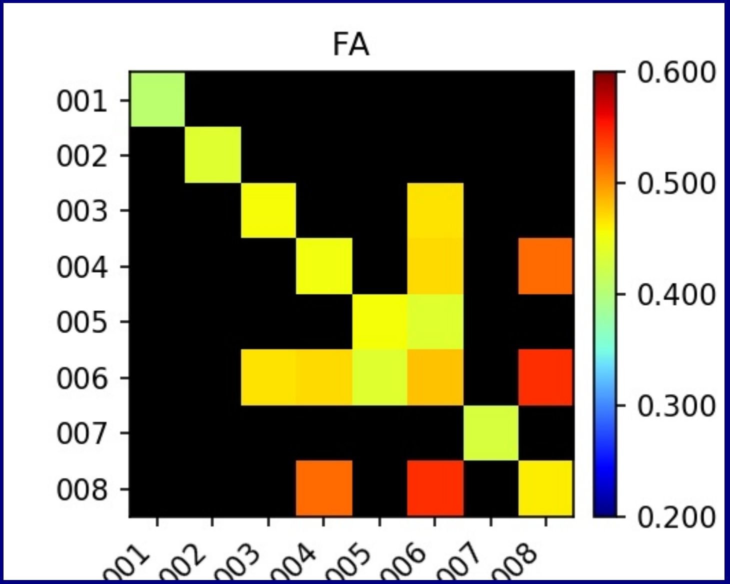
Introduction to:
investigating networks with multivariate modeling

AFNI Bootcamp (SSCC, NIMH, NIH)



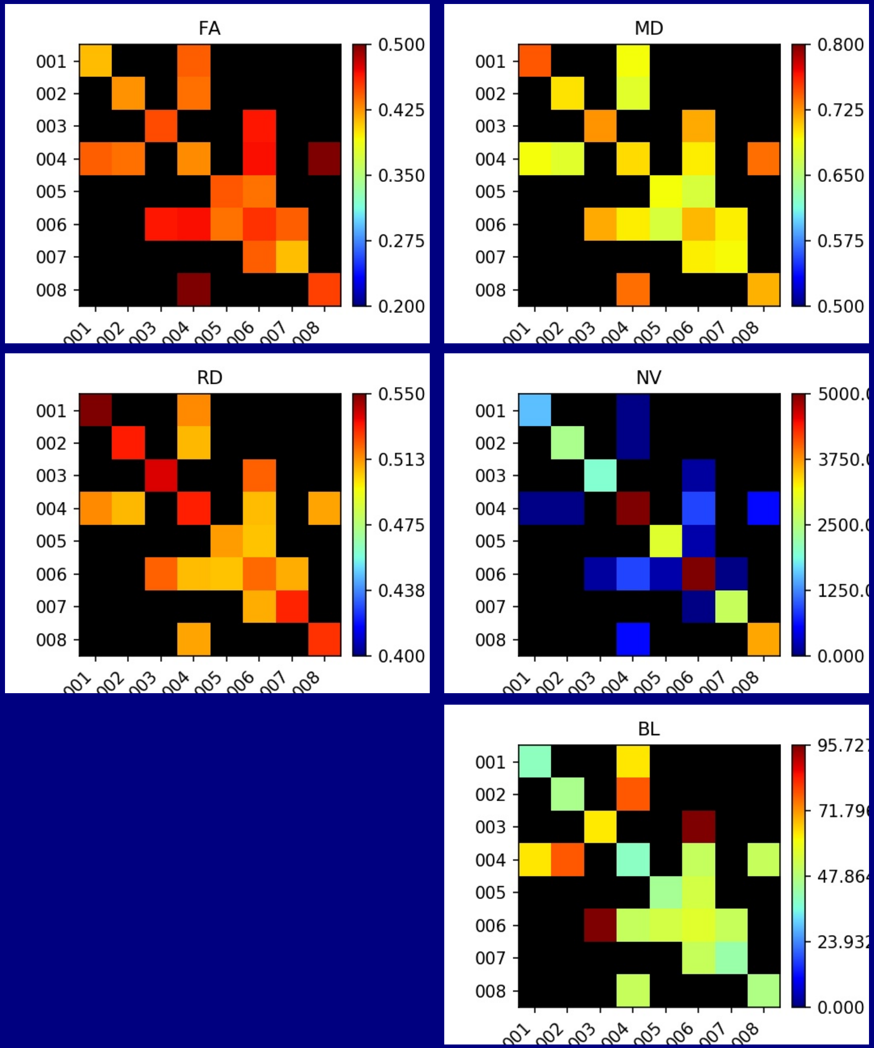
Outline

+ We describe combining DTI or FMRI network results (matrices) with non-MRI data (e.g., age, test scores, characteristics, etc.) for group analysis.
+ General motivation for multivariate modeling (MVM)
+ Case study example

WMC Quantities

For pairs of targets in a network, have an average WMC 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.



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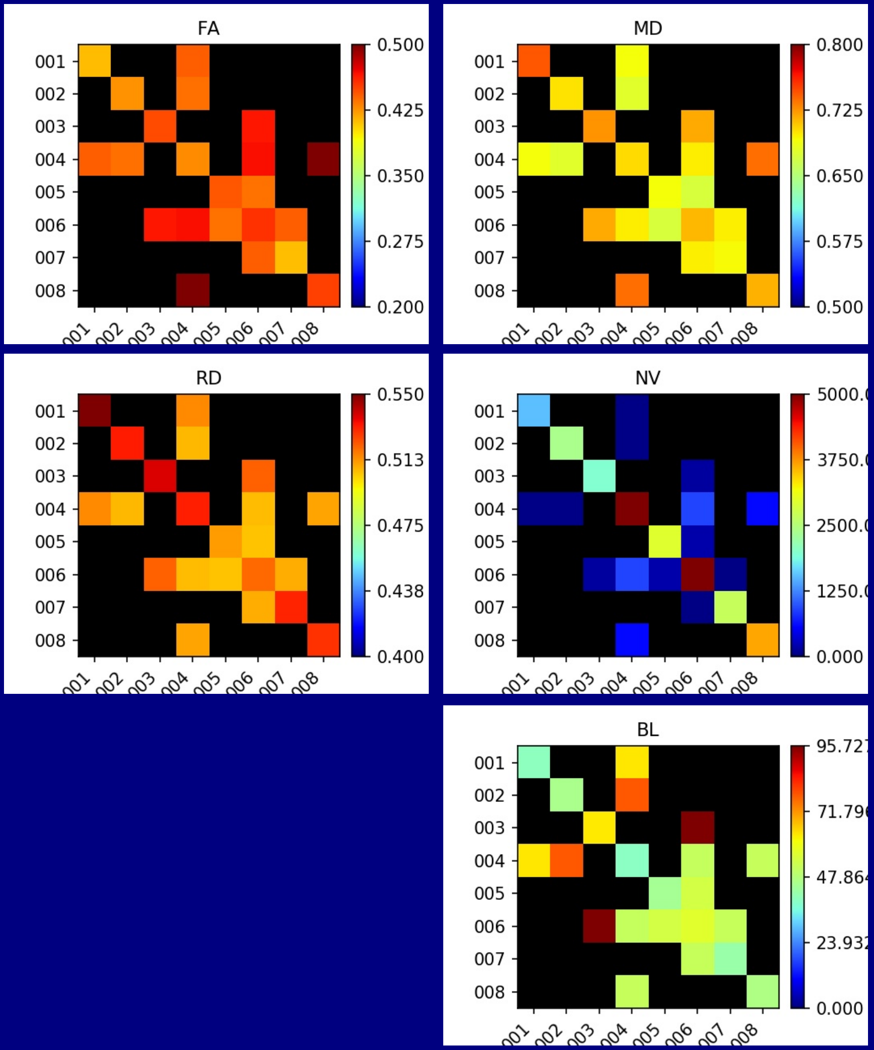
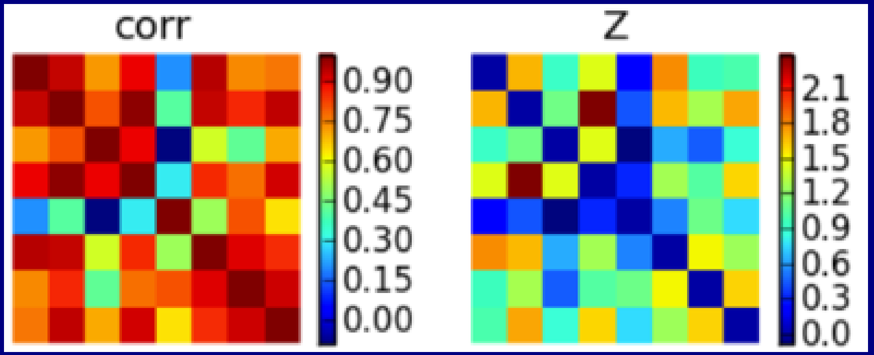


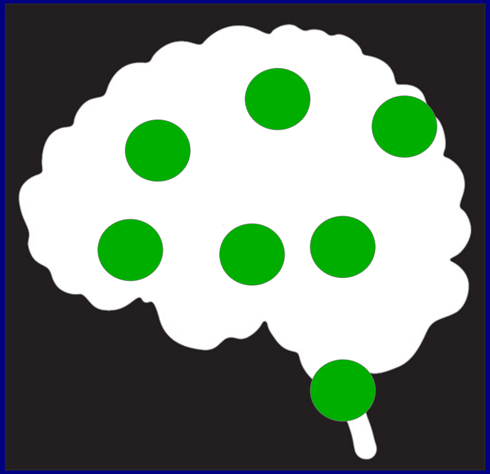
Have produced sets of localized structural/anatomical quantities for comparison with functional values or behavioral scores, genetics, etc.

Also works for GM quantities (FC)
3dNetCorr: correlation matrices of average time series in ROIs (e.g., uninflated GM ROIs from 3dROIMaker)



Group Analysis Steps

1) Place network targets



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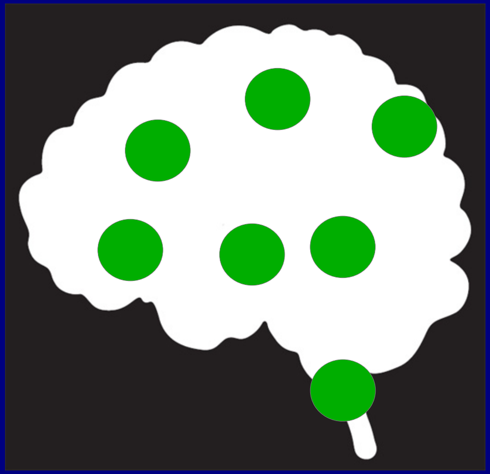
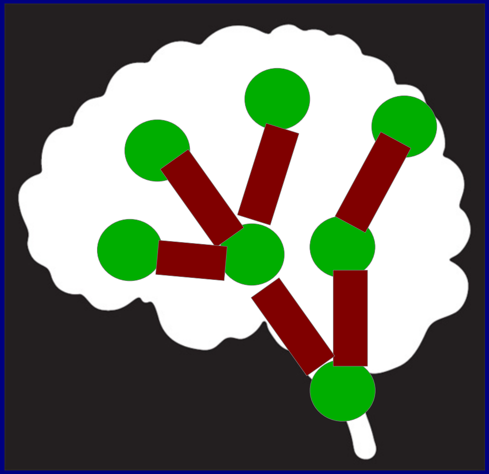


2) Probabilistic tracking



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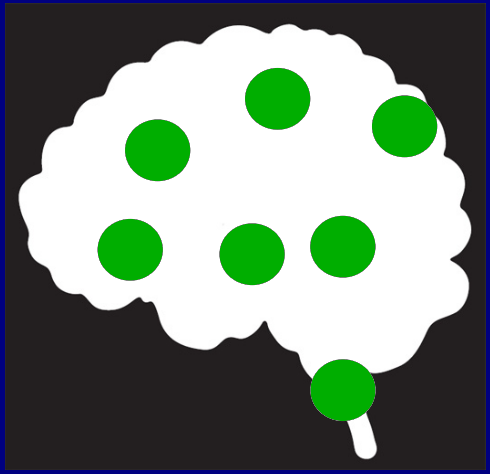

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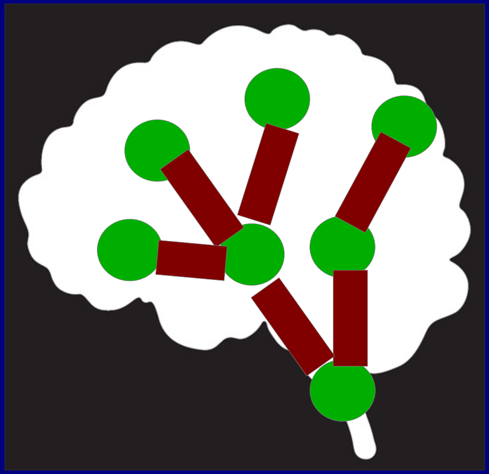
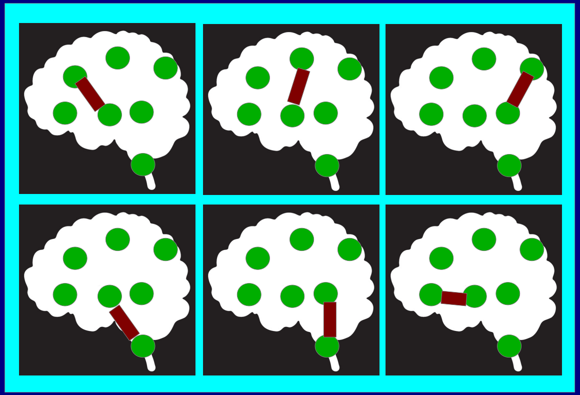


3) set of WM ROIs → set of simultaneous measures



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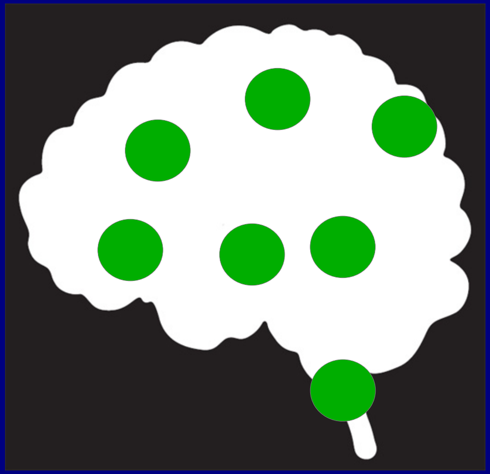

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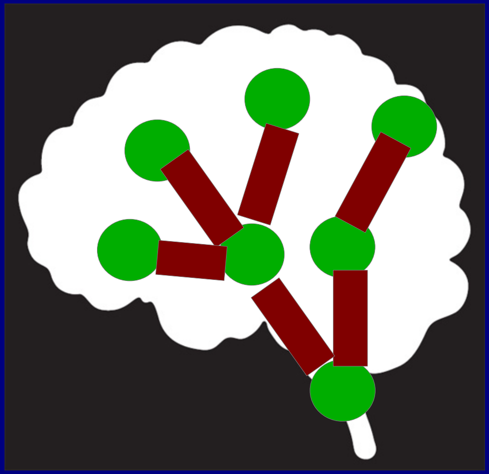

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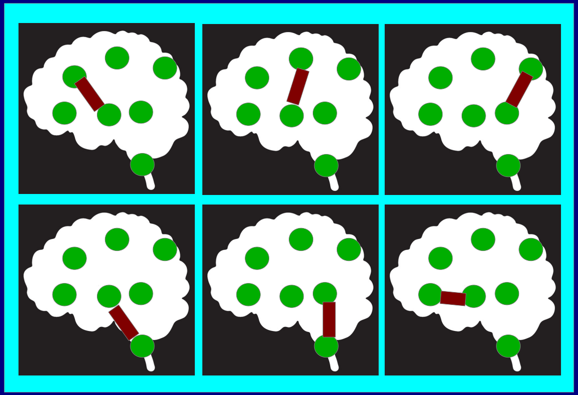
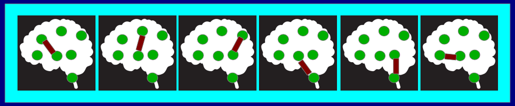


4) Network-level test: multivariate model (MVM)



$\{FA_1, FA_2, FA_3, ...\}$
$\sim var1 + var2 + var3 ...$

➡ AFNI's 3dMVM, written by G. Chen

Group Analysis Steps

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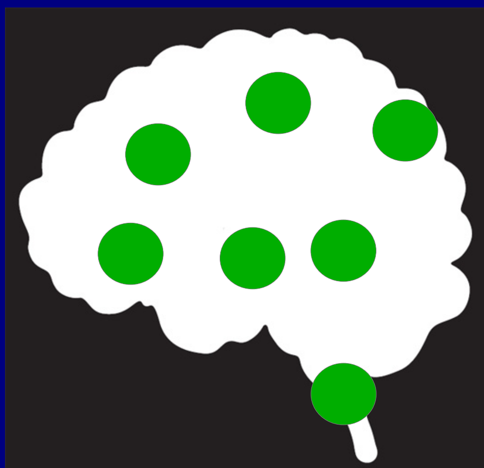

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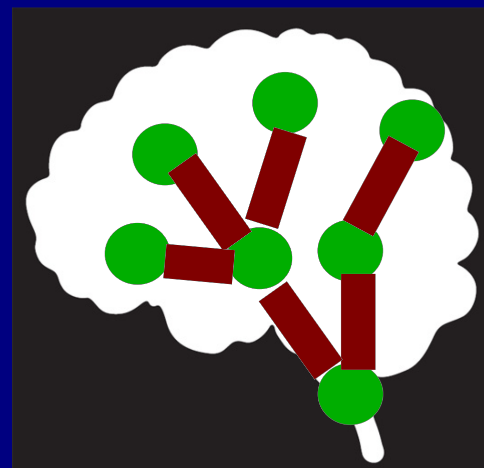

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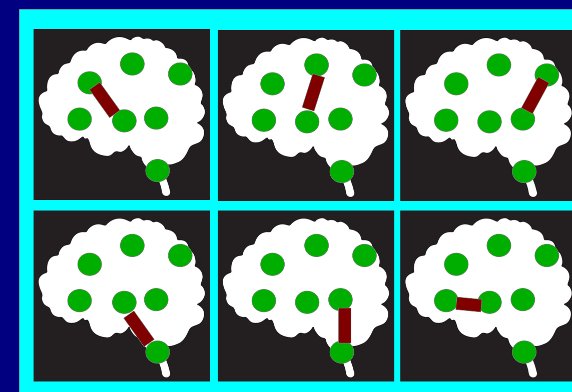

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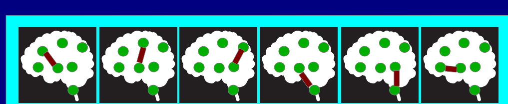
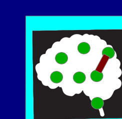


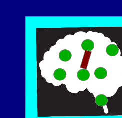
$\{FA_1, FA_2, FA_3, ...\}$
$\sim$ var1 + var2 + var3 ...

5) WMC-level / ROI-level tests: follow-up GLM for each WMC

$FA_1 \sim$ var1 + var2 + var3 … ,



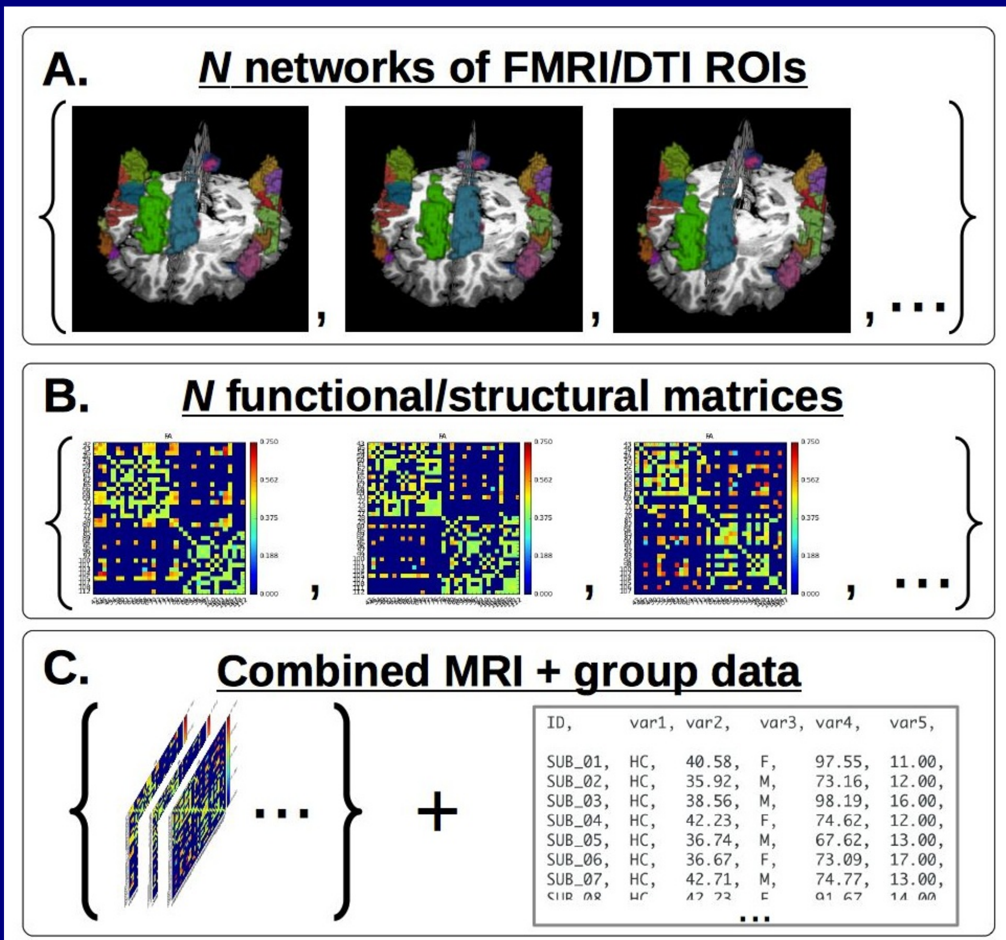
$FA_2 \sim$ var1 + var2 + var3 … ,



...

AFNI's 3dMVM, written by G. Chen

Group Analysis: Summary



D. User-defined model(s)

'measure1 ~ var1 + var2 + var3*var4 + …'

'measure2 ~ var1 + var2 + var3*var4 + …'

...

E. Network-level statistics for each model

ANOVA table of χ^2, DF, and p-value:

```
# RESULTS: ANOVA table - FA
5 # Number of effects
   # Chisq DF   Pr(>Chisq)
  4.9457216  1 2.615532e-02 # var1
  0.8453055  1 3.578838e-01 # var2
  0.6640459  1 4.151352e-01 # var3
  0.8097606  1 3.681910e-01 # var4
  2.1255675  1 1.448591e-01 # var3:var4
```

F. Set of ROI statistics for each model

Post hoc table of value, t-stat, DF and 2-sided p:

```
# RESULTS: Post hoc tests - FA
54 # Number of tests
      # value          t-stat DF    2-sided-P
 -0.0044778181 -0.62834967 14 5.398911e-01 # 001__002-var1(+HC-IL)
 -0.0002940607 -0.23287694 14 8.192272e-01 # 001__002-var2
  0.0011186177  2.13603173 14 5.082097e-02 # 001__002-var3(+F-M)-var4
 -0.0069573895 -1.12411575 14 2.798695e-01 # 001__002-var3(+F-M)
  0.0004507261  1.54181323 14 1.454148e-01 # 001__002-var4
  0.0130966286  1.51536073 14 1.519300e-01 # 003__004-var1(+HC-IL)
  0.0010852927  0.70869270 14 4.901486e-01 # 003__004-var2
```

(Taylor, Chen, Cox & Saad, 2016, BC)

Helper functions

Combine data: **fat_mvm_prep.py**

+ make a data table combining:
  - a CSV (~XLS) file of subject data with
  - a set of 3dTrackID “*.grid” (or 3dNetcorr “*.netcc”) files
+ automatically determines matrix elements found across all subj (*some* missing data allowed with LME modeling)

Specify model + GLTs: **fat_mvm_scripter.py**

+ define a statistical model of MRI data from CSV columns
+ build a 3dMVM command for both
  - the network-level model, and
  - the follow-up GLTs (to investigate individual elements)

See demo and readme file in FAT-MVM demo, installable via cmd: **@Install_FATMVM_DEMO**

Example:
Group analysis of tracked networks
using multivariate statistics

from study:
A DTI-Based Tractography Study of Effects on Brain Structure Associated with Prenatal Alcohol Exposure in Newborns,
Taylor, Jacobson, van der Kouwe, Molteno, Chen, Wintermark, Alhamud, Jacobson, Meintjes (2015, HBM)

Prenatal alcohol exposure (PAE)

- Alcohol is a teratogen, disrupting healthy embryonic and fetal development.
  → leads to various Fetal Alcohol Spectrum Disorders (FASD)

- FASD occurs in children whose pregnant mothers binge drank
  - e.g., ≥4 drinks/occasion and/or ≥14 drinks/wk

- Results in *poor*:
  - academic performance
  - language/math skills
  - impulse control
  - abstract reasoning
  - memory, attention

  and facial and skeletal dysmorphology

Goals of this study

To:

1) Use neuroimaging to compare structural brain development
   in newborns with PAE to that of HC newborns.
2) Quantitatively examine WM properties across the brain
3) Relate changes in (localized) WM properties with PAE,
   controlling for several confounding effects
   → examine several, and see which is/are (most) significant

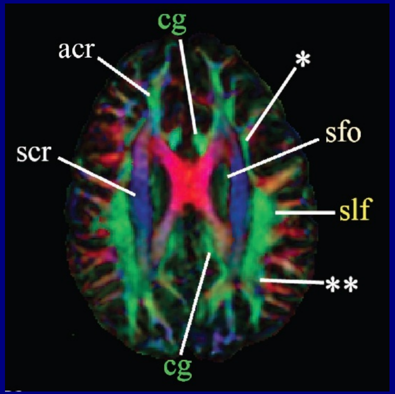
Tools: diffusion tensor imaging (DTI) + tractography

A) delineate similar WM ROIs across all subjects

B) quantify structural properties (FA, MD, T1, …)

C) statistical modeling for comparisons

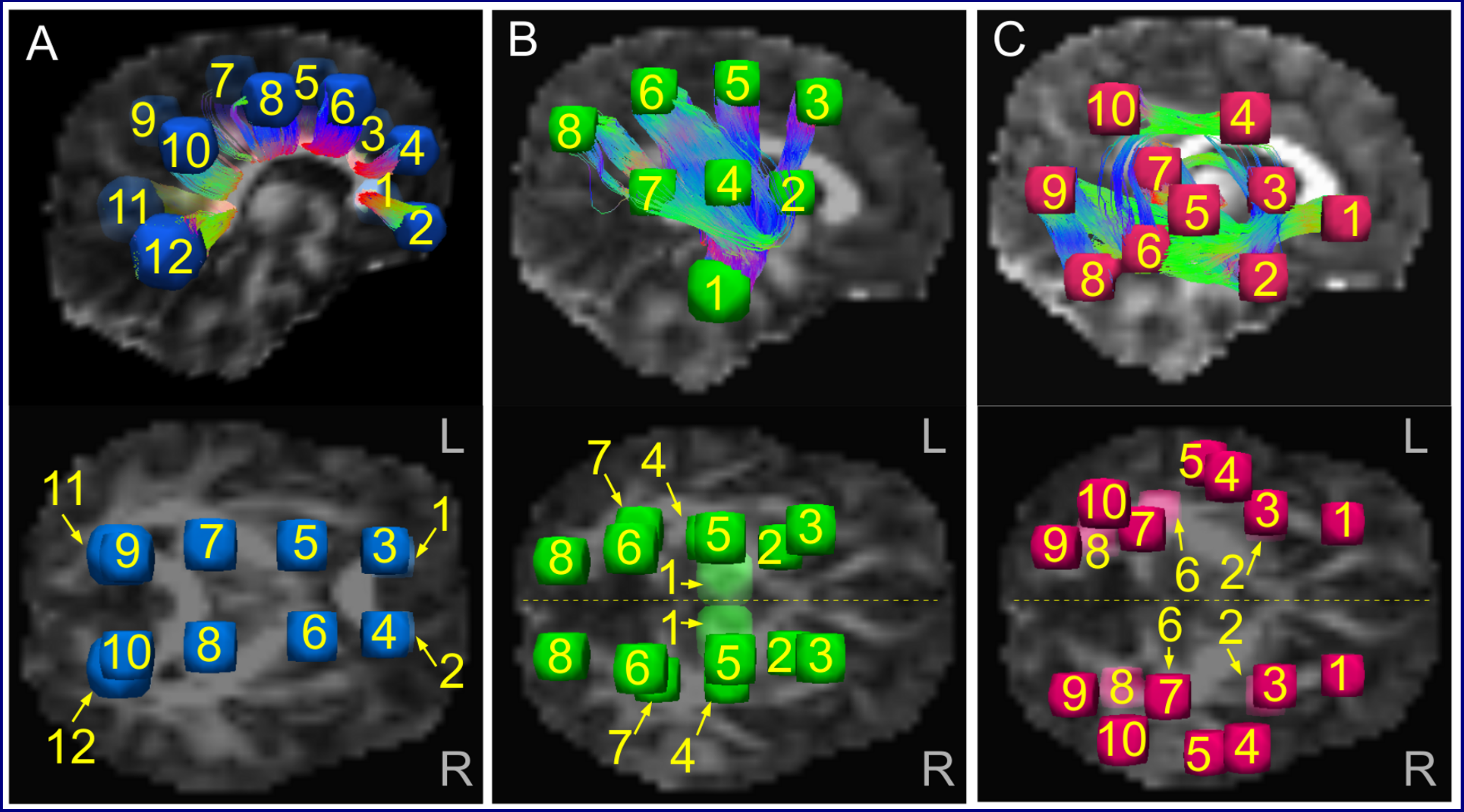
- at whole brain, network and ROI levels



Setting up DTI-tractography

Location of targets for tractography: 5 WM networks.

CC and Cor. Rad. (CCCR) | Projection (L/R-PROJ) | Association (L/R-ASSOC)



II) Results: network level

The questions:

1) which WM networks are affected by PAE?

2) which parameters show effects most strongly?

Answer using:

MVM for each network:

{set of DTI parameters} ~
alcohol (frequency: binge/wk) +
infant age (wks since conception) +
infant sex (M/F) +
maternal age (yrs) +
maternal cigarette smoking (cig/day).

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Parameters showing at least trends (p<0.1) →

↓ Networks

	FA				MD				AD				PD			
Network	**var.**	β_{med}	F (df_N, df_D)	p	**var.**	β_{med}	F (df_N, df_D)	p	**var.**	β_{med}	F (df_N, df_D)	p	**var.**	β_{med}	F (df_N, df_D)	p
CCCR					**alc**	-0.70	8.6 (1, 14)	**0.011***	**alc**	-0.72	14.0 (1, 14)	**0.002****				
									cig	-0.27	2.5 (6, 9)	0.101	cig	0.47	3.5 (1, 14)	0.083
					mat_age	0.56	5.5 (1, 14)	**0.034***	**mat_age**	0.53	6.3 (1, 14)	**0.025***				
L-PROJ					**alc**	-0.41	3.9 (10, 140)	**0.000*****	**alc**	-0.52	4.1 (10, 140)	**0.000*****				
	cig	0.12	4.2 (11, 4)	0.091									cig	0.52	4.0 (1, 14)	0.066
					mat_age	0.37	4.4 (1, 14)	0.056	**mat_age**	0.44	6.5 (1, 14)	**0.023***				
R-PROJ					**alc**	-0.41	1.9 (12, 168)	**0.035***	**alc**	-0.45	2.7 (12, 168)	**0.002****				
													cig	0.48	3.4 (1, 14)	0.085
	age	0.33	8.6 (13, 2)	0.109	**age**	-0.41	5.8 (1, 14)	**0.031***	**age**	-0.39	5.3 (1, 14)	**0.038***				
					sex	-0.20	4.3 (1, 14)	0.056	**sex**	-0.39	5.9 (1, 14)	**0.029***				
	mat_age	-0.16	9.2 (13, 2)	0.103												
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													cig	0.49	3.6 (1, 14)	0.080
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					mat_age	0.44	3.8 (1, 14)	0.071	**mat_age**	0.43	4.7 (1, 14)	**0.048***				
R-ASSOC	alc	0.23	1.8 (7, 98)	0.090	**alc**	-0.62	10.2 (1, 14)	**0.007****	**alc**	-0.67	14.1 (1, 14)	**0.002****				
									cig	-0.29	3.9 (1, 14)	0.068	cig	0.5	3.5 (1, 14)	0.082

**** p<0.05; ** p<0.01; *** p<0.001.***

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** p<0.05; ** p<0.01; *** p<0.001.*

→ Statistically significant alcohol exposure associations in ~every WM network

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** p<0.05; ** p<0.01; *** p<0.001.*

**→ Increased alcohol exposure:
decreased AD
(and decreased MD)**

III) Results: ROI level

The question:

1) where are most significant AD-alcohol relations in each network?

Answer using:

Follow-up GLT for each WMC:

WMC DTI parameter ~
alcohol (frequency: binge/wk) +
infant age (wks since conception) +
infant sex (M/F) +
maternal age (yrs) +
maternal cigarette smoking (cig/day).

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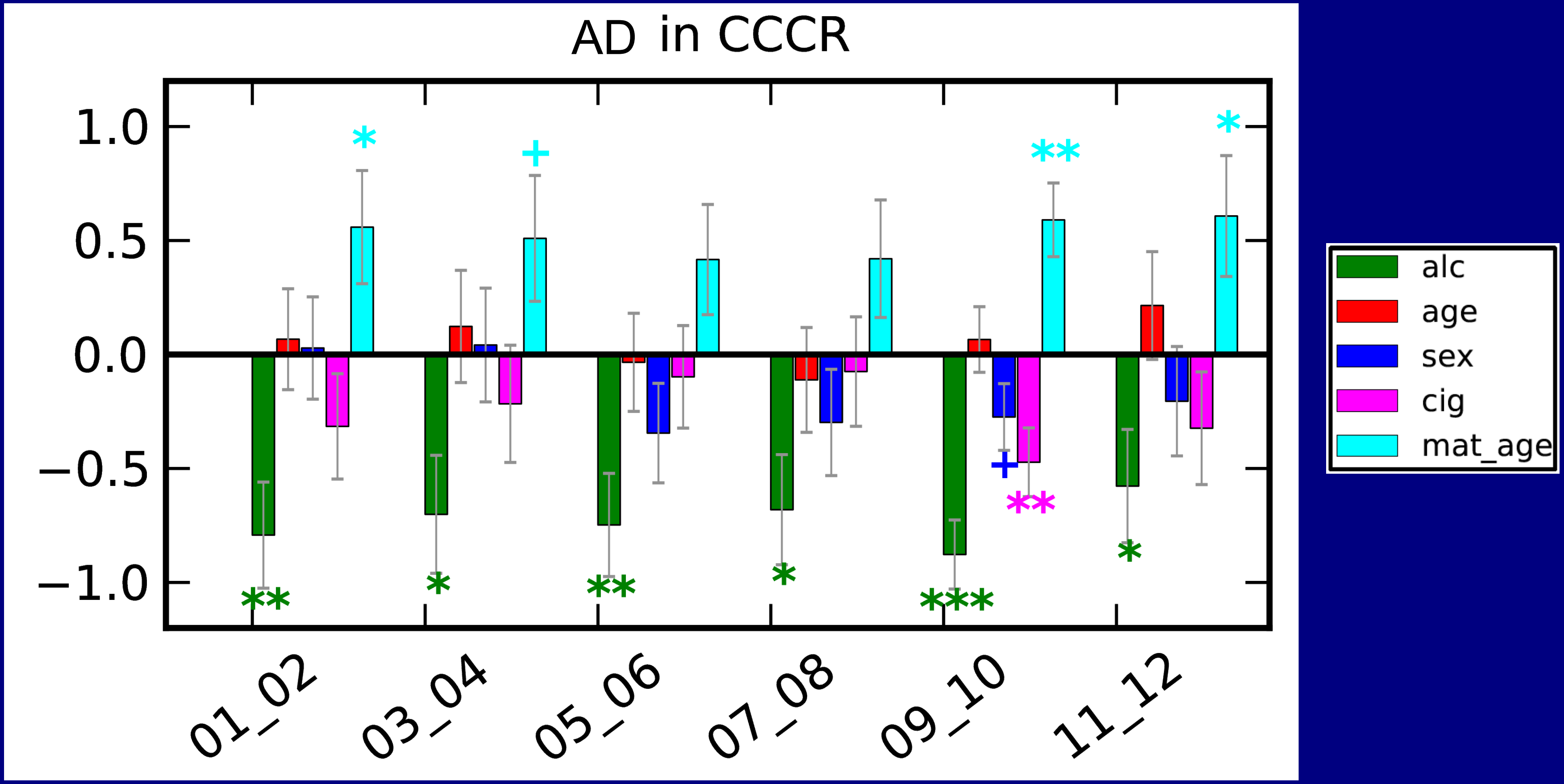
Transcallosal (CC and corona radiata)

GLM β



anterior → **posterior**

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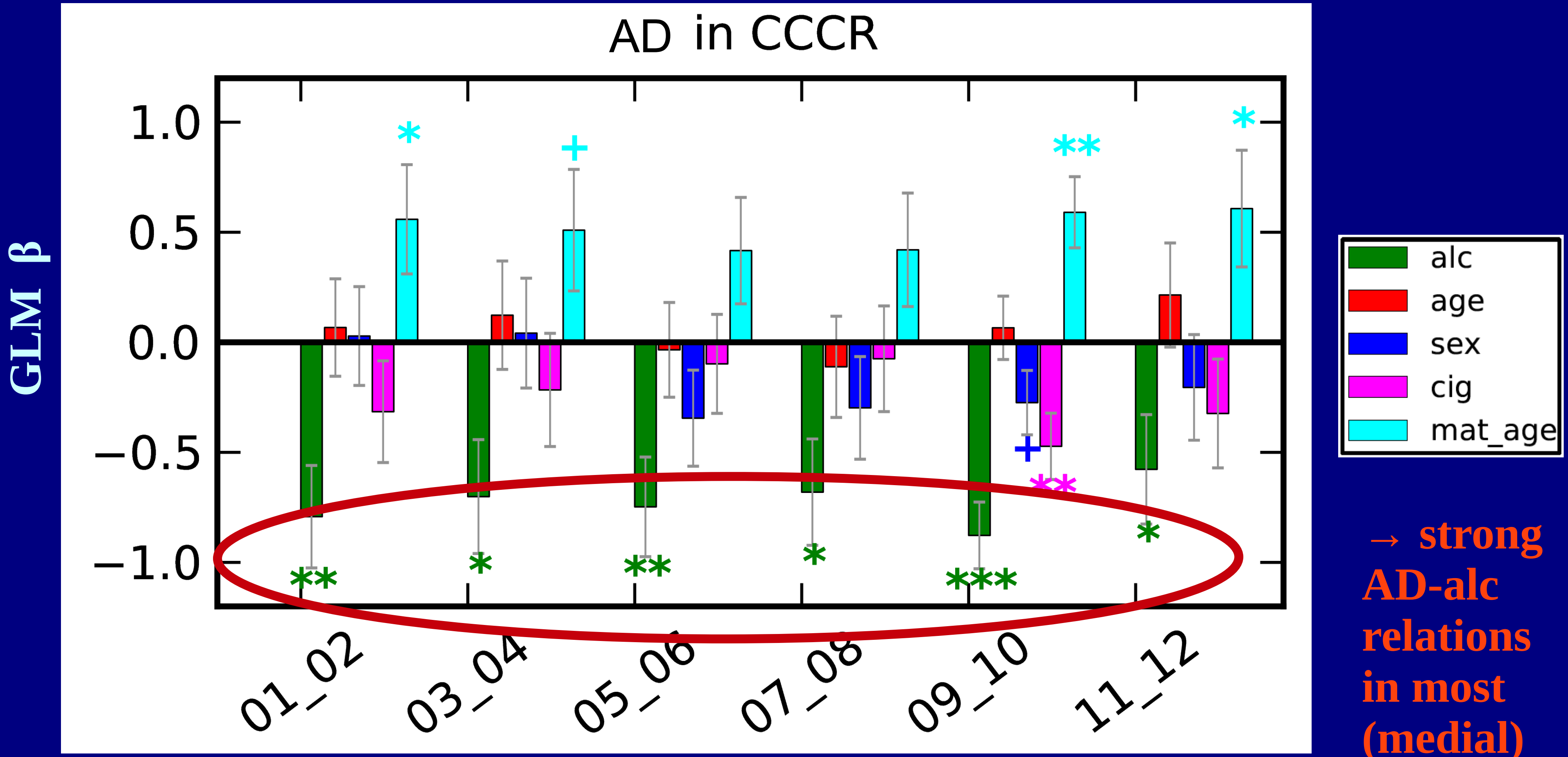

anterior → posterior

→ strong AD-alc relations in most (medial) WM ROIs

SUMMARY

+ Tracking allows one to compare and investigate properties first at a network level, and then “zoomed in” at WMC level
  - Same applies for FC matrices (e.g., from 3dNetCorr)
+ MVM modeling provides omnibus *F*-statistic for network level, and GLTs for follow-up
+ FATCAT functions help combine MRI data (*.grid or *.netcc files) with subject characteristics (*.xls -> *.cxv file)
+ Additional functions help specify the model for 3dMVM