A DTI-based tractography study of effects on brain structure associated with prenatal alcohol exposure in newborns

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Outline

- Prenatal alcohol exposure (PAE) in brief
- Methods: diffusion tensor imaging (DTI) and tractography
- Setup for this DTI – PAE newborn study
- Newborn infant study results

$\rightarrow$ see also Taylor et al. poster #3241, W/<u>Th</u>

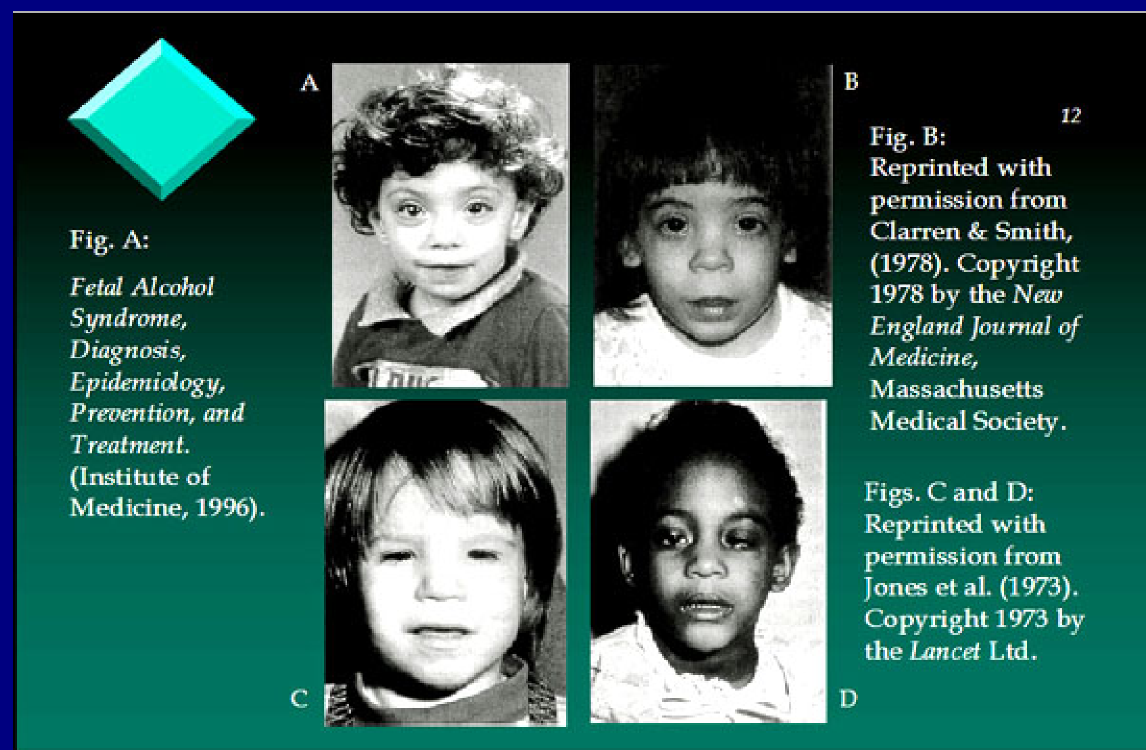
Prenatal alcohol exposure (PAE)

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

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

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

  and facial and skeletal dysmorphology



PAE and FASD assessment

Traditional/clinical assessments:

- the degree of facial and skeletal dysmorphology
  - For example, changes in lip, philtrum and nasal structures

Different racial/ethnic groups typically show varied changes

- cognitive deficits
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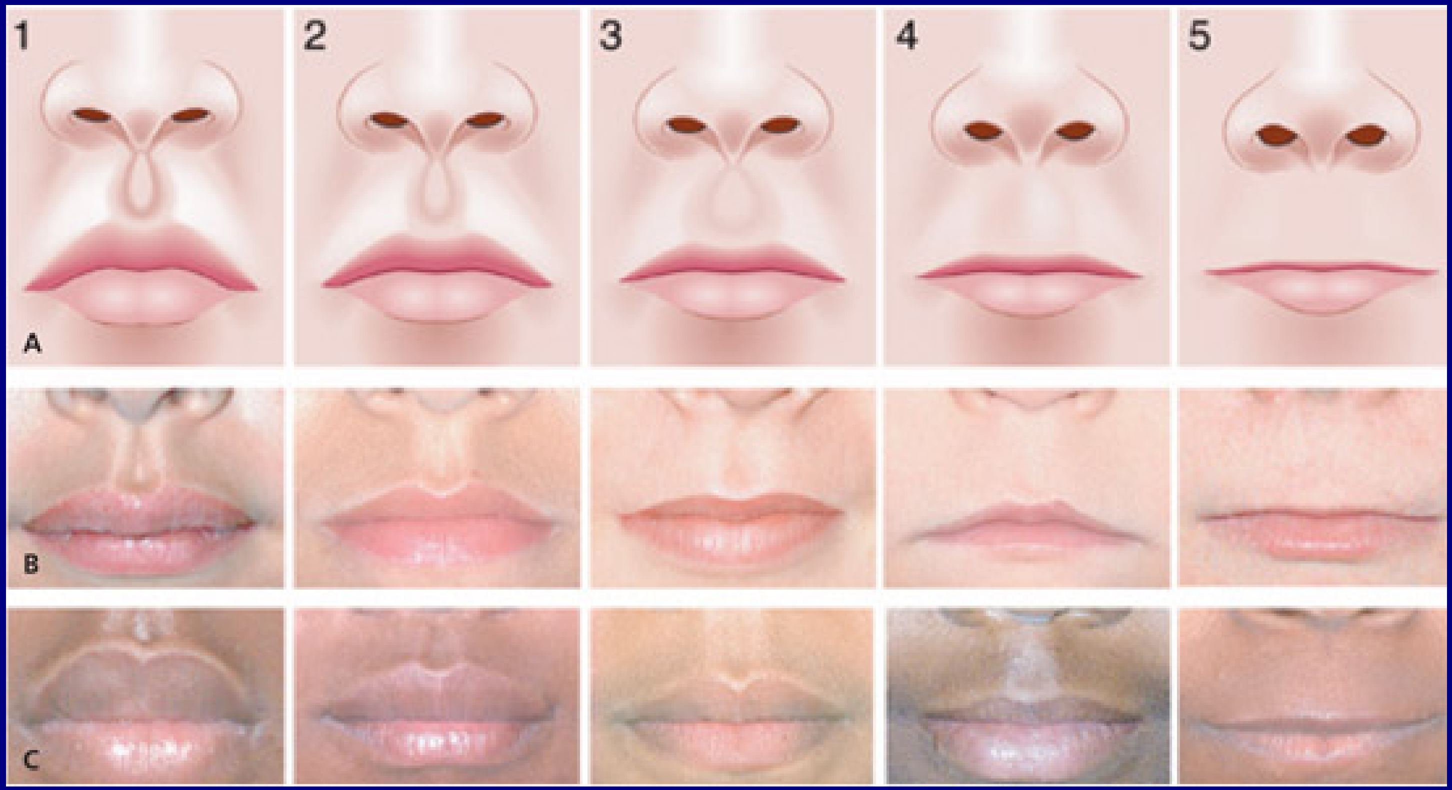

Different racial/ethnic groups typically show varied changes

- cognitive deficits
- eye-blink conditioning

→ semi-quantitative, convolve many factors (upbringing, education, etc.), and do not locate brain changes

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
   $\rightarrow$ examine several, and see which is/are (most) significant

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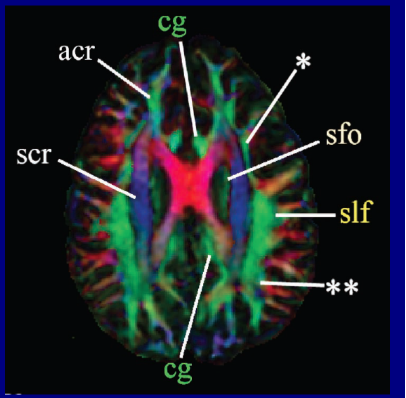
Tools: diffusion tensor imaging (DTI) + tractography

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



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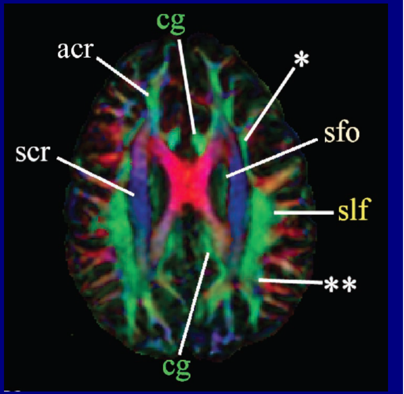
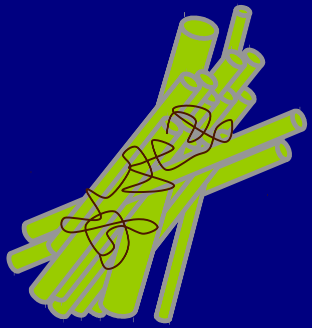


This is the first study to use DTI and tractography to examine PAE effects in the neonatal/infant period.

Local structure via diffusion MRI



(In brief)

1) Random motion of molecules affected by local structures

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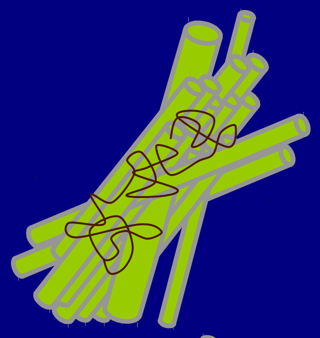

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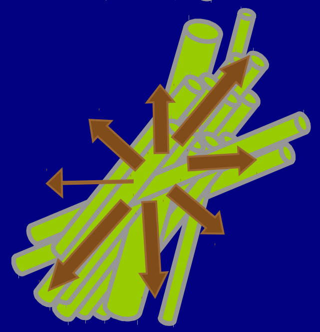

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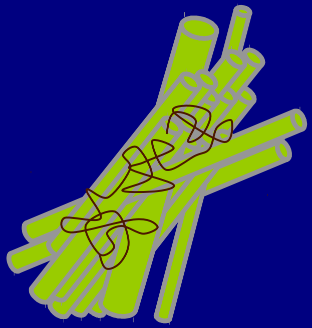

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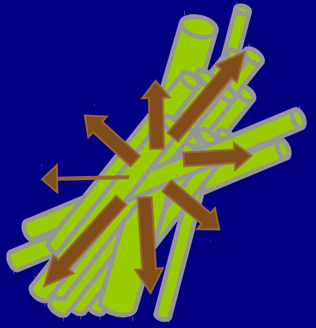
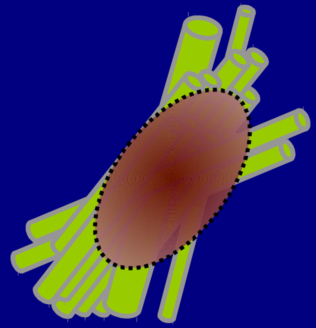


3) Bulk features of local structure approximated with various reconstruction models, mainly grouped by number of major structure directions/voxel:

+ one direction:
  DTI (Diffusion Tensor Imaging) $\rightarrow$ ellipsoid



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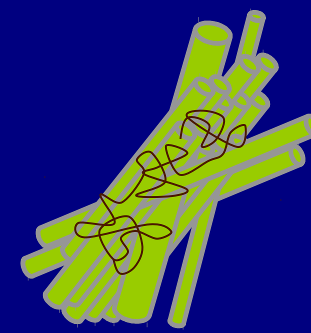

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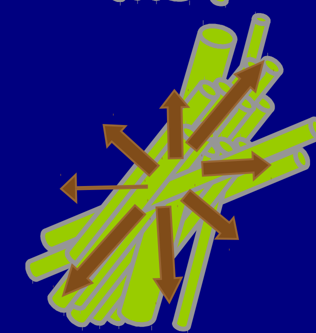

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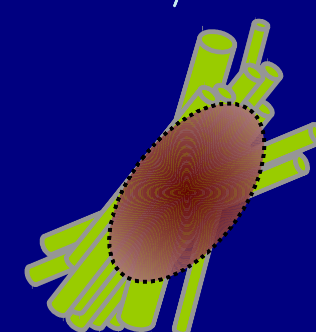

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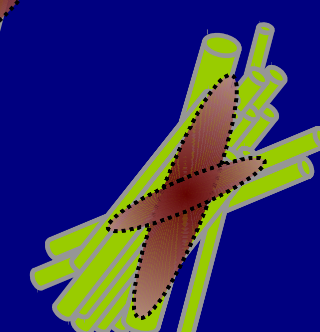

+ >=1 direction:
  HARDI (High Angular Resolution Diffusion Imaging)
  Qball, DSI, ODFs, ball-and-stick, multi-tensor, CSD, ...

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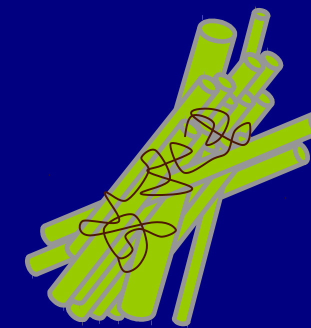

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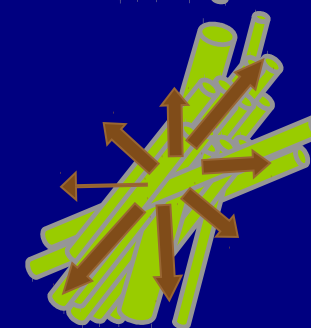

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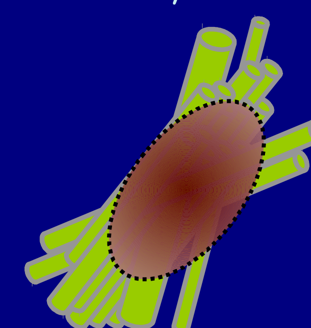

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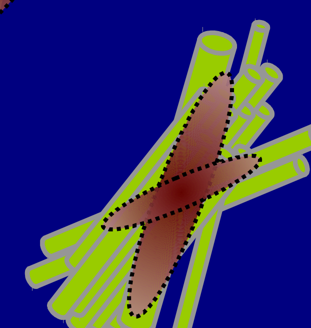
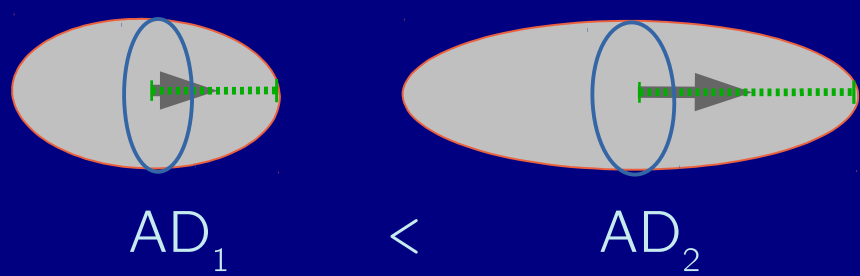


"Big 5" DTI ellipsoid parameters

Main quantities of diffusion (motion) surface

first eigenvalue, L1
= λ_1, parallel/axial diffusivity, AD



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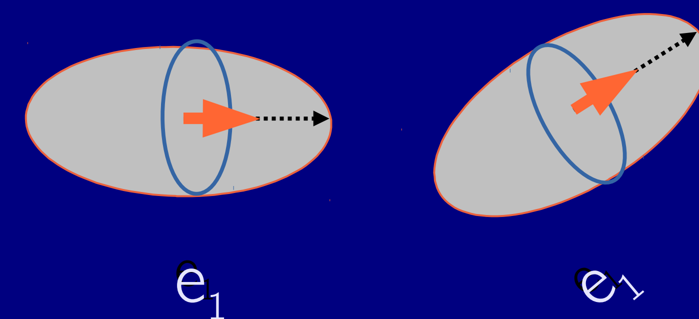
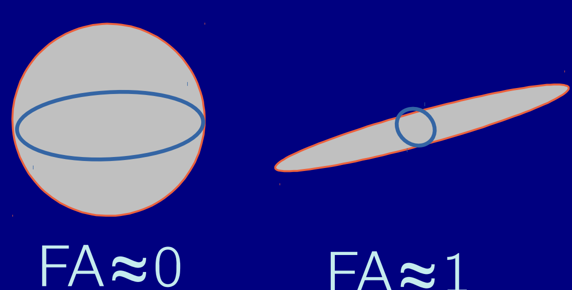
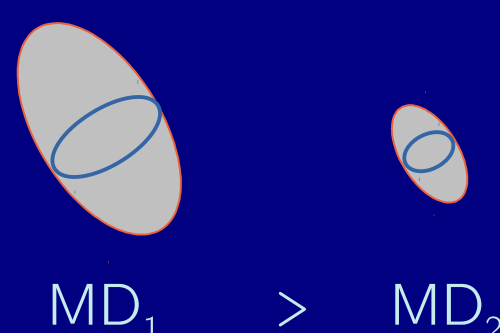


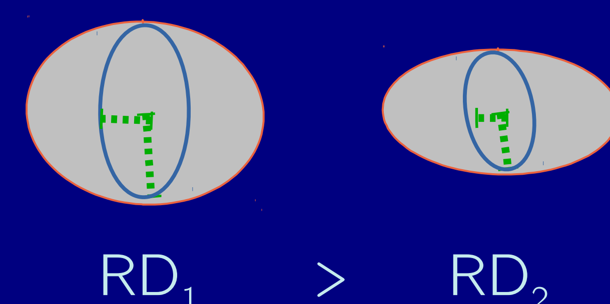
Fractional anisotropy, FA



Mean diffusivity, MD



Radial diffusivity, RD



Interpreting DTI parameters

General literature:

FA: measure of fiber bundle coherence and myelination

- in adults, FA>0.2 is proxy for WM
- in infants, FA>0.1 is proxy for WM[1]

MD, AD, RD: local density of structure

e_1: orientation of major bundles

[1] *e.g., Dubois et al., 2006*

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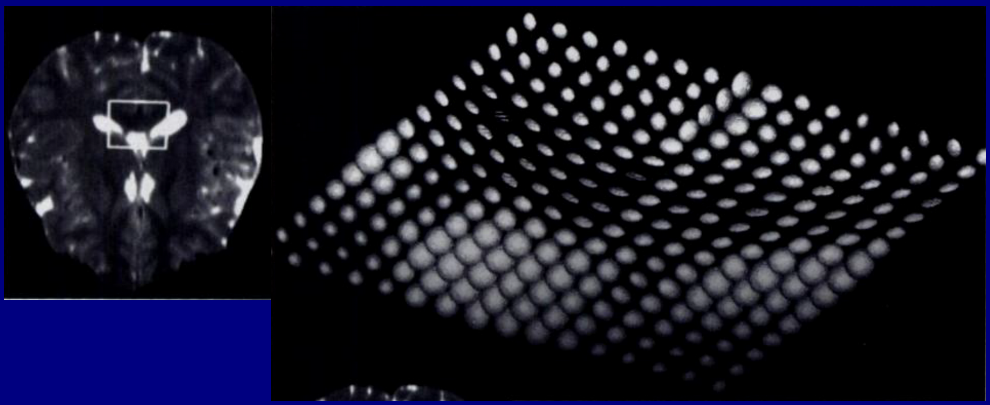
Cautionary notes:

- Degeneracies of structural interpretations
- Changes in myelination may have small effects on FA
- WM bundle diameter << voxel size
  - don't know location/multiplicity of underlying structures
- More to diffusion than just structure-- i.e., fluid properties
- Noise, distortions, etc. in measures

[1] *e.g., Dubois et al., 2006*

Local DTs $\rightarrow$ extended tracts

Field of local diffusion parameters



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Field of local diffusion parameters

$\longrightarrow$ individual ellipsoids

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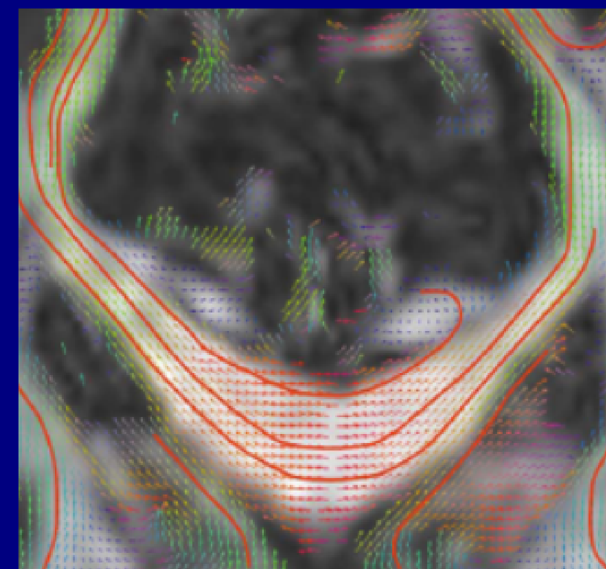
Field of local diffusion parameters

Connect to form extended tracts

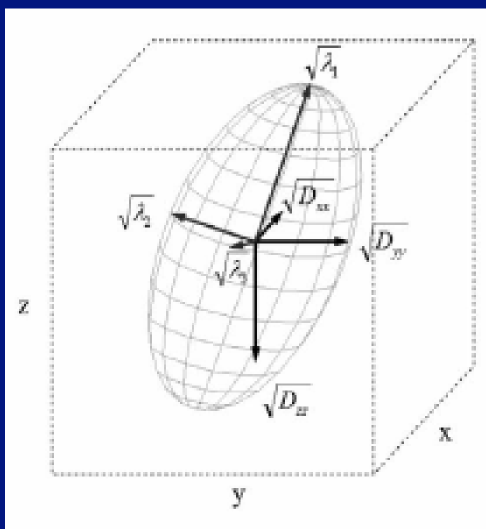


$\longrightarrow$ individual ellipsoids

$\longrightarrow$ linked structures

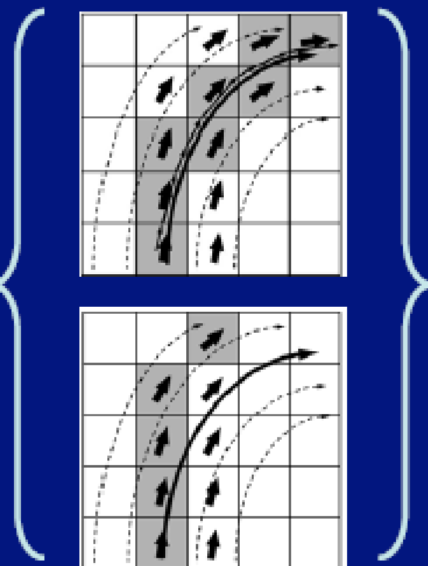
Tractography

Estimate WM structure (fiber tract locations)



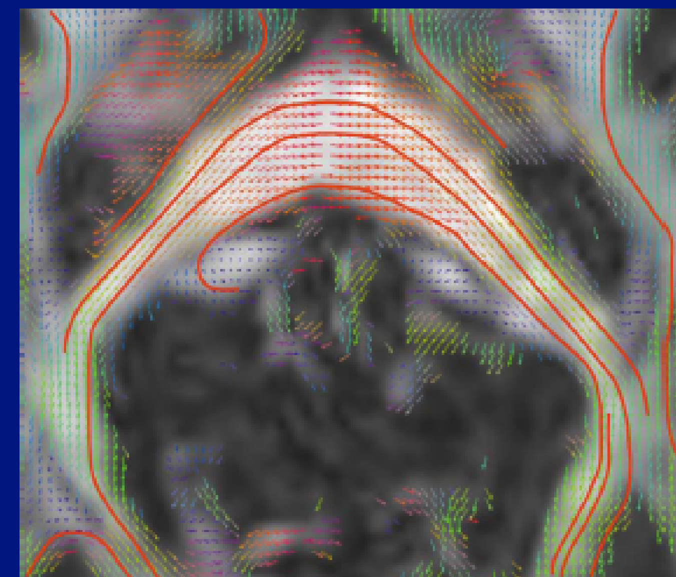
ellipsoid measures (~*smoothing of real structures*)

\+



some kind of algorithm for connecting

=



estimate spatial extents of WM 'tracts' in vivo

(images from Bammer et al. 2003)

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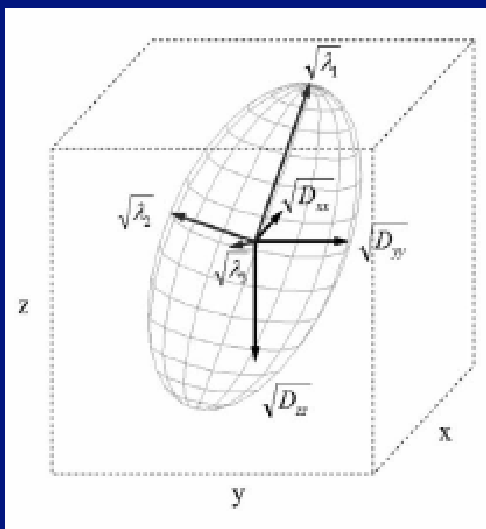

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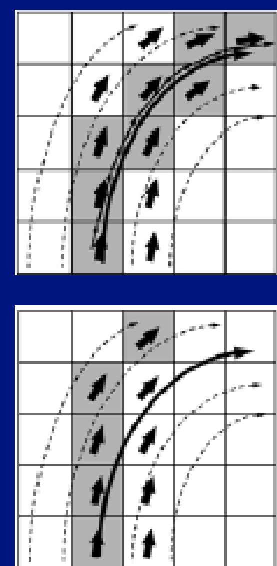

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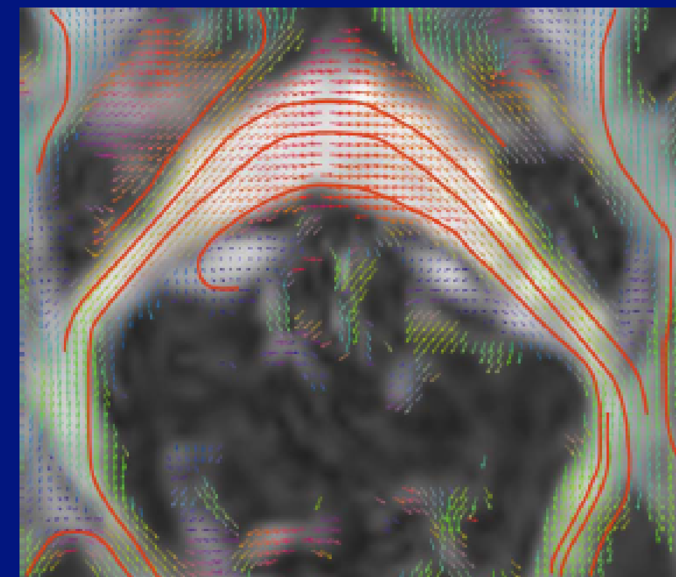

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(images from Bammer et al. 2003)

Tracking WM fibers

Tracking can be a useful alternative to maps/atlases for finding characteristic subsets, families or networks of the same WM bundles within each subject, for example[1]:

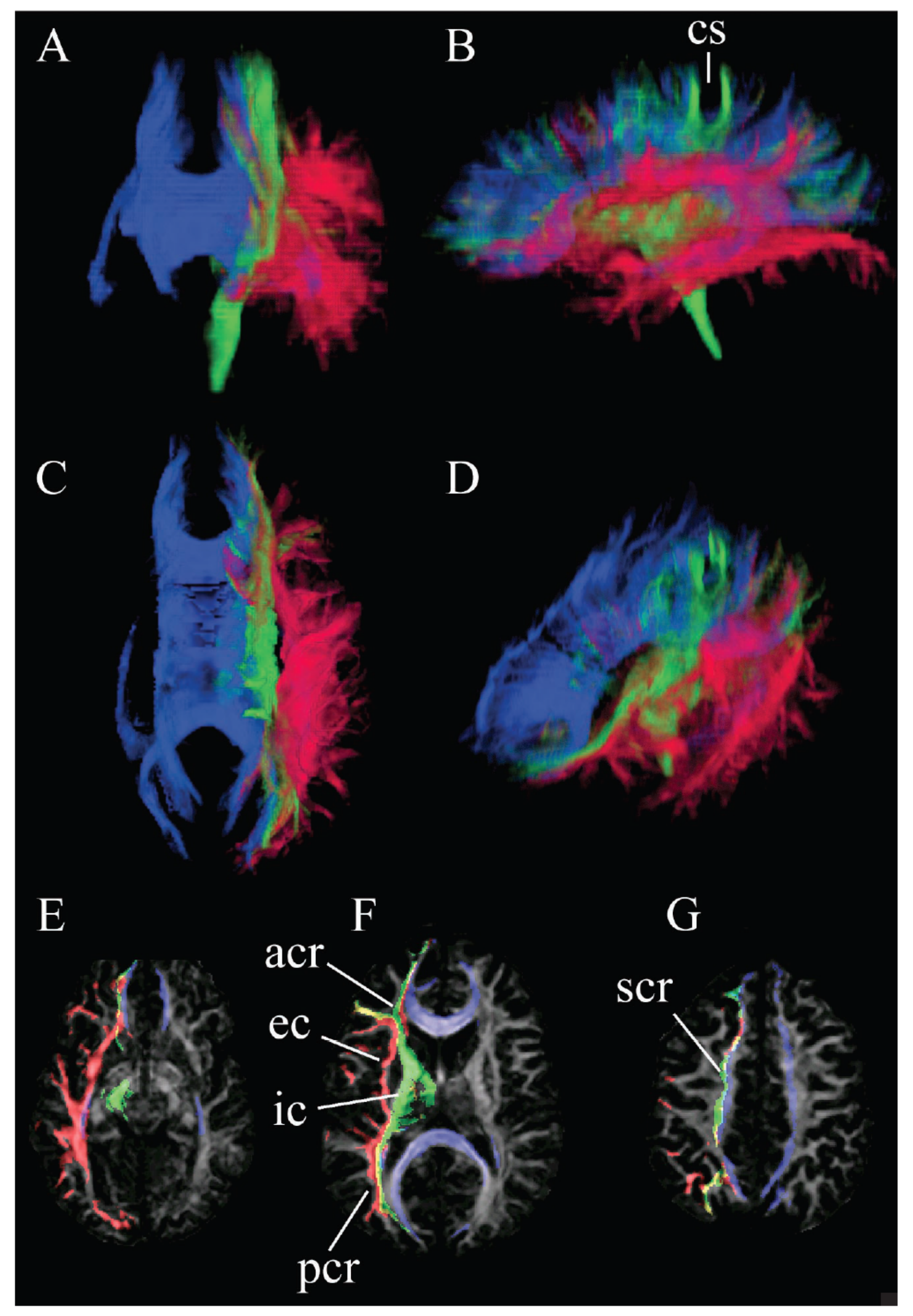
Transcallosal

Projection

Association

Here, we use the FATCAT[2] tracking tools available in AFNI.

→ see Saad et al. poster #3543 W/Th



[1]*Wakana, et al., 2004;* [2]*Taylor & Saad, 2013*

The subjects

- Nonsedated newborn subjects (<47 days after birth), same community
  - 11 PAE (6 female, 5 male)
    postconception age range 36-44 wk (median 42 wk)
  - 9 HC (3 female, 6 male)
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- Recruited as part of the Cape Town FASD Newborn Neuroimaging Study (Western Cape, SA)
  - communities around wine regions have some of highest rates of alcoholism/PAE in the world[1]

[1] *May et al., 2007*

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- Characteristics from followback interviews[2] and checkups include:
  - maternal detailed drinking, cigarette use, age at scan.
  - infant postconception age, sex, intracranial volume.

[1]*May et al., 2007;* [2]*Jacobson et al., 2002*

The scanning

- 3T Siemens Allegra + 170.9 mm circ. polarized birdcage RF coil

- Diffusion weighted imaging (DWI)
  - 2 mm isotropic voxels, whole brain coverage
  - Twice-refocused SE-EPI sequence
  - Two DWI sets with opposite phase (AP/PA) encoding
    + each: 4 b=0 and 30 b=1000 s mm^{-2} images
  - Processing included:
    motion correction using FSL, susceptibility-distortion correction[1,2], outlier rejection.

- Anatomical images
  - 1 mm isotropic voxels, whole brain coverage
  - multiecho FLASH sequence[3]
  - T1 and PD maps generated with Freesurfer-mri_ms_fitparms

[1]*Andersson et al., 2003;* [2]*Rohde et al., 2004;* [3]*van der Kouwe et al., 2008*

The measures

fractional anisotropy, FA

mean diffusivity, MD

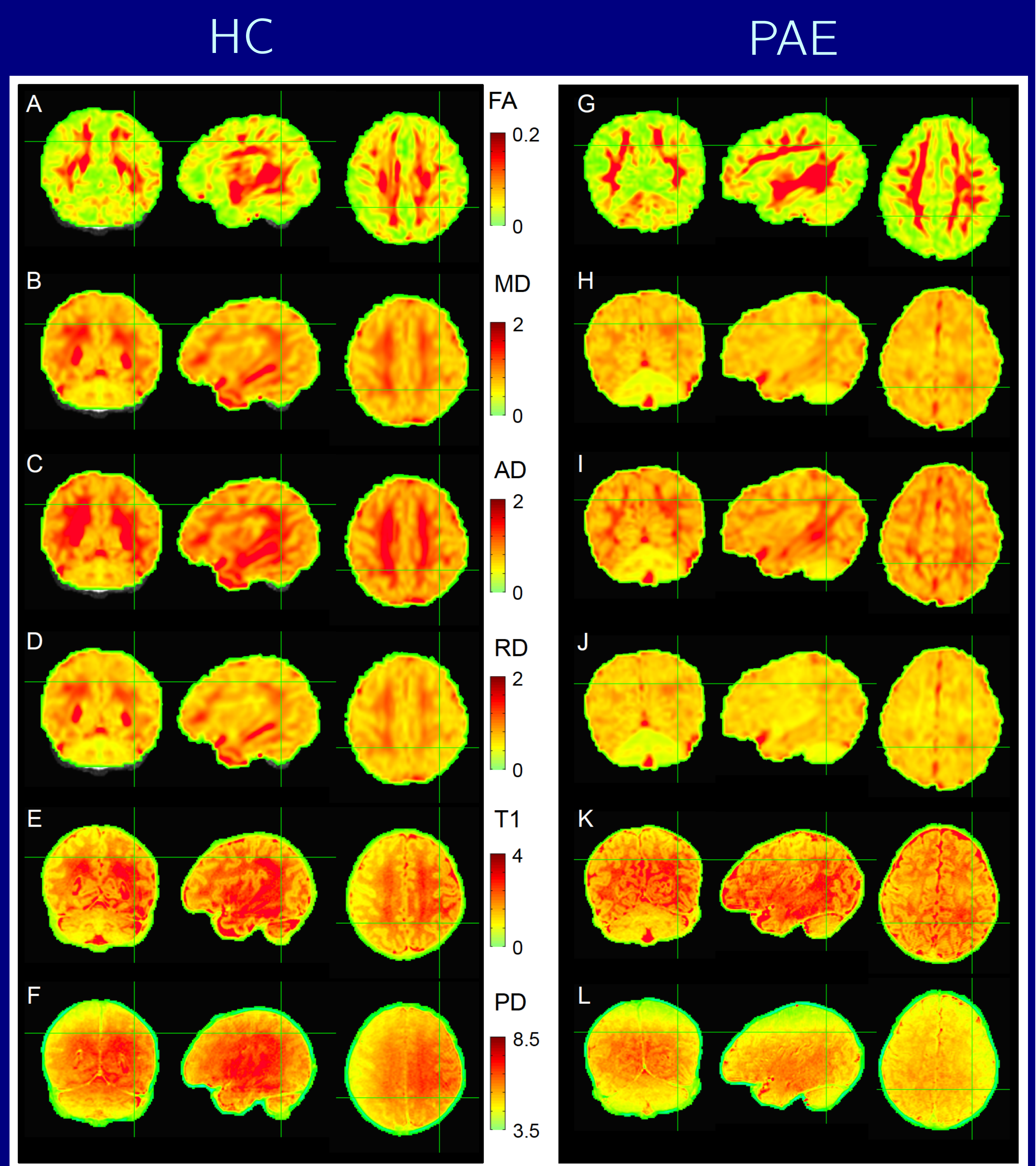
axial diffusivity, AD (i.e., L1)

radial diffusivity, RD

T1 relaxation time, T1

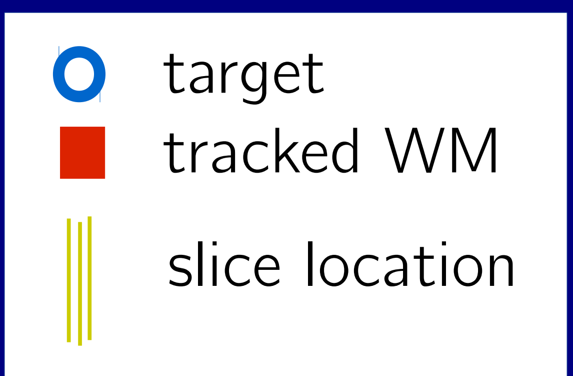
proton density, PD

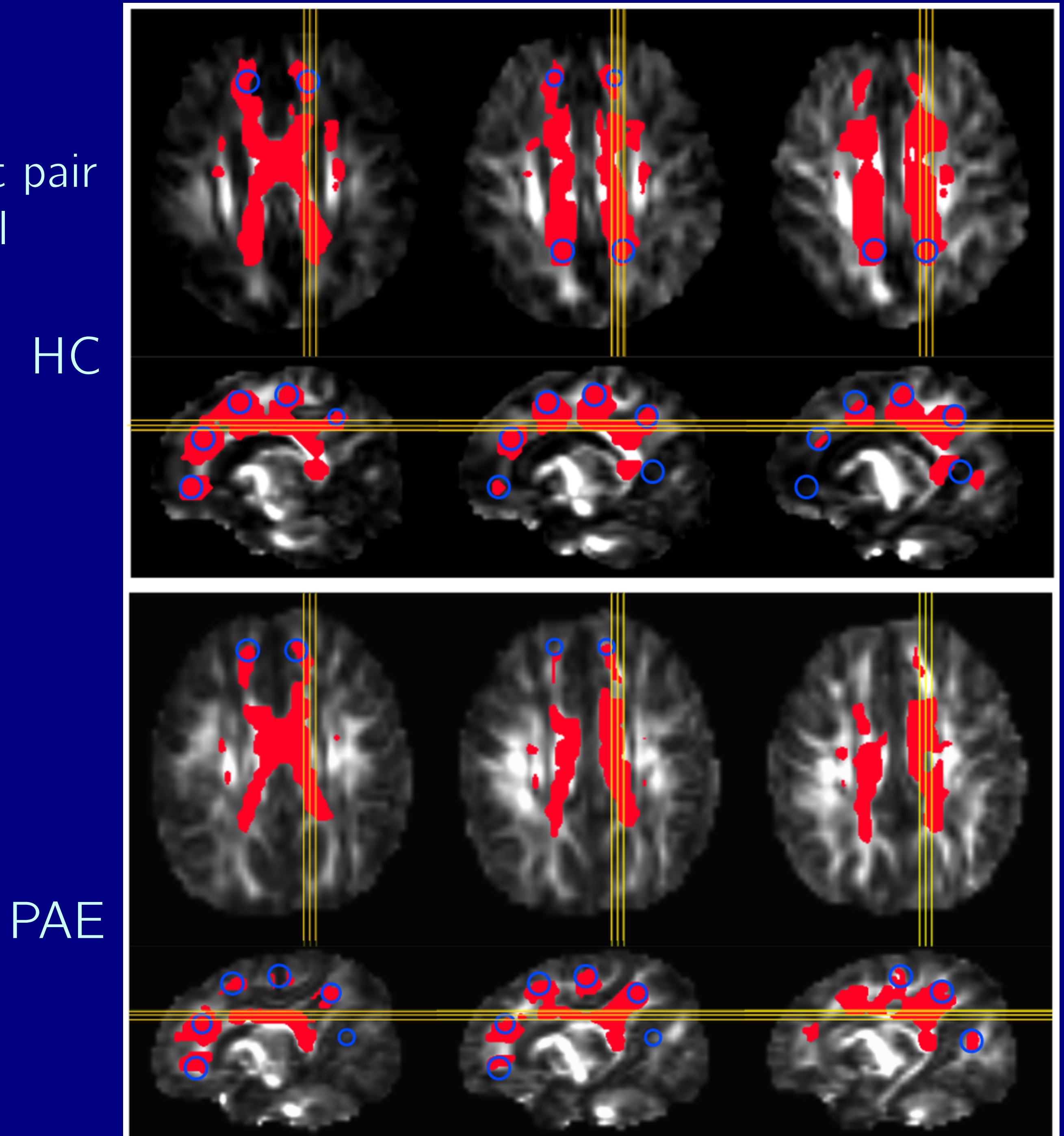
...



The measures

... and normalized volumes (= the number of voxels in a WM ROI connecting a target pair divided by subject intracranial volume)

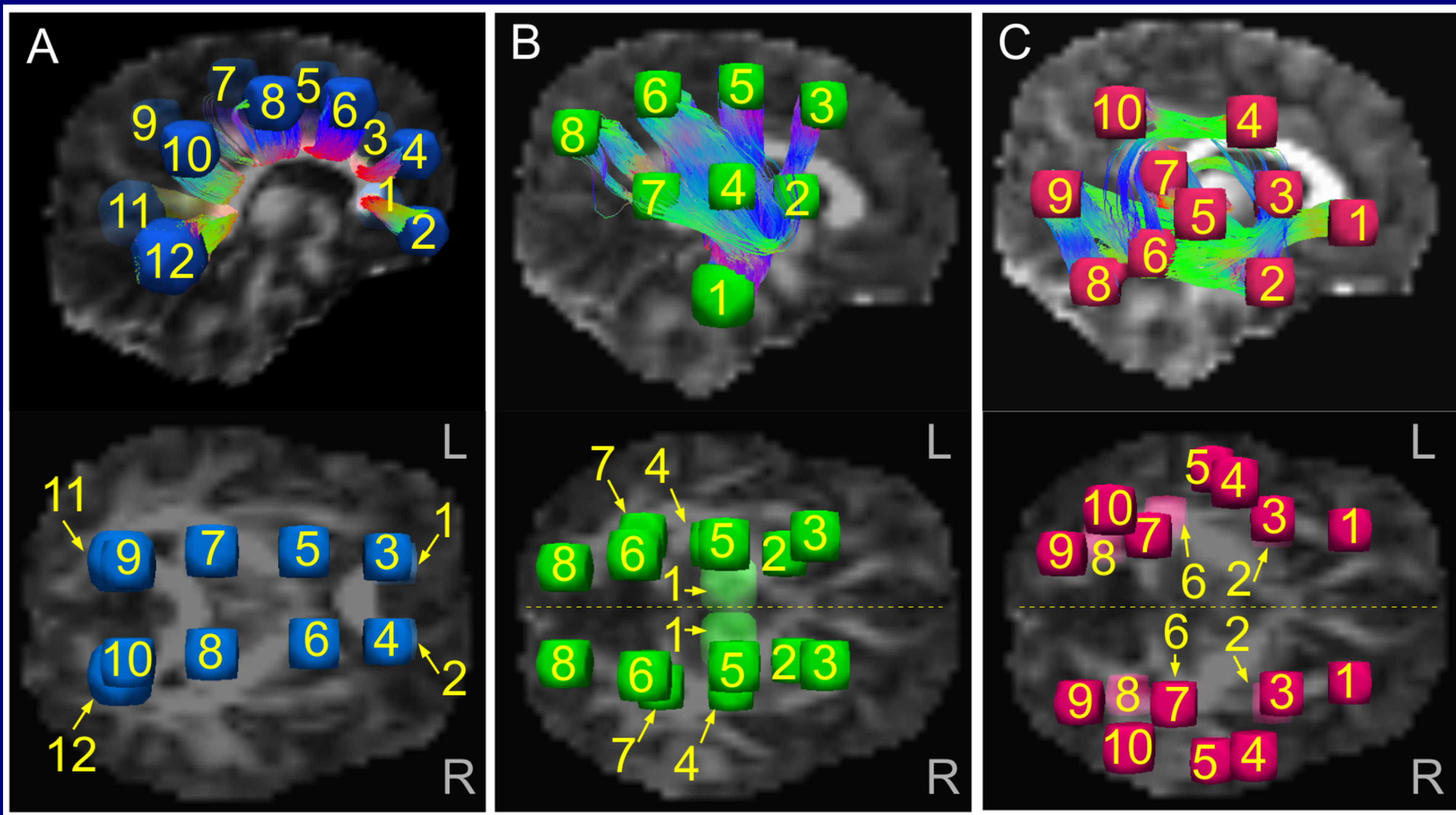




Setting up DTI-tractography

Location of targets for tractography: 5 WM networks.

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



Analysis Steps

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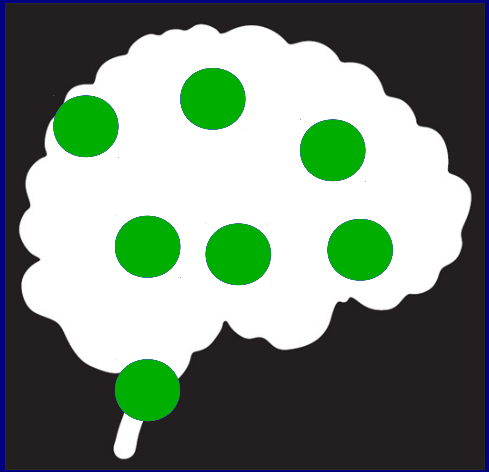

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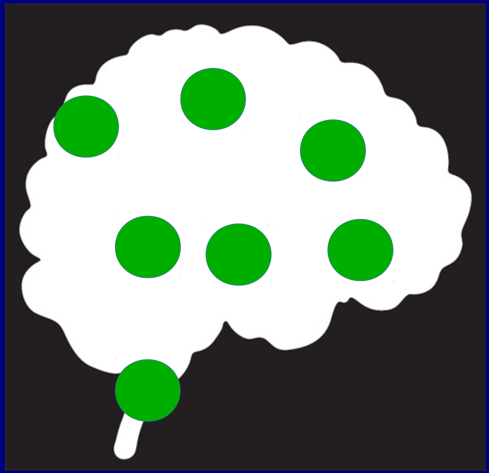
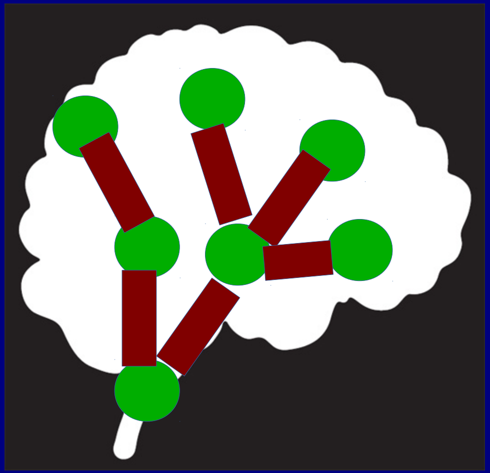


2) Probabilistic tracking



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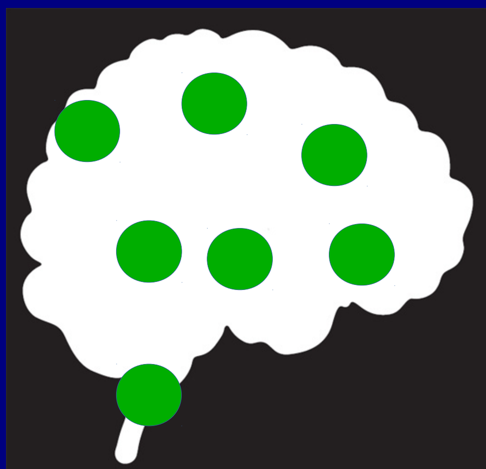

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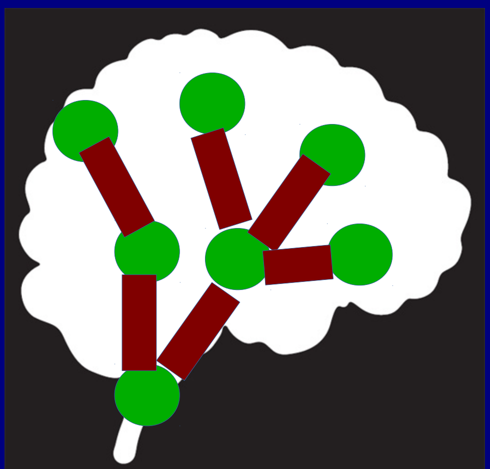
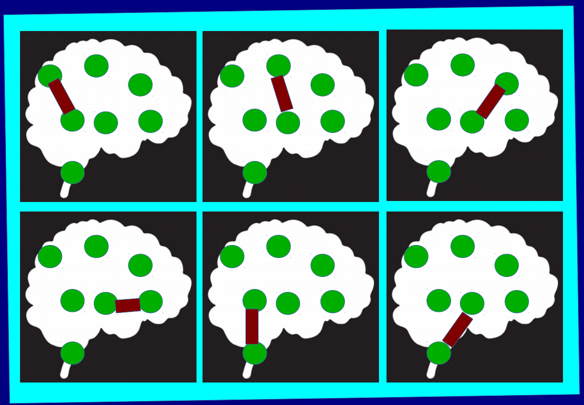


3) set of WM ROIs $\rightarrow$ set of repeated measures



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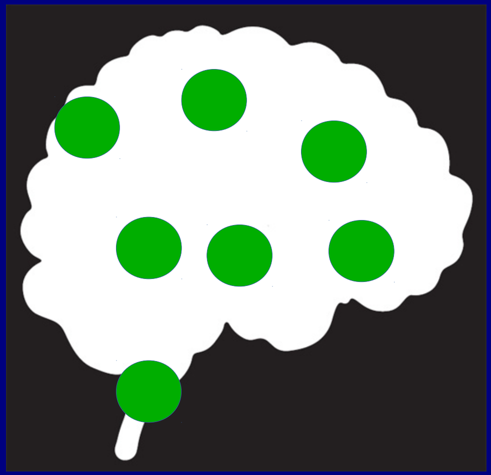

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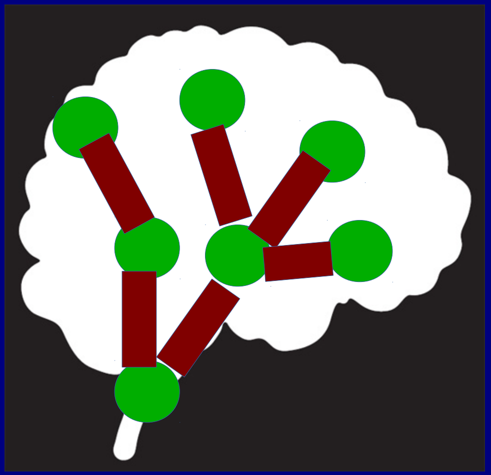

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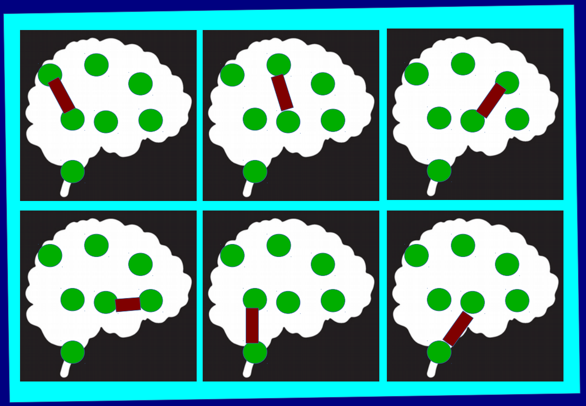

4) Multivariate model

- FA_1, FA_2, FA_3, ...
- alc
- infant age
- infant sex
- maternal age
- maternal cig/day

→ see Chen et al. poster #3606 W/Th

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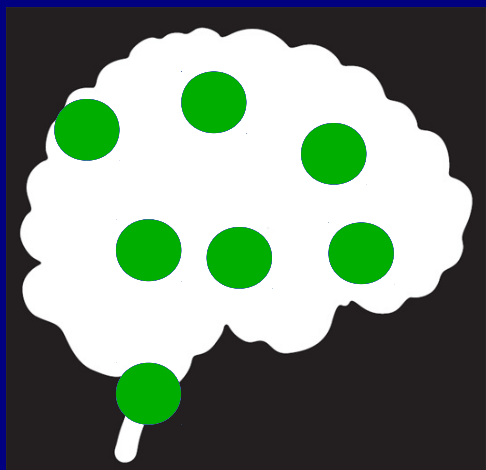

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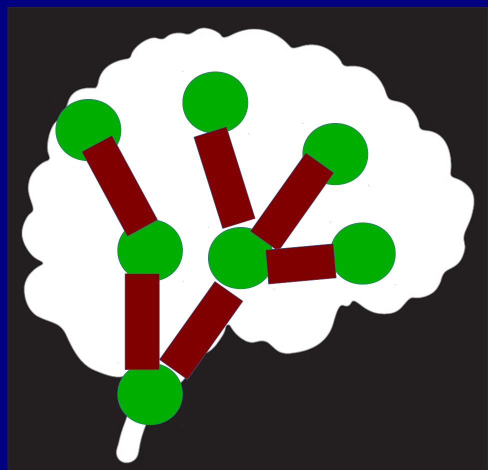

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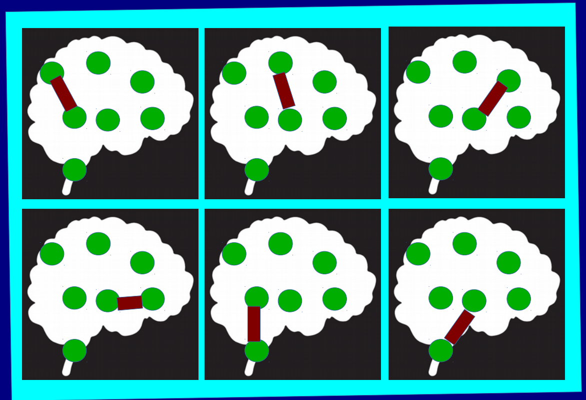

4) Multivariate model
- FA_1, FA_2, FA_3, ...
- alc
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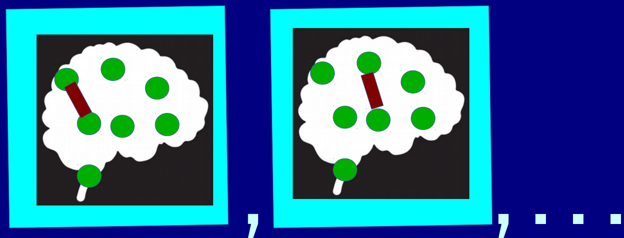
- maternal cig/day

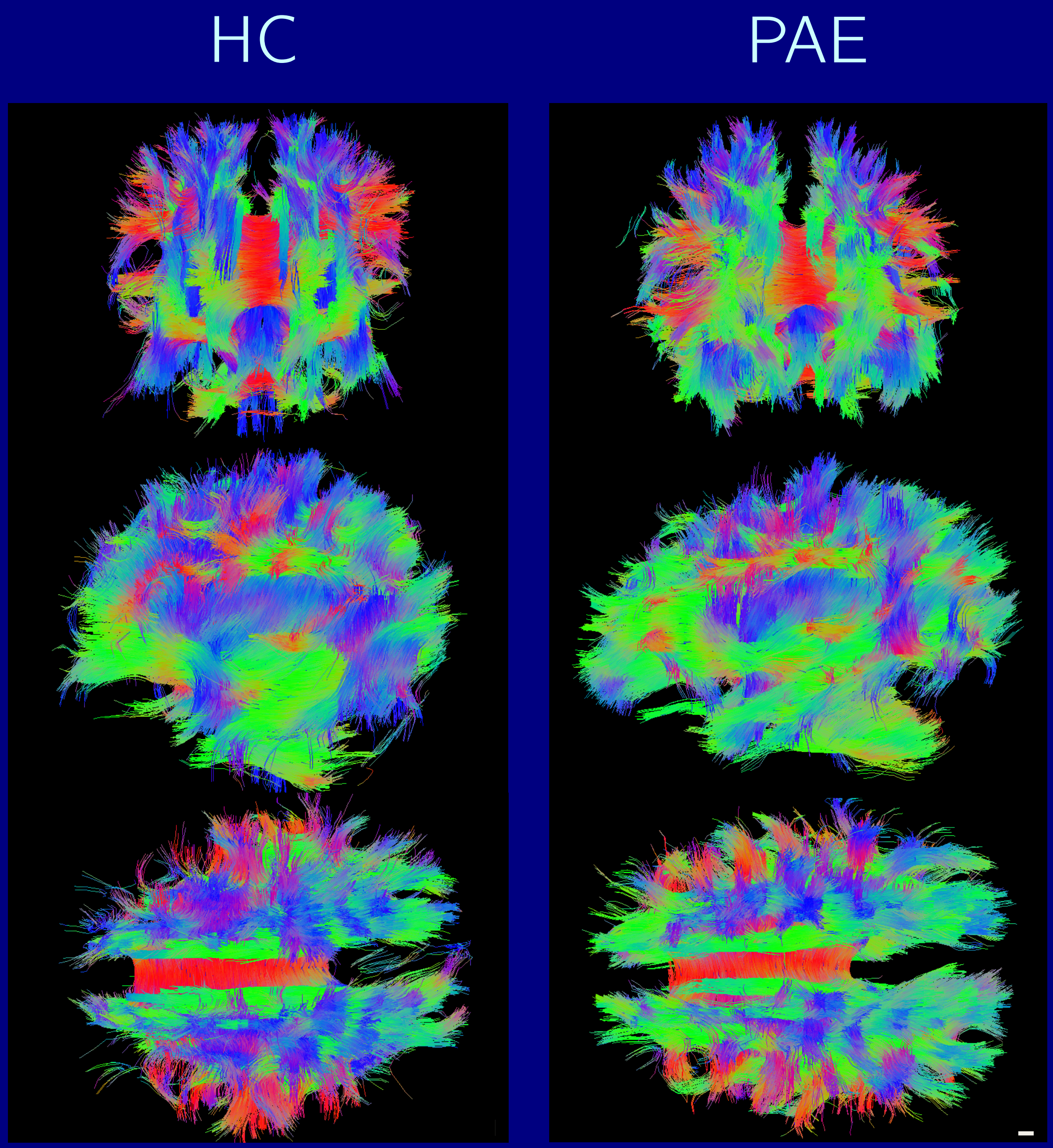
5) Follow-up GLM for each WM ROI
- FA
- alc
- infant age
- infant sex
- maternal age
- maternal cig/day



→ see Chen et al. poster #3606 W/Th

I) Results: whole brain

A) Preliminary whole brain tracking:
- no major obvious differences
- no missing regions



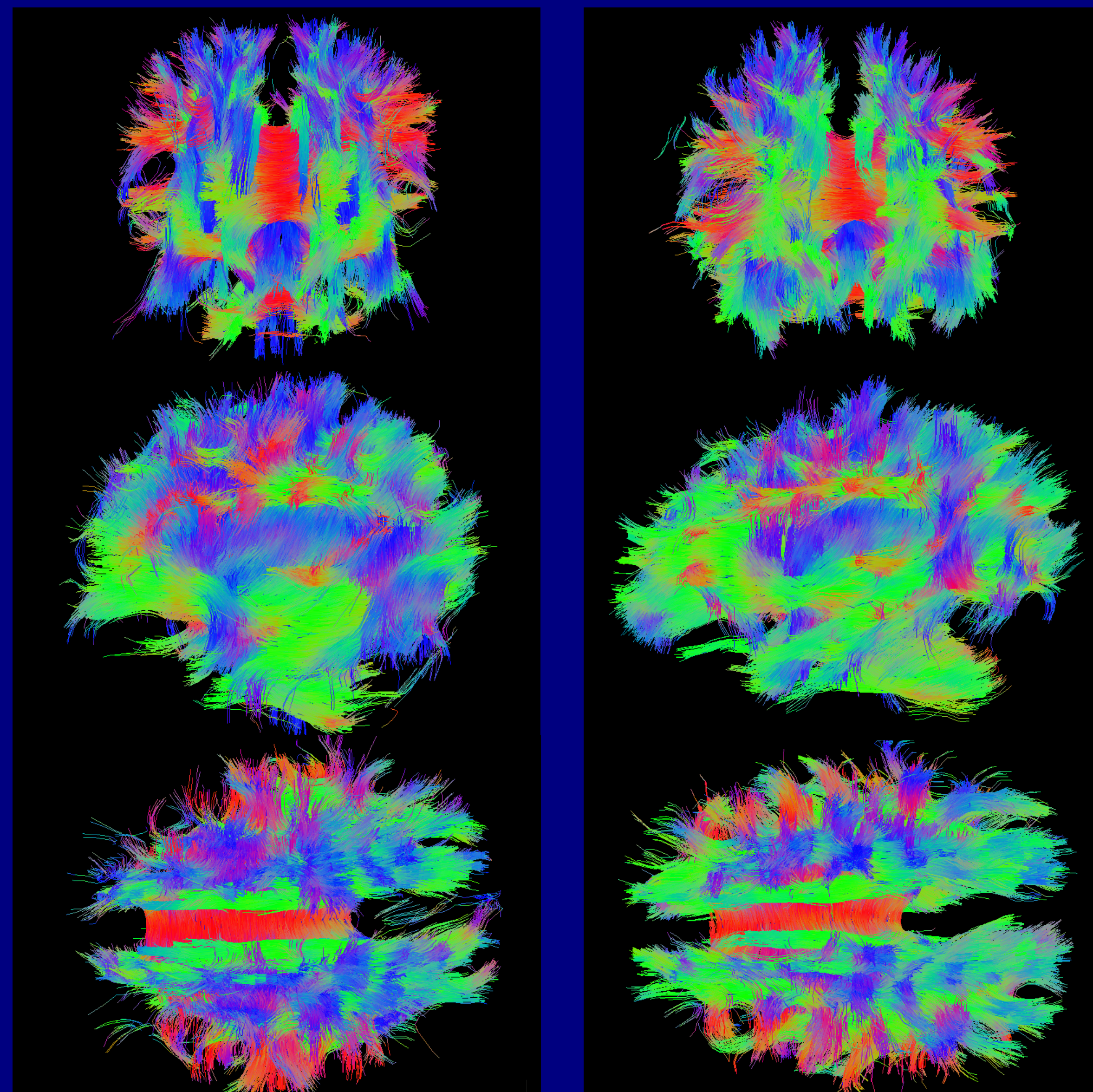
I) Results: whole brain

A) Preliminary whole brain tracking:
- no major obvious differences
- no missing regions

B) Brain volume and WM volume strongly associated with age.

C) Brain volume associated (negatively) with alcohol exposure

HC PAE



II) Results: network level

The questions:

1) which WM networks are affected by PAE?
2) which parameters show effects most strongly?

Answer using:

- (for each network) a multivariate GLM for
  - 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).

II) Results: network level

The questions:

1) which WM networks are affected by PAE?
2) which parameters show effects most strongly?

Parameters showing at least trends ($p<0.1$) $\rightarrow$

$\leftarrow$ 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												
L-ASSOC					**alc**	-0.65	6.0 (7, 8)	**0.011***	**alc**	-0.66	8.1 (1, 14)	**0.013***				
													cig	0.49	3.6 (1, 14)	0.080
									age	-0.16	2.5 (6, 84)	**0.030***				
					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

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

II) Results: network level

The questions:

1) which WM networks are affected by PAE?
2) which parameters show effects most strongly?

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					sex	-0.20	4.3 (1, 14)	0.056	**sex**	-0.39	5.9 (1, 14)	**0.029***				
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									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.*

→ Statistically significant alcohol exposure associations in ~every WM network

II) Results: network level

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Parameters showing at least trends ($p<0.1$) →

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

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

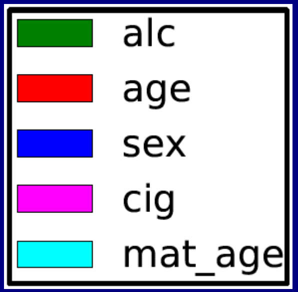
III) Results: ROI level

The question:

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

Answer using:

- (for each ROI) a GLM for
  - single DTI parameter
  - alcohol (frequency: binge/wk)
  - infant age (wks since conception)
  - infant sex (M/F)
  - maternal age (yrs)
  - maternal cigarette smoking (cig/day).

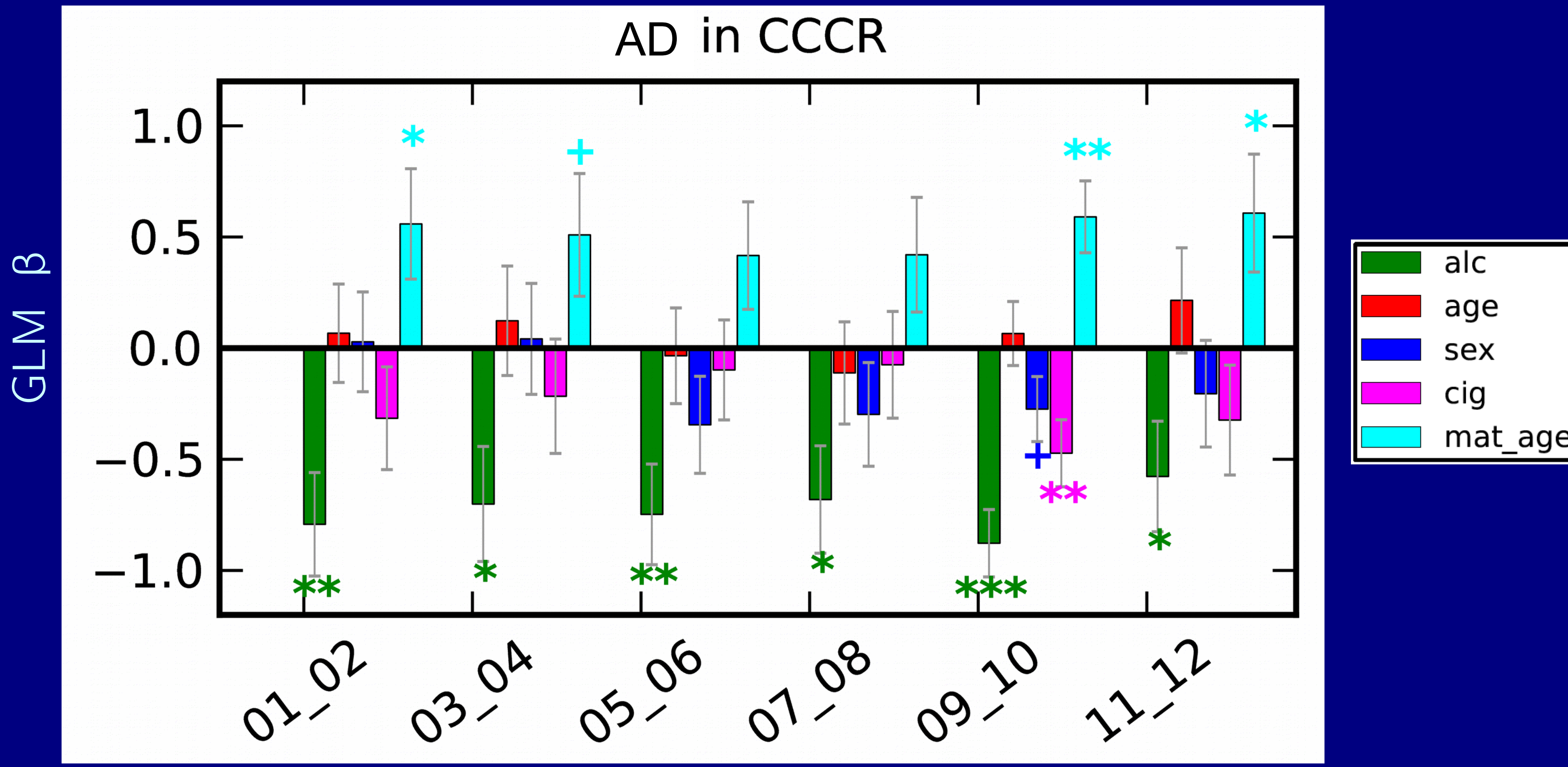


III) Results: ROI level

The question:

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

Transcallosal (CC and corona radiata)



anterior → posterior

III) Results: ROI level

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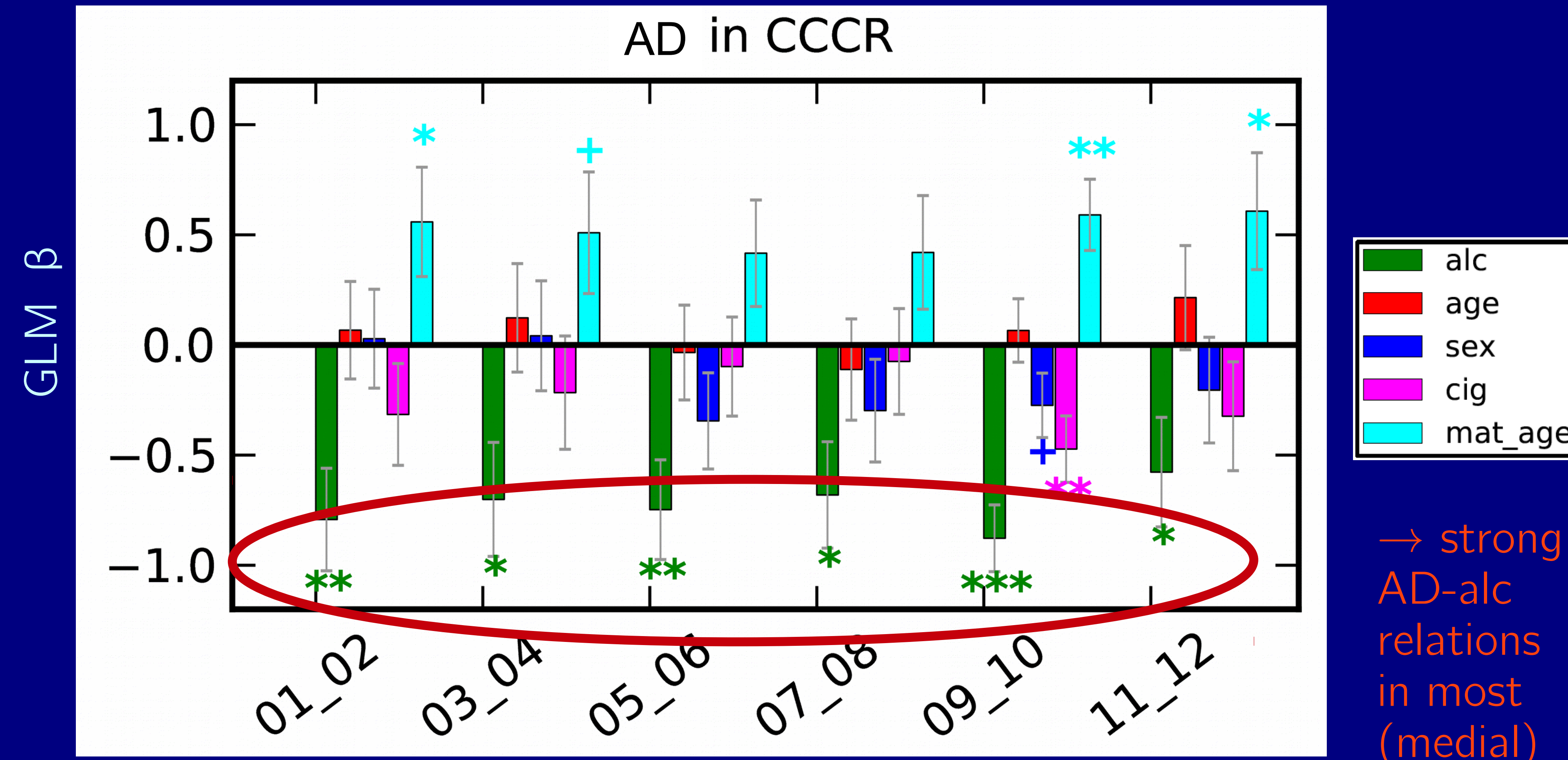
Transcallosal (CC and corona radiata)



anterior → posterior

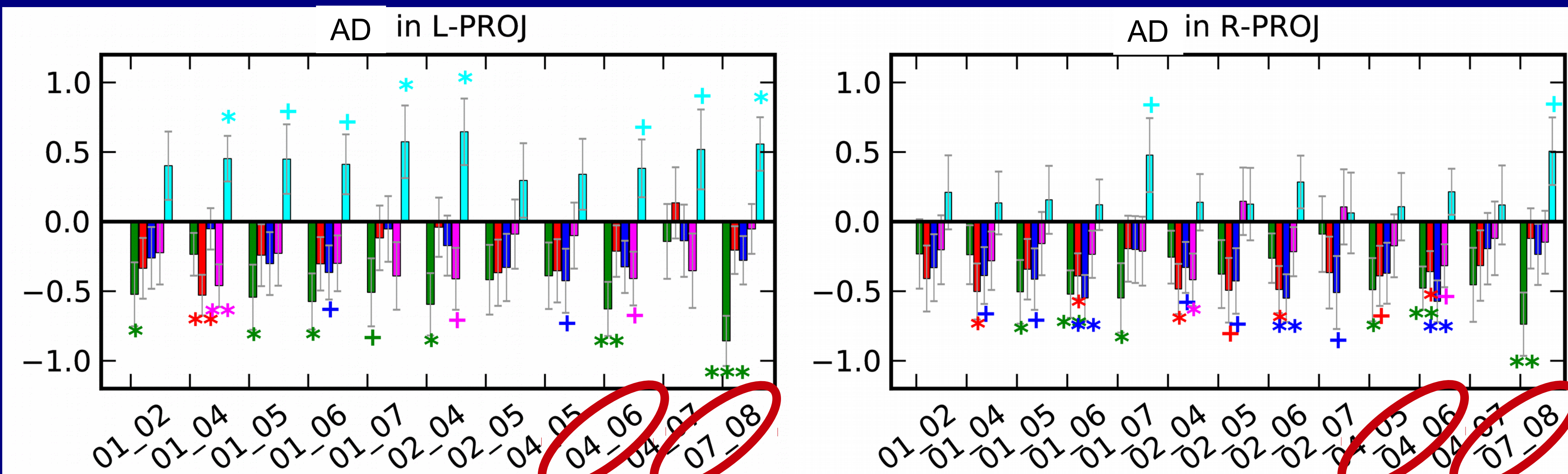
→ strong AD-alc relations in most (medial) WM ROIs

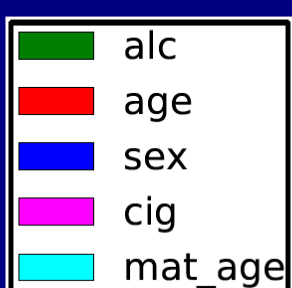
III) Results: ROI level

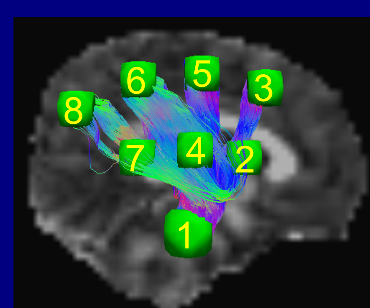
The question:

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

L and R Projection





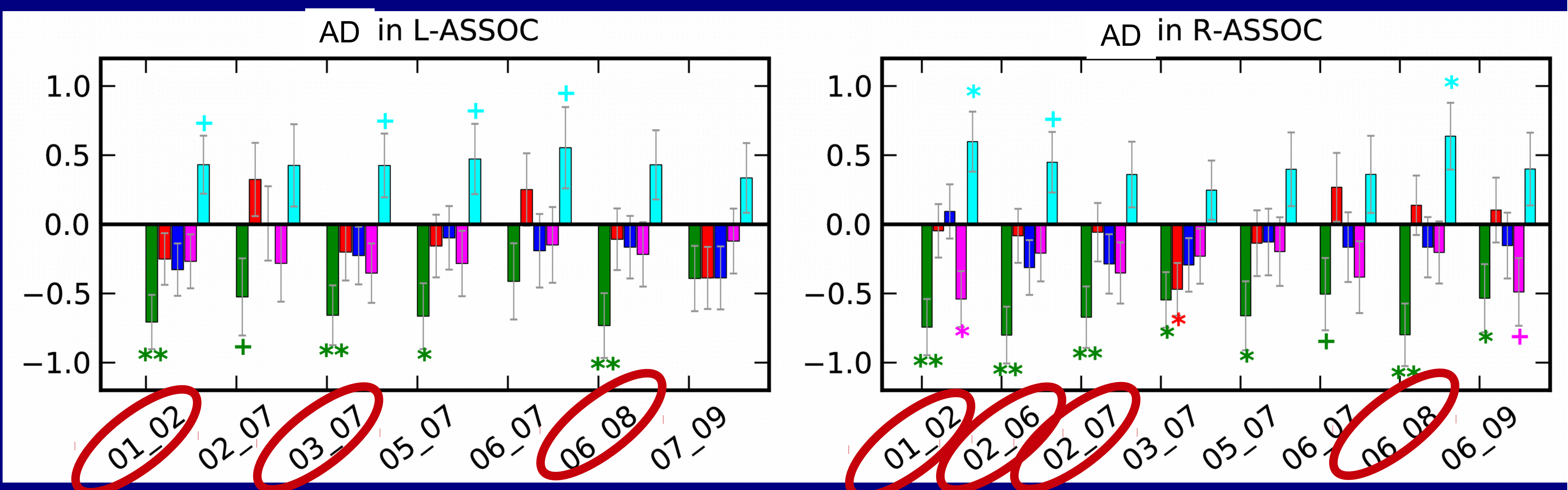


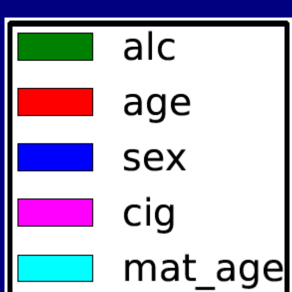
→ strong (symmetric) AD-alc relations in posterior WM ROIs

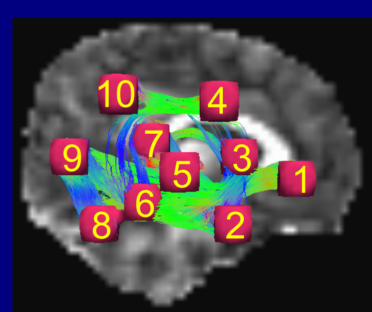
III) Results: ROI level

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

L and R Association







→ strong AD-alc relations
in (symmetric) ~medial or
inferior WM ROIs

Conclusions

- PAE in newborns is associated with widespread structural/WM changes
- Effects are seen across transcallosal, projection and association fibers

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    $\longrightarrow$ likely due to locations of early WM maturation/myelination
  - decreased AD has been associated with WM inflammation and damage in animal models; disruption of linear neurofilaments; reduction of fast transport; and axolemmal atrophy[1,2].

[1] *Wu et al., 2007; Beaulieu et al. 2002*

Conclusions

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  - decreased AD has been associated with WM inflammation and damage in animal models; disruption of linear neurofilaments; reduction of fast transport; and axolemmal atrophy[1,2].
- Further work will continue with more newborn subjects and investigating, e.g., lateralization; as well as with older (pediatric) subjects to investigate developmental WM trajectories.

[1] *Wu et al., 2007; Beaulieu et al. 2002*

Many thanks to all study coauthors:

UCT, South Africa
Ernesta M. Meintjes
Chris Molteno
Ali Alhamud

Mass. General Hosp, USA
Andre van der Kouwe

Montréal Children's Hosp, Can.
Pia Wintermark

NIMH/NIH, USA
Gang Chen

Wayne State University, USA
Sandra W. Jacobson
Joseph L. Jacobson

Extra info.

	HC ($n = 9$) Mean/%	SD	PAE ($n = 11$) Mean/%	SD	p-value
Infant characteristics					
Sex (% female)	33.3		54.5		0.075
Gestational age at birth (wk)	38.7	1.9	38.6	2.0	0.939
Postpartum age at scan (wk)	3.0	1.6	2.6	1.5	0.589
Postconception age at scan (wk)	41.6	2.1	41.2	2.3	0.658
Birthweight (g)	2753.3	478.4	2754.1	413.5	0.997
Maternal characteristics					
Maternal age at delivery (yr)	24.0	4.7	29.8	4.6	0.012 *
Parity	1.2	1.2	2.3	1.5	0.105
Education[†] (yr)	10.6	0.9	9.7	1.0	0.807
Marital status (% married)	33.3		18.2		0.176
Smoking (cig/day)	4.3	2.5	6.5	4.8	0.218
Marijuana (days/wk)	0.0	0.1	0.2	0.5	0.509
Extent of alcohol consumption					
At conception					
oz AA/day[‡]	0.02	0.05	2.25	1.89	0.002 **
oz AA/occasion[‡]	0.13	0.38	4.70	3.51	0.001 **
frequency (days/wk)	0.02	0.05	0.42	0.30	0.001 ***
Across pregnancy					
oz AA/day[‡]	0.01	0.03	1.68	1.52	0.004 **
oz AA/occasion[‡]	0.13	0.40	4.66	1.35	0.000 ***
frequency (days/wk)	0.01	0.03	0.33	0.26	0.001 **
Infant global parameters					
Number DWIs[a]	21.7	4.4	22.4	3.6	0.698
Total intracranial volume (cm^3)	469.4	60.8	434.6	43.5	0.152
WM volume (cm^3)	200.7	23.0	182.9	25.6	0.123
WM fraction	0.43	0.04	0.42	0.03	0.535

HC = healthy control; PAE = prenatal alcohol exposure; SD = standard deviation; AA = absolute alcohol; * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

[†]Education missing for one HC mother.

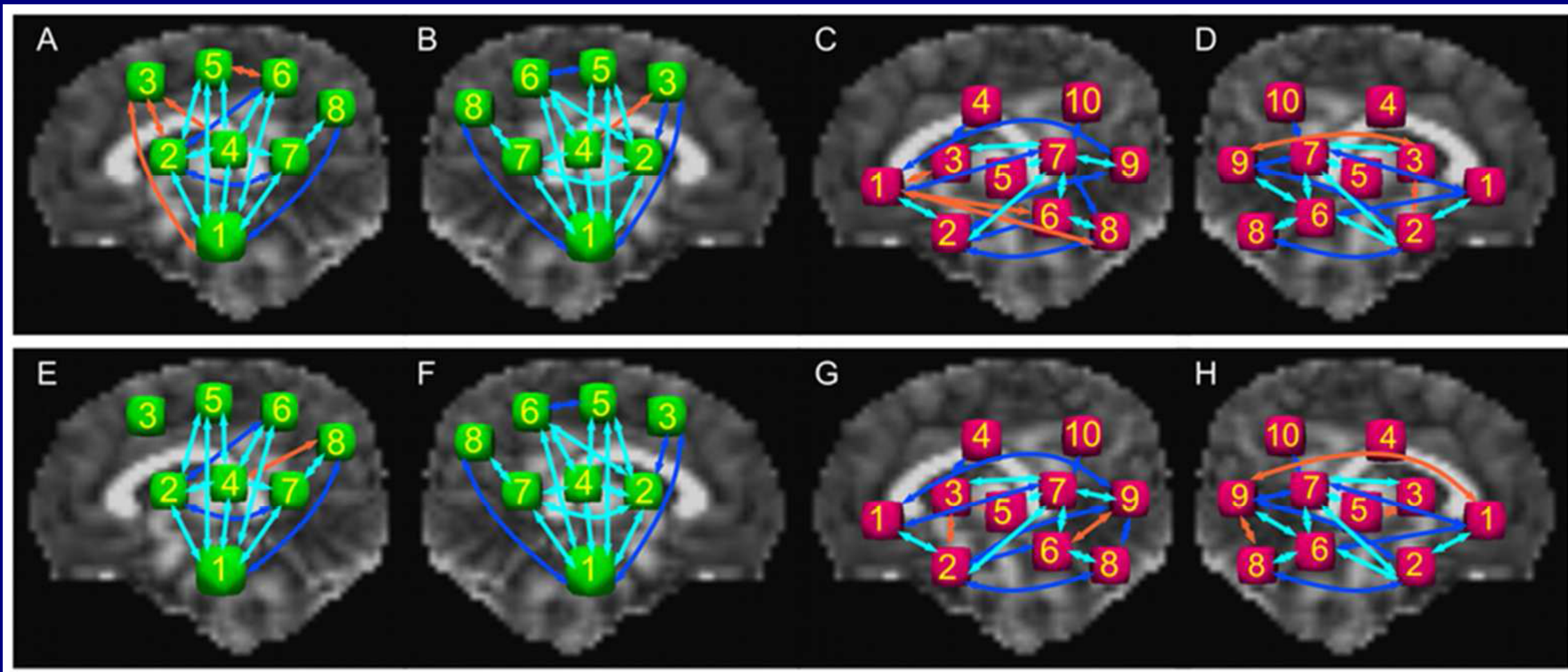
[‡]Measures of oz AA for one PAE mother were Winsorized (values >3 SD above mean were recoded).

[a]Number of diffusion weighted images (DWIs) after deleting any dropout/motion-corrupted volumes.

Variable	alc		age		sex		cig		mat_age	
	r	β	*r*	β	*r*	β	*r*	β	*r*	β
Brain volume	-0.26	-0.36*	0.76***	0.77***	-0.39	-0.21	-0.08	-0.14	-0.40	-0.13
WM volume	-0.30	-0.21	0.65**	0.54*	-0.35	-0.24	-0.07	-0.03	-0.51*	-0.23
WM fraction	-0.14	0.12	0.03	-0.15	-0.04	-0.09	-0.04	-0.11	-0.30	-0.52

Predictors

For each predictor, r represents the simple correlation between each predictor and the outcome; β is the standardized regression coefficient after adjustment for all the other predictors; * $p<0.05$; ** $p<0.01$; *** $p<0.001$. alc = frequency of maternal drinking; age = infant age since conception; sex: male=0, female=1; cig = maternal smoking (cig/day); mat_age = maternal age at delivery.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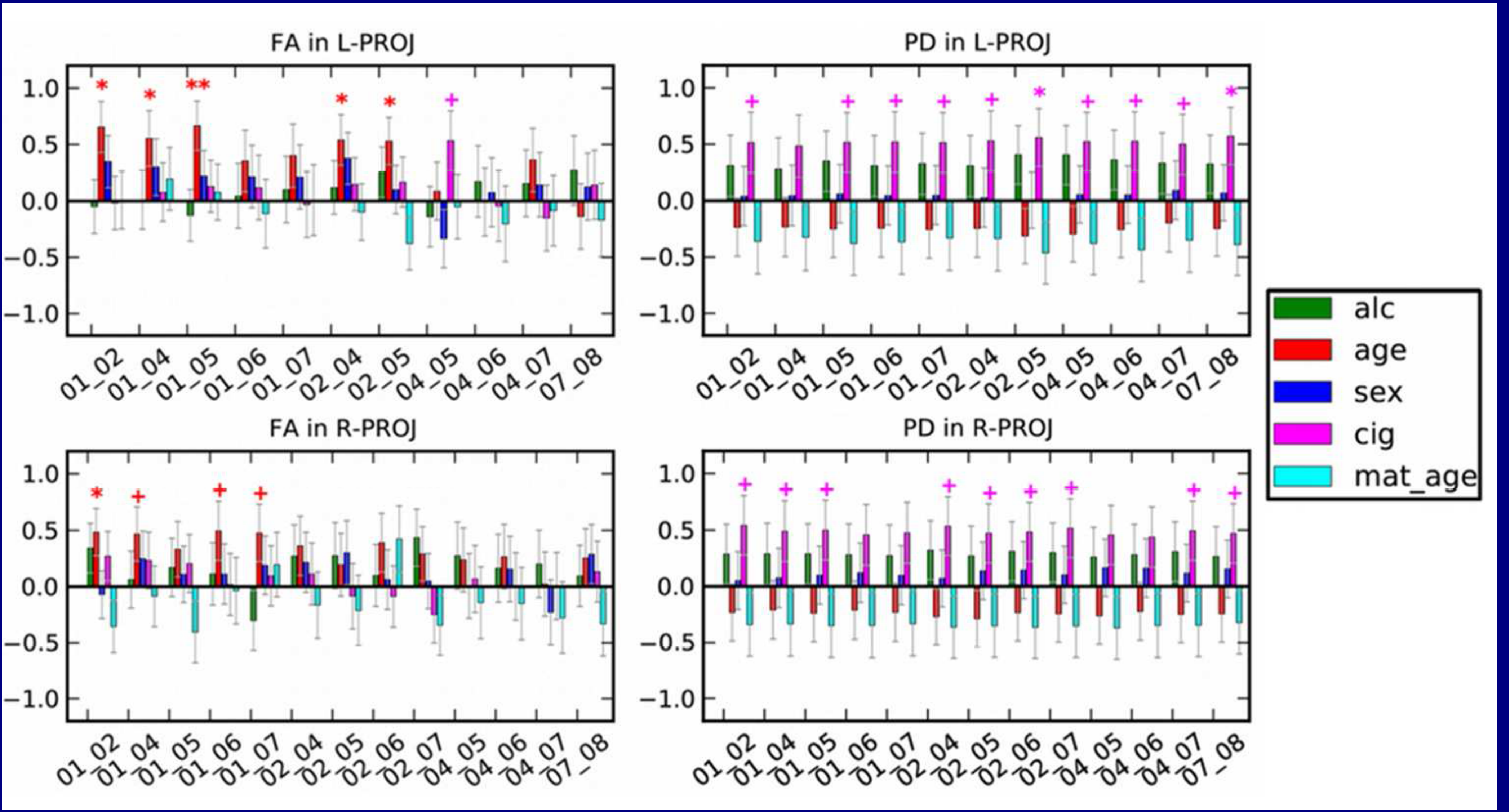
FA in L-PROJ
PD in L-PROJ
FA in R-PROJ
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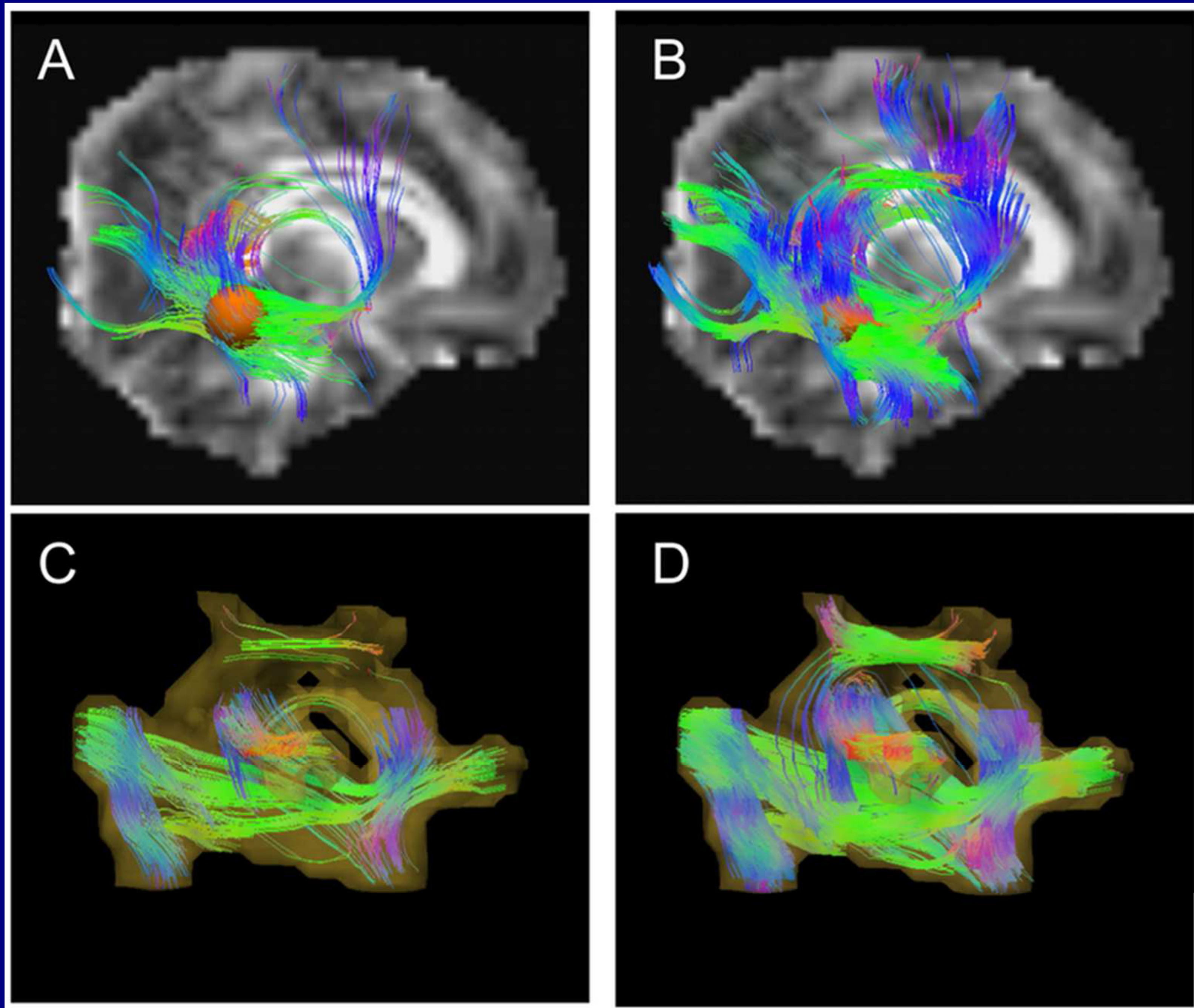
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