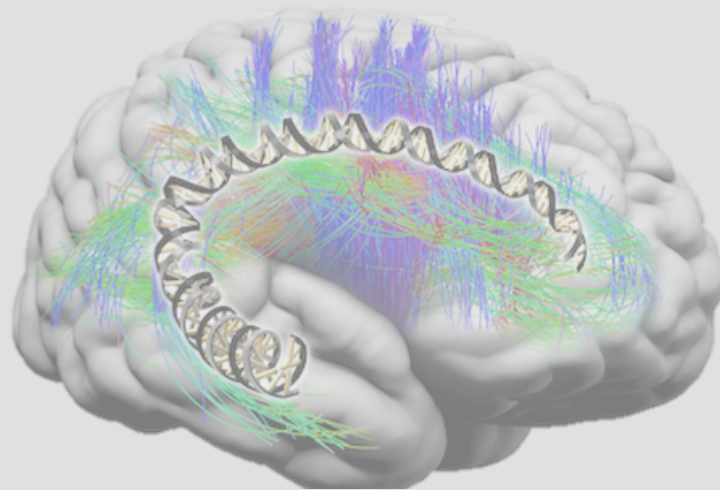


Genetic Mega and Meta analysis:

Variance components models of heritability and
Fixed-Effects models of SNP associations



International Imaging Genetics Conference
SOLAR Workshop

Neda Jahanshad
January 20, 2015



How did we use SOLAR eclipse?

- I. Joint analysis of imaging studies to improve power for discovery
- II. Creating a pedigree matrix for mega analysis
- III. Comparing mega and meta-analysis approaches
 - variance components and fixed-effects

```
[njahansh@hpc200-01 SOLAR_POLY]$ ./solar
```

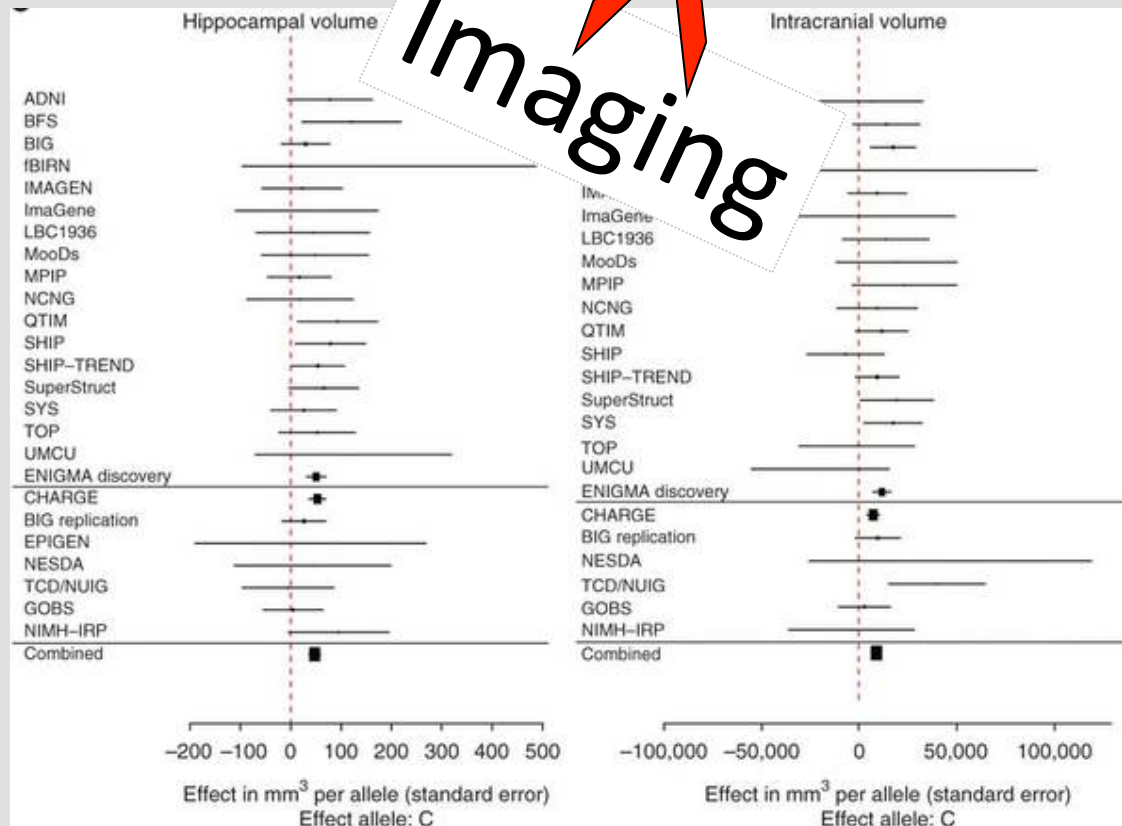
```
SOLAR version 7.2.0 (Experimental), last updated on October 11, 2013  
Copyright (c) 1995-2013 Texas Biomedical Research Institute  
Enter help for help, exit to exit, doc to browse documentation.
```

```
solar> █
```

Meta analysis for genetic studies

- A search for “meta-analysis” revealed 400+ articles in Nature Genetics in the last 10 years!
 - ~20%!!
 - 1350 google scholar results for 2015
 - 1200 this time in 2014 for meta analysis and human genetics
- What is meta-analysis?
- WHY?
- GWAS-MA → Important genetic discoveries for:
 - Cardiovascular diseases
 - Glaucoma
 - Cancer
 - Obesity
 - Alzheimer’s disease
 - Schizophrenia

Meta analysis for genetic studies

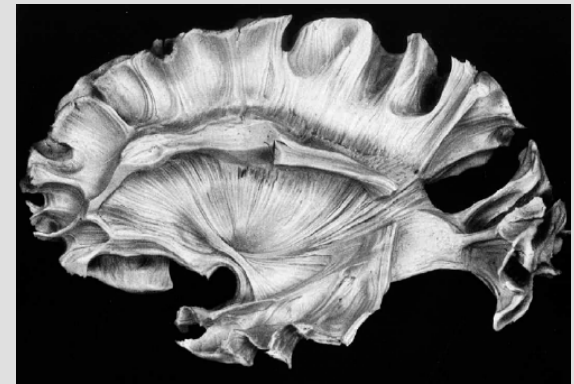


Stein et al., Nat Gen 2012
Bis et al., Nat Gen 2012
Ikram et al., Nat Gen 2012
Taal et al., Nat Gen 2012
Hibar et al., Nature 2015

What about the Brain's White Matter microstructure?

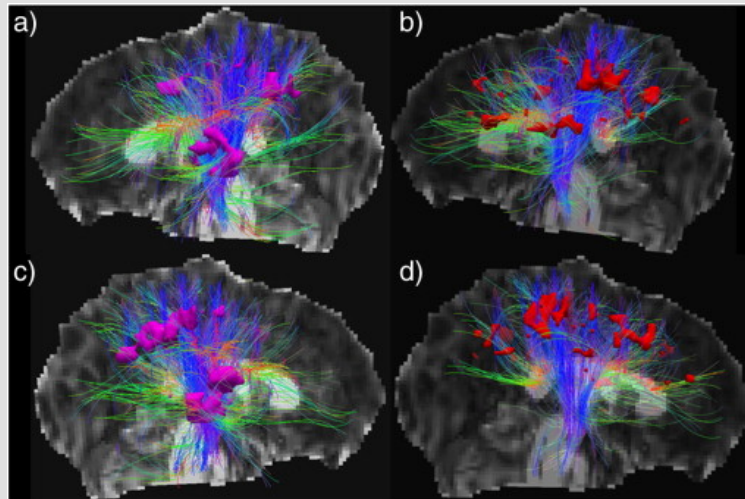
Bundles of myelinated axons connecting gray matter regions

- Neurodegeneration
 - Alzheimer's Disease
 - Huntington's Disease
- Psychiatric Disorders:
 - Schizophrenia
 - Depression
- Microstructure depends on many complex processes in development and plasticity
- Genetically influenced



Ludwig & Klingler (1956)

Diffusion Weighted Imaging



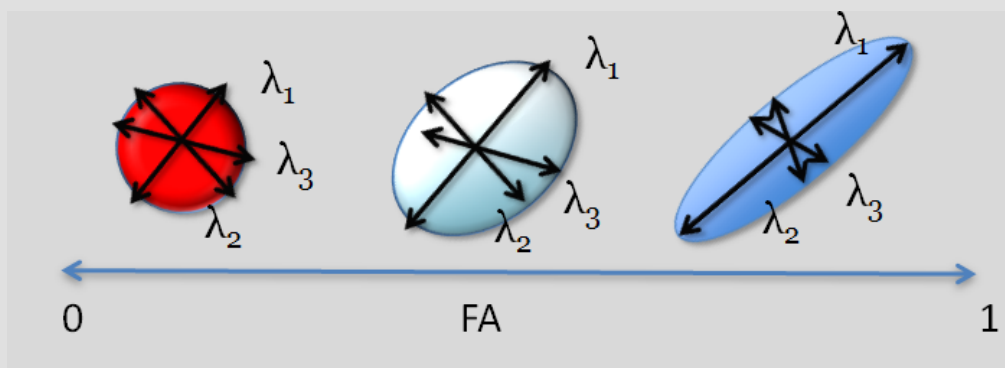
- Diffusion weighted imaging (DWI) is MRI-based
 - Magnetic gradients are applied in various directions
 - Signal change between two opposite pulses reflects distance protons have moved in time interval
 - Simplest model - diffusion tensor is calculated in each voxel
 - → Diffusion tensor imaging

$$\mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

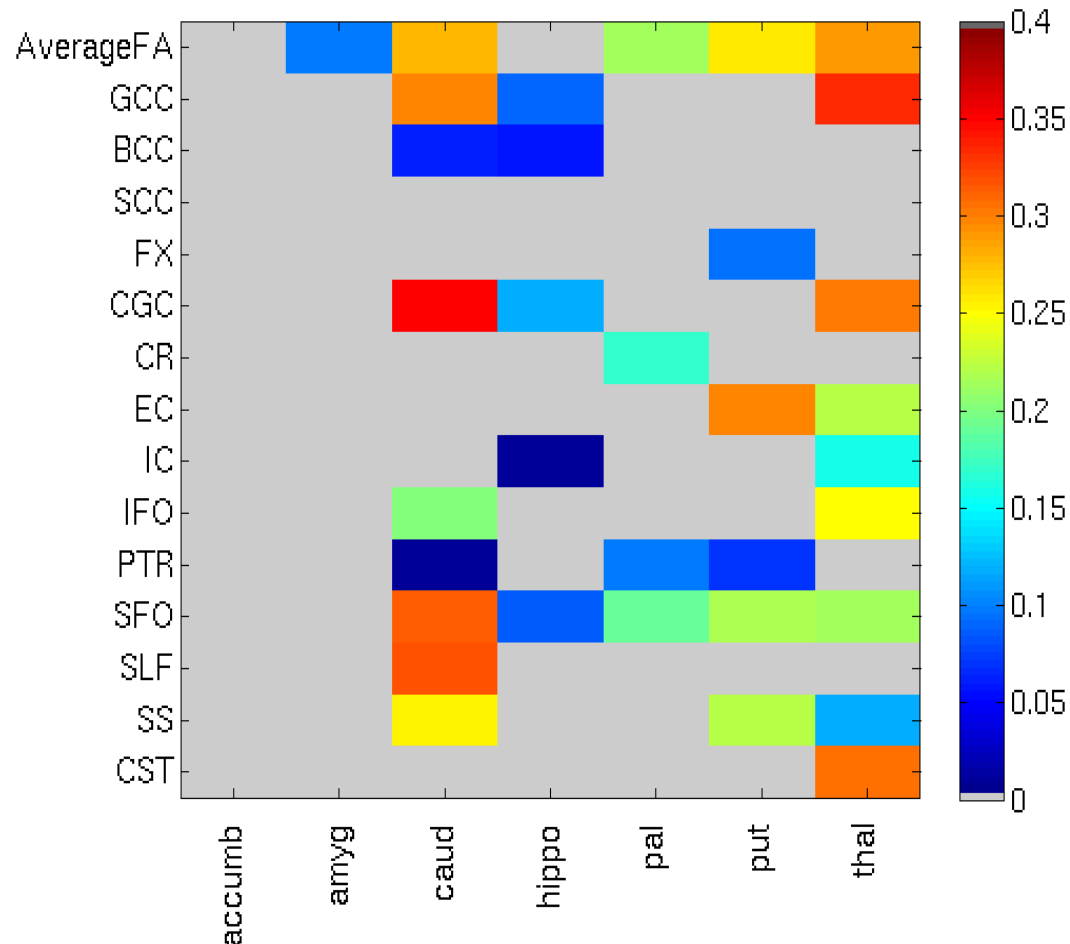
Fractional Anisotropy

- Extent to which water diffusion is directionally constrained
- Higher FA reflects higher fiber density, increased coherence and heavier myelination

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$



Genetic correlations with subcortical volumes?



Genetic overlap between white matter integrity and psychiatric disorders

- FA reduced in unaffected relatives

- Bipolar disorder

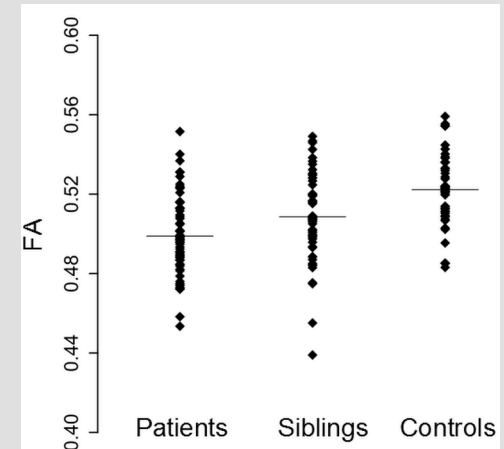
- (Mahon et al., 2012; Skudlarski et al., 2013; Sprooten et al., 2011, 2013)*

- Major depressive disorder

- (Huang et al., 2010; Keedwell et al., 2012)*

- Schizophrenia

- (Hao et al., 2009; Hoptman et al., 2008; Knöchel et al., 2012; Munoz-Maniega et al., 2008; Boos et al., 2013)*



- Polygenic risk scores *(Whalley et al., 2013)*

- Negative association between FA and polygenic risk score for depression, derived from PGC case-control GWAS

GWAS using DTI phenotypes

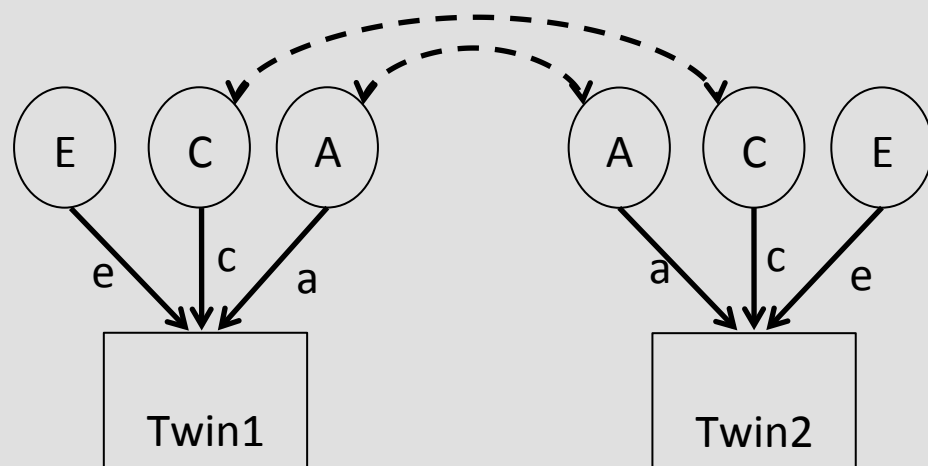
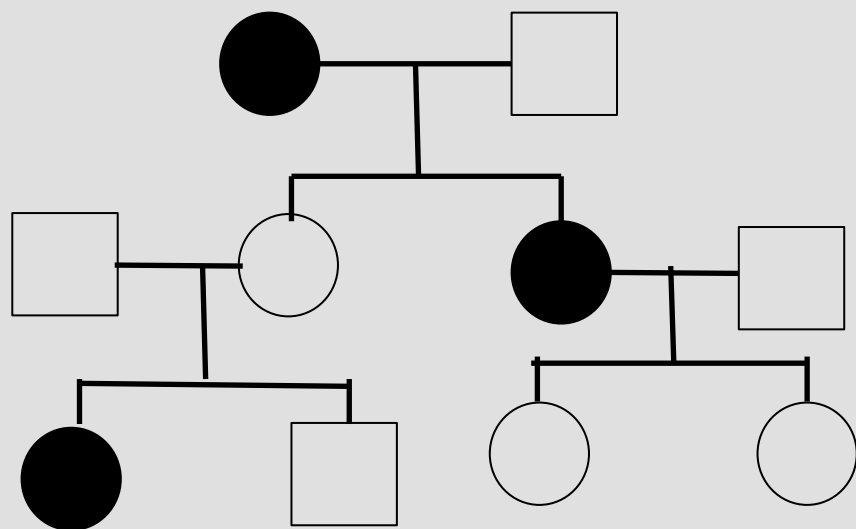
- Single site GWAS of white matter
 - Global measure of FA
 - General factor of FA
 - Extent of connections between regions
- Top SNPs in candidate pathways
- Relatively small sample sizes
 - $N \sim 150$, $N \sim 700$

Multi-site DTI-GWAS...

- Greatly increase the number of subjects!
 - Genome wide significance?
- Would a tract from one study be the same as a tract from another?
- How reliable are the tracts in terms of imaging protocol and resolution
- Would tracts from different populations even be similarly heritable?
- How effective would they be as endophenotypes?

Let's find out!

- Multi-site heritability analysis
 - Meta-analysis
 - Run each site independently and jointly analyze results
 - Mega analysis
 - Combine studies and run a single analysis



5 cohorts:

	<i>GOBS</i>	<i>QTIM</i>	<i>TAOS</i>	<i>BrainSCALE</i>	<i>NTR</i>
N Subjects	814	625	319	199	246
Sex	350M/464F	231M/394F	158M/161F	100M/99F	93M/153F
Age range (yrs.)	19-85	21-29	12-15	9-10	18-45
Scanner	Siemens	Bruker	Siemens	Achieva	Intera
N-acquisitions	1	1	1	2	1
Field Strength	3T	4T	3T	1.5T	3T
Voxel size (mm)	1.7x1.7x3.0	1.8x1.8x2.0	1.7x1.7x3.0	2.5x2.5x2.5	2.5x2.5x2.5
N-gradients	55	94	55	32	32
N-b₀	3	11	3	8	1
<i>b</i>-value (s/mm²)	700	1159	700	1000	1000

Can ALL this be run with SOLAR?

Combining DTI - Initial Steps

- Create common template
- Tract based spatial statistics skeletonization
- ROI extraction
- SOLAR statistics
 - Voxelwise and on a ROI basis

<http://enigma.ini.usc.edu/ongoing/dti-working-group/>

Creating SOLAR Pedigree Files for individual group analysis

Pedigree

ID	FA	MO	SEX	MZTWIN	HHID	genoID	PEDIGREE NUMBER
801101	801106	801102	F			801101	1
801102	801104	801103	F				1
801106	801125	801124	M				1
801113	801106	801102	M			801113	1
801114	801106	801102	M			801114	1
801115	801106	801102	M			801115	1
801118	801106	801102	F			801118	1
801120	801123	801101	F			801120	1

Twins

ID	MO	FA	SEX	FAMID	MZTWIN
8003201	8003203	8003204	2	80032	80032
8003202	8003203	8003204	2	80032	80032
8003301	8003303	8003304	1	80033	
8003302	8003303	8003304	2	80033	
8003304			1	80033	
8003303			2	80033	
8003204			1	80032	
8003203			2	80032	

MEGA Pedigree files

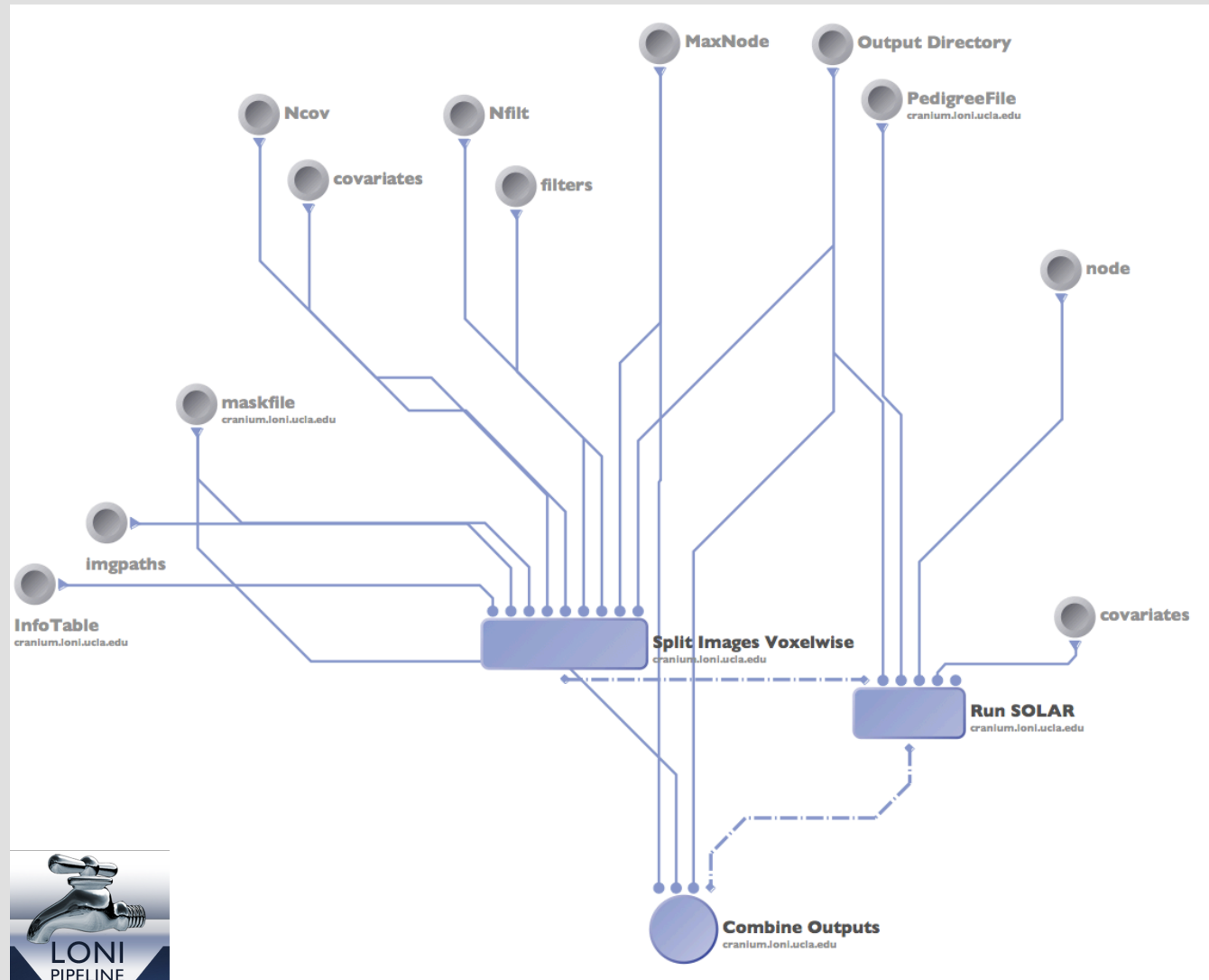
ID	FA	MO	SEX	FAMID	MZTWIN	HHID	genoID	PEDIGREE NUMBER	CLASS
801101	801106	801102	F				801101	1	0
A44012			F					101	0
A44101			M					202	0
Q44160			F					204	0
8003201	8003204	8003203	2	80032	80032		1		1
8003202	8003204	8003203	2	80032	80032		1		1
8003301	8003304	8003303	1	80033			2		1
8003302	8003304	8003303	2	80033			2		1
8948803			2	89488					1
8948804			1	89488					1
200101	200103	200102	F	2001					2
281702			F	2817					2
281802			F	2818					2
UMCU15	UMCFA1	UMCMO1	F	UMCUFA	UMCUFAID1				3
UMCU141	UMCFA1	UMCMO1	F	UMCUFA	UMCUFAID1				3
UMCFA87			M	UMCUFAID87					3
UMCFA92			M	UMCUFAID92					3
UI205	UIFAID1	UIMOID1	M	UIFMID1					4
UI201	UIFAID1	UIMOID1	F	UIFMID1					4
UI13	UIFAID12	UIMOID12	F	UIFMID1	UIFMID123				4
UI112	UIFAID12	UIMOID12	F	UIFMID1	UIFMID123				4
UIMOID123			F	UIFMID123					4

Running SOLAR voxelwise

After creating pedigree files...

- 1) Split images and create individual SOLAR files
- 2) RUN SOLAR voxelwise
- 3) Combine results

LONI Pipeline for voxelwise processing

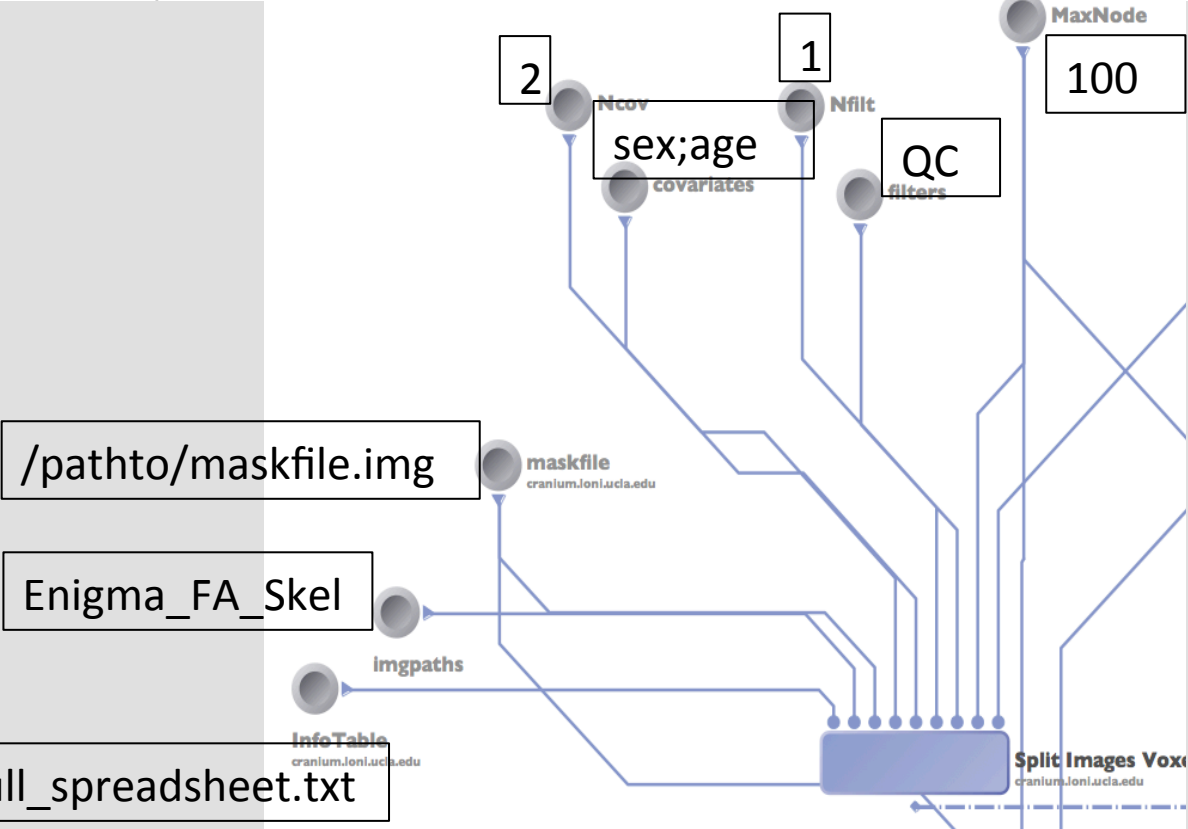


1) Create SOLAR phenotype files

- Keep all subject information in a table and call what you need by columns!
- Tell the pipeline how many nodes to use (into how many pieces to break up the images)

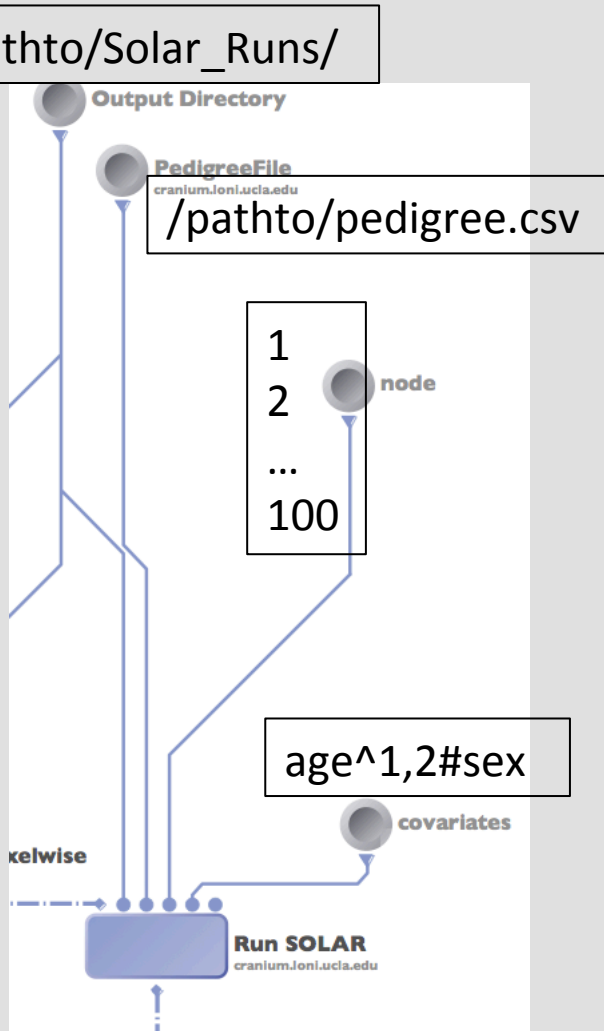
full_spreadsheet.txt

familyID	subjectID	zygosity	Enigma_FA_Skel	age	sex	bmi	ROI_1	QC
80032	8003201	1	/path/to/8003201_FAskel.img	22.38	2	32	0.5238	1
80033	8003301	2	/path/to/8003301_FAskel.img	24.24	1	20	0.4908	NA
80572	8057201	2	/path/to/8057201_FAskel.img	22.88	2	21	0.5012	1



mrid	id	age	sex	VOXEL_31_107_105	VOXEL_31_107_107	VOXEL_31_108_104	VOXEL_31_109_103
8003201	8003201	22.38	2	0.4183	0.234	0.4373	0.3544
8057201	8057201	22.88	2	0.4838	0.374	0.4183	0.4183

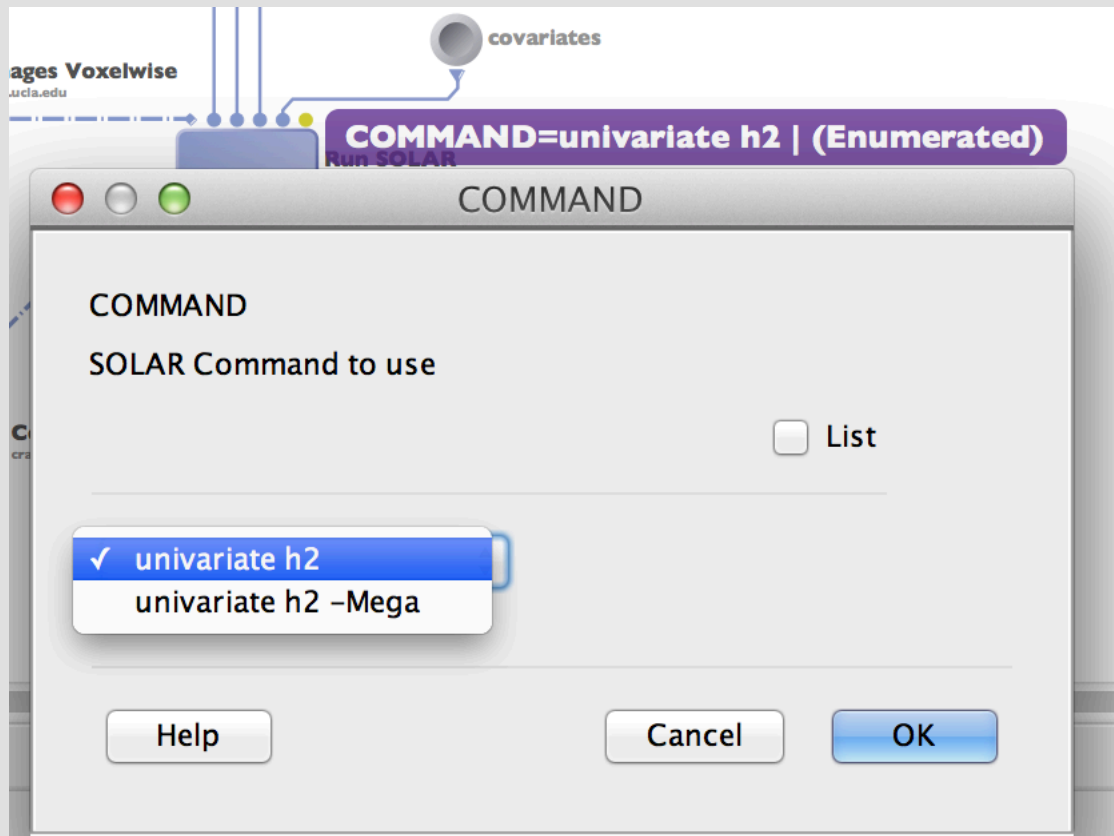
2) Run SOLAR commands



- Where to write out the files
- Import pedigree csv
- Tell the pipeline how many nodes to use (into how many pieces to break up the images)
 - List out the instances
- Type in covariates you used just as you want SOLAR to process them

2) Run SOLAR Commands

- What type of model to run



mrid	id	age	sex	VOXEL_31_107_105	VOXEL_31_107_107	VOXEL_31_108_104	VOXEL_31_109_103
mrid	id	age	sex	VOXEL_31_107_105	VOXEL_31_107_107	VOXEL_31_108_104	VOXEL_31_109_103
mrid	id	age	sex	VOXEL_31_107_105	VOXEL_31_107_107	VOXEL_31_108_104	VOXEL_31_109_103
8003201	8003201	22.38	2	0.4183	0.234	0.4373	0.3544
8057201	8057201	22.88	2	0.4838	0.374	0.4183	0.4183

```
Pedi load pedigree_file.csv
pheno load node_1.csv
set SE_FOUT_NAME node_1_results.txt
```

```
model new
covar age^1,2#sex
```

```
define VOXEL_31_107_105_INORM =
inorm_VOXEL_31_107_105
trait VOXEL_31_107_105_INORM
se_univ_polygenic
```

```
define VOXEL_31_107_107_INORM =
inorm_VOXEL_31_107_107
trait VOXEL_31_107_107_INORM
se_univ_polygenic
```

1 file for
each node
created in a
separate
subfolder

SOLAR outputs

- Each subfolder has a file which writes out the individual voxel outputs in series...

Node1_results.txt

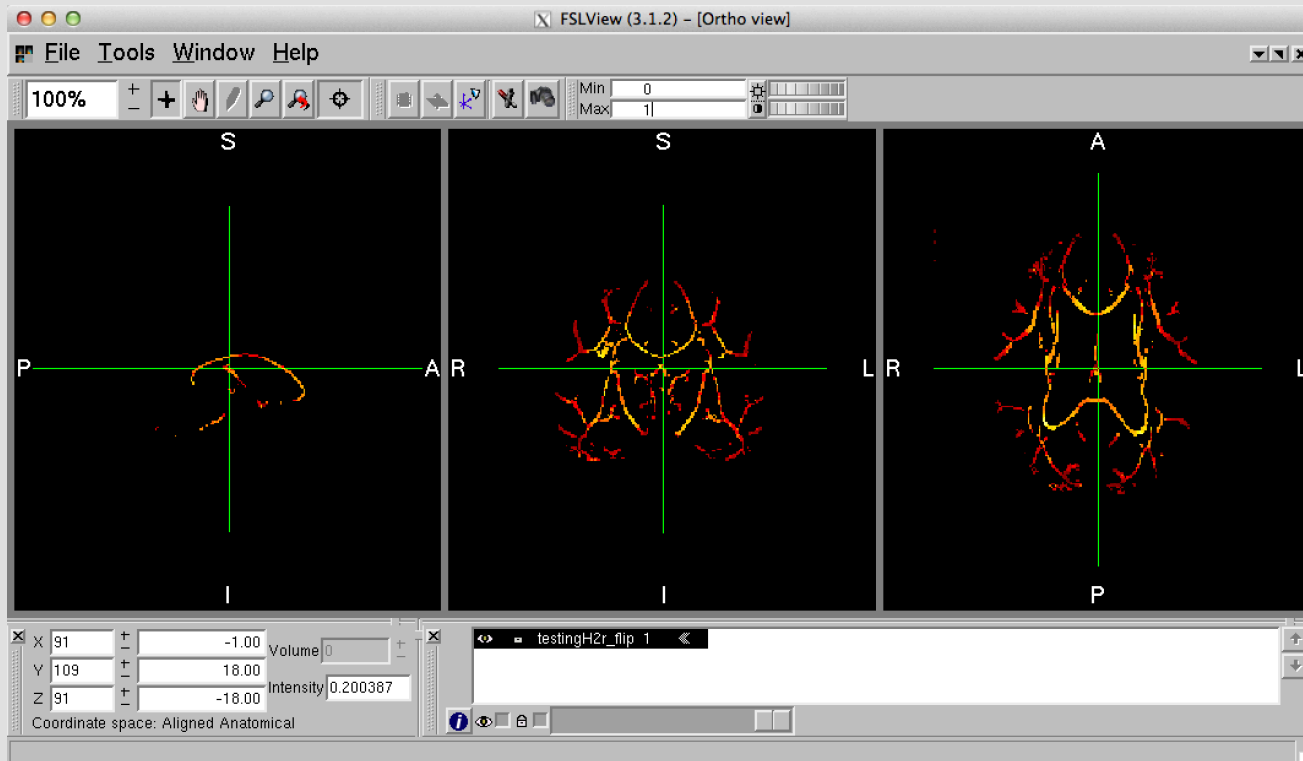
Trait	VOXEL_31_107_107_INORM H2r	0.3281639	SE 0.0945206	P	0.0007434	%CovVarianceExpl	0.0161728
Trait	VOXEL_31_110_103_INORM H2r	0.0498169	SE 0.1073933	P	0.3219608	%CovVarianceExpl	0.0111192
Trait	VOXEL_31_111_102_INORM H2r	0.1393968	SE 0.1067673	P	0.0988901	%CovVarianceExpl	0.0152693

SE_Trait	VOXEL_31_107_105_INORM H2r	0.0486776	SE 0.0614070	P	0.2052666	%CovVarianceExpl	0.0455025
tH2rClO	0	SE	0	H2Cl1	0	SE	0
CombinedP	1.295e-05						
SE_Trait	VOXEL_31_107_107_INORM H2r	0.3631914	SE 0.0709515	P	0.0000001	%CovVarianceExpl	0.0533894
tH2rClO	0.2127420575593708	SE	0.09272003333585752	H2Cl1	0.2916855190539751	SE	0.0900410693836886
CombinedP	0.374768800000000001						
SE_Trait	VOXEL_31_108_104_INORM H2r	0.0791948	SE 0.0645077	P	0.0961782	%CovVarianceExpl	0.0449088
tH2rClO	0.01267095447067678	SE	0.06714660375759364	H2Cl1	0	SE	0
CombinedP	0.00028725000000000002						

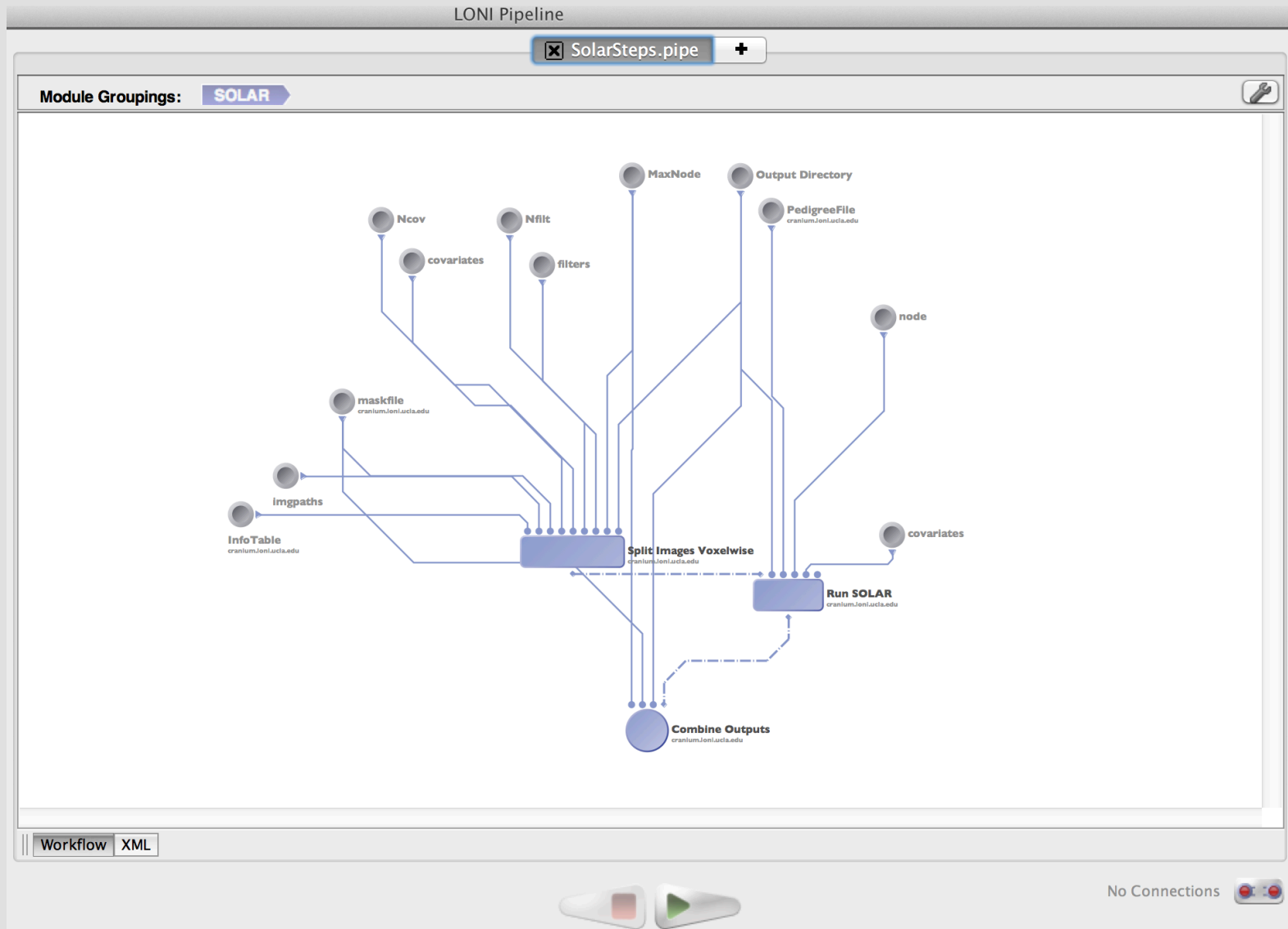
3) Combine Outputs

Takes already inputted data –
Mask, Folder, Nodes

And combines all voxels in all subfolders to
create as many nifti images as the output
files have outputs!



Pipeline for voxelwise SOLAR processing



5 cohorts:

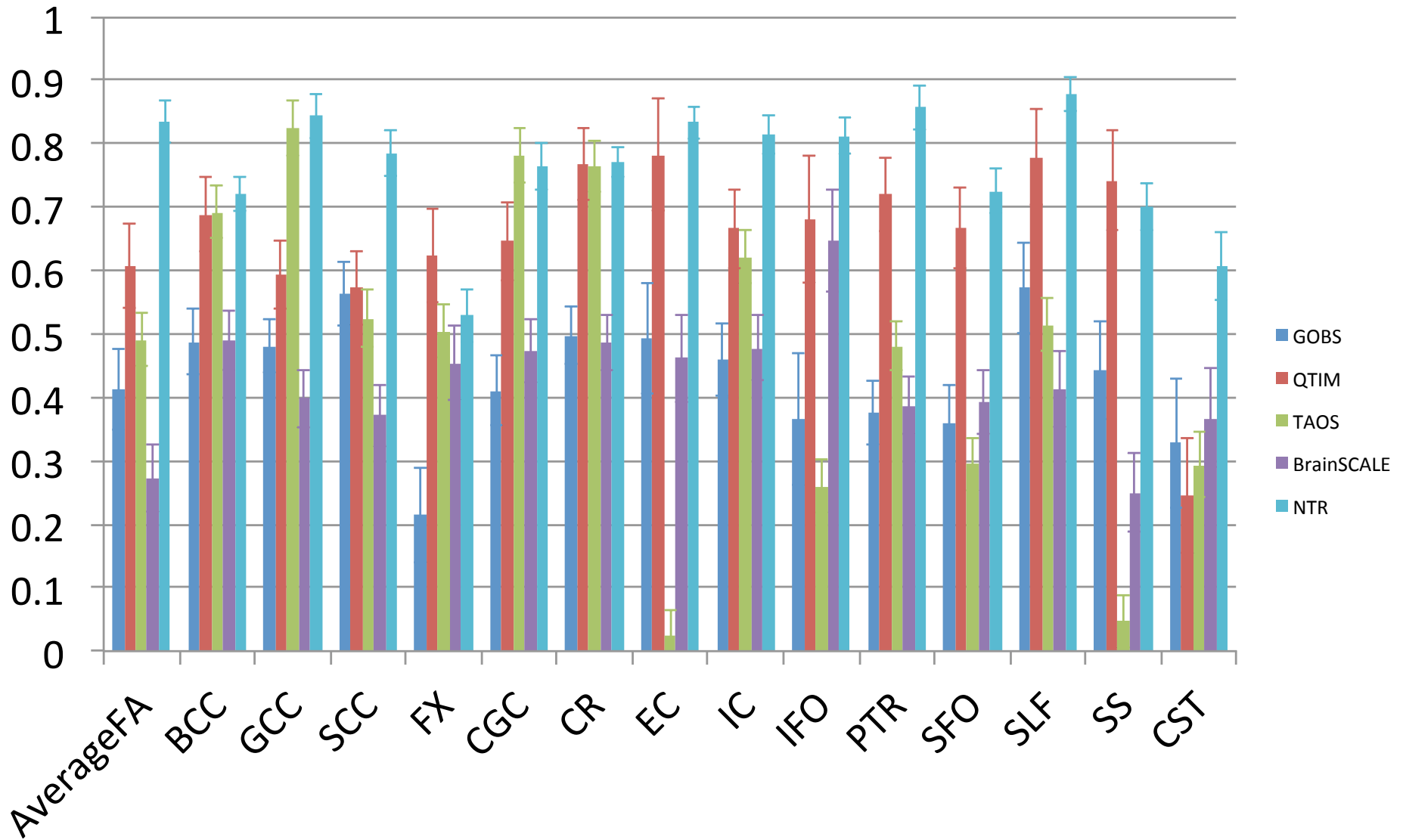
Family types – twins/siblings/pedigree

Age range – narrow (9-10) to wide (19-85)

A variety of acquisition parameters!?!

	<i>GOBS</i>	<i>QTIM</i>	<i>TAOS</i>	<i>BrainSCALE</i>	<i>NTR</i>
N Subjects	814	625	319	199	246
Sex	350M/464F	231M/394F	158M/161F	100M/99F	93M/153F
Age range (yrs.)	19-85	21-29	12-15	9-10	18-45
Scanner	Siemens	Bruker	Siemens	Achieva	Intera
N-acquisitions	1	1	1	2	1
Field Strength	3T	4T	3T	1.5T	3T
Voxel size (mm)	1.7x1.7x3.0	1.8x1.8x2.0	1.7x1.7x3.0	2.5x2.5x2.5	2.5x2.5x2.5
N-gradients	55	94	55	32	32
N-b_0	3	11	3	8	1
b-value (s/mm²)	700	1159	700	1000	1000

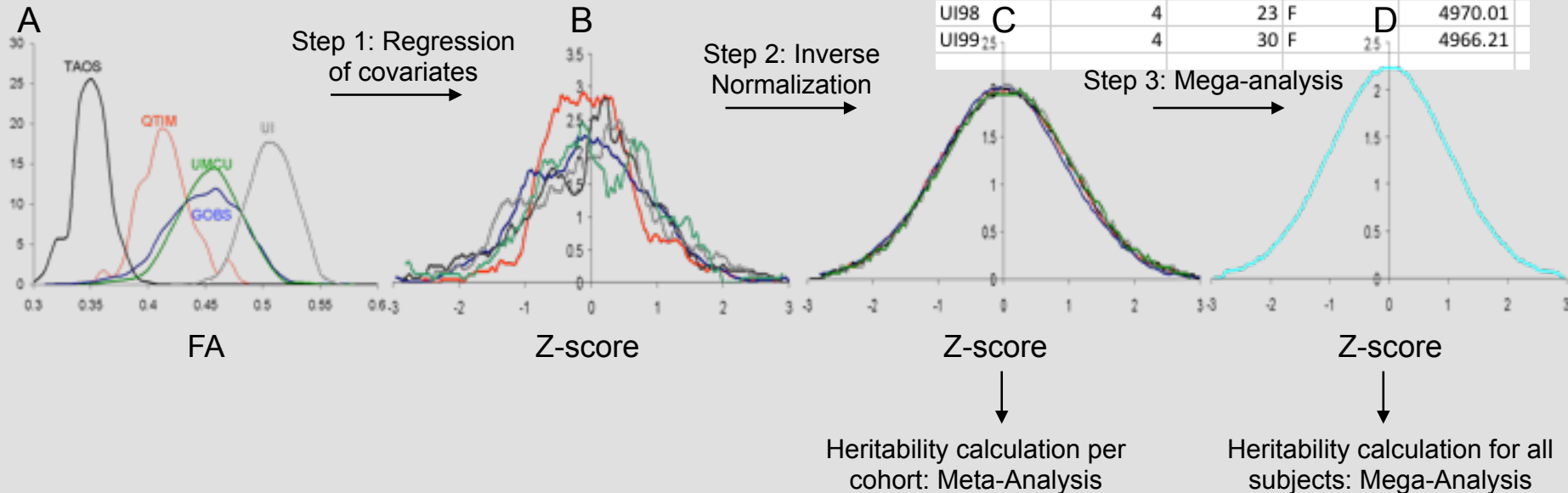
Individual Site Heritability



Mega- Analysis

ID	FA	MO	SEX	FAMID	MZTWIN	HHID	genoID	PEDIGREE NUMBER	CLASS
801101	801106	801102	F				801101	1	0
A44012			F					101	0
A44101			M					202	0
Q44160			F					204	0
8003201	8003204	8003203	2	80032	80032		1		1
8003202	8003204	8003203	2	80032	80032		1		1
8003301	8003304	8003303	1	80033				2	1
8003302	8003304	8003303	2	80033			2		1
8948803			2	89488					1
8948804			1	89488					1
200101	200103	200102	F	2001					2
281702			F	2817					2
281802			F	2818					2
UMCU15	UMCFA1	UMCMO1	F	UMCUFA	UMCUFAID1				3
UMCU141	UMCFA1	UMCMO1	F	UMCUFA	UMCUFAID1				3
UMCFA87			M		UMCUFAID87				3
UMCFA92			M		UMCUFAID92				3
UI205	UIFAID1	UIMOID1	M	UIFMID1					4
UI201	UIFAID1	UIMOID1	F	UIFMID1					4
UI13	UIFAID12	UIMOID12	F	UIFMID1	UIFMID123				4
UI112	UIFAID12	UIMOID12	F	UIFMID1	UIFMID123				4
UIMOID123			F	UIFMID123					4

id	Class	Age	Sex	AverageFA
A32067	0	52	1	3419.52
A01650	0	48	1	4009.48
A01574	0	31	2	4483.02
A32069	0	28	2	4426.44
A32001	0	70	1	4229.04
A32064	0	52	2	4169.51
A20026	0	30	1	4440.72
8057201	1	23.2	2	0.38969
8057202	1	23.2	2	0.435831
8069102	1	25.98	2	0.382811
8898651	1	21.13	2	0.39339
8901050	1	24.38	1	0.385784
8909250	1	21.68	2	0.305713
8916351	1	23.82	2	0.387703
202201	2	14.6	F	3537.34
201201	2	14.5	F	3305.49
255601	2	14.4	F	3504.28
281001	2	14	M	3489.01
281801	2	14.8	F	3659.46
281701	2	13.7	F	3475.13
UMCU1	3	9.32	F	4614.65
UMCU202	3	9.15	M	4583.06
UMCU203	3	9.18	F	4314.87
UI101	4	38	F	4899.95
UI97	4	40	F	4977.08
UI98	4	23	F	4970.01
UI99	4	30	F	4966.21



Meta-Analysis – heritability estimate

- Calculate a weighted mean, meta-analyzed heritability and standard errors based on individual cohort results.
 - 2 methods for weighting h^2 and its variance in MA
 - Sample size and Standard Error:

$$h_{\text{MA-N}}^2(v) = \frac{\sum_j n_j h_j^2(v)}{\sum_j n_j}$$

$$\text{Var}(h_{\text{MA-N}}^2(v)) = \frac{\sum_j n_j^2 \text{se}_j^2(v)}{(\sum_j n_j)^2}$$

$$h_{\text{MA-SE}}^2(v) = \frac{\sum_j \text{se}_j^{-2} h_j^2(v)}{\sum_j \text{se}_j^{-2}}$$

$$\text{Var}(h_{\text{MA-SE}}^2(v)) = \frac{1}{\sum_j \text{se}_j^{-2}(v)}$$

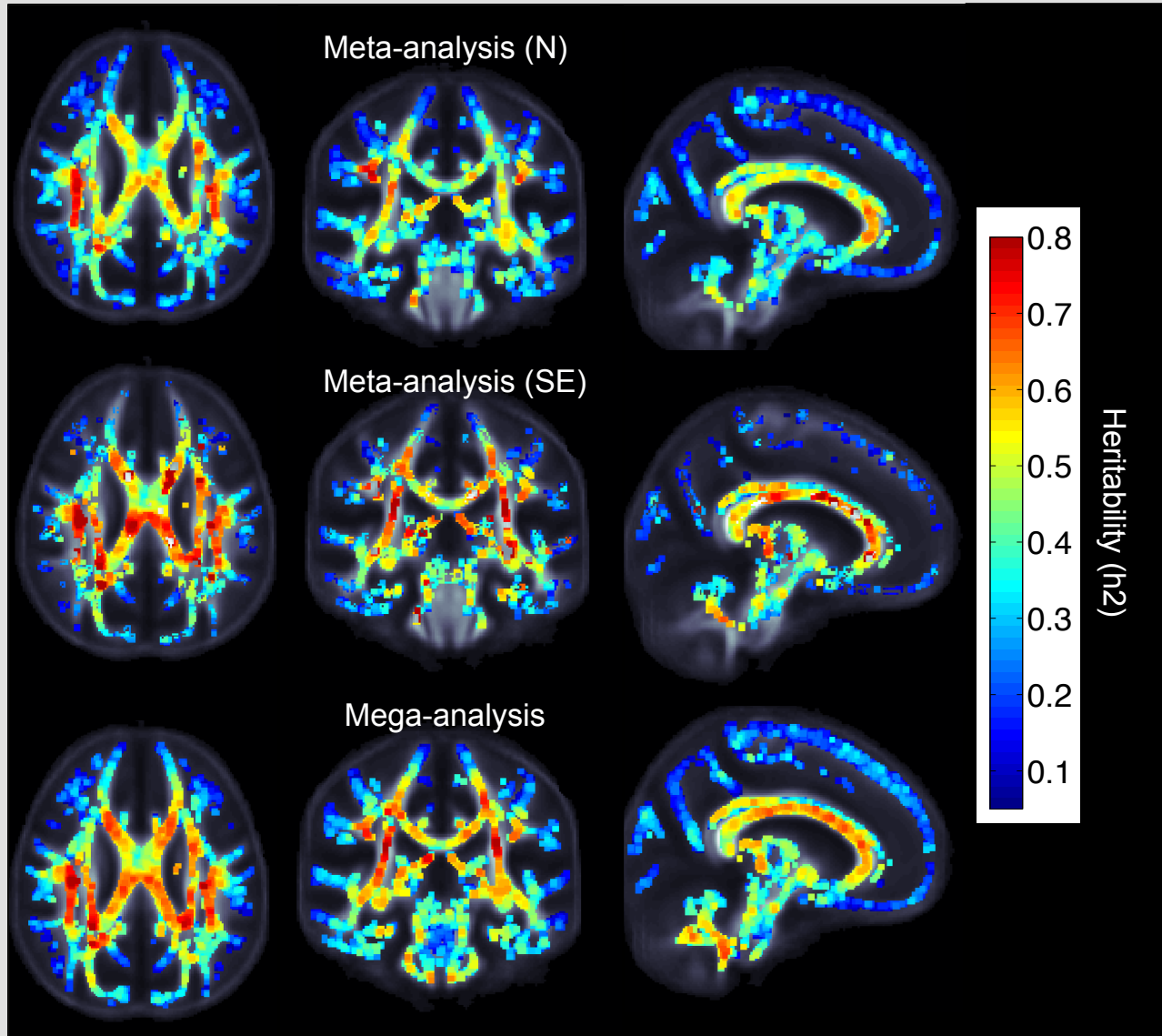
MA– p -value estimate

- No standard for variance component based meta-analysis!
- Let's test 2 approaches:
 - Base on individual cohort p -values:

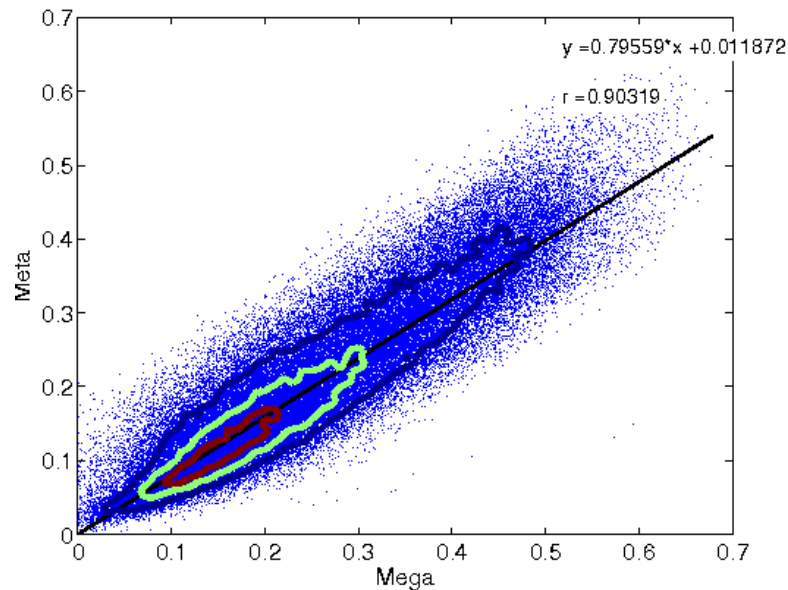
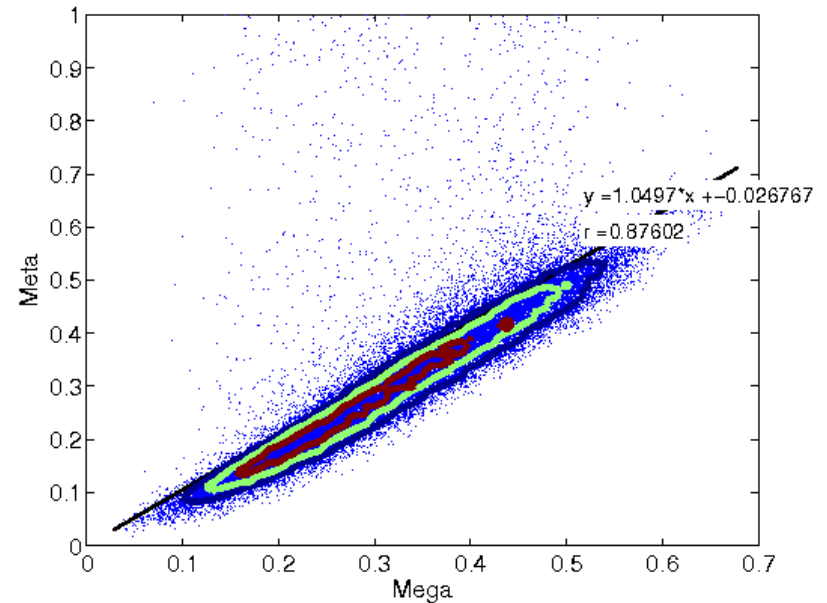
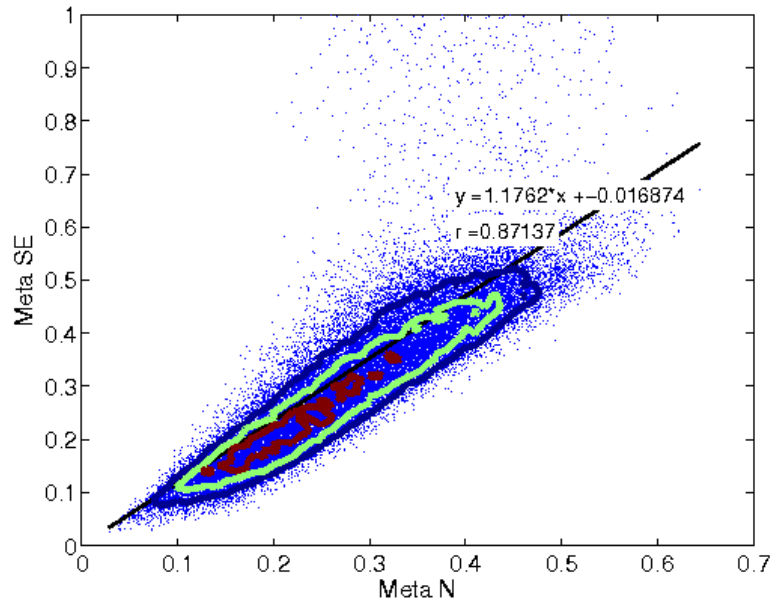
$$Z_{\text{MA-N}}(v) = \frac{\sum_j z_j(v) \sqrt{n_j}}{\sqrt{\sum_j n_j}} \quad Z_{\text{MA-SE}}(v) = \frac{\hat{\beta}(v)}{\text{SE}(\hat{\beta}(v))} = \frac{\sum_j \hat{\beta}_j(v) \times \text{se}_j^{-2}(v) / \sum_j \text{se}_j^{-2}(v)}{\sqrt{1 / \sum_j \text{se}_j^{-2}(v)}}$$

- where $z_j(v) = \Phi^{-1}(\bar{p}_j(v))$ $\hat{\beta}_j(v) = z_j(v) \times \text{se}_j(v)$
- Based on meta h^2 and meta SE
 - Compute Z-scores (ratio of meta h^2 to meta SE) and convert to p -values

Voxelwise Results



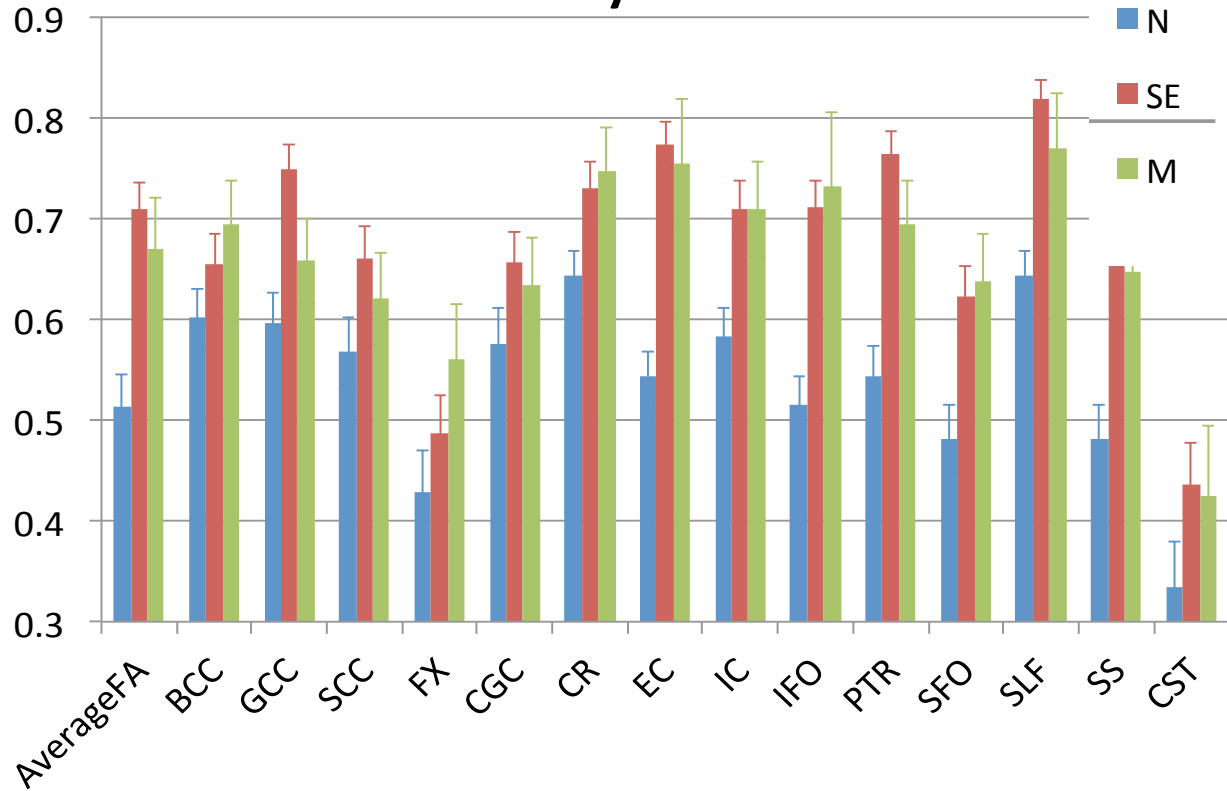
Joint Study Voxelwise Results



	% significantly heritable*	Bonferroni critical p-value*	minimum p-value
Meta-N	10.15, 35.75	4.3×10^{-7}	$p < 10^{-10}$
Meta-SE	34.87, 49.86	4.3×10^{-7}	$p < 10^{-10}$
Mega	53.1	4.3×10^{-7}	$p < 10^{-10}$
*total voxels in mask = 116524			

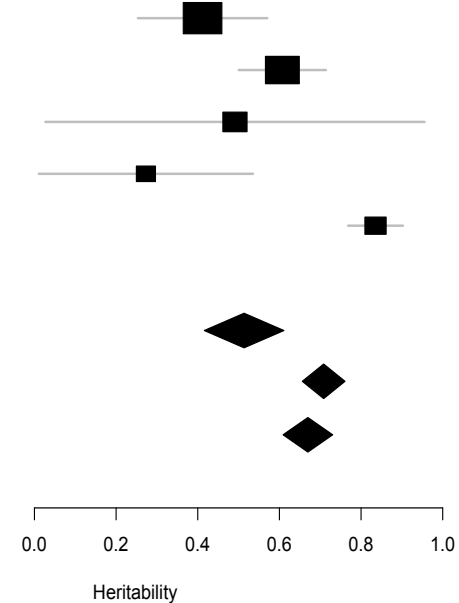
Joint Study ROI Results

Joint Analytic Methods



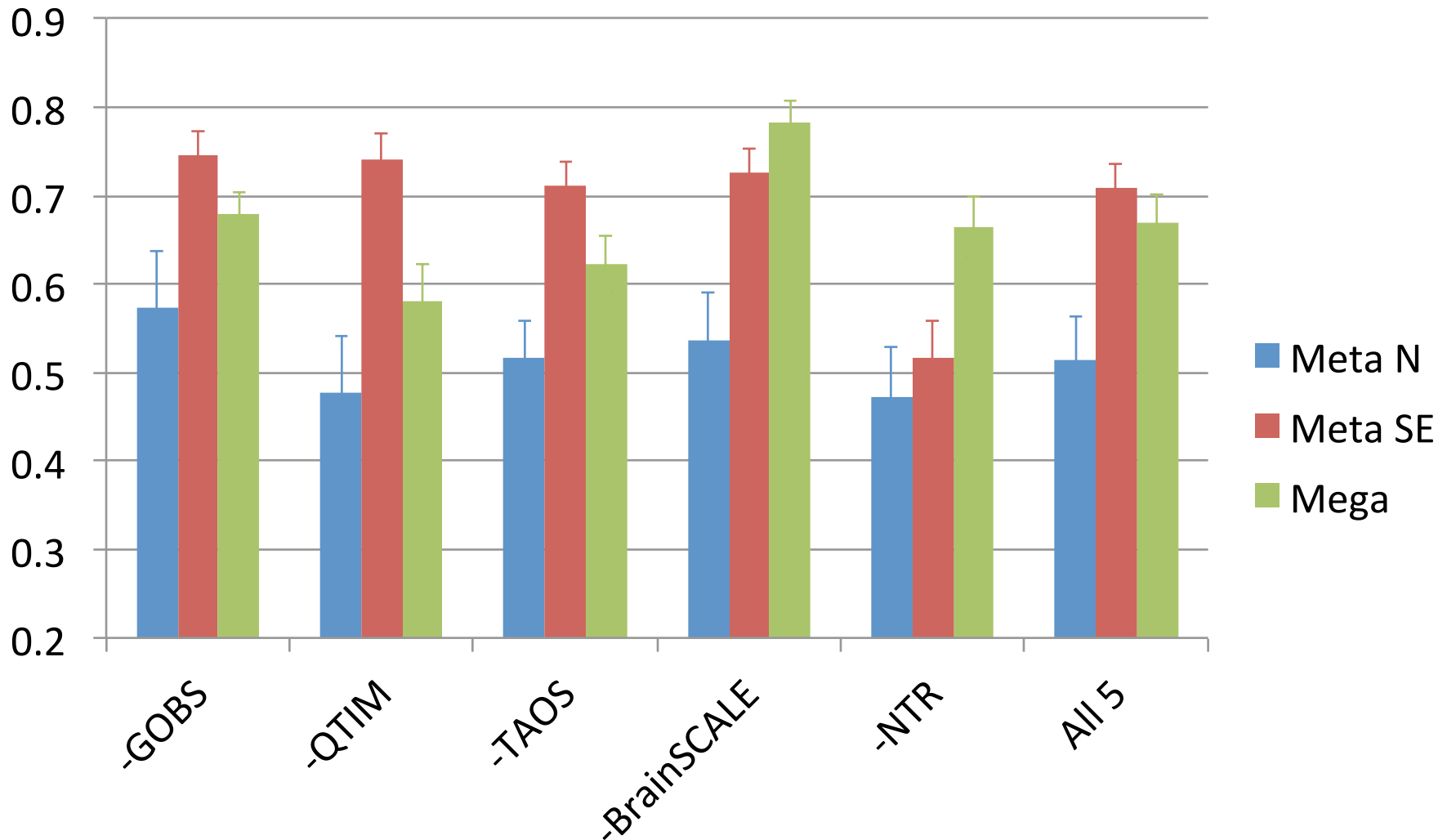
GOBS
QTIM
TAOS
BrainSCALE
NTR

MA-N
MA-SE
Mega



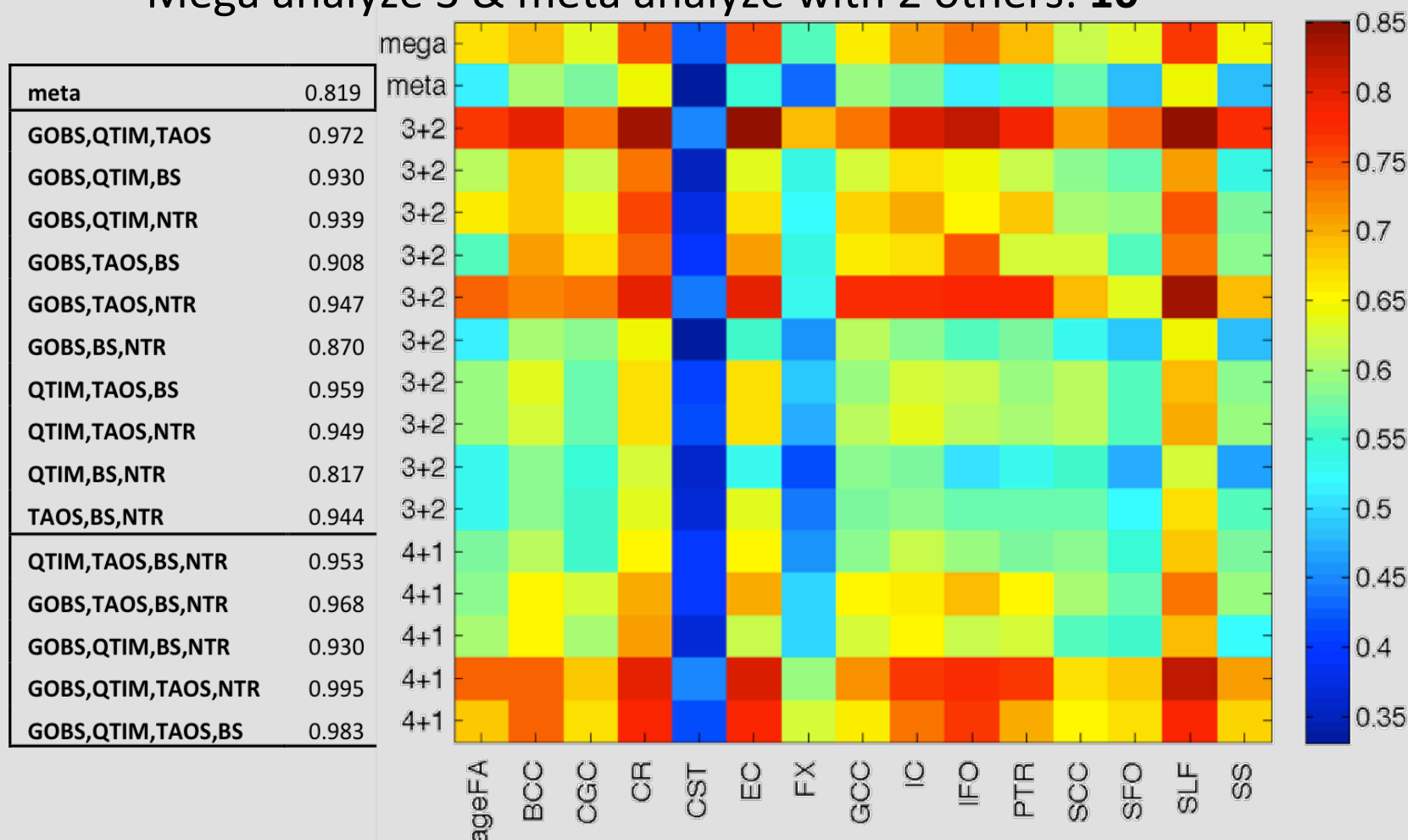
Robustness – removing one site

Average FA



Partial mega and meta!

- How many combinations??
 - Mega analyze 4 & meta analyze with remainder: **5**
 - Mega analyze 3 & meta analyze with 2 others: **10**



Partial mega and meta!

	5-Mega	5-Meta	3Mega+2Meta	4Mega+1Meta
AverageFA	7.65E-49	5.38E-25	6.62E-31	1.42E-43
BCC	1.40E-55	3.61E-42	1.72E-45	9.31E-67
CGC	9.71E-41	2.06E-35	2.51E-35	4.94E-47
CR	3.39E-58	1.25E-52	5.51E-56	5.55E-84
CST	6.44E-19	2.54E-06	1.08E-07	7.52E-09
EC	1.91E-59	1.29E-17	1.56E-18	4.35E-27
FX	1.21E-31	4.71E-15	9.21E-17	1.41E-21
GCC	1.28E-46	8.30E-45	4.10E-51	3.58E-60
IC	3.53E-51	5.64E-35	4.01E-39	2.57E-57
IFO	1.68E-51	1.80E-12	2.07E-13	7.83E-20
PTR	2.90E-54	1.15E-36	1.99E-39	2.45E-59
SCC	4.24E-41	6.70E-36	2.21E-39	1.34E-49
SFO	8.78E-44	1.14E-23	2.27E-26	1.00E-36
SLF	8.09E-62	2.06E-31	1.31E-32	1.93E-47
SS	1.85E-43	5.86E-17	5.84E-18	7.50E-23

Meta, Mega and their combinations

- All results are significant and fairly stable
 - Even partial mega analysis leads to lower p-values than meta
 - In general partial mega also provides higher estimates of heritability
- ... what does it mean to combine heritability results from different populations??
- ... is mega analysis appropriate??
- **DTI-FA estimates are heritable and reliable!!!**

What about with Fixed-Effects?

- Many candidate SNPs have been associated with DTI white matter differences
- ENIGMA approach = meta analysis
- Are we missing something?
- Mega analysis more powerful?
- Data sharing requirements + IRBs + HIPAA + MTAs... are they worth it?
- Lets find out!

10 sites == 5,000+ scans

- Candidate disease SNPs previously published to have associations with DTI measures in groups of ~100s
- 3,000 CEU – largest single ethnicity group
 - CEU analysis + full group analysis
- Family based cohorts – requires mixed model associations with kinship matrices

All Groups

- **DNC (Duke U)
 - N=700
- *GOBS (Yale U/UMD)
 - N=808
- IMAGEN (multi-site EU)
 - N=1360
- LBC (U Edinburgh)
 - N=592
- NeurolIMAGE (Nijmegen)
 - N=423
- ***NIDA (NIH/UMD)
 - N=337
- QTIM (QIMR/USC)
 - N=525
- **TAOS (UMD)
 - N=306

* Not included in CEU only analysis

** Filtered based on distance of PC1 and PC2 from CEU population (from HM3mds2R.csv file from imputation)

***Only about 10 CEU in NIDA, so removed full cohort for CEU only analysis

ENIGMA – DTI

15 Candidate SNPs– N=5,000+ with DTI

2 imaging based searches

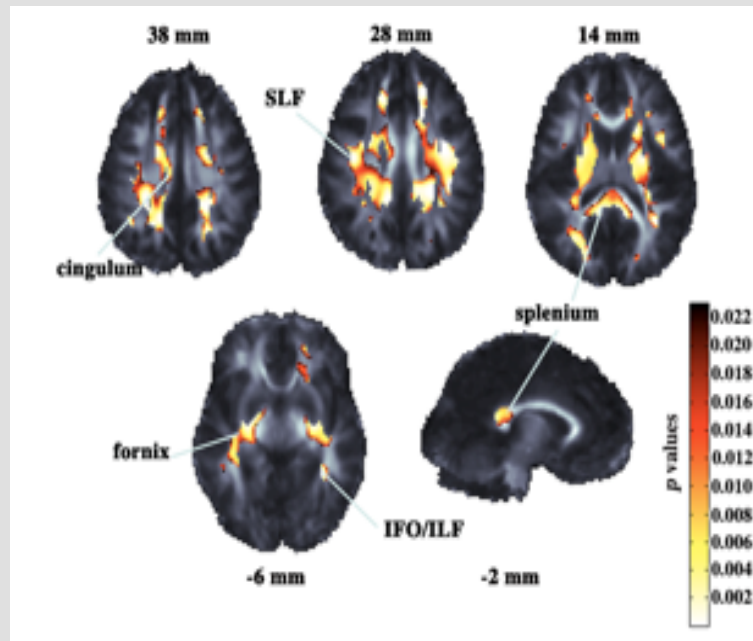
3 AD

- *APOE4*
- *CLU*
- *HFE*

~~11~~ 10 Scz/MDD/
psychosis

- *DTNBP1*

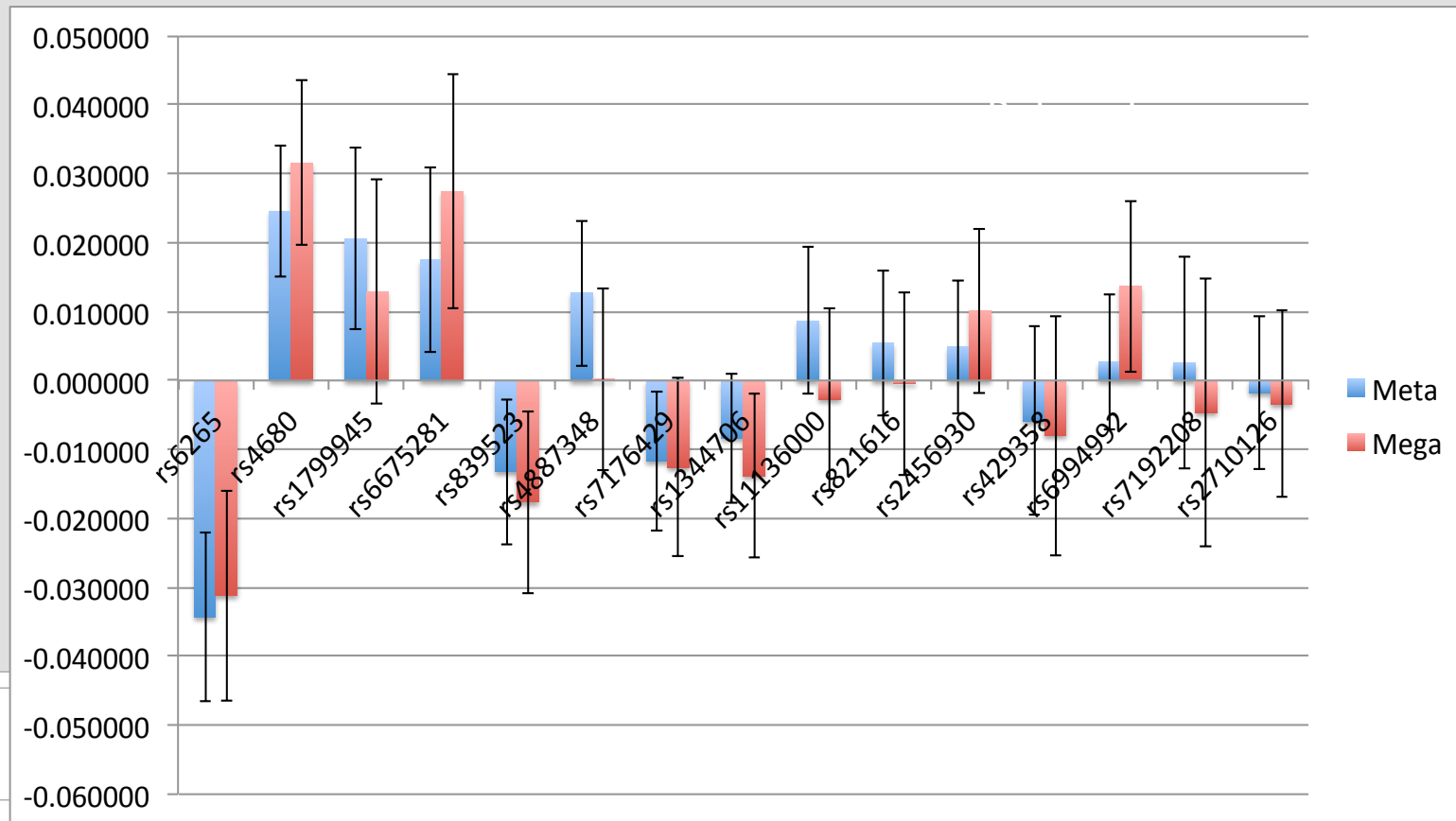
- *ZNF804A*
- *CNTNAP2*
- *COMT*
- *NTRK-3*
- *BDNF*
- *DISC1*
- *ErbB4*



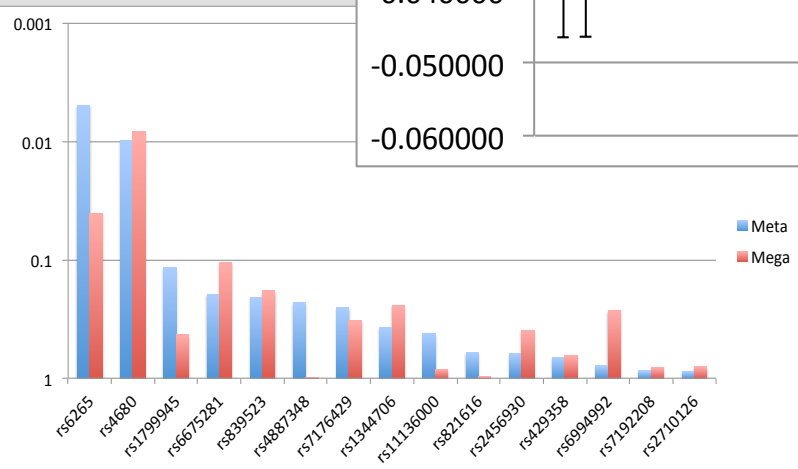
Site Genetic Frequency Breakdown

CEU	QTIM			TAOS			DUKE			IMAGEN			NeuroIMAG E			LBC		
	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
rs1018381	1	73	451	0	24	122	2	49	247	7	212	1141	0	0	0	6	85	471
rs11136000	76	294	155	27	67	52	44	149	105	172	743	481	57	205	161	120	266	206
rs1344706	101	235	189	26	75	45	44	146	108	230	666	500	84	193	146	95	270	227
rs1799945	20	145	360	6	31	109	11	74	213	31	348	1017	9	104	310	10	142	381
rs2456930	101	258	166	19	65	62	50	133	114	208	653	535	57	209	157	89	296	207
rs2710126	122	239	164	32	71	43	73	135	89	288	724	384	17	371	35	31	413	147
rs429358	11	122	392	1	39	106	7	66	190	26	346	1024	15	122	286	15	162	415
rs4680	119	272	134	31	62	53	93	132	73	323	712	361	86	210	127	134	246	119
rs4887348	47	199	279	13	55	78	31	112	155	101	530	765	20	167	236	37	220	335
rs6265	31	158	336	3	40	103	12	89	197	49	443	904	15	140	268	10	167	324
rs6675281	12	130	383	2	38	106	4	59	235	27	334	1035	14	120	289	9	151	432
rs6994992	57	287	181	28	68	50	46	153	99	225	624	547	76	192	155	74	301	217
rs7176429	37	237	251	14	67	65	41	123	134	128	619	649	34	157	232	49	242	301
rs7192208	1	93	431	4	30	112	2	60	236	10	258	1128	9	87	327	5	122	465
rs821616	39	227	259	9	69	68	31	103	164	107	586	703	28	187	208	50	231	311
rs839523	42	226	257	12	61	73	33	97	168	87	525	784	21	160	242	62	224	306

CEU only - Candidate SNPs Results



Meta
Mega



Mega Standard Error >> Meta

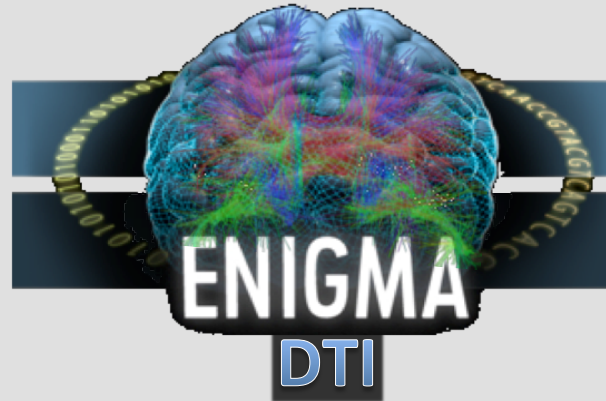
ENIGMA-DTI SfN 2014

By Site Breakdown

<u>AverageFA</u>	<u>CEU</u>		<u>AverageFA</u>	<u>ALL</u>	
<u>BDNF</u>	<u>p</u>	<u>B</u>	<u>BDNF</u>	<u>p</u>	<u>B</u>
QTIM	0.11	-0.089	GOBS	0.93	0.005
TAOS	0.29	0.144	QTIM	0.11	-0.089
DUKE	0.75	0.011	TAOS	0.73	0.03
IMAGEN	0.02	-0.039	NIDA	0.93	-0.004
NeuroIMAGE	0.09	-0.05	DUKE	0.91	0.002
LBC	0.29	0.03	IMAGEN	0.02	-0.039
			NeuroIMAGE	0.09	-0.05
			LBC	0.29	0.03

Now we are ready for GWAS-MA!

- But need more groups for a large joint analysis across multiple sites
 - 10,000+ images from groups with interest
- Mega analysis will require sharing data, may be more powerful, but may be confounded by site heterogeneity
- Meta analysis will be performed in most cases if ***data is not shared*** and can lead to important findings



1. Preprocessing
 - Initial quality control (motion/artifacts)
 - Creating FA maps
2. Registration to template and skeletonization
 - Intermediate QC
 - Projection distance
3. ROI extraction
4. Final quality control
 - Visual inspection of images
 - Histograms and outlier detection
5. GWAS / Other analysis

Summary

I. Joint analysis to improve power of genetic discovery

II. Creating a pedigree matrix for mega analysis

III. Comparing mega and meta-analysis approaches

```
[njahansh@hpc200-01 SOLAR_POLY]$ ./solar
```

```
SOLAR version 7.2.0 (Experimental), last updated on October 11, 2013  
Copyright (c) 1995-2013 Texas Biomedical Research Institute  
Enter help for help, exit to exit, doc to browse documentation.
```

```
solar> █
```

Future Extensions and Applications

- Vertex-wise analysis of shape morphometry

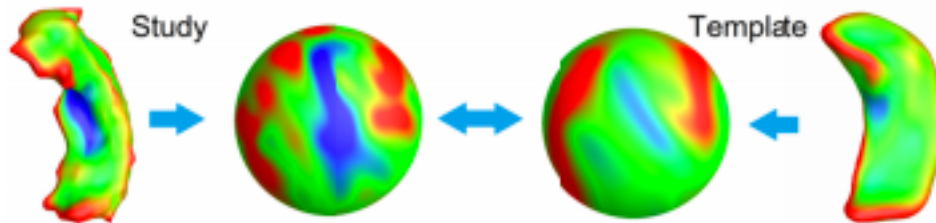


Figure 1. Mapping a subcortical structure to a template by matching spherical curvature maps.

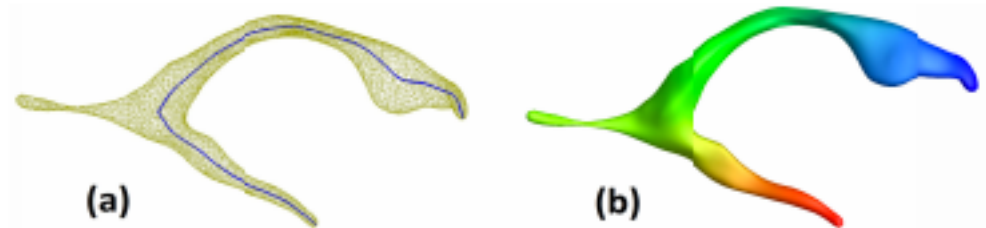


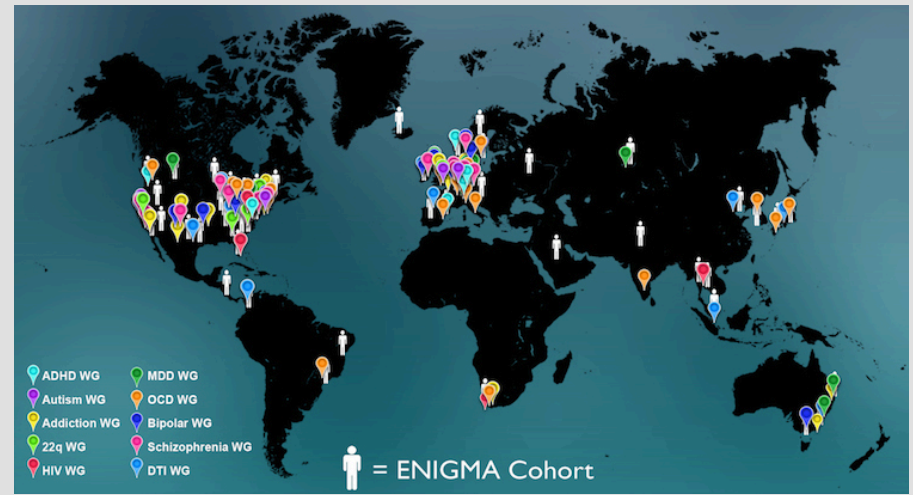
Figure 2. (a) Medial curve of a left lateral ventricular surface; (b) The resulting global orientation function.

Future Extensions and Applications

- Vertex-wise analysis of shape morphometry
 - QTIM: 1040 subjects
 - HCP: 440 subjects
 - 7 subcortical regions
- SOLAR – Eclipse pipeline
 - Modified for vertices

Thank you!

- **Peter Kochunov**
- **Thomas E Nichols**
- **John Blangero**
- **Bennett A Landman**
- **Paul M Thompson**
- **David C Glahn**



+10,000 subjects about to participate in
ENIGMA-DTI's GWAS