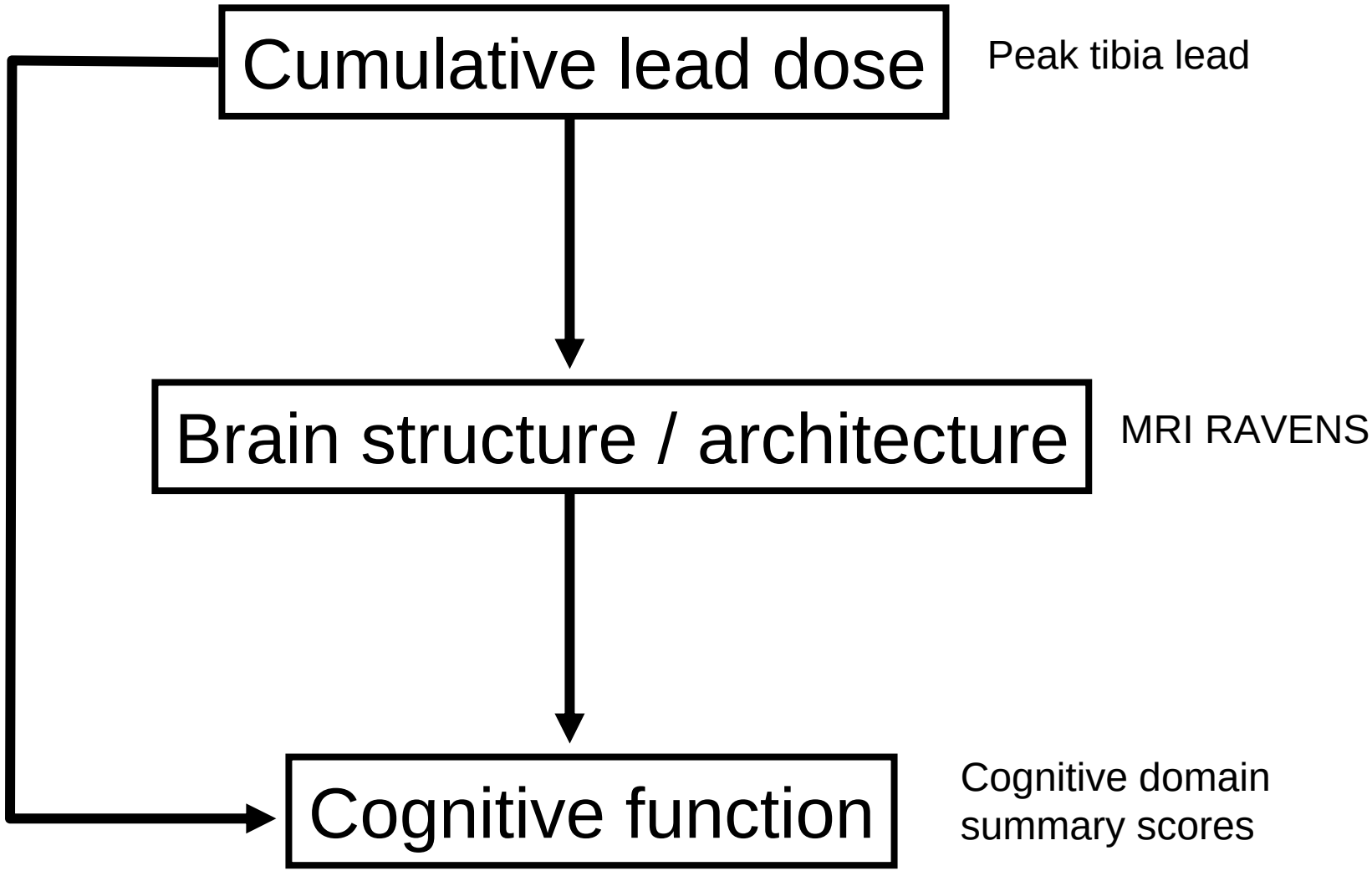
IS MRI Based Structure a Mediator for Lead's Effect on Cognitive Function?

Brian Caffo, Sining Chen, Brian Schwartz

Department of Biostatistics and Environmental Health Sciences
Johns Hopkins University


Cumulative lead dose
Peak tibia lead
Brain structure / architecture
MRI RAVENS
Cognitive function
Cognitive domain
summary scores

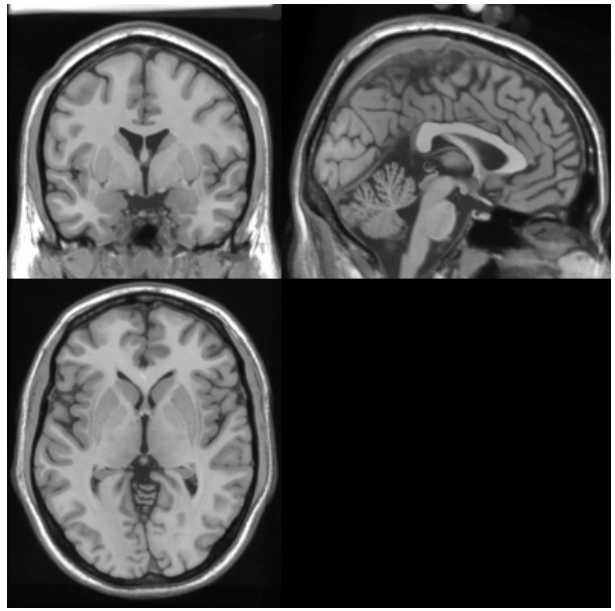
- Around 500 male organo-lead workers
- Peak tibia lead measured by extrapolating from recent lead levels using a compartmental model
- Cognitive function measured by a battery of psychological tests collapsed into six domain scores

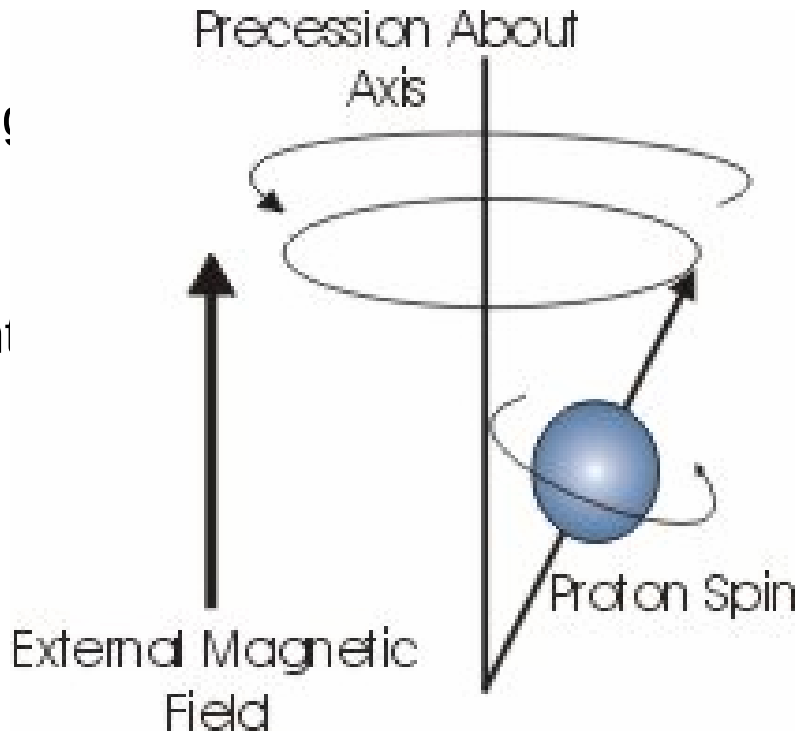
1. VM - Visual memory
2. VC - Visuo construction
3. VML - Verbal memory and learning
4. EF - Executive function
5. EHC - Eye-hand coordination
6. PSP - Processing speed

Variable	**Summary**			
Age (years)	Mean(sd, range) 60.390 (7.93, 34.70, 78.30)			
Year enrolled (n)	1994	1995	1996-97	2001-03
	107	199	35	171
Domain scores	Mean (sd, range)			
VC	-0.36 (1.03, -4.51, 1.73)			
VML	0.26 (0.80, -2.40, 1.87)			
VM	0.15 (0.92, -2.40, 2.19)			
EF	-0.16 (0.76, -3.76, 1.64)			
EHC	-0.10 (0.88, -4.93, 1.61)			
PSP	-0.16 (0.77, -4.40, 2.07)			
Brain volume(cm^3)	Mean (sd, range)			
Total	1150.32 (105.10, 733.56, 1487.99)			
Grey	588.39 (60.05, 314.35, 762.85)			
White	561.92 (59.03, 389.48, 748.22)			

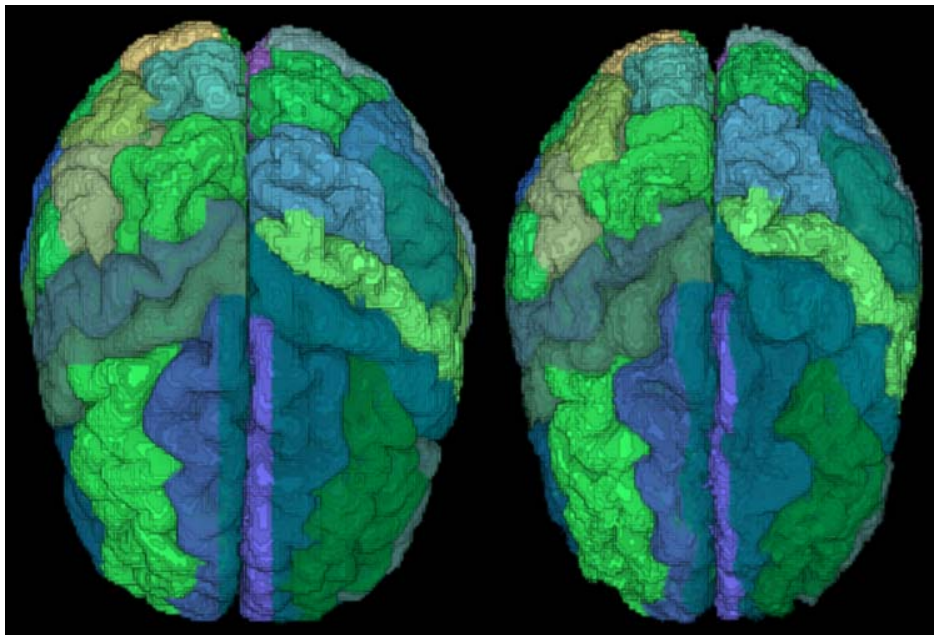
MRI

- Nuclear magnetic resonance
  - Uniform magnetic field
  - Protons align in the direction of the magnetic field
  - RF pulse knocks some protons out of alignment
  - Protons snap back into place emitting RF pulse
  - Emitted RF differs by tissue type
  - Weighting shows contrast of different types

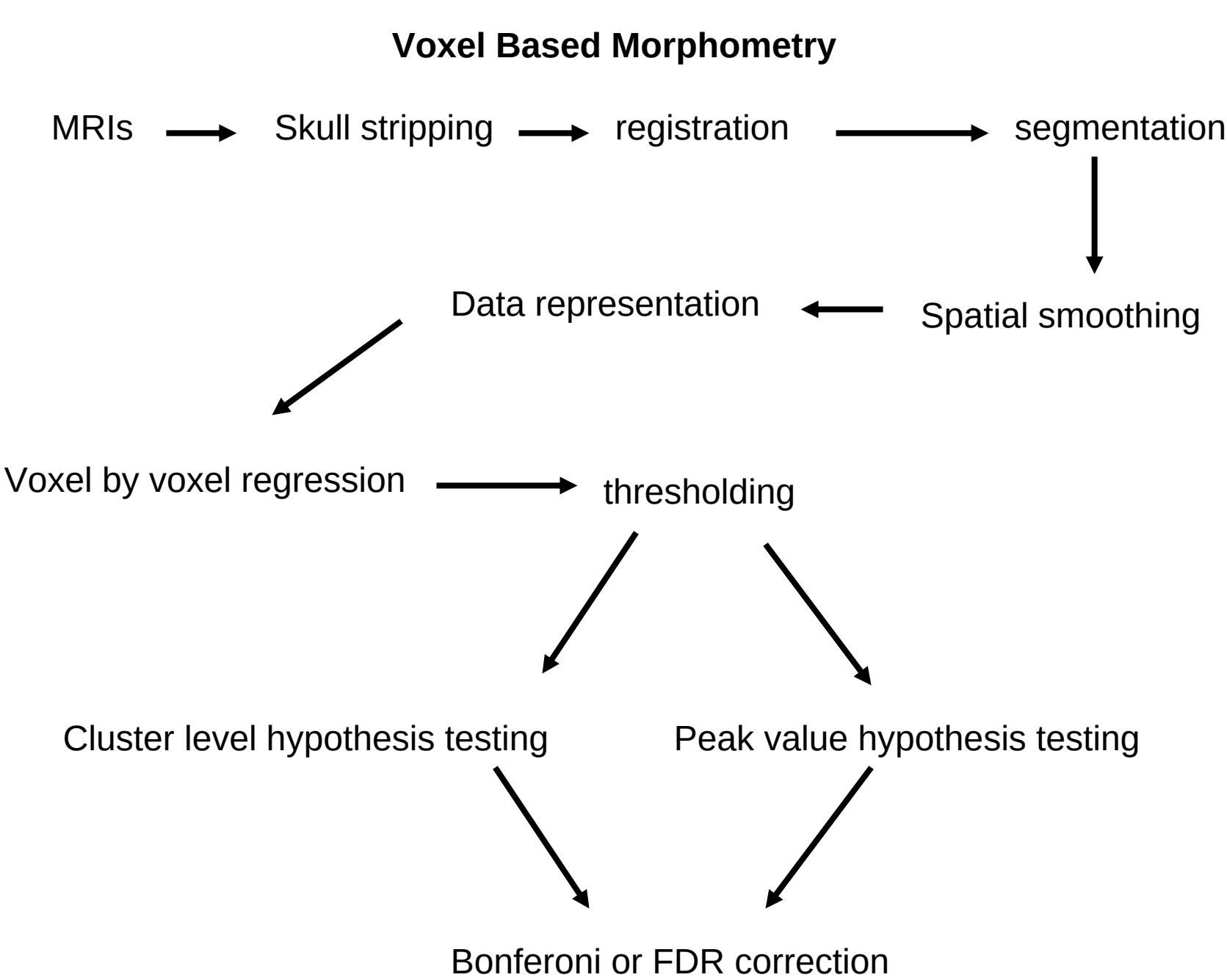




Regions of interest analysis



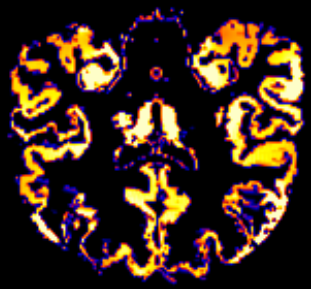
- Processed brains are registered with a labeled template
- Subject-specific volume summaries are calculated for anatomical regions of interest
- ROI summaries analyzed using standard methods

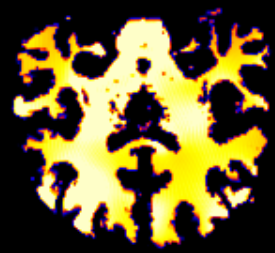

Voxel Based Morphometry
MRIs
Skull stripping
registration
segmentation
Spatial smoothing
Data representation
Voxel by voxel regression
thresholding
Cluster level hypothesis testing
Peak value hypothesis testing
Bonferoni or FDR correction

RAVENS maps

- Images are skull stripped, segmented and registered to a common template
- Intensity in a voxel the image represents volume (in mm^3) of the original images
- Original intensity lost
- Using VBM we investigate cross-sectional volume changes

Ravens maps





Grey

White

Image representation

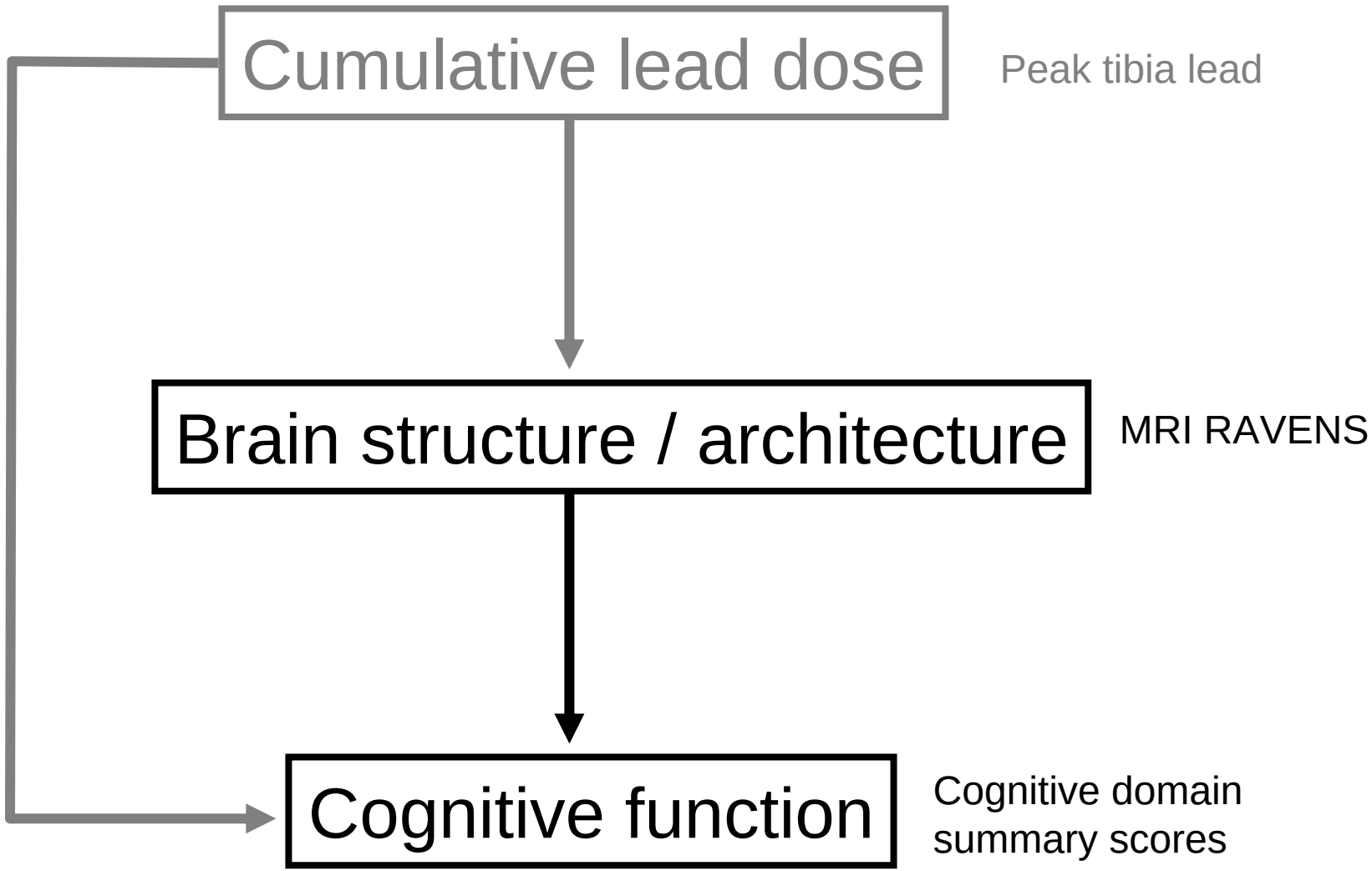
- Images are stored in Analyze format
  - Binary image “.img” file
  - Header “.hdr” file
  - Header file contains (among other things)
    - Voxel dimensions
    - Array dimensions
    - Image center
  - Same header file for all images
  - Images need to be rotated by 90 degree pitch to be in standard format

More on the images

- Images are registered to a template, but the template is rotated from the standard SPM template
- Imperfect registration implies some benefit from smoothing
  - Images were smoothed using a 10mm FWHM Gaussian kernel smoother in SPM
- Multiplying the value in a voxel by .94x.94x1.5 / 1000 converts it to mm^3

Conversion to rda files

- The (around) 600 smoothed images are represented 256x256x256 arrays
- These images were processed into 256 separate rda files each containing a 256x256x600 array and the associated subject indices
- This representation allows for easy parallel processing of the VBM analysis


Cumulative lead dose
Peak tibia lead
Brain structure / architecture
MRI RAVENS
Cognitive function
Cognitive domain
summary scores

Voxel-level model

NBT = Voxel + Age + VI + Height + Ed + Db + Smk + Alc

- Proportional versus absolute?
- TBV?
- Outliers with abnormalities?

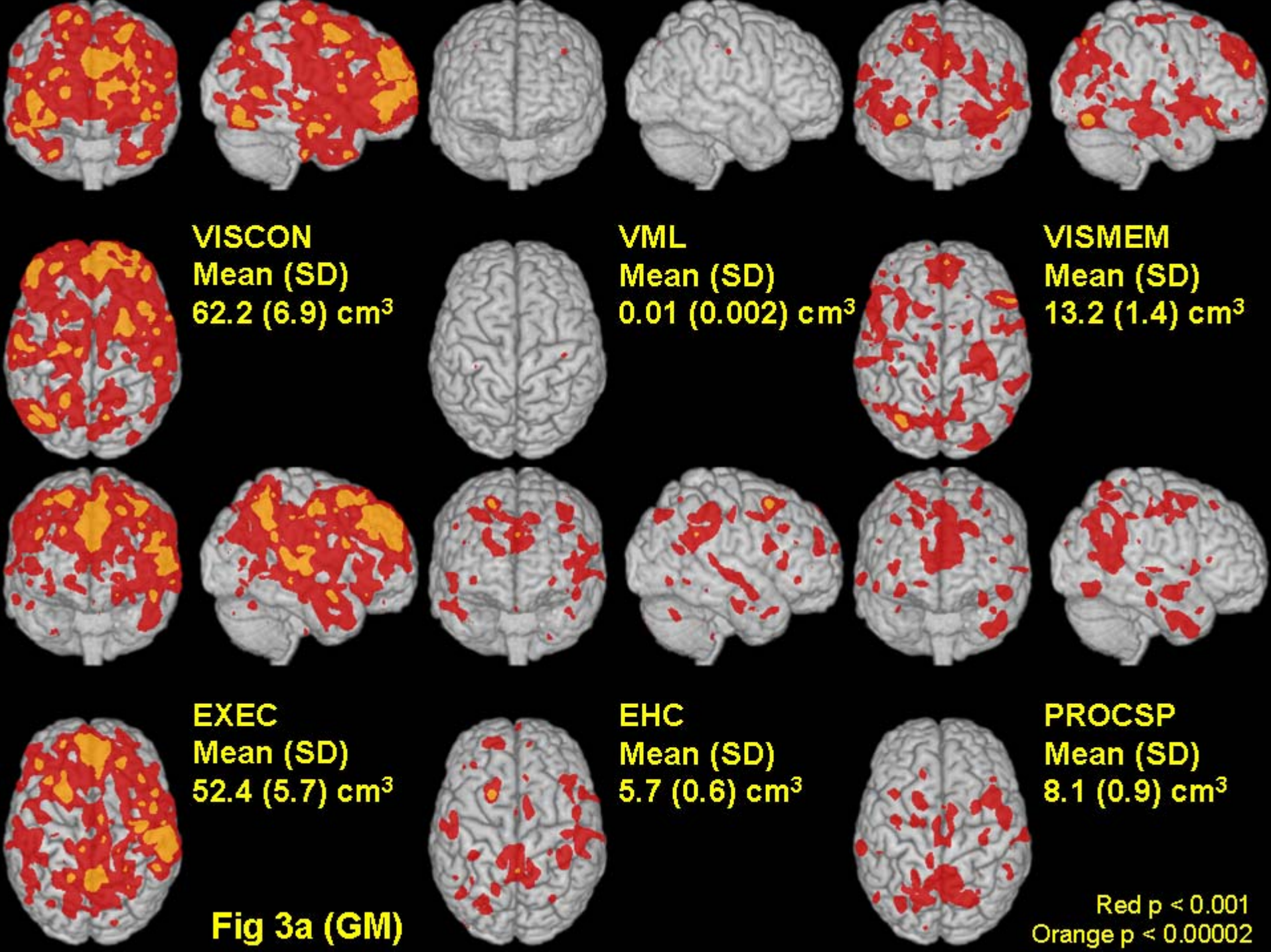

VISCON
Mean (SD)
62.2 (6.9) cm3
VML
Mean (SD)
0.01 (0.002) cm3
VISMEM
Mean (SD)
13.2 (1.4) cm3
EXEC
Mean (SD)
52.4 (5.7) cm3
EHC
Mean (SD)
5.7 (0.6) cm3
PROCSP
Mean (SD)
8.1 (0.9) cm3
Red p < 0.001
Orange p < 0.00002

Fig 3a (GM)

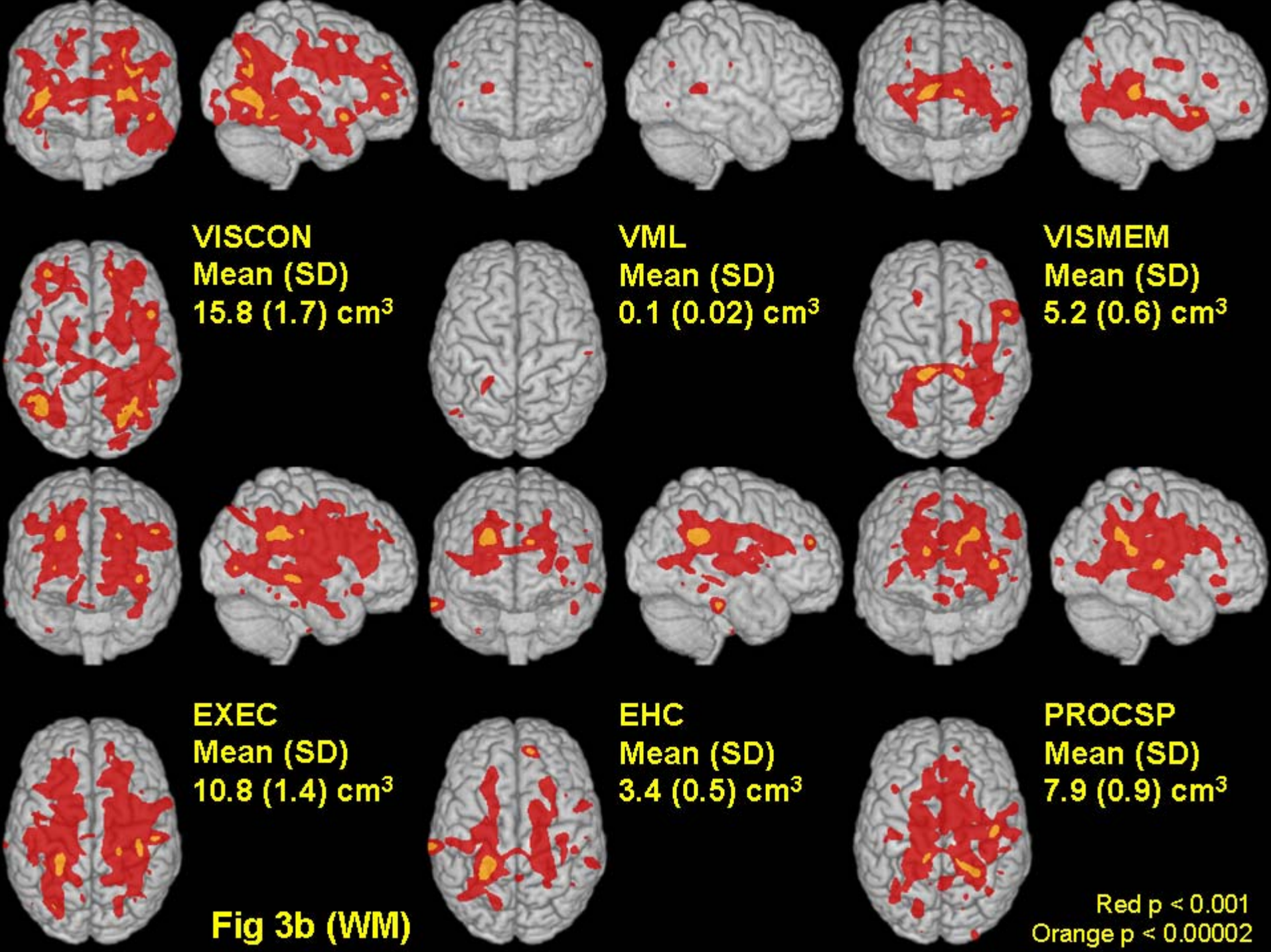
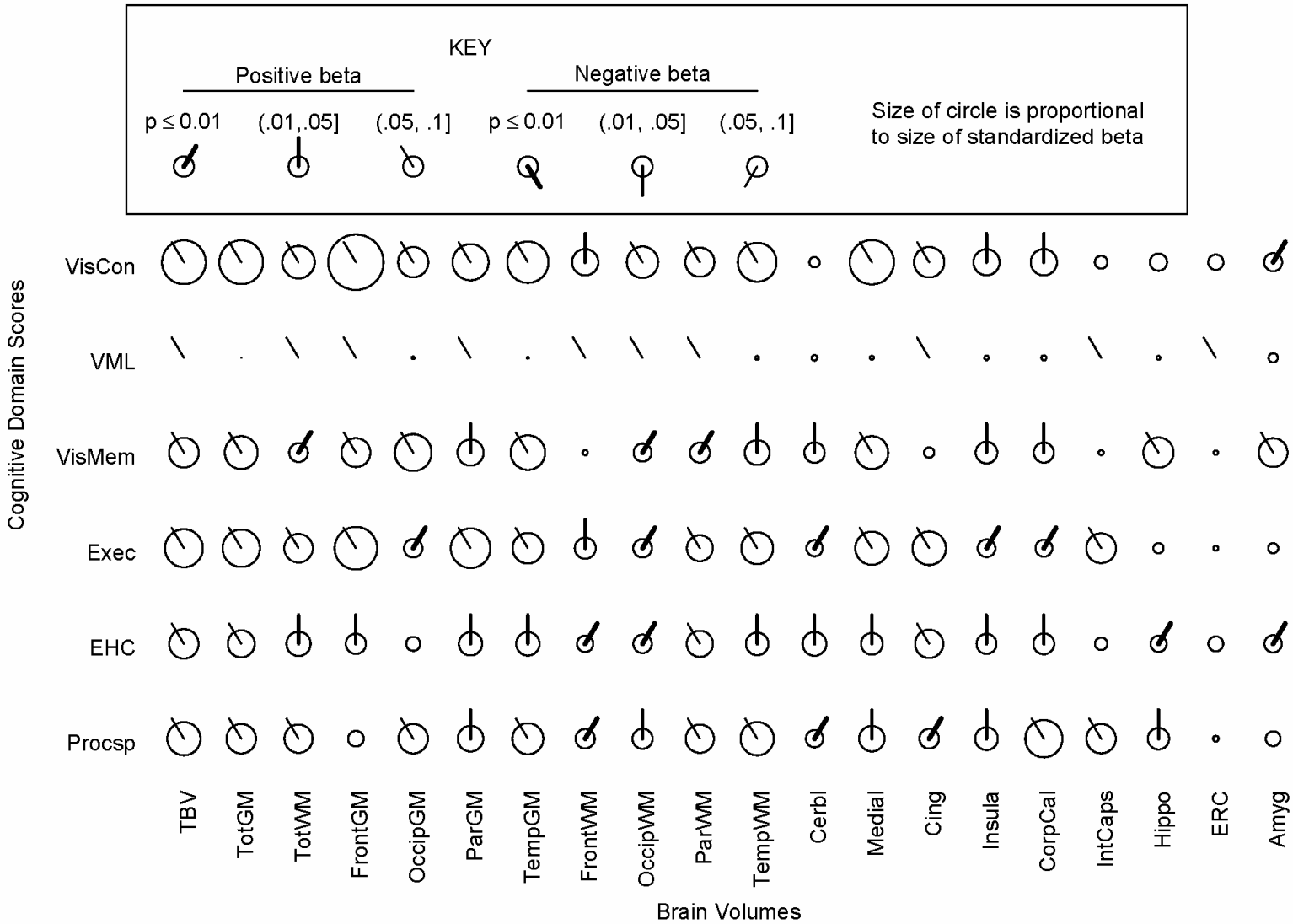

VISCON
Mean (SD)
15.8 (1.7) cm3
VML
Mean (SD)
0.1 (0.02) cm3
VISMEM
Mean (SD)
5.2 (0.6) cm3
EXEC
Mean (SD)
10.8 (1.4) cm3
EHC
Mean (SD)
3.4 (0.5) cm3
PROCSP
Mean (SD)
7.9 (0.9) cm3
Fig 3b (WM)
Red p < 0.001
Orange p < 0.00002

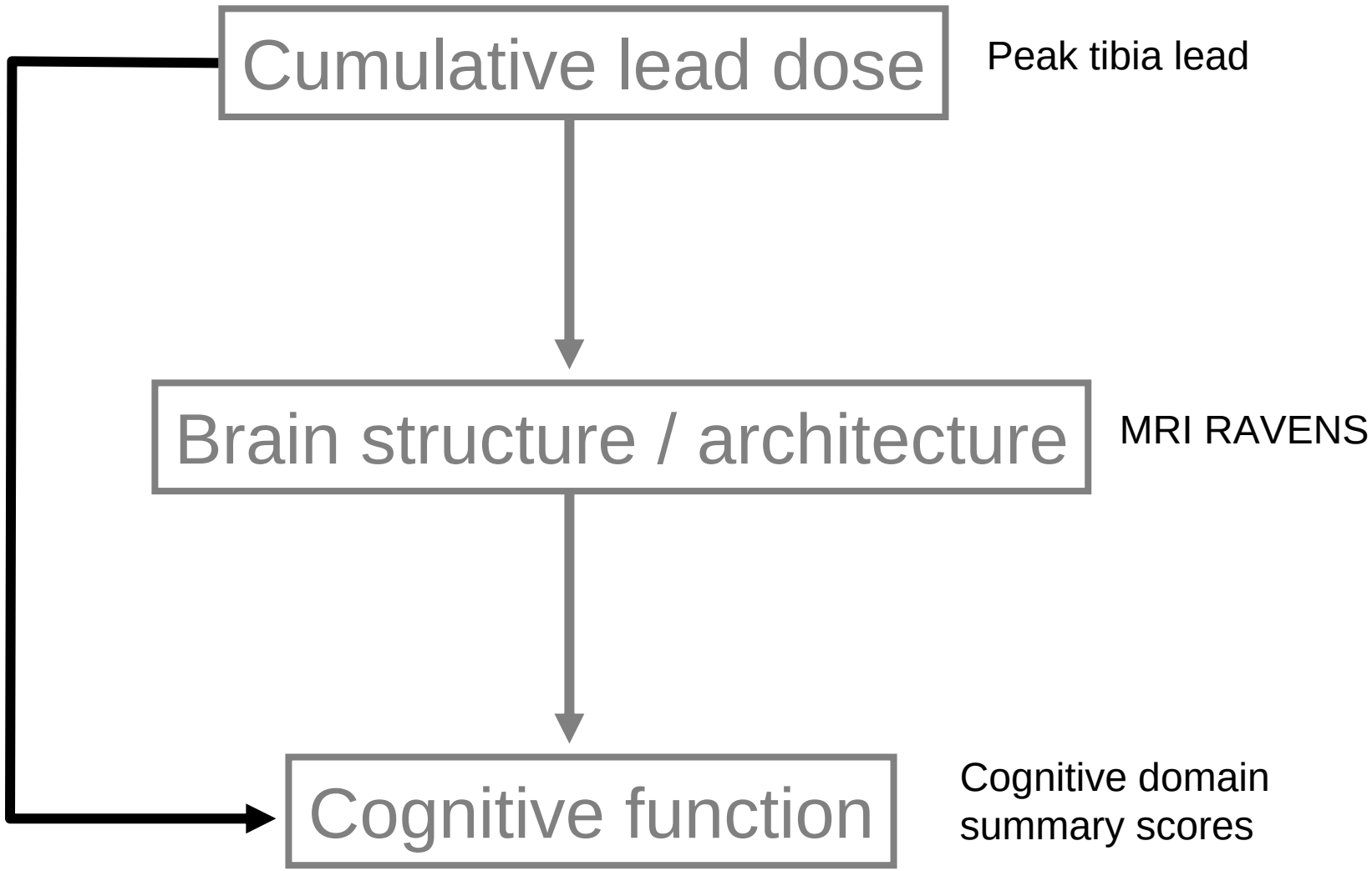
Figure 2


KEY
Positive beta
Negative beta
p ≤ 0.01
(.01, .05]
(.05, .1]
p ≤ 0.01
(.01, .05]
(.05, .1]
Size of circle is proportional to size of standardized beta
Cognitive Domain Scores
VisCon
VML
VisMem
Exec
EHC
Procsp
TBV
TotGM
TotWM
FrontGM
OccipGM
ParGM
TempGM
FrontWM
OccipWM
ParWM
TempWM
Cerbl
Medial
Cing
Insula
CorpCal
IntCaps
Hippo
ERC
Amyg
Brain Volumes

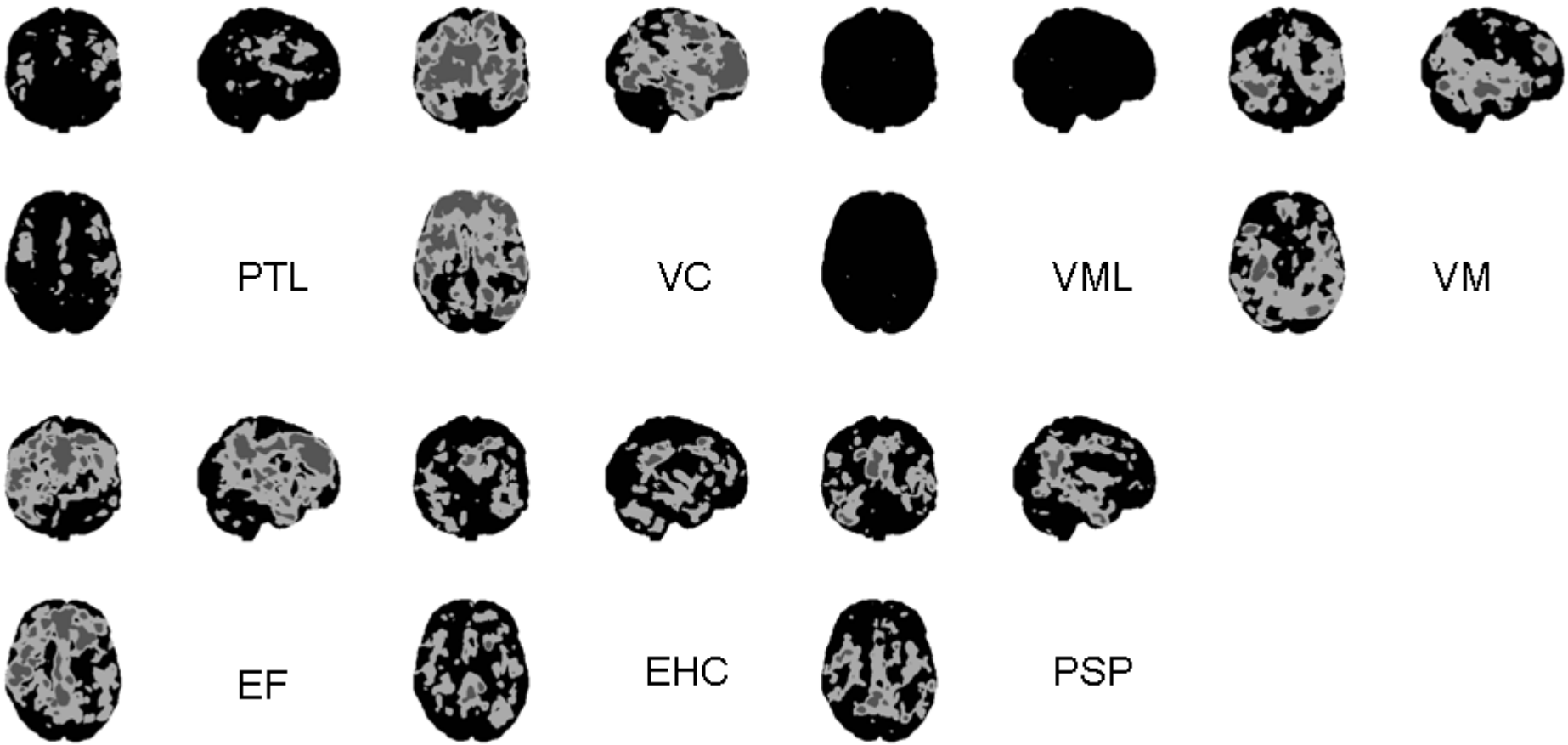
Domain	Expected Anatomical Site	ROI	VBM
Visuoconstruction (ROCF, BD)	frontal-parietal-occipital	frontal WM	frontal-parietal-occipital GM parietal WM
Verbal Memory (RAVLT, Serial Digit)	Temporal-parietal L>R, hippocampus, prefrontal, ACC, thalamus, precuneas	------	-------
Visual Memory (ROCF, symbol digit)	Bilateral hippocampus, R>L;	Total WM Parietal GM, WM, temporal WM, corpus callosum, cerebellum, insula	Occipital, inferior parietal GM, WM, corpus callosum
Executive Function (Purdue Assembly, Stroop C-A, Trails B)	Pre-frontal, ACC, DLPFC; Trails B – medial temporal	Occipital GM, frontal WM, occipital WM, insula, corpus callosum	frontal-parietal-occipital GM, parietal, ACC, WM
Eye-Hand Coordination (Trails A, Purdue)	WM hyperintensities,	Total WM, frontal GM, WM, parietal GM, temporal GM,WM, occipital WM, cerebellum, insula, amygdale, medial	Parietal WM, GM
Processing Speed (Reaction Time)	DLPFC, ventral pre-motor	Frontal GM, WM, parietal GM, occipital WM, medial, cingulate, insula, hippocampus	Occipital GM, parietal-occiptial WM

General strategy

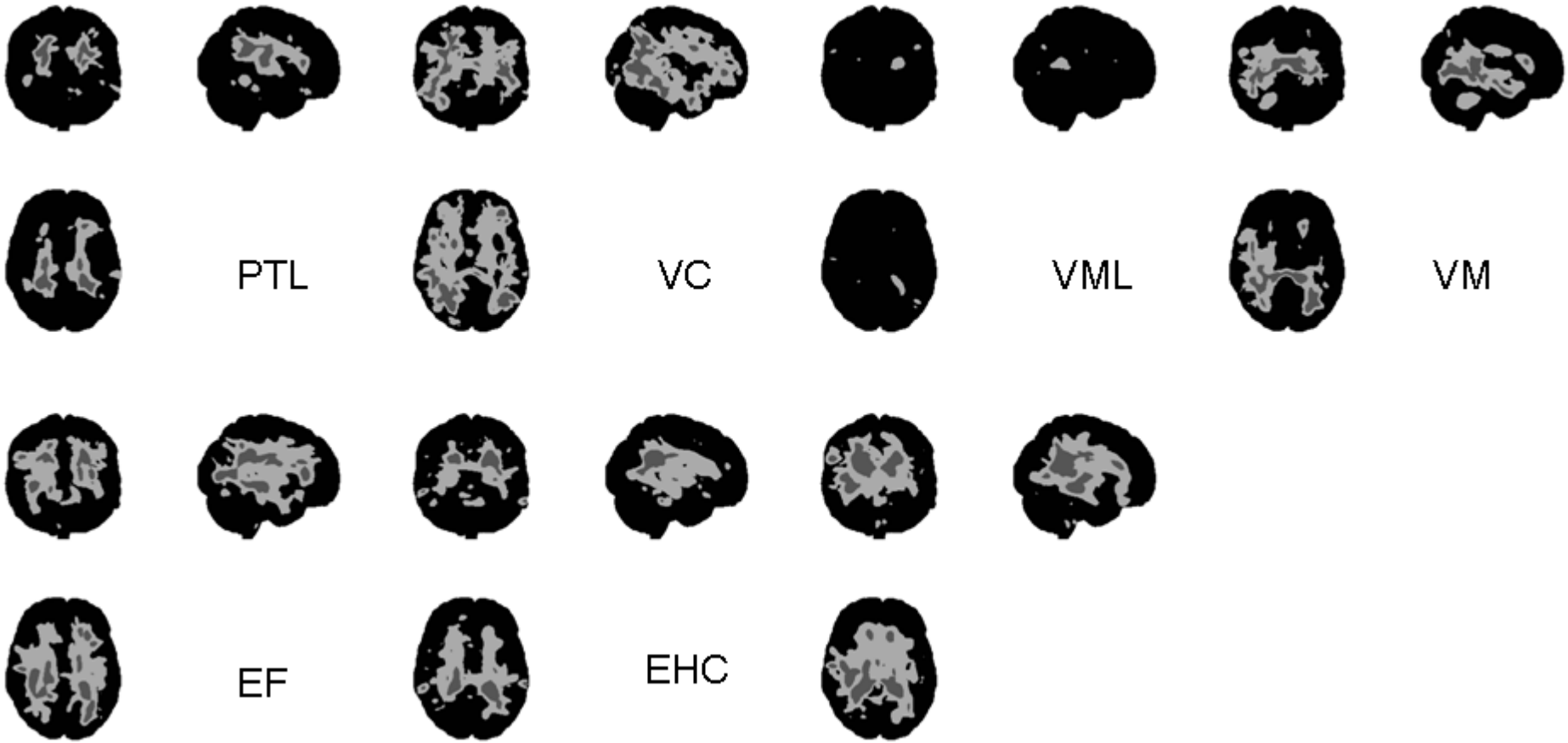
- Apply VBM regressing PTL or Domain on volume
- Threshold the resulting T statistic map to create a lead based mask
  - Ideally represents those areas most associated with lead or domain across subjects
- Apply the mask to each subject and sum the resulting voxels creating subject-specific ROIs
- Raises concerns over multiplicity

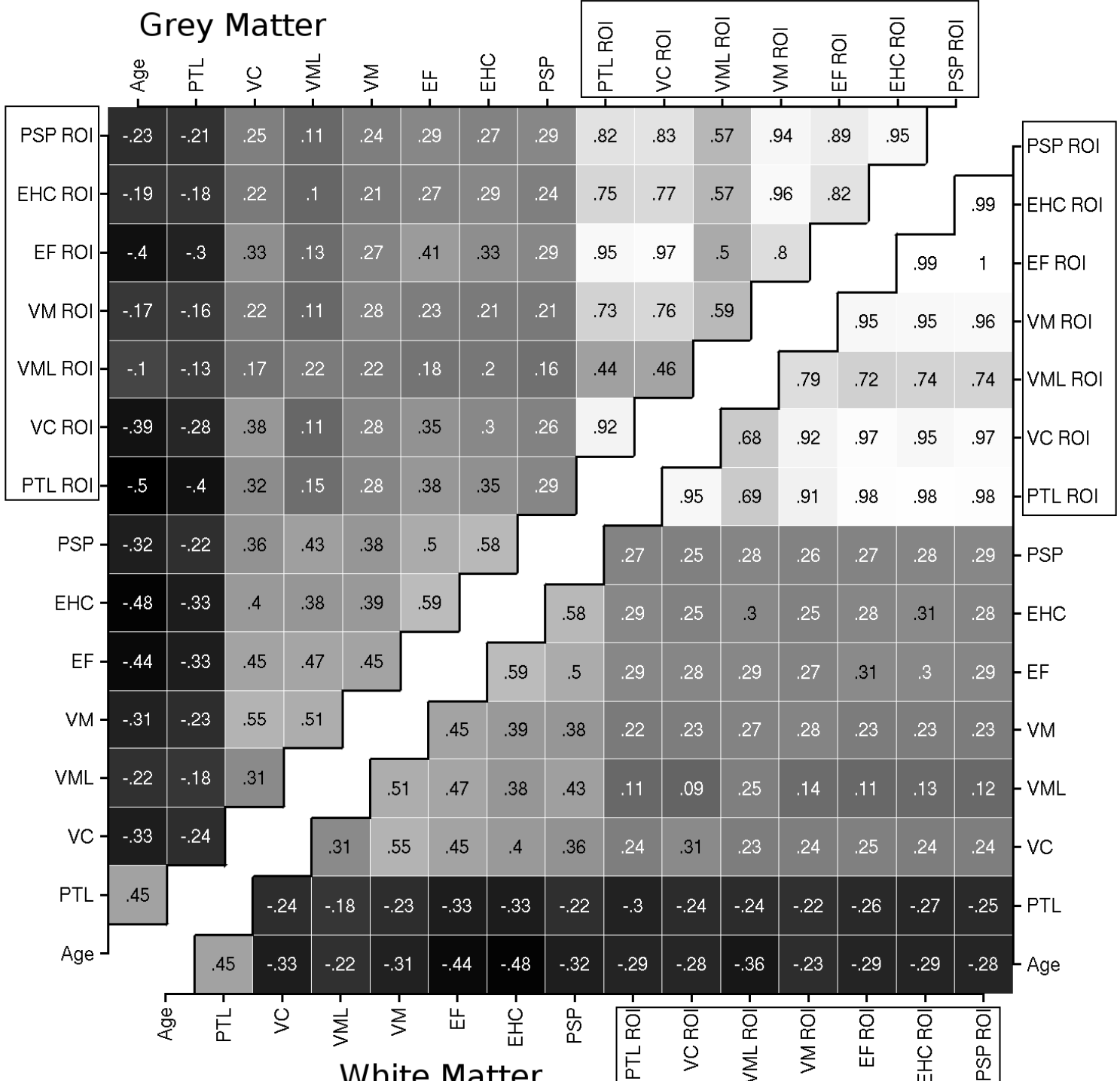

Cumulative lead dose
Peak tibia lead
Brain structure / architecture
MRI RAVENS
Cognitive function
Cognitive domain
summary scores

Grey matter glass brain images



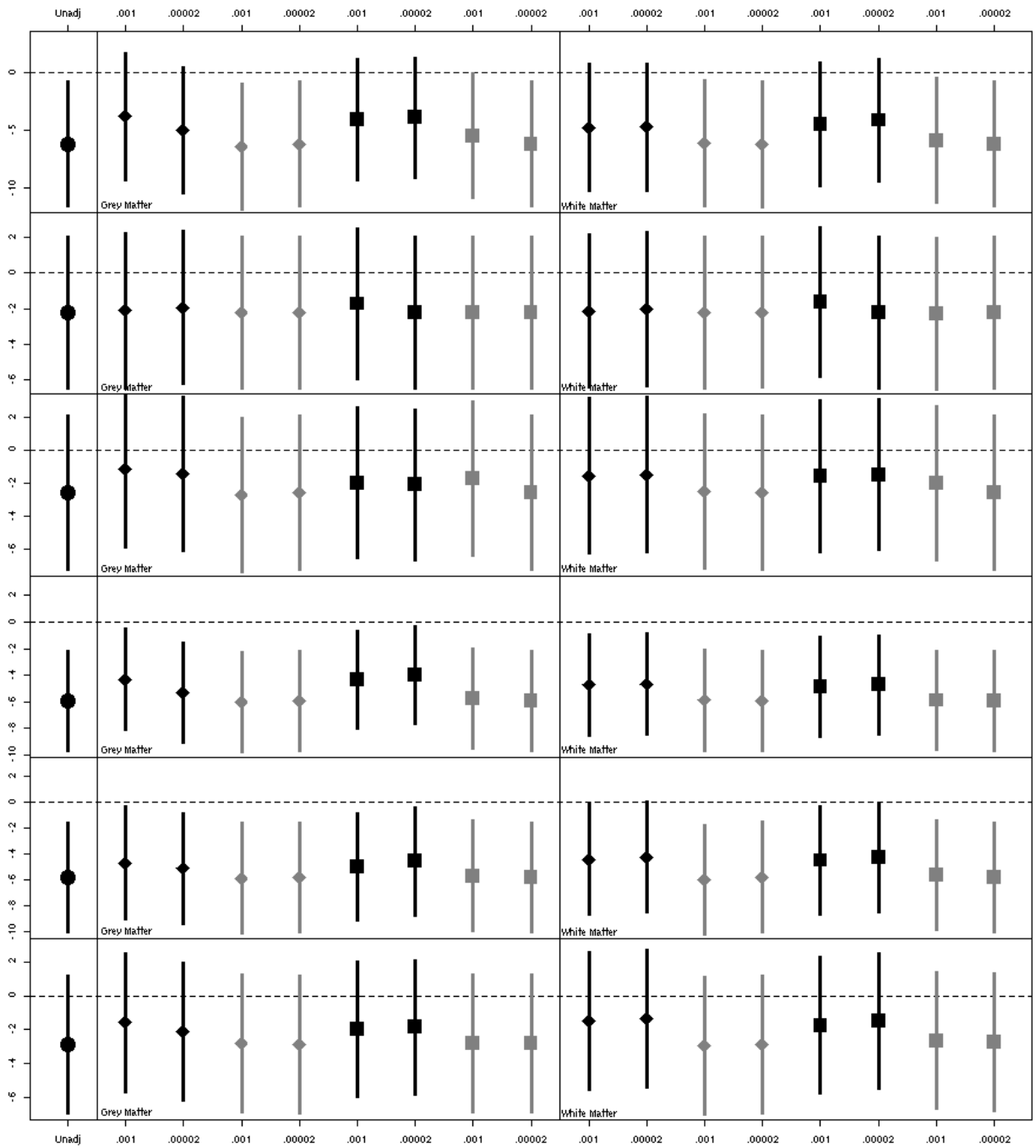
White matter glass brain images




Grey Matter
White Matter
Age
PTL
VC
VML
VM
EF
EHC
PSP
PTL ROI
VC ROI
VML ROI
VM ROI
EF ROI
EHC ROI
PSP ROI
PSP ROI -.23 -.21 .25 .11 .24 .29 .27 .29 .82 .83 .57 .94 .89 .95
EHC ROI -.19 -.18 .22 .1 .21 .27 .29 .24 .75 .77 .57 .96 .82 .99
EF ROI -.4 -.3 .33 .13 .27 .41 .33 .29 .95 .97 .5 .8 .99 1
VM ROI -.17 -.16 .22 .11 .28 .23 .21 .21 .73 .76 .59 .95 .95 .96
VML ROI -.1 -.13 .17 .22 .22 .18 .2 .16 .44 .46 .79 .72 .74 .74
VC ROI -.39 -.28 .38 .11 .28 .35 .3 .26 .92 .68 .92 .97 .95 .97
PTL ROI -.5 -.4 .32 .15 .28 .38 .35 .29 .95 .69 .91 .98 .98 .98
PSP -.32 -.22 .36 .43 .38 .5 .58 .27 .25 .28 .26 .27 .28 .29
EHC -.48 -.33 .4 .38 .39 .59 .58 .29 .25 .3 .25 .28 .31 .28
EF -.44 -.33 .45 .47 .45 .59 .5 .29 .28 .29 .27 .31 .3 .29
VM -.31 -.23 .55 .51 .45 .39 .38 .22 .23 .27 .28 .23 .23 .23
VML -.22 -.18 .31 .51 .47 .38 .43 .11 .09 .25 .14 .11 .13 .12
VC -.33 -.24 .31 .55 .45 .4 .36 .24 .31 .23 .24 .25 .24 .24
PTL .45 -.24 -.18 -.23 -.33 -.33 -.22 -.3 -.24 -.24 -.22 -.26 -.27 -.25
Age .45 -.33 -.22 -.31 -.44 -.48 -.32 -.29 -.28 -.36 -.23 -.29 -.29 -.28

Permutation analysis

- Investigate the impact of multiplicity and using the same subjects to both create the mask and evaluate significance
- Permute subject labels, perform the VBM analysis again, threshold the t-map, apply the mask to each subject
- Now each subjects ROI value represents only chance associations


Unadj
.001
.00002
.001
.00002
.001
.00002
.001
.00002
.001
.00002
.001
.00002
.001
.00002
.001
.00002
Grey Matter
White Matter

Structural equation modeling

- Domain = a + b PTL + c Volume + OC + error
- Volume = d + e PTL + OC + error
- Direct effect of PTL on Domain = b
- Indirect effect of PTL on Domain = ec
- Total effect of PTL on Domain = b + ec
- Proportion direct = b / (b + ec)
- Estimated by the sem package in R

Proportion of direct effect

roi	size	matter	VC	VML	VM	EXEC	EHC	PSP
lead	**0.001**	**Grey**	0.544	0.802	0.621	0.631	0.698	0.583
domain	**0.001**	**Grey**	0.595	0.850	0.829	0.683	0.868	0.753
lead	**0.00002**	**Grey**	0.730	0.804	0.695	0.793	0.803	0.711
domain	**0.00002**	**Grey**	0.566	1.000	0.851	0.648	0.850	0.755
lead	**0.001**	**White**	0.769	0.896	0.79	0.803	0.811	0.707
domain	**0.001**	**White**	0.732	0.710	0.779	0.809	0.805	0.719
lead	**0.00002**	**White**	0.790	0.887	0.8	0.816	0.819	0.710
domain	**0.00002**	**White**	0.703	1.000	0.78	0.778	0.816	0.696