

MSKIDS Scanner Harmonization

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Overview

- MSKIDS data summary
- PNC analysis: ROIs [Males vs Females], GAMs
- Harmonization of scanner effects with ComBat-GAM

Section 1

MSKIDS data summary

MSKIDS: All participants

Participants: 168

Per scanner:

site	n
CHP	57
HSC-SIEMENSPRISMAFIT	86
HSC-SIEMENSTIMTRIO	25

Per sex and site:

sex	site	n
FEMALE	CHP	42
FEMALE	HSC-SIEMENSPRISMAFIT	54
FEMALE	HSC-SIEMENSTIMTRIO	20
MALE	CHP	15
MALE	HSC-SIEMENSPRISMAFIT	32
MALE	HSC-SIEMENSTIMTRIO	5

Totals: Females = 116; Males = 52

MSKIDS: HC only

Participants: 101

Per site:

site	n
CHP	36
HSC-SIEMENSPRISMAFIT	58
HSC-SIEMENSTIMTRIO	7

Per sex and site:

sex	site	n
FEMALE	CHP	24
FEMALE	HSC-SIEMENSPRISMAFIT	37
FEMALE	HSC-SIEMENSTIMTRIO	5
MALE	CHP	12
MALE	HSC-SIEMENSPRISMAFIT	21
MALE	HSC-SIEMENSTIMTRIO	2

Totals: Females = 66; Males = 35

MSKIDS: MS only

Participants: 67

Per site:

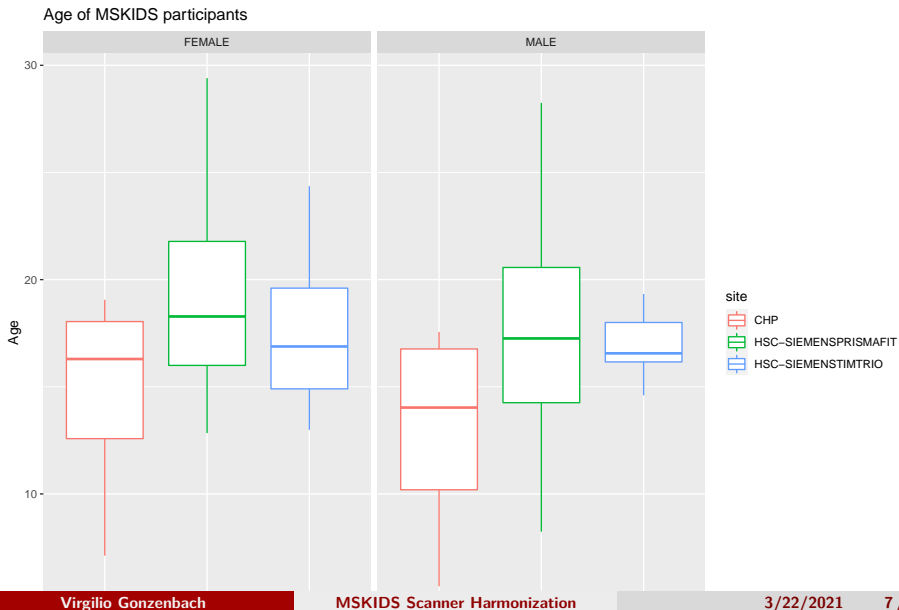
site	n
CHP	21
HSC-SIEMENSPRISMAFIT	28
HSC-SIEMENSTIMTRIO	18

Per sex and site:

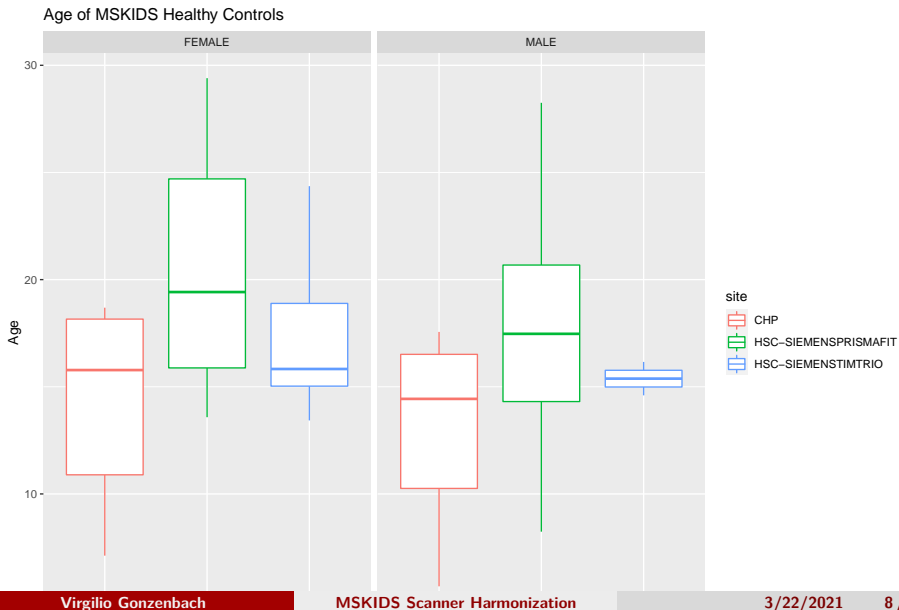
sex	site	n
FEMALE	CHP	18
FEMALE	HSC-SIEMENSPRISMAFIT	17
FEMALE	HSC-SIEMENSTIMTRIO	15
MALE	CHP	3
MALE	HSC-SIEMENSPRISMAFIT	11
MALE	HSC-SIEMENSTIMTRIO	3

Totals: Females = 50; Males = 17

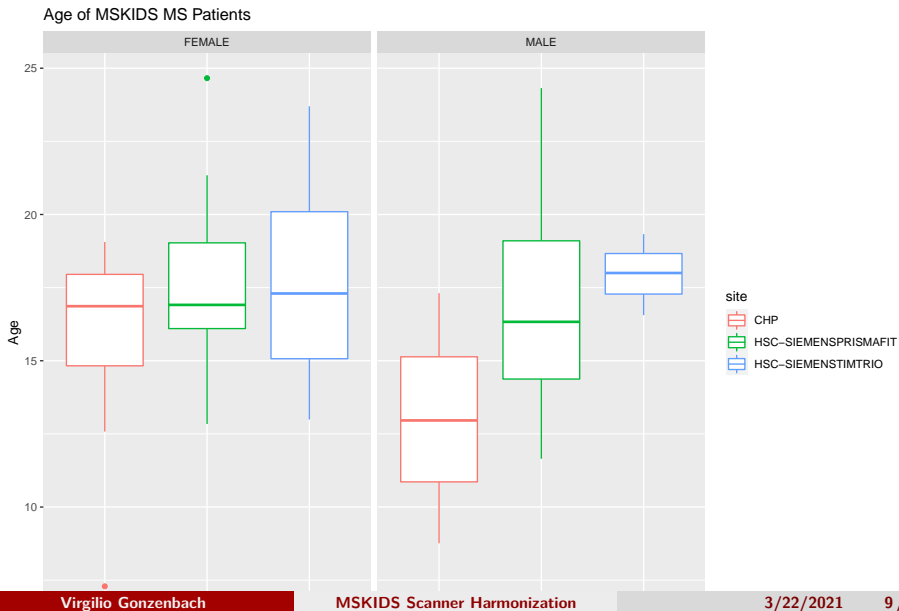
MSKIDS: Age [All participants]



MSKIDS: Age [HC only]



MSKIDS: Age [MS only]



Section 2

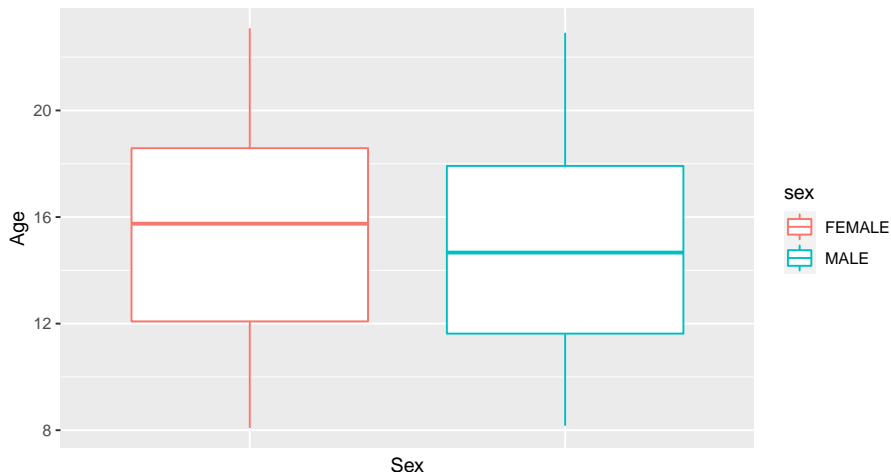
PNC Analysis

Overview

- Objective: To inform harmonization approach by
- Determining Age-ROI, ICV-Age, ICV-ROI relationships in Males and Females
 - Ascertaining non-linear age trends in select ROIs

Age by Sex

Age of the Philadelphia Neurodevelopment Cohort



Females: 630 Males : 555

Age descriptives

Full dataset:

	n	mean	sd	median	min	max
age	1185	15.12	3.742	15.33	8.083	23.08

Males:

	n	mean	sd	median	min	max
age	555	14.78	3.717	14.67	8.167	22.92

Females:

	n	mean	sd	median	min	max
age	630	15.42	3.741	15.75	8.083	23.08

ICV: Models by Sex

Table 4

<i>Dependent variable:</i>		
	Intracranial Volume	
	Males	Females
	(1)	(2)
Age	0.118** (0.035, 0.201)	−0.037 (−0.116, 0.041)
Constant	−0.000 (−0.083, 0.083)	0.000 (−0.078, 0.078)
R ²	0.014	0.001

Note:

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

Stargazer

White Matter: Models by Sex

Table 5

<i>Dependent variable:</i>		
	White Matter Volume	
	Males	Females
	(1)	(2)
Age	0.467*** (0.393, 0.541)	0.374*** (0.302, 0.447)
Constant	−0.000 (−0.074, 0.074)	−0.000 (−0.072, 0.072)
R ²	0.218	0.140

Note:

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

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Gray Matter: Models by Sex

Table 6

<i>Dependent variable:</i>		
	Gray Matter Volume	
	Males	Females
	(1)	(2)
Age	−0.245*** (−0.326, −0.164)	−0.402*** (−0.473, −0.330)
Constant	0.000 (−0.081, 0.081)	−0.000 (−0.072, 0.072)
R ²	0.060	0.161

Note:

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

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CSF (in ventricles): Models by Sex

Table 7

<i>Dependent variable:</i>			
Cerebrospinal Fluid Volume			
Males		Females	
(1)		(2)	
Age	0.284*** (0.204, 0.364)	0.171*** (0.094, 0.248)	
Constant	−0.000 (−0.080, 0.080)	0.000 (−0.077, 0.077)	
R ²	0.081	0.029	

Note:

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

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Comparison of GAMs vs Linear models across all 145 ROIs

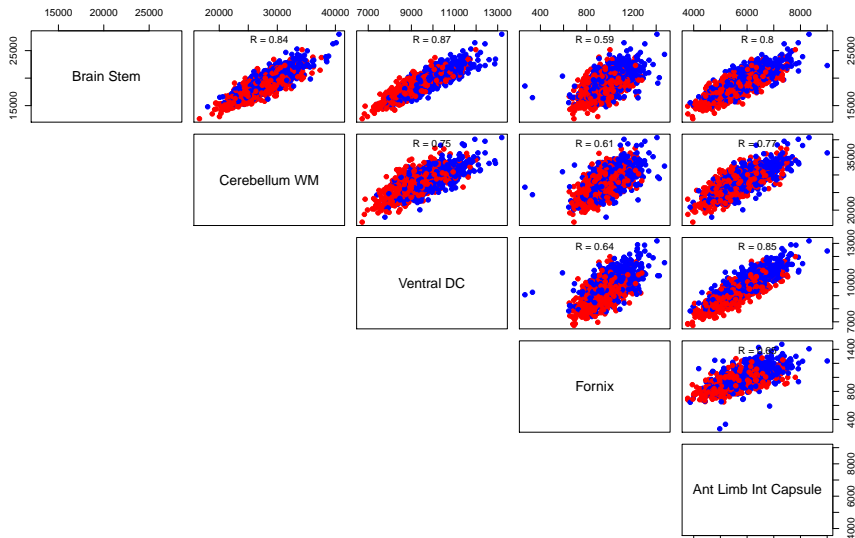
- Model 1: $\text{ROI} = \text{sex} + \text{age} + \text{age} * \text{sex}$
- Model 2: $\text{ROI} = \text{sex} + s(\text{age}, \text{by} = \text{sex})$, where $s()$ denotes the smooth function(s) fitted separately within each sex.

ROIs w/ non-linear age trends (FDR-adjusted):

ROI_INDEX	ROI_NAME	HEMISPHERE	TISSUE_SEG
35	Brain Stem	Both	NONE
40	Right Cerebellum White Matter	Right	WM
41	Left Cerebellum White Matter	Left	WM
61	Right Ventral DC	Right	WM
62	Left Ventral DC	Left	WM
89	fornix right	Right	WM
90	fornix left	Left	WM
91	anterior limb of internal capsule right	Right	WM
92	anterior limb of internal capsule left	Left	WM

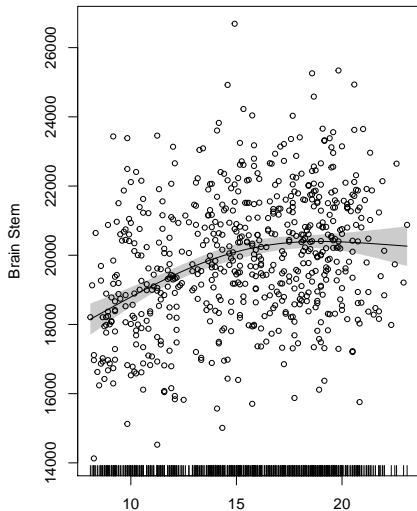
Pairwise Correlations

Pairwise correlations of significant ROIs (GAM)

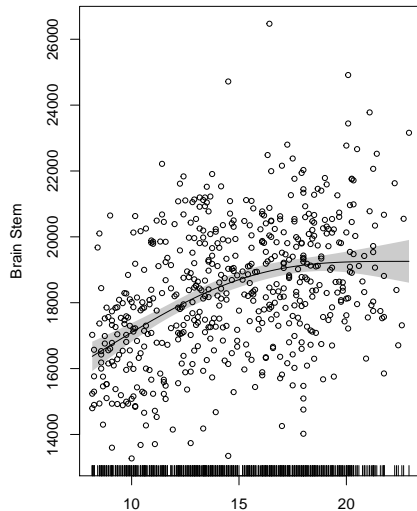


Brain Stem: GAM Plot

Females



Males



Brain Stem: Linear Models by Sex

Table 9

	<i>Dependent variable:</i>	
	Brain Stem Volume	
	Males (1)	Females (2)
Age	0.410*** (0.334, 0.485)	0.283*** (0.207, 0.358)
Age (Squared)	-0.131*** (-0.207, -0.056)	-0.137*** (-0.213, -0.062)
Constant	0.000 (-0.075, 0.075)	0.000 (-0.074, 0.074)
R ²	0.182	0.116

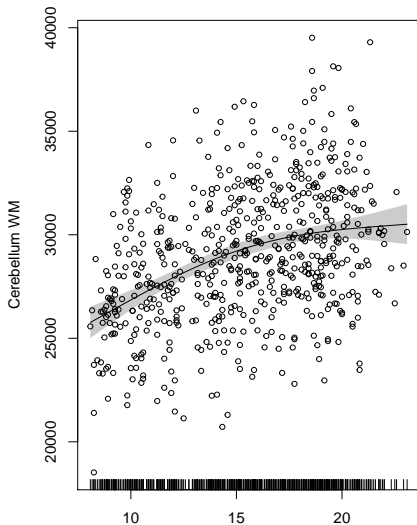
Note:

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

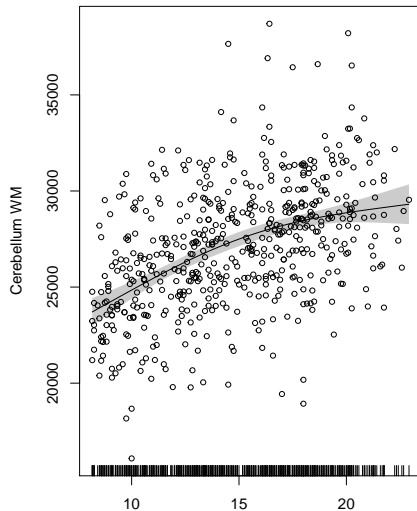
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Cerebellum WM: GAM plot

Females



Males



Cerebellum WM: Linear Models by Sex

Table 10

	<i>Dependent variable:</i>	
	Cerebellum WM	
	Males (1)	Females (2)
Age	0.464*** (0.390, 0.537)	0.365*** (0.291, 0.438)
Age (Squared)	-0.099** (-0.173, -0.026)	-0.106** (-0.179, -0.032)
Constant	0.000 (-0.074, 0.074)	0.000 (-0.072, 0.072)
R ²	0.222	0.161

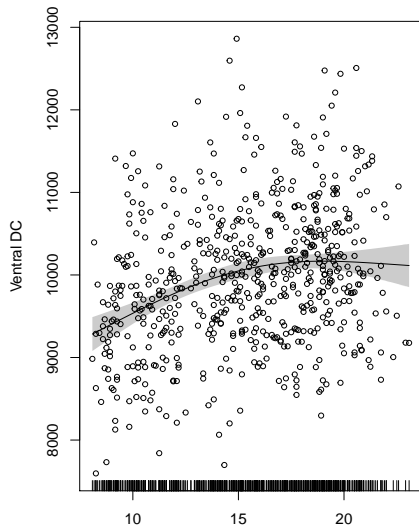
Note:

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

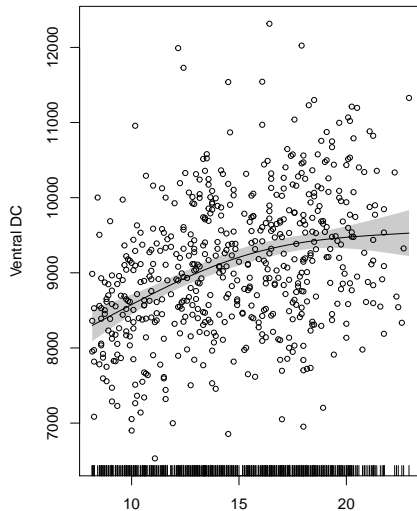
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Ventral Diencephalon: GAM Plot

Females



Males



Ventral DC: Linear Models by Sex

Table 11

	<i>Dependent variable:</i>	
	Ventral DC	
	Males (1)	Females (2)
Age	0.370*** (0.292, 0.447)	0.247*** (0.170, 0.323)
Age (Squared)	-0.099* (-0.176, -0.022)	-0.124** (-0.201, -0.048)
Constant	0.000 (-0.077, 0.077)	-0.000 (-0.075, 0.075)
R ²	0.144	0.089

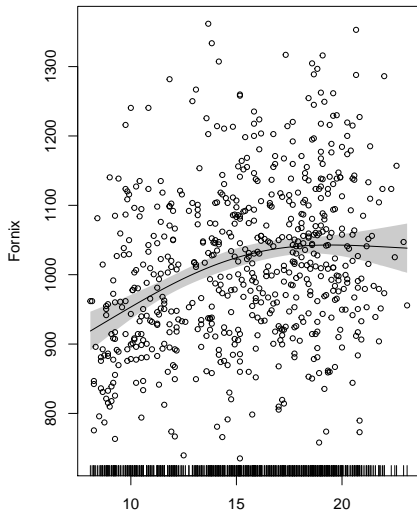
Note:

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

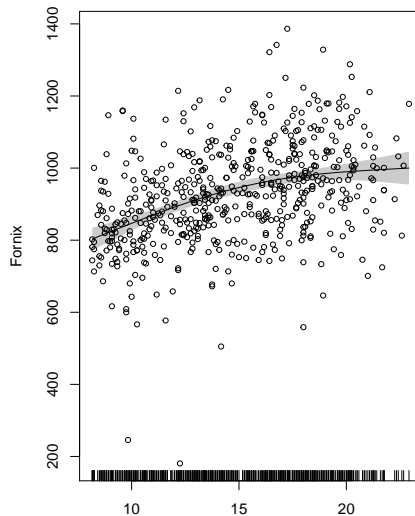
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Fornix: GAM Plot

Females



Males



Fornix: Linear Models by Sex

Table 12

	<i>Dependent variable:</i>	
	Fornix	
	Males (1)	Females (2)
Age	0.389*** (0.313, 0.466)	0.260*** (0.184, 0.337)
Age (Squared)	-0.097* (-0.174, -0.020)	-0.119** (-0.195, -0.042)
Constant	0.000 (-0.076, 0.076)	0.000 (-0.074, 0.074)
R ²	0.158	0.095

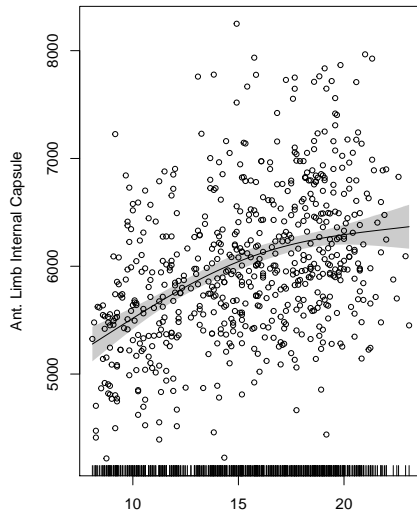
Note:

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

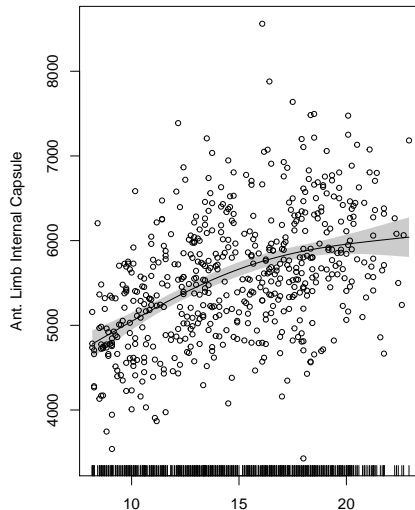
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Anterior Limb of Internal Capsule (ALIC): GAM Plot

Females



Males



ALIC: Linear Models by Sex

Table 13

<i>Dependent variable:</i>		
	Ant. Limb Internal Capsule	
	Males	Females
	(1)	(2)
Age	0.465*** (0.392, 0.539)	0.390*** (0.318, 0.463)
Age (Squared)	-0.109** (-0.183, -0.036)	-0.104** (-0.176, -0.031)
Constant	0.000 (-0.073, 0.073)	-0.000 (-0.071, 0.071)
R ²	0.225	0.180

Note:

*p<0.05; **p<0.01; ***p<0.001
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Section 3

Harmonization

Factors guiding harmonization approach

- Differential Age confound in Males vs. Females
- ICV, ROI volume differences in Males vs. Females
- Differential relationships (e.g., ROI-age, ROI-ICV) in Males vs. Females
- Non-linear age trends in ROIs

Harmonization Approach

Adjusted data are shown for the following approach:

- Join HC and MS data into one dataset
- Split this dataset into 2 according to sex.
- Harmonize (Step 1): Run ComBat-GAM with ICV as target.
- Harmonize (Step 1): Run ComBat-GAM with 145 as target with harmonized ICV as added covariate.

Models used in harmonization

- GAM: $s(\text{age}) + \text{MS} + \text{MSxage}$

Testing for site effects

ANOVAs were run on each of the 145 ROIs comparing two versions of covariate model: with and without the inclusion of a site/scanner variable.

Site effects: MS + HC

Number of ROIs showing site effects:

Raw data:

[1] “~ ICV + age + age2 + sex + *sexage* + *sexage2* + MS + *MSage* + *MSage2*”

FDR	Bonferroni	Uncorrected P
35	18	55

Harmonized data:

[1] “~ ICV + age + age2 + sex + *sexage* + *sexage2* + MS + *MSage* + *MSage2*”

FDR	Bonferroni	Uncorrected P
0	0	0

Site effects: MS + HC [Females]

Raw:

[1] “~ ICV + age + age2 + MS + MSage + MSage2”

FDR	Bonferroni	Uncorrected P
28	13	44

Harmonized:

[1] “~ ICV + age + age2 + MS + MSage + MSage2”

FDR	Bonferroni	Uncorrected P
0	0	0

Site effects: MS + HC [Males]

Raw:

[1] “~ ICV + age + age2 + MS + MSage + MSage2”

FDR	Bonferroni	Uncorrected P
2	1	29

Harmonized: [1] “~ ICV + age + age2 + MS + MSage + MSage2”

FDR	Bonferroni	Uncorrected P
0	0	0

Site effects: MS

Raw:

[1] “~ ICV + age + age2 + sex + *sexage* + *sexage2*”

FDR	Bonferroni	Uncorrected P
20	8	33

Harmonized: [1] “~ ICV + age + age2 + sex + *sexage* + *sexage2*”

FDR	Bonferroni	Uncorrected P
0	0	1

Site effects: MS [Females]

Raw: [1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
3	1	27

Harmonized:

[1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
0	0	0

Site effects: MS [Males]

Raw:

[1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
0	0	4

Harmonized:

[1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
0	0	4

Site effects: HC

Raw:

[1] “~ ICV + age + age2 + sex + sexage + sexage2”

FDR	Bonferroni	Uncorrected P
23	10	32

Harmonized:

[1] “~ ICV + age + age2 + sex + sexage + sexage2”

FDR	Bonferroni	Uncorrected P
0	0	0

Site effect: HC [Females]

Raw

[1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
12	5	33

Harmonized:

[1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
0	0	0

Site effects: HC [Males]

Raw: [1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
1	1	21

Harmonized: [1] “~ ICV + age + age2”

FDR	Bonferroni	Uncorrected P
0	0	0

Harmonization Conclusions

Insert conclusions