

Hearing loss meta-analysis

Francis Manno PhD & Raúl R. Cruces PhD

09 March, 2020

Contents

Methods	3
Eligibility Criteria	3
Estimation of heterogeneity per model	4
Total included studies	4
Table of included studies (Figure 1.A)	4
Relation between hearing loss (dB) and age (Figure 2.D)	6
Studies characteristics (Figure 2.E, 2.F)	7
Brain structure (GM, WM) and MRI measures	8
Frequency table: Brain structure (GM, WM) and MRI measures	8
Brain structure (GM, WM) and side	9
Brain structure (GM, WM) by MRI measure (volume) and ROI	9
Studies characteristics (Figure 2.A, 2.B): Brain structure (GM, WM) by MRI measure (volume and FA)	10
MRI measures by ROI (Figure 2.C)	10
Relations of all MRI measurements of GM and WM with age	11
Gray matter relation with Age by volume (Figures 3.A and 3.B)	12
White matter relation with Age by volume and FA (Figures 3.C, 3.D and 3.F)	13
Gray and White matter relation with Age by asymmetry	13
Table of estimates and meta-regression: WM and GM relation with age by MRI measures (volume and FA)	14

Meta-regression: Variables by Etiology, Brain matter and MRI measure	15
Gray Matter Volume: Random effects model no intercept covariated by Big area	16
ACQUIRED - Meta-regressions of Gray Matter by Volume	19
CONGENITAL - White Matter by VOLUME	21
ACQUIRED - White Matter by VOLUME (ONLY BILATERAL)	24
.	25
bilateral Total Cortex 0.2239 0.2691 0.8321 -0.3035 0.7514	25
CONGENITAL - White Matter by FA fractional anisotropy	25
ACQUIRED - White Matter by FA fractional anisotropy (ONLY RIGHT)	28
Supplementary material: heterogeneity per model	31
Heterogeney: GM volume Right	31
Heterogeney: GM volume Left	32
Heterogeney: WM FA Right	33
Heterogeney: WM FA Left	34
Heterogeney: WM volume Right	35
Heterogeney: WM volume Left	36
Meta-regressions of Gray Matter Volume & Brain Areas: Random effects model no intercept covariated by Side	37
Meta-regressions of White Matter FA & Brain Areas: Random effects model no intercept covariated by Side	48
Meta-regressions of White Matter Volume & Brain Areas: Random effects model no intercept covariated by Side	56
Supplementary material: Forest-plots of other Measures	62
Hesch gyrus FA white matter	62
STG Volume White matter	63
Measures of White matter Integrity	64
White matter: RD	64
White matter: MD	65
White matter: Mean Kurtosis	66
White matter: AD	67
Other Measures of White Matter	68
White matter: Thickness	68
White matter: VBM	69

Meta Plots	69
The L'Abbé plot	69
Baujat plot to identify studies contributing to heterogeneity	69
Galbraith plot	69
Resources	70

Methods

Eligibility Criteria

We included peer-review publications in English, involving patients with bilateral congenital and mixed hearing loss and controls with structural Magnetic Resonance Imaging. We included cross-sectional studies with control groups, that investigated the structural relation between MRI changes and the hearing loss. The most common MRI measures were **volume, FA, VBM and thickness**. Each measure was assigned to a specific ROI and to a big brain area. (eg. HG and superior temporal lobe belong to **temporal lobe**). A total of 59 studies were included, 6 of them contained incomplete information. A total of 2778 patients and 4214 controls.

Notes for inclusion:

1. I excluded Xia et al. Chin J Rad, 2008 because I don't understand chinese and it appears to be the same data as Xia et al. Chin J Med Img Tech, 2008.
2. Kim et al. Hear Res 2014 used two groups prelingual deaf and post lingual deaf, I used the average for the main table.
3. Xia et al. Chin J Med Img Tech, 2008 had a total of 40 patients, two groups 9-12 years and 19-22 years, no controls.
4. Zheng et al. Sci Rep, 2017 this variables change; Con rangeLow Con rangeHigh. Why? I didn't find them on the original paper.

Effect size direction was directly include in the Cohen's D value by mutiplying by -1 if the effect was decrease and by 1 if it was none of increased. Forests plots were generated form the meta-regression with subgroups left and right. We measure a general regression for white and gray mater by Etiology (congenital and acquired) with subgroups (left and right).

Effects were summarized across studies using the generic inverse-variance weighting method with DerSimonian and Laird random effects. Studies were weighted by $1/SE^2$ (where SE is the standard error). For the effect size we used Hedges'G, wich takes into account the sample size.

$$Hedges'G = \frac{X_1 - X_2}{\sqrt{\frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1 + n_2 - 2}}}$$

Assumptions:

1. We assume that the calculation of the cohen's D is correct.
2. We assume that the direction of the effect is correct.

3. Variance was estimated using the cohen's D and sample size of each study. Our estimated variance was used for all meta-regressions, therefore we could have an additional bias in-between studies variance and heterogeneity calculations. We should have calculated the effect size from the mean and standard deviation from each study. Variance was estimated using the following formula:

$$Variance = \frac{n1 + n2}{n1 \times n2} + \frac{Hedges'G^2}{2 \times (n1 + n2 - 2)}$$

Estimation of heterogeneity per model

We estimated heterogeneity in results using the τ statistic, which represents the standard deviation in the meta-regression models, we used the heterogeneity test x^2 and I^2 .

We performed a multi-level meta-analytic model, over our multiple effect size estimates nested with variables: Etiology, side and Big brain area. We expected that the underlying true effects are more similar for the same level of the grouping variables than true effects arising from different levels.

We can account for the correlation in the true effects by adding a random effect to the model at the level corresponding to the grouping variable.

The dataset contains the result from 54 studies, each comparing different measurements between patients and controls. The difference of between groups was quantified in terms of Hedges'G and Cohen's D.

Total included studies

Table 1: Total unique studies 54

	Hearing Loss	Healthy
Total number of patients	2778	4214
Number mean	47.08	71.42
Number sd	128.5	250.6
Age mean	33.07	30.96
Age SD	22.66	20.5
%Female mean	50.02	55.71
%Female sd	12.05	12.78

Table 2: Acquired studies 13

	Hearing Loss	Healthy
Total number of patients	1766	3146
Number mean	110.4	196.6
Number sd	239	468.2
Age mean	64.6	55.27
Age SD	7.863	13.85
%Female mean	45.1	56.52
%Female sd	15.09	12.9

Table 3: Congenital studies 41

	Hearing Loss	Healthy
Total number of patients	1012	1068
Number mean	23.53	24.84
Number sd	17.18	15.04
Age mean	21.06	20.99
Age SD	12.48	13.06
%Female mean	51.83	55.41
%Female sd	10.37	12.88

Table of included studies (Figure 1.A)

Table 4: Studies with incomplete information (NA)

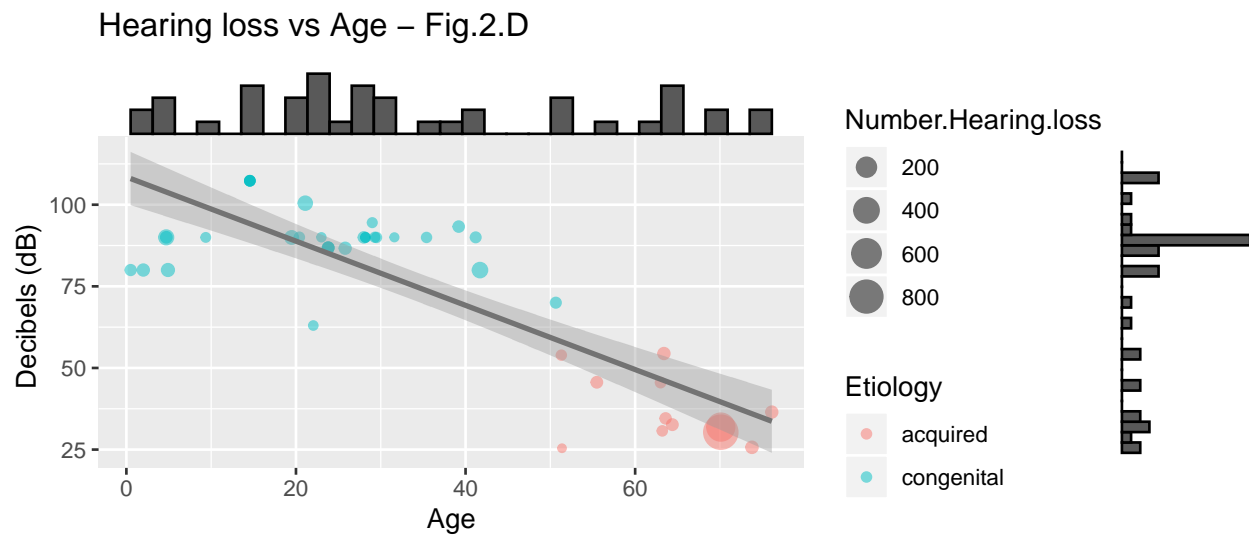
	Source	MRI Tesla	all.techniques	all.measures
5	2006, Kara et al. J Neuroradiol	1.5	VBM	length, Thickness, volume
9	2008, Xia et al. Chin J Med Img Tech	1.5	VBM	volume
12	2010, Husain et al. Brain Res	3	DTI, VBM	FA, volume
26	2014, Lyness et al. Neuroimage	1.5	DTI	FA, MD, RD
41	2017, Karns et al. Hear Res	3	DTI	AD, FA, RD, volume
48	2018, Kumar U, Mishra M. Brain Res	3	VBM	Thickness, VBM

Table 5: Included studies

	Source	MRI Tesla	all.techniques	all.measures
1	2000, Bavelier et al. J Neurosci	1.5	VBM	volume
2	2003, Emmorey et al. PNAS	1.5	VBM	asymmetry, GM+WM, ratio GM/WM, volume
3	2003, Penhune et al. Neuroimage	1.5	VBM	asymmetry, ratio GM/WM, volume
4	2004, Chang et al. Neuroreport	3	DTI	asymmetry, FA
6	2007, Meyer et al. Restor Neurol Neurosci	3	VBM	volume
7	2007, Shibata DK. Am J Neuroradiol	1.5	VBM	volume
8	2008, Allen et al. J Neurosci	1.5	VBM	asymmetry, ratio GM/WM, Vol proportion, volume
10	2009, Kim et al. Neuroreport	3	DTI, VBM	FA, volume
11	2009, Wang et al. Chin J Med Img Tech	3	DTI	FA
13	2010, Leporé et al. Hum Brain Mapp	1.5	VBM	VBM
14	2010, Li, et al. J Clin Rad	1.5	VBM	volume
15	2010, Liu et al. Chin J Med Img Tech	3	CT	FA
16	2011, Smith et al. Cereb Cortex	3	VBM	asymmetry, ratio GM/WM, volume
17	2012, Li et al. Brain Res	3	CT	Thickness
18	2012, Li et al. Hum Brain Mapp	3	DTI	AD, FA, RD
19	2013, Allen et al. Front Neuroanat	1.5	VBM	asymmetry, volume
20	2013, Boyen et al. Hear Res	3	VBM	volume
21	2013, Miao et al. Am J Neuroradiol	3	DTI	FA, RD
22	2013, Pénicaud et al. Neuroimage	1.5	VBM	volume
23	2014, Hribar et al. Hear Res	3	DTI, VBM	AD, FA, Thickness
24	2014, Kim et al. Hear Res	3	VBM	volume
25	2014, Lin et al. Neuroimage	1.5	VBM	volume
27	2014, Olulade et al. J Neurosci	3	VBM	volume
28	2014, Profant et al. Neuroscience	3	DTI, VBM	AD, CT, FA, MD, RD, Surface, volume
29	2014, Profant et al. Neuroscience	3	DTI, VBM	AD, CT, FA, MD, RD, Surface, volume
30	2015, Huang et al. PLoS One	1.5	DTI	FA, MD
31	2015, Tae Investig Magn Reson Imaging	1.5	VBM	VBM
32	2016, Amaral et al. Eur J Neurosci	3	VBM	asymmetry, Thickness
33	2016, Chinnadurai et al. Magn Reson Imaging	1.5	DTI	AD, Axial Kurtosis, FA, Mean Kurtosis, Radial Kurtosis, RD
34	2016, Ma et al. AJNR Am J Neuroradiol	3	DTI	AD, FA, MD, RD
35	2016, Shi et al. Neuroreport	3	VBM	volume
36	2016, Shiell et al. Neural Plasticity	3	CT	Thickness
37	2016, Smittenaar et al. Open Neuroimag J	1.5	CT	CT

	Source	MRI Tesla	all.techniques	all.measures
38	2016, Wu et al. Brain Res	1.5	VBM	ADC, FA
39	2016, Wu et al. Brain Res	1.5	VBM	ADC, FA
40	2016, Wu et al. Brain Res	1.5	VBM	ADC, FA
42	2017, Kim et al. Neuroreport	3	DTI	FA
43	2017, Shiell & Zatorre. Hear Res	3	DTI	AD, MD, RD, volume
44	2017, Zheng et al. Sci Rep	3	DTI	FA, Mean Kurtosis
45	2018, Benetti et al. Neuroimage	4	DTI	AD, FA, RD
46	2018, Chen et al. Behav Neurosci	3	VBM	volume
47	2018, Feng et al. PNAS	3	VBM	VBM
49	2018, Park et al. Biomed Res Int	3	DTI	FA
50	2018, Pereira-Jorge et al. Neural Plast	1.5	VBM	volume
51	2018, Ren et al. Front Neurosci	3	CT, VBM	Thickness, volume
52	2018, Uchida et al. Front Aging Neurosci	3	VBM	volume
53	2018, Uchida et al. Front Aging Neurosci	3	VBM	volume
54	2018, Zou et al. Otol Neurotol	3	DTI	AK, FA, MK, RK
55	2019, Belkhiria et al. Front. Aging Neurosci	3	VBM	CT, volume
56	2019, Belkhiria et al. Front. Aging Neurosci	3	VBM	CT, volume
57	2019, Luan et al. Front Neurosci	3	DTI, VBM	FA, MD, volume
58	2019, Ponticorvo et al. Hum Brain Mapp	3	VBM	volume
59	2019, Xu et al. J Magn Reson Imaging	3	VBM	volume

Relation between hearing loss (dB) and age (Figure 2.D)



Studies characteristics (Figure 2.E, 2.F)



Fig.2.E – Severity

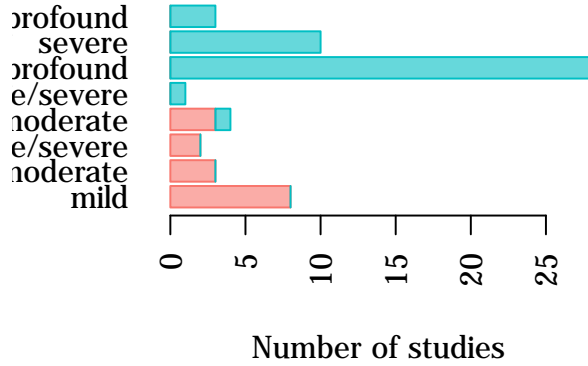
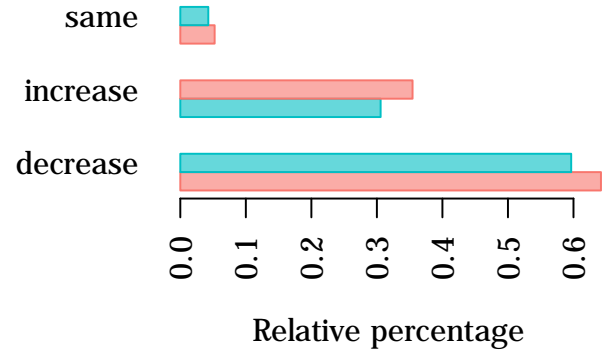


Fig.2.F – Effect direction



Brain structure (GM, WM) and MRI measures

Highlights

- Most of the studies that measured Gray matter focus on cortical changes (volume, thickness and VBM).
- White matter studies are more heterogeneous in their measurements.
- Diffusion tensor (DT) derived measurements are the most frequent in white matter, followed by volume.
- It is harder to interpret a meta-analysis of multiple white matter measurements because its effect varies widely in different directions. The measurements derived from DT have the most differences.

We conduct our meta-analysis using the **TWO** most frequent measurements for gray and white matter. We use *volume* for GM and *fractional anisotropy* for WM.

Further meta regressions can be found in the supplementary material.

Gray Matter

- thickness
- VBM

White Matter integrity

- mean diffusivity MD
- radial diffusivity RD
- axial diffusivity AD
- mean kurtosis

White Matter volume

- thickness (I am unsure how they did this)
- VBM
- volume

Biletareal - GM volume

- WM volume
- WM fractional anisotropy

Frequency table: Brain structure (GM, WM) and MRI measures

Table 6: Matter vs measure (continued below)

	AD	ADC	AK	asymmetry	Axial Kurtosis	CT	FA	GM+WM
GM	0	0	2	9	0	23	8	0
WM	39	12	2	8	3	0	117	0

Table 7: Table continues below

	length	MD	Mean Kurtosis	MK	Radial Kurtosis	ratio GM/WM	RD
GM	0	2	0	2	0	0	0
WM	1	17	27	2	3	0	26

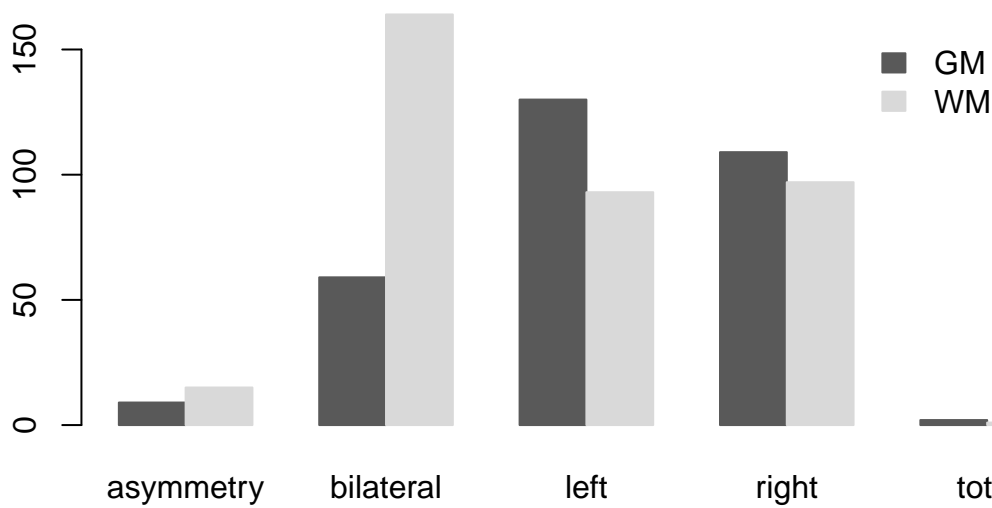
	RK	Surface	Thickness	VBM	Vol proportion	volume
GM	2	4	14	43	6	194
WM	2	0	10	16	6	79

Table 9: Matter vs Side

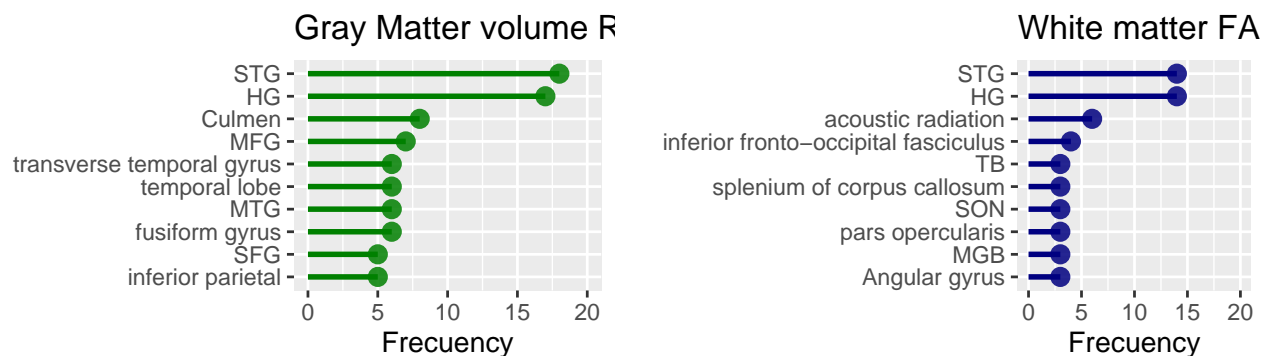
	asymmetry	bilateral	left	right	total
GM	9	59	130	109	2
WM	15	164	93	97	1

Brain structure (GM, WM) and side

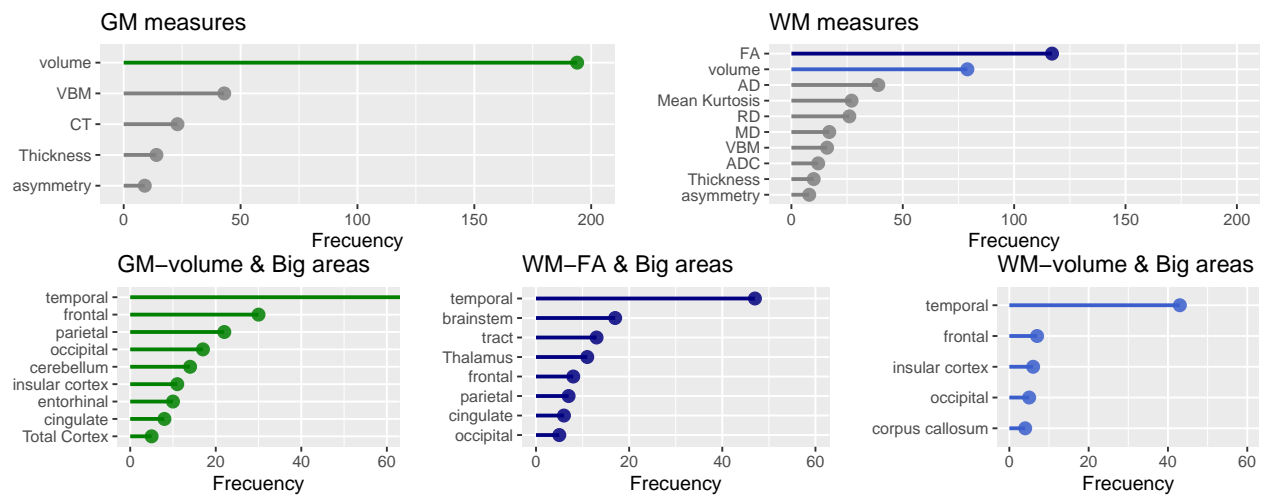
Matter vs Side



Brain structure (GM, WM) by MRI measure (volume) and ROI



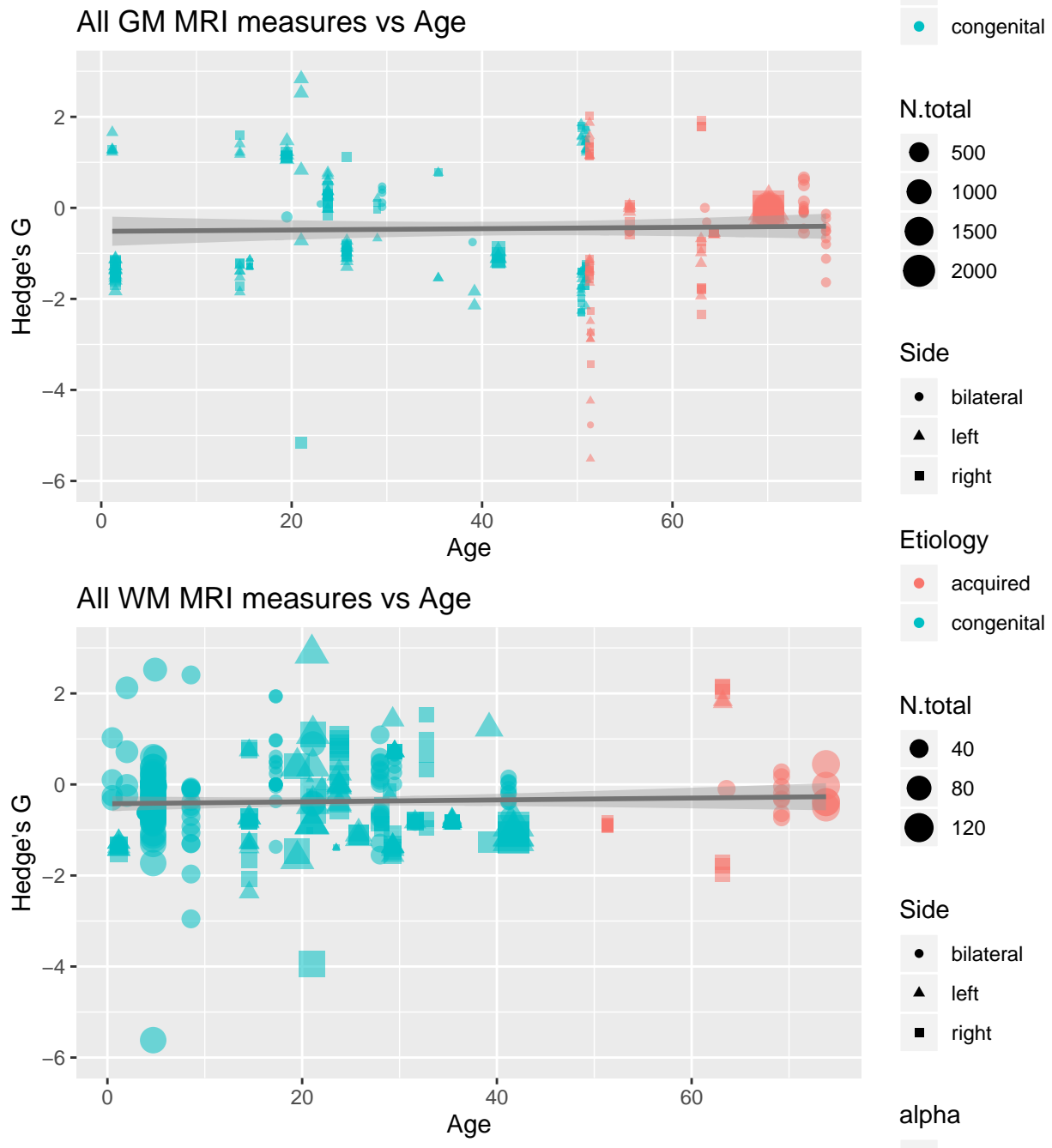
Studies characteristics (Figure 2.A, 2.B): Brain structure (GM, WM) by MRI measure (volume and FA)



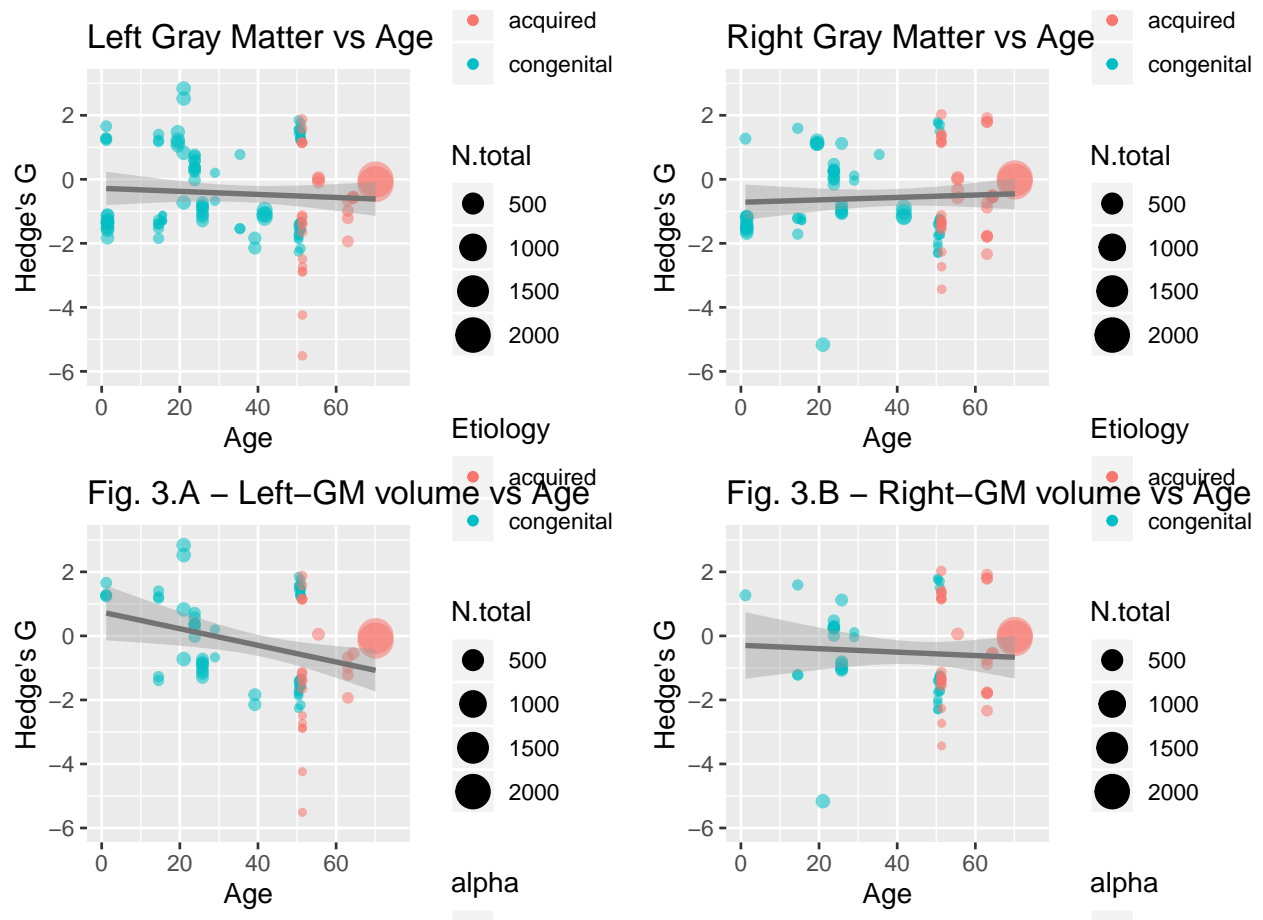
MRI measures by ROI (Figure 2.C)



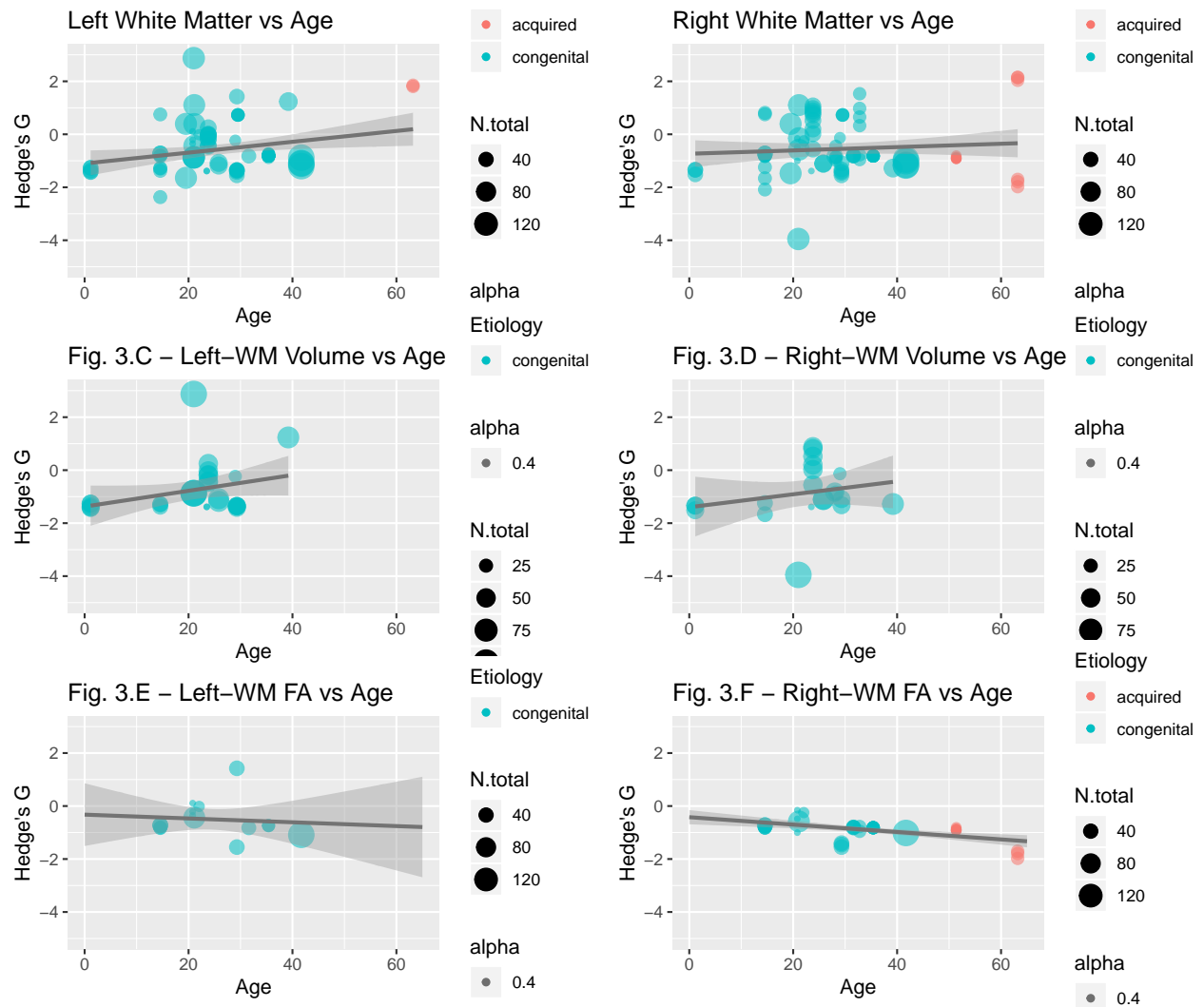
Relations of all MRI measurements of GM and WM with age



Gray matter relation with Age by volume (Figures 3.A and 3.B)



White matter relation with Age by volume and FA (Figures 3.C, 3.D and 3.F)



Gray and White matter relation with Age by asymmetry

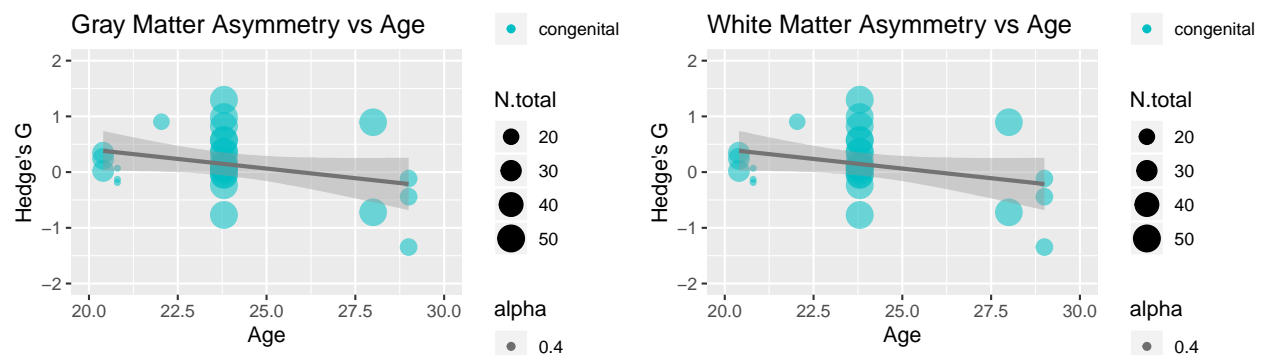
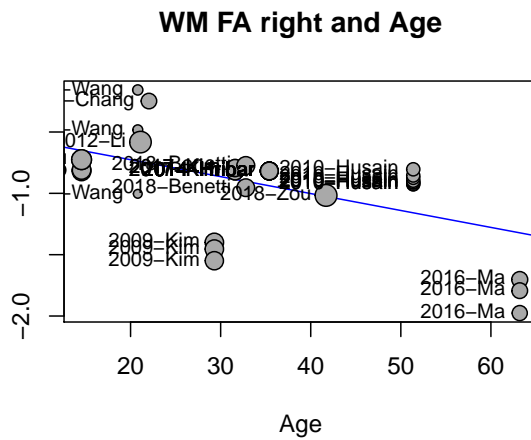


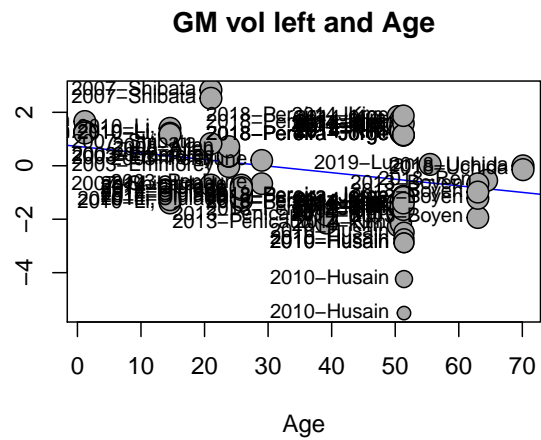
Table of estimates and meta-regression: WM and GM relation with age by MRI measures (volume and FA)

Model	r	p-value	t.stat	df
GM.vol.L	-0.27	0.0103	-2.62	85
WM.vol.L	0.26	0.1687	1.41	28
WM.fa.L	-0.09	0.7393	-0.34	13
GM.vol.R	-0.07	0.5343	-0.62	69
WM.vol.R	0.23	0.316	1.03	19
WM.fa.R	-0.55	2e-04	-4.04	38

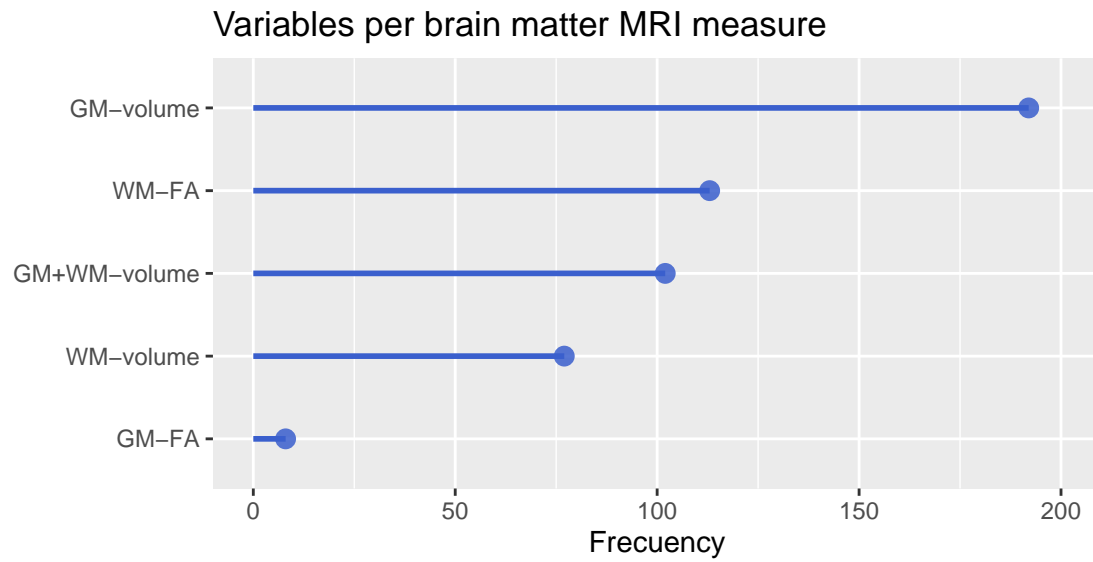
Treatment effect (standardised mean difference)

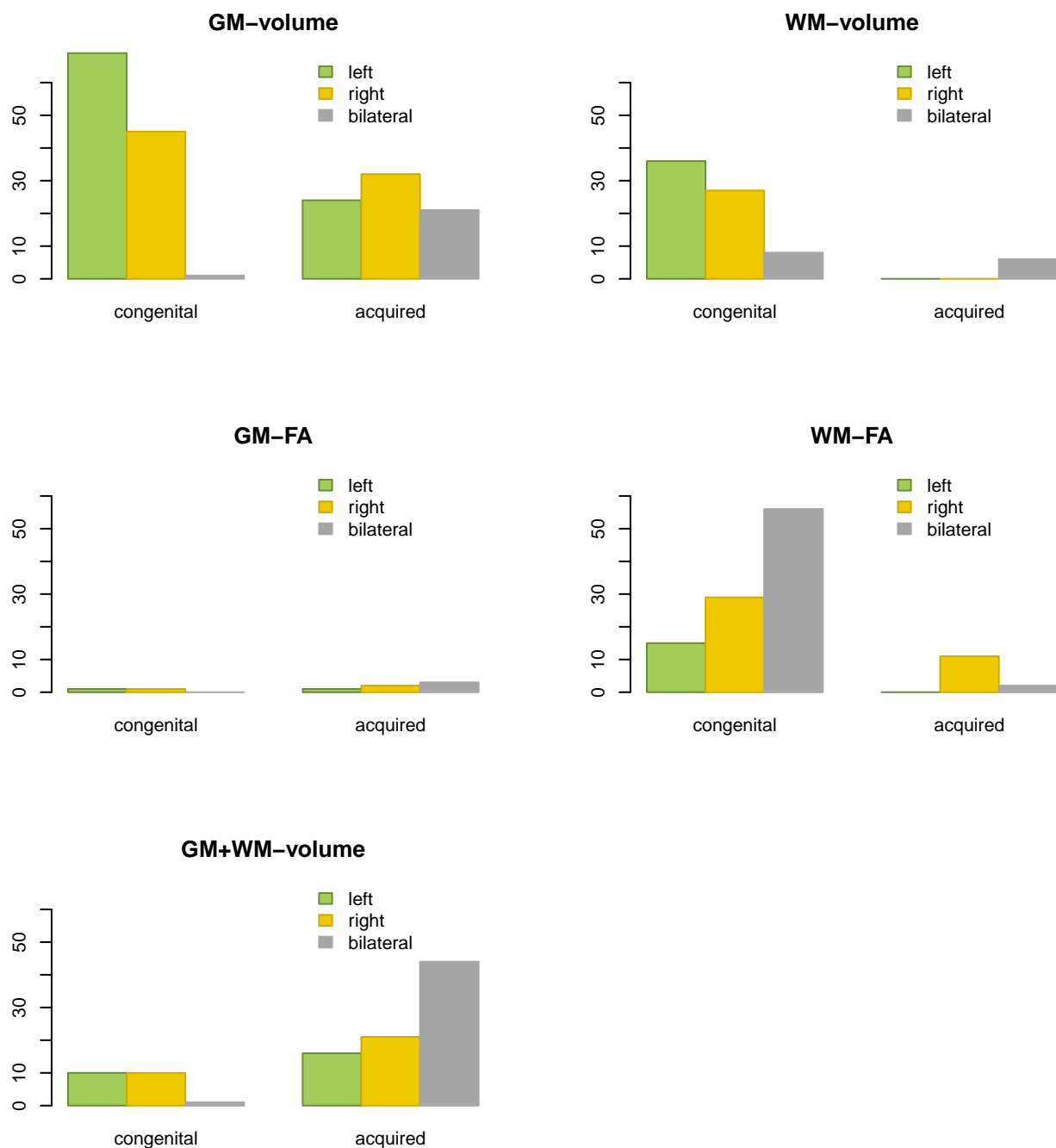


Treatment effect (standardised mean difference)



Meta-regression: Variables by Etiology, Brain matter and MRI measure





Gray Matter Volume: Random effects model no intercept covariated by Big area

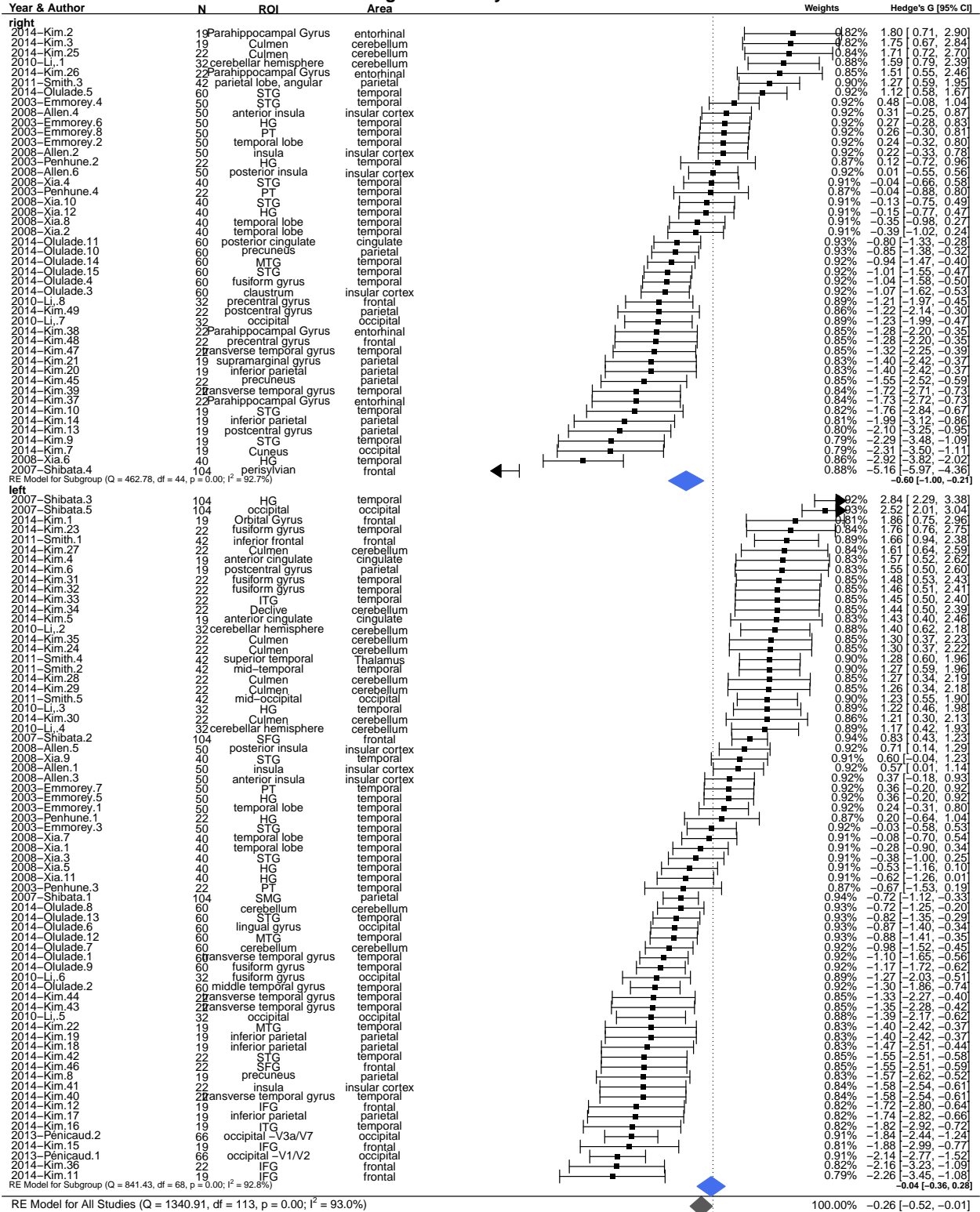
Table 11: Table continues below

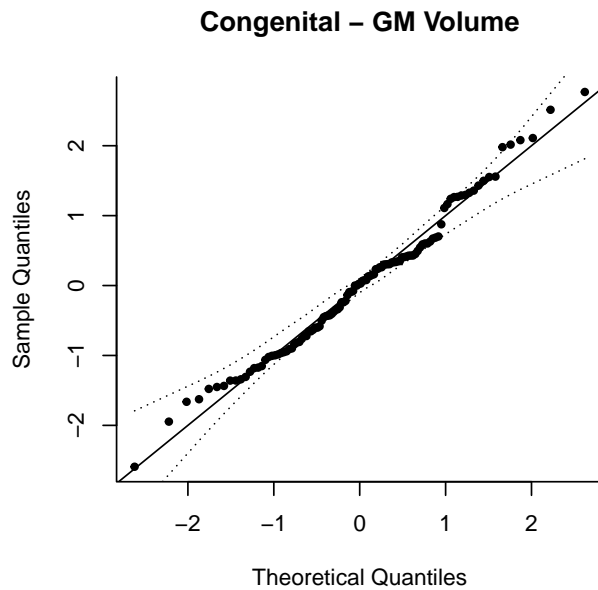
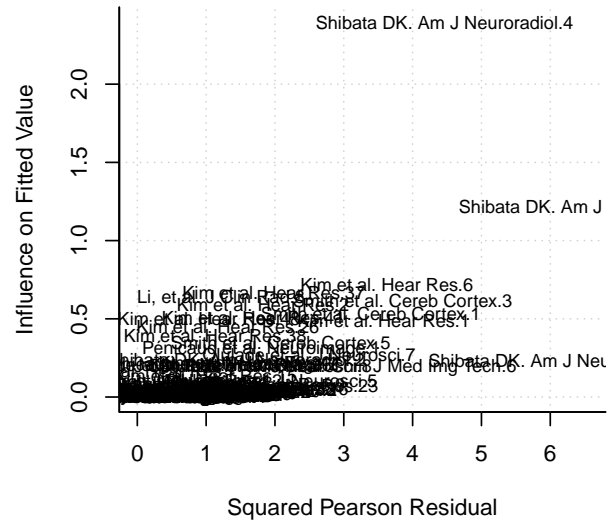
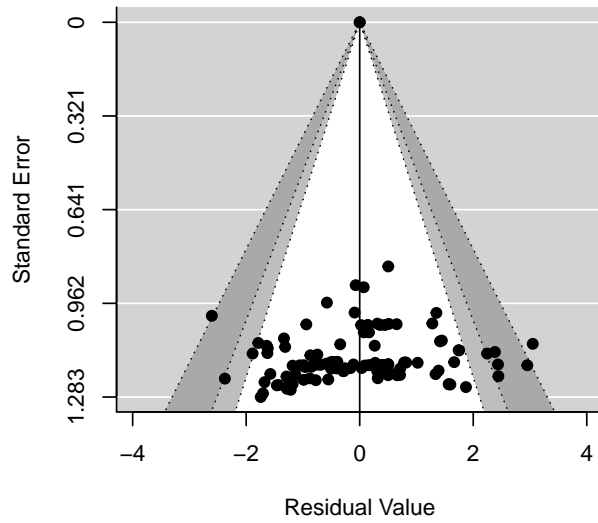
	HedgeG	se	zval	ci.lo	ci.up
left cerebellum	0.9013	0.3735	2.413	0.1693	1.633
left cingulate	1.5	0.9037	1.66	-0.2712	3.271
left frontal	-0.588	0.4468	-1.316	-1.464	0.2877
left insular cortex	0.0628	0.6065	0.1035	-1.126	1.252
left occipital	-0.5252	0.4567	-1.15	-1.42	0.3699
left parietal	-0.8875	0.5149	-1.724	-1.897	0.1217
left temporal	-0.116	0.2235	-0.5189	-0.554	0.3221
left Thalamus	1.282	1.213	1.056	-1.097	3.66
right cerebellum	1.682	0.7284	2.309	0.254	3.109

	HedgeG	se	zval	ci.lo	ci.up
right cingulate	-0.8018	1.193	-0.6721	-3.14	1.536
right entorhinal	0.05865	0.6339	0.09251	-1.184	1.301
right frontal	-2.559	0.7143	-3.583	-3.959	-1.159
right insular cortex	-0.1339	0.598	-0.2239	-1.306	1.038
right occipital	-1.73	0.8957	-1.932	-3.486	0.02545
right parietal	-1.113	0.4445	-2.503	-1.984	-0.2413
right temporal	-0.5427	0.2729	-1.989	-1.078	-0.007815

	pval	N
left cerebellum	0.01581	11
left cingulate	0.09694	2
left frontal	0.1882	8
left insular cortex	0.9175	4
left occipital	0.2502	7
left parietal	0.08478	6
left temporal	0.6039	30
left Thalamus	0.2909	1
right cerebellum	0.02096	3
right cingulate	0.5015	1
right entorhinal	0.9263	4
right frontal	0.0003399	3
right insular cortex	0.8228	4
right occipital	0.05341	2
right parietal	0.01233	8
right temporal	0.04675	20

Congenital – Gray Matter Volume





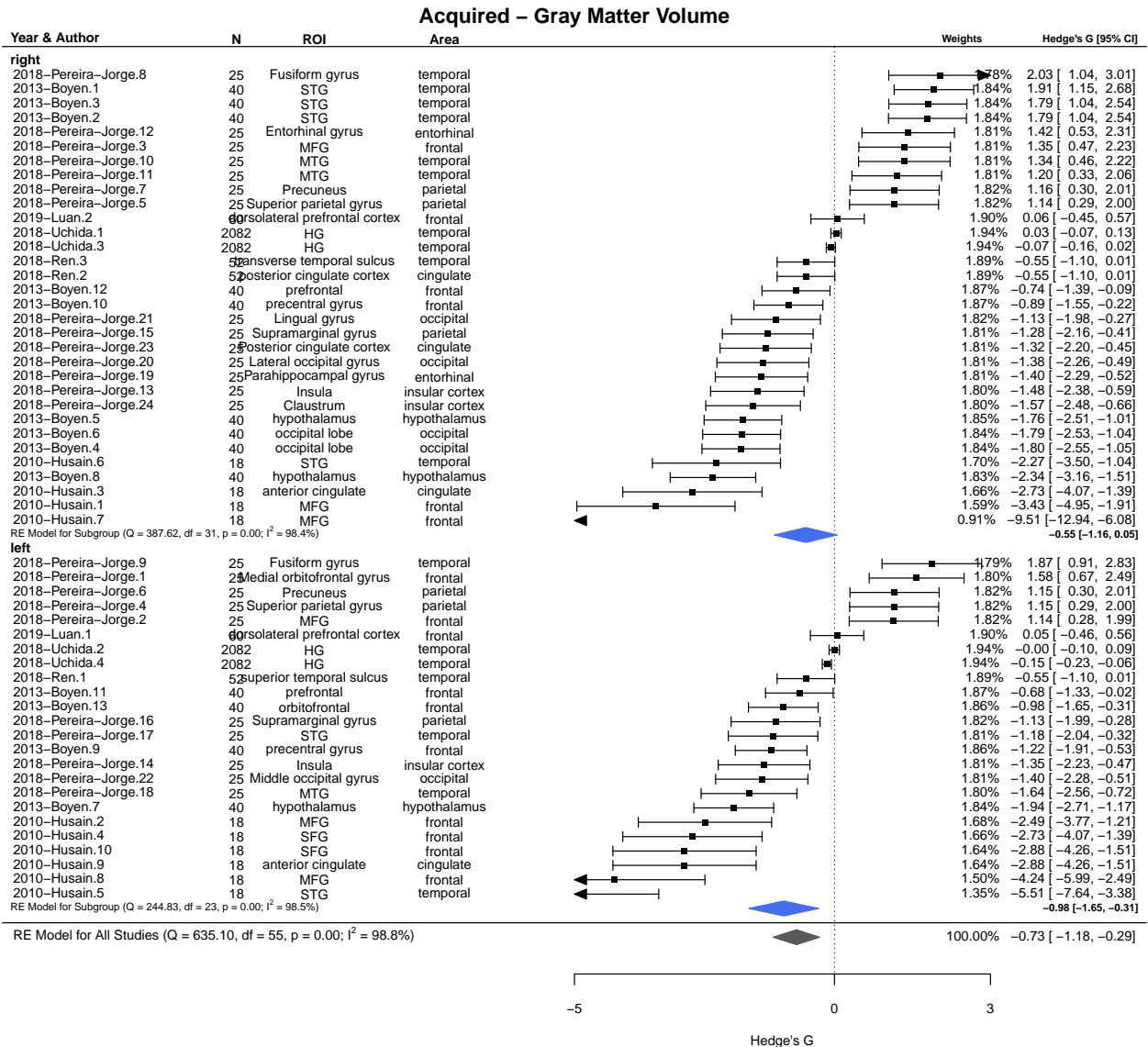
ACQUIRED - Meta-regressions of Gray Matter by Volume

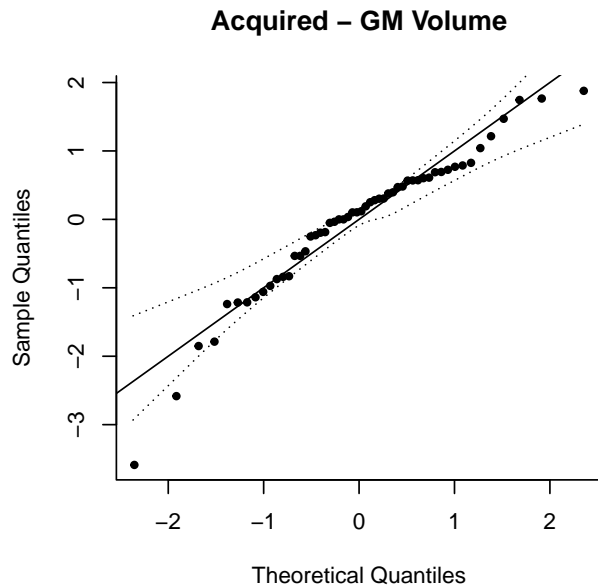
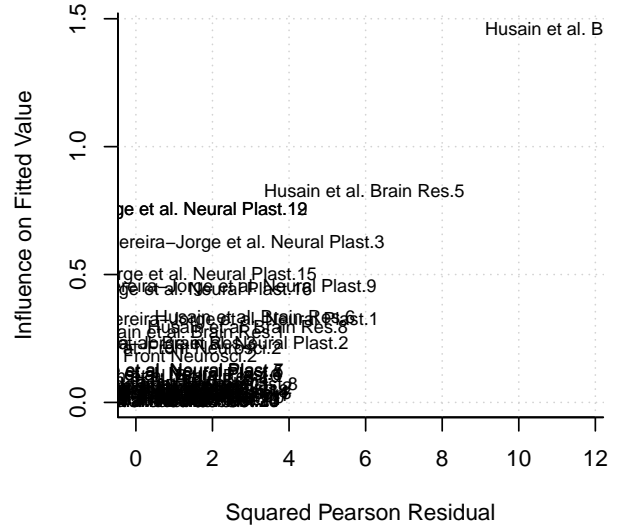
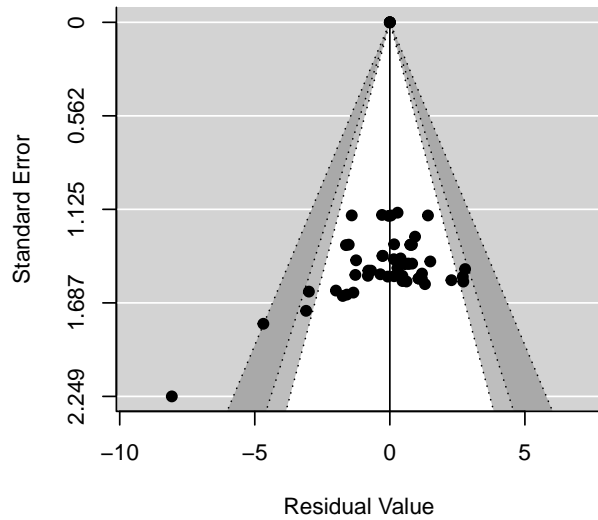
Random effects model no intercept covariated by Big area

Table 13: Table continues below

	HedgeG	se	zval	ci.lo	ci.up
left cingulate	-2.883	1.728	-1.669	-6.269	0.5024
left frontal	-1.14	0.5268	-2.164	-2.173	-0.1076
left hypothalamus	-1.937	1.626	-1.191	-5.124	1.25
left insular cortex	-1.353	1.641	-0.8248	-4.57	1.863
left occipital	-1.398	1.642	-0.8514	-4.616	1.82
left parietal	0.3896	0.9454	0.4121	-1.463	2.243
left temporal	-0.8302	0.6236	-1.331	-2.052	0.3921
right cingulate	-1.483	0.954	-1.554	-3.352	0.3872
right entorhinal	0.007072	1.161	0.006091	-2.269	2.283
right frontal	-1.438	0.7012	-2.05	-2.812	-0.06331
right hypothalamus	-2.047	1.151	-1.778	-4.304	0.2095
right insular cortex	-1.525	1.163	-1.311	-3.803	0.7542
right occipital	-1.524	0.8158	-1.868	-3.123	0.07522
right parietal	0.3405	0.9459	0.36	-1.513	2.194
right temporal	0.727	0.5141	1.414	-0.2806	1.735

	pval	N
left cingulate	0.09509	1
left frontal	0.03045	10
left hypothalamus	0.2335	1
left insular cortex	0.4095	1
left occipital	0.3945	1
left parietal	0.6803	3
left temporal	0.1831	7
right cingulate	0.1202	3
right entorhinal	0.9951	2
right frontal	0.04034	6
right hypothalamus	0.0754	2
right insular cortex	0.1898	2
right occipital	0.0618	4
right parietal	0.7189	3
right temporal	0.1573	10





CONGENITAL - White Matter by VOLUME

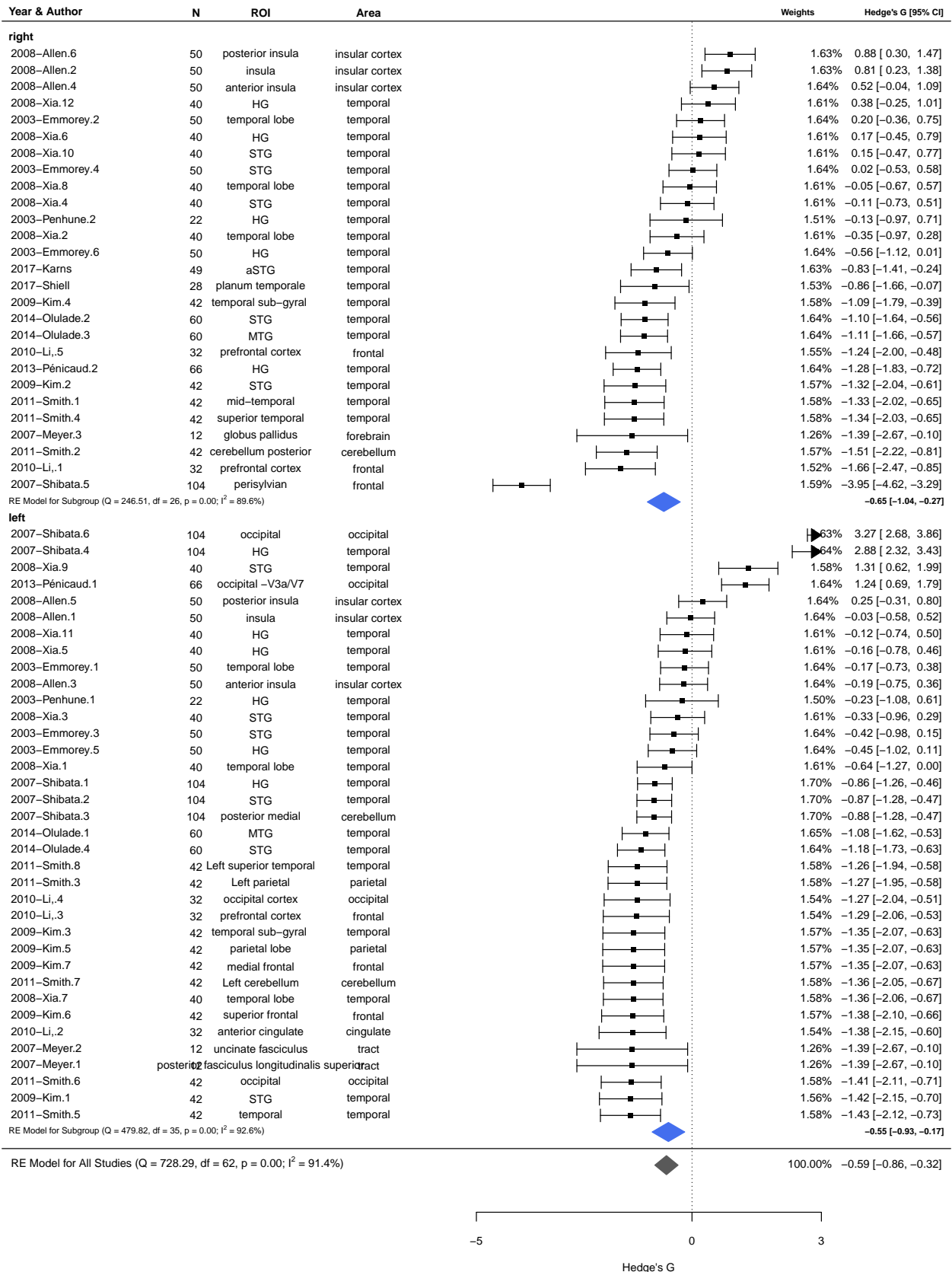
Random effects model no intercept covariated by Big area

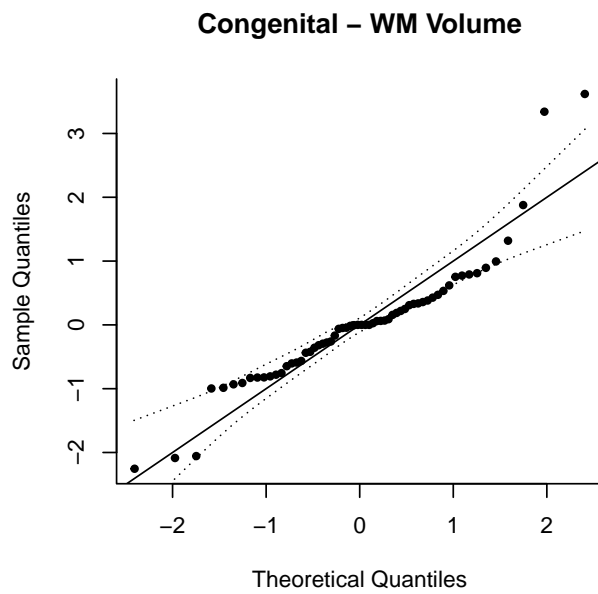
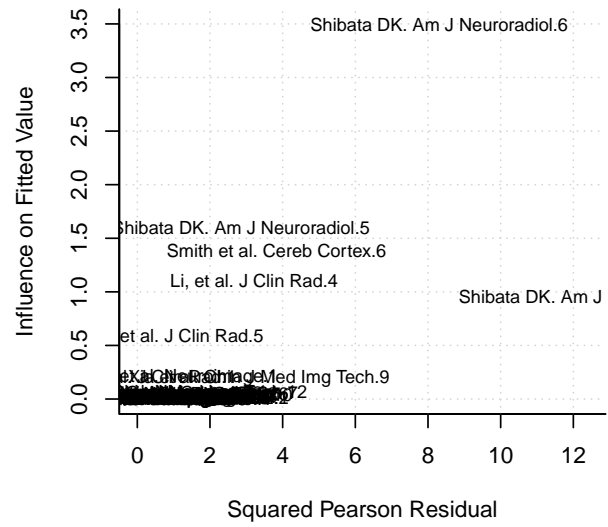
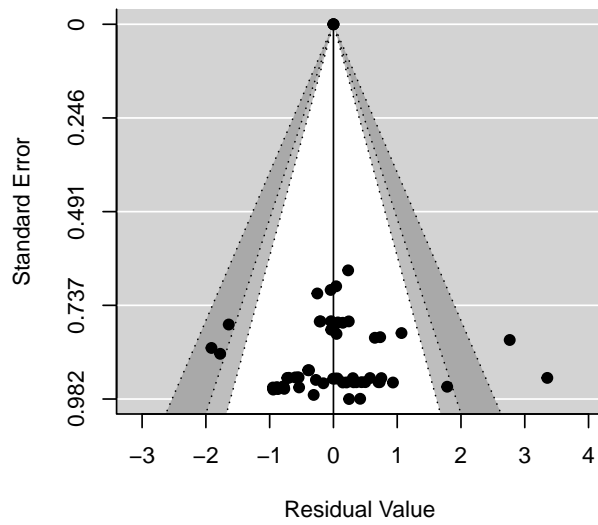
Table 15: Table continues below

	HedgeG	se	zval	ci.lo	ci.up
left cerebellum	-1.107	0.6745	-1.641	-2.429	0.2149
left cingulate	-1.379	0.9926	-1.389	-3.324	0.5668
left frontal	-1.34	0.5684	-2.358	-2.454	-0.2262
left insular cortex	0.007913	0.5504	0.01438	-1.071	1.087
left occipital	0.5024	0.4846	1.037	-0.4475	1.452
left parietal	-1.308	0.6914	-1.892	-2.663	0.04705
left temporal	-0.478	0.2211	-2.163	-0.9113	-0.04478
left tract	-1.386	0.7931	-1.747	-2.94	0.1688
right cerebellum	-1.513	0.9789	-1.546	-3.432	0.4051
right forebrain	-1.386	1.122	-1.235	-3.584	0.8126
right frontal	-2.31	0.5697	-4.055	-3.426	-1.193
right insular cortex	0.737	0.5521	1.335	-0.3451	1.819
right temporal	-0.5529	0.2218	-2.493	-0.9875	-0.1183

	pval	N
left cerebellum	0.1007	2
left cingulate	0.1649	1
left frontal	0.01838	3
left insular cortex	0.9885	3
left occipital	0.2999	4
left parietal	0.0585	2
left temporal	0.03058	19
left tract	0.08061	2
right cerebellum	0.1221	1
right forebrain	0.2167	1
right frontal	5.021e-05	3
right insular cortex	0.1819	3
right temporal	0.01266	19

Congenital White Matter Volume

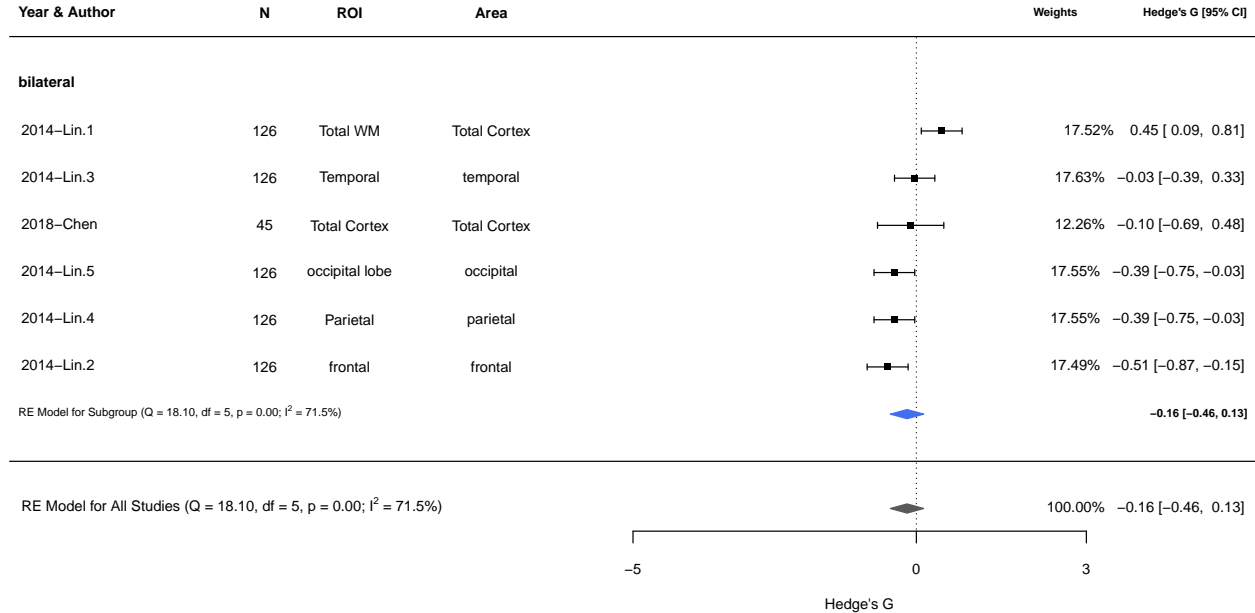




ACQUIRED - White Matter by VOLUME (ONLY BILATERAL)

Not enough values for the Random effects model no intercept covariated by Big area and Side (left or right)

acquired White Matter Volume



	HedgeG	se	zval	ci.lo	ci.up
bilateral frontal	-0.5069	0.35	-1.448	-1.193	0.1792

bilateral occipital -0.3876 0.3494 -1.109 -1.073 0.2972

bilateral parietal -0.3876 0.3494 -1.109 -1.073 0.2972

bilateral temporal -0.02982 0.3486 -0.08555 -0.713 0.6534

bilateral Total Cortex 0.2239 0.2691 0.8321 -0.3035 0.7514

Table 18: Table continues below

	pval	N
bilateral frontal	0.1476	1
bilateral occipital	0.2673	1
bilateral parietal	0.2673	1
bilateral temporal	0.9318	1
bilateral Total Cortex	0.4053	2

Nothing is significant

CONGENITAL - White Matter by FA fractional anisotropy

Random effects model no intercept covariated by Big area

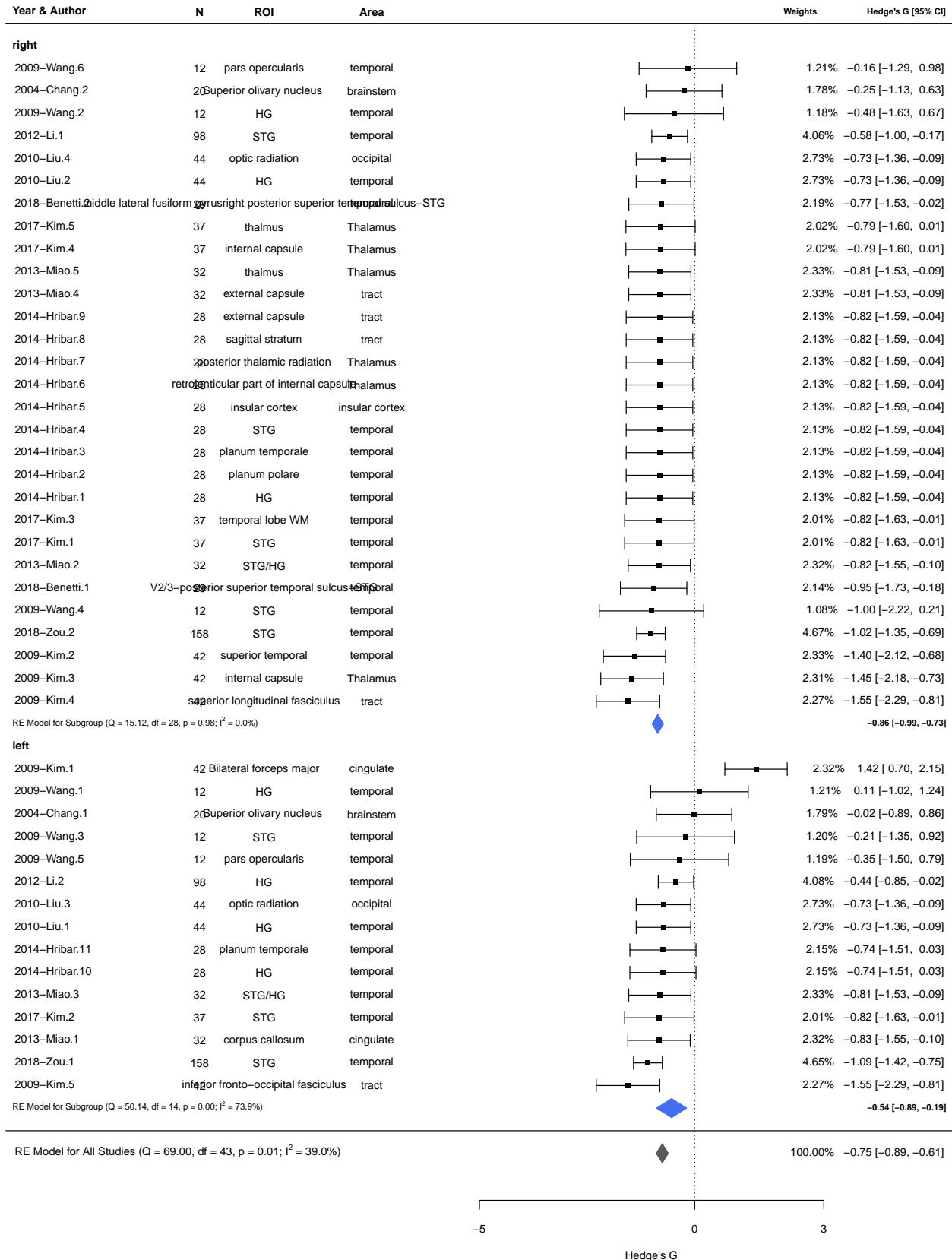
Table 19: Table continues below

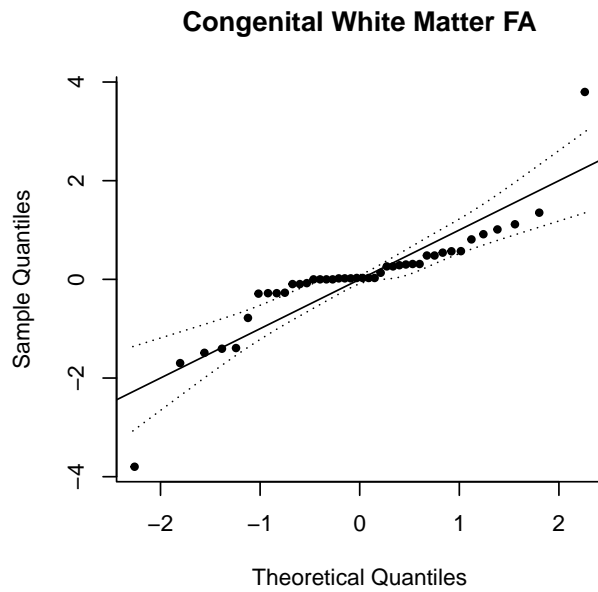
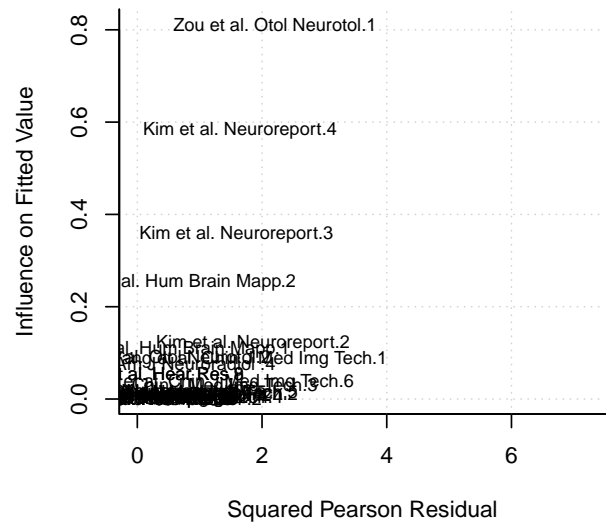
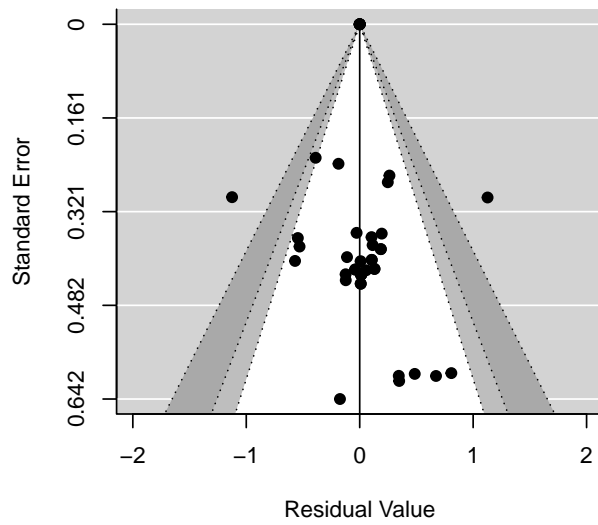
	HedgeG	se	zval	ci.lo	ci.up
left brainstem	-0.01557	0.4891	-0.03183	-0.9742	0.9431
left cingulate	0.297	0.2965	1.002	-0.2841	0.8781
left occipital	-0.7254	0.3791	-1.914	-1.468	0.01755
left temporal	-0.698	0.1265	-5.518	-0.946	-0.4501
left tract	-1.549	0.425	-3.645	-2.382	-0.7163
right brainstem	-0.2476	0.4908	-0.5044	-1.21	0.7145
right insular cortex	-0.8178	0.4415	-1.852	-1.683	0.04759
right occipital	-0.7254	0.3791	-1.914	-1.468	0.01755

	HedgeG	se	zval	ci.lo	ci.up
right temporal	-0.8298	0.1036	-8.013	-1.033	-0.6269
right Thalamus	-0.9238	0.1789	-5.164	-1.274	-0.5732
right tract	-1.004	0.2156	-4.656	-1.427	-0.5813

	pval	N
left brainstem	0.9746	1
left cingulate	0.3165	2
left occipital	0.05566	1
left temporal	3.421e-08	10
left tract	0.000267	1
right brainstem	0.614	1
right insular cortex	0.064	1
right occipital	0.05566	1
right temporal	1.121e-15	16
right Thalamus	2.416e-07	6
right tract	3.226e-06	4

Congenital White Matter FA



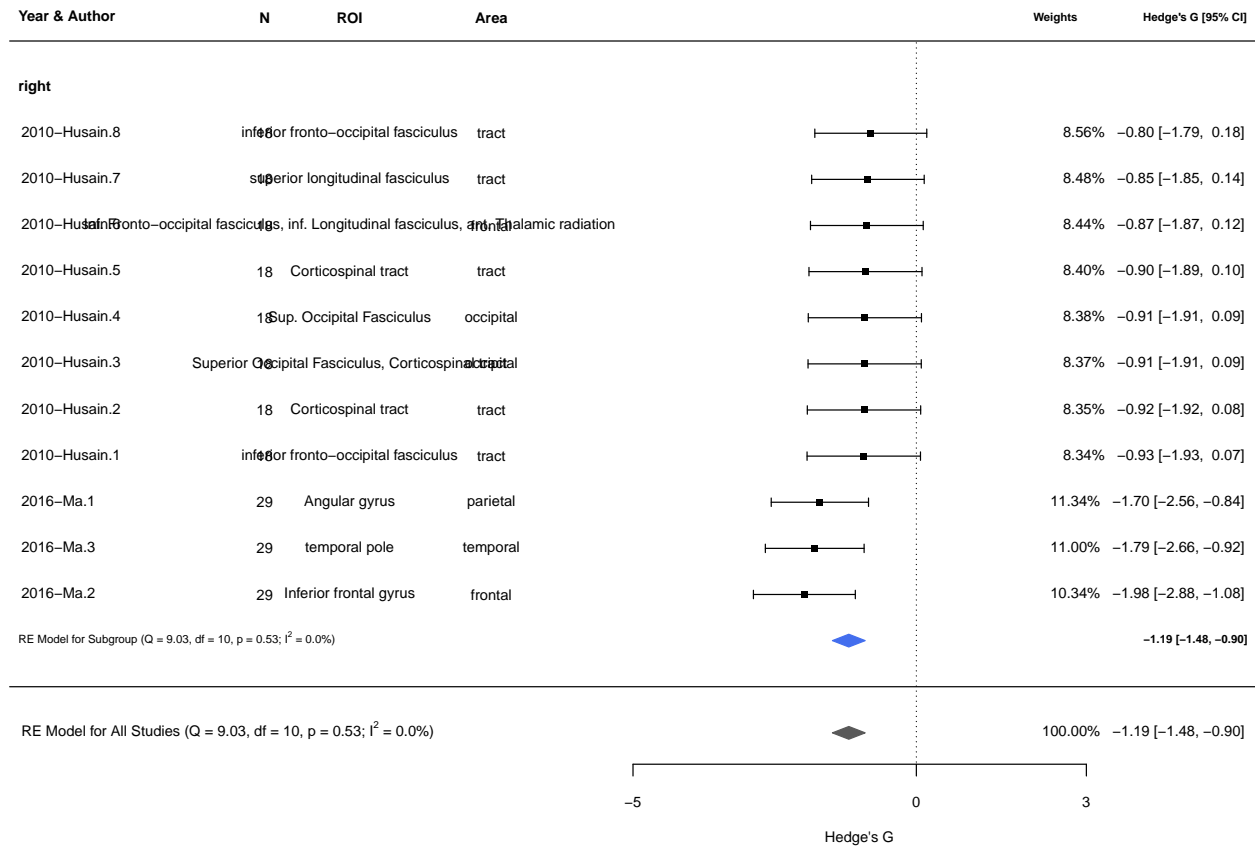


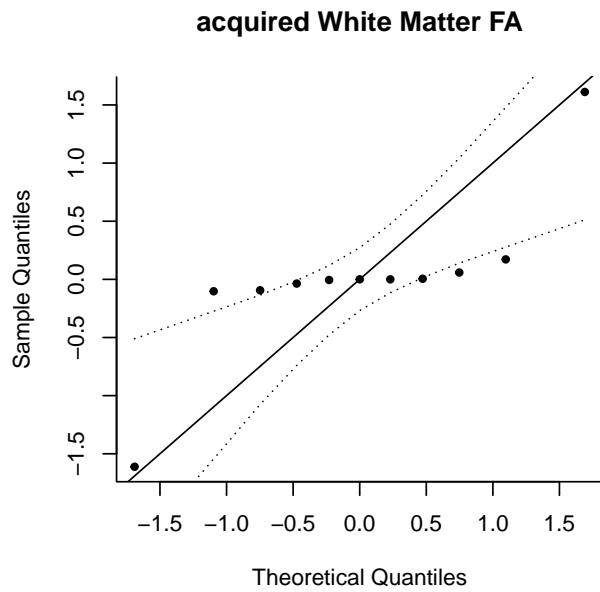
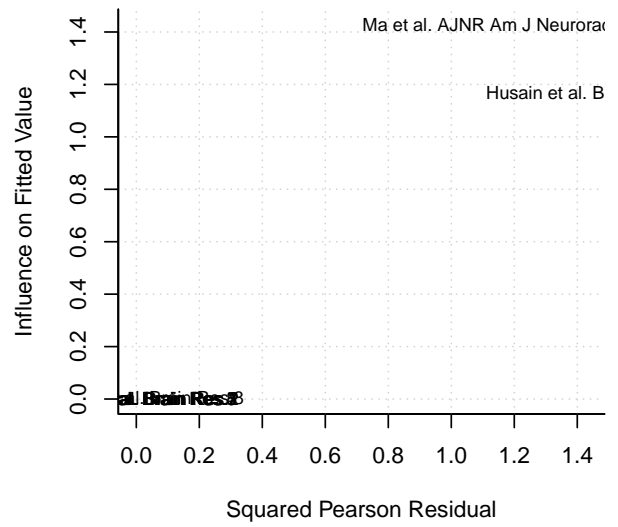
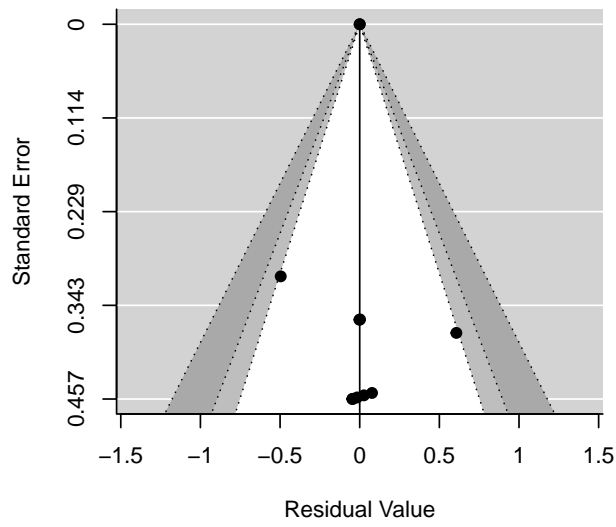
ACQUIRED - White Matter by FA fractional anisotropy (ONLY RIGHT)

Random effects model no intercept covariated by Big area

	HedgeG	se	zval	ci.lo	ci.up	p.val	N
right frontal	-1.48	0.3403	-4.35	-2.147	-0.8134	1.36e-05	2
right occipital	-0.9105	0.3603	-2.527	-1.617	-0.2042	0.01151	2
right parietal	-1.703	0.4379	-3.888	-2.561	-0.8443	0.0001011	1
right temporal	-1.793	0.4446	-4.034	-2.665	-0.922	5.488e-05	1
right tract	-0.8812	0.2272	-3.878	-1.326	-0.4359	0.0001052	5

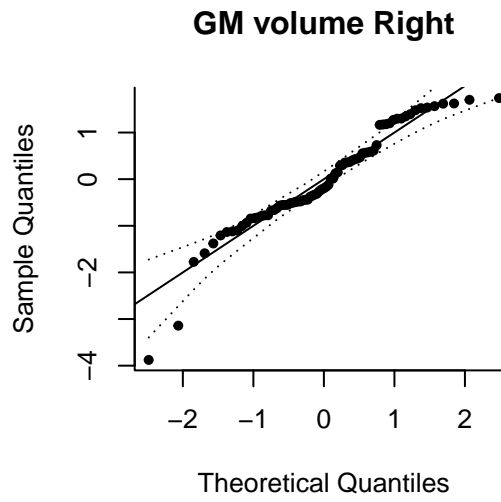
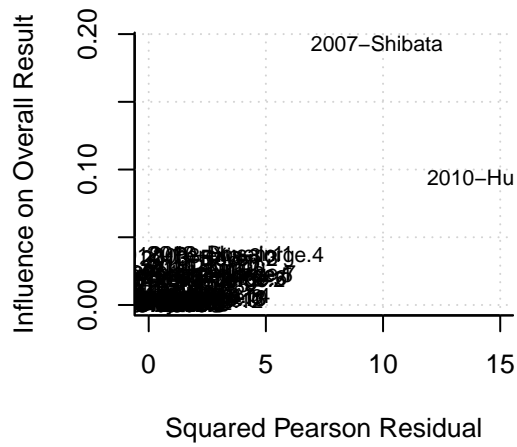
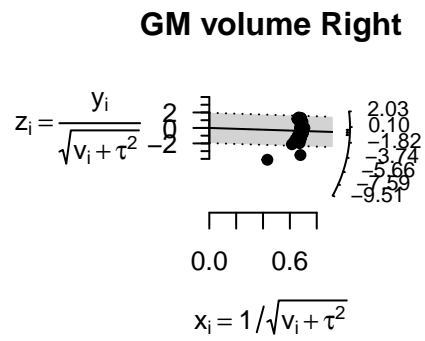
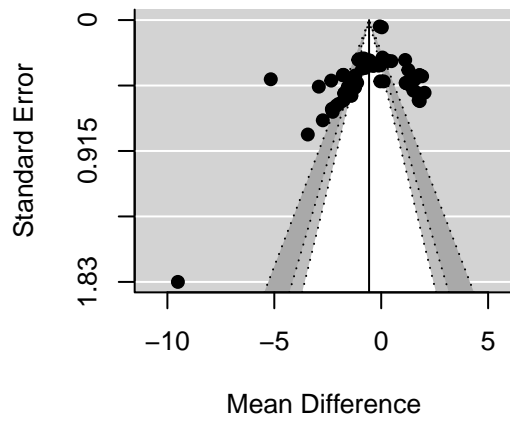
acquired White Matter FA



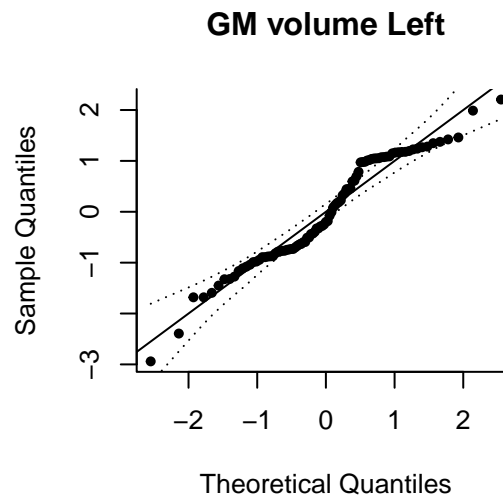
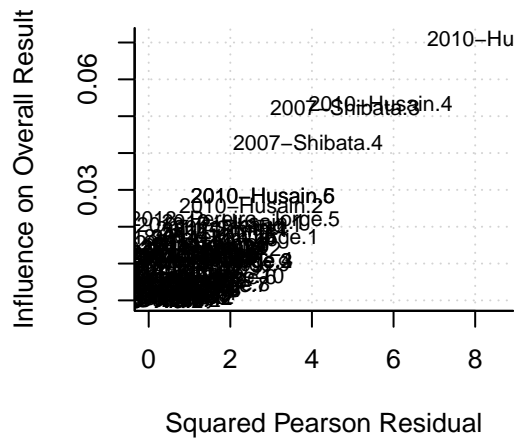
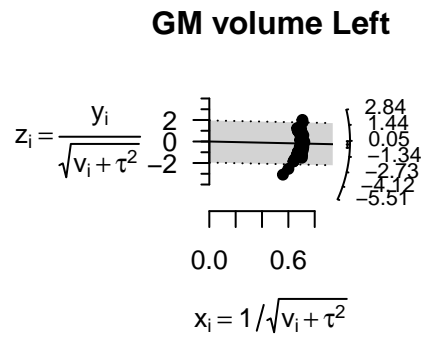
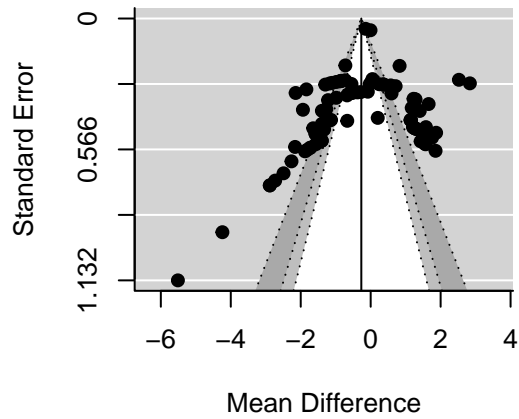


Supplementary material: heterogeneity per model

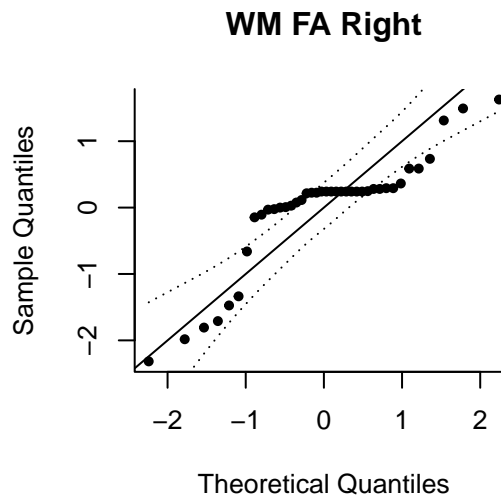
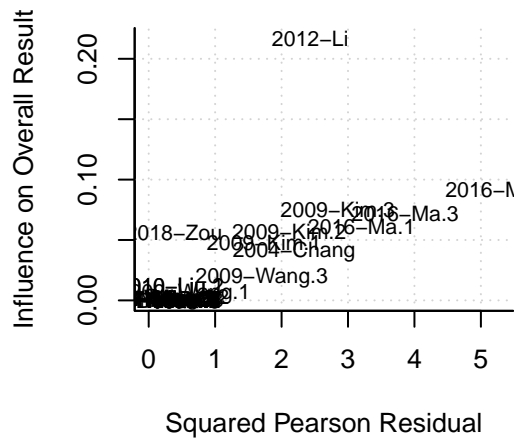
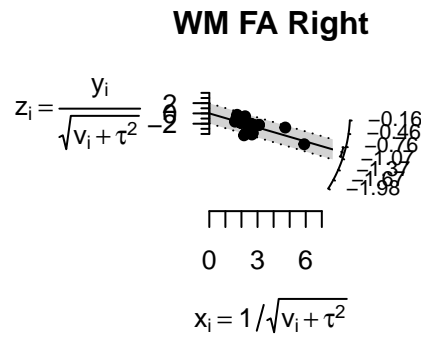
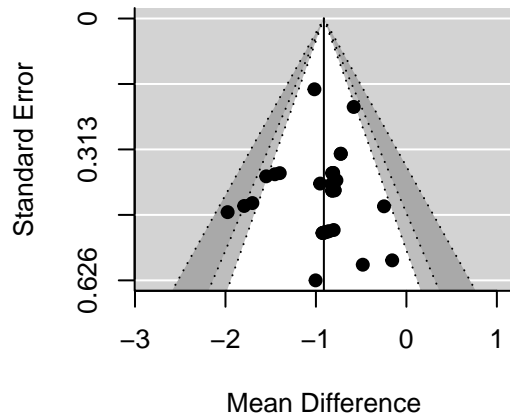
Heterogeneity: GM volume Right



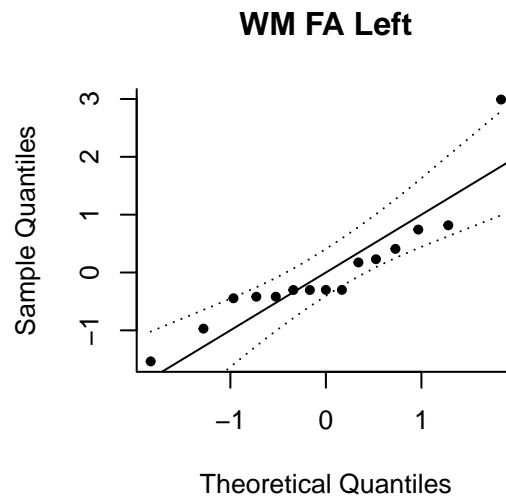
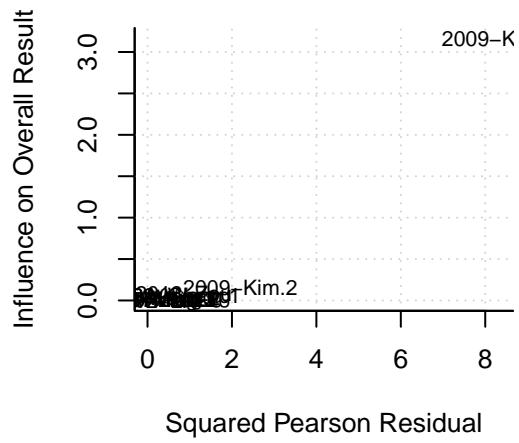
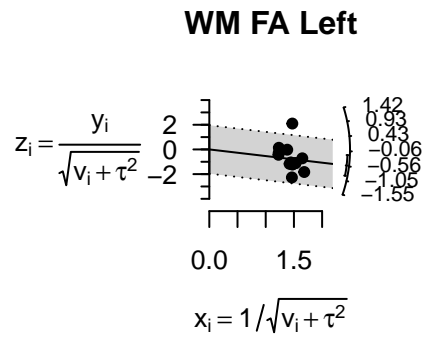
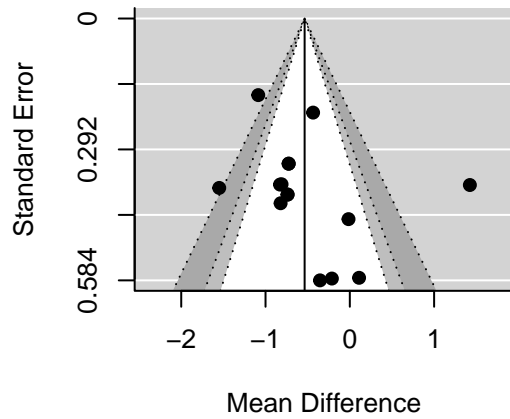
Heterogeney: GM volume Left



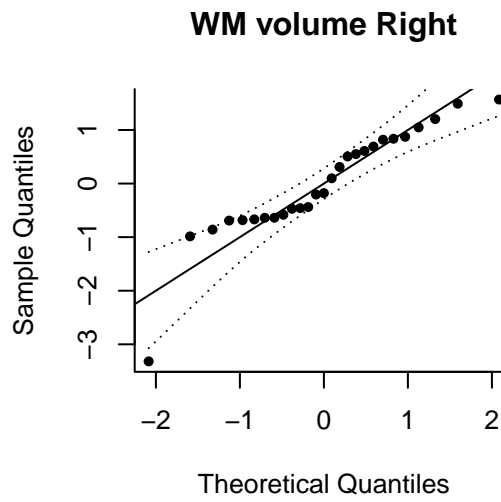
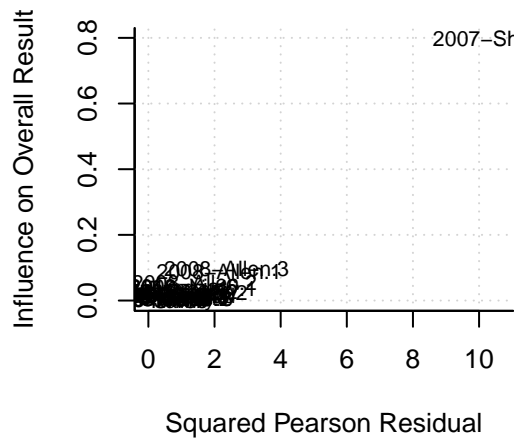
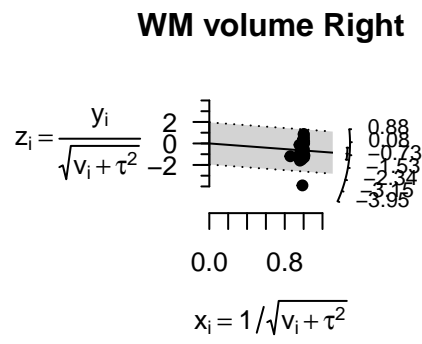
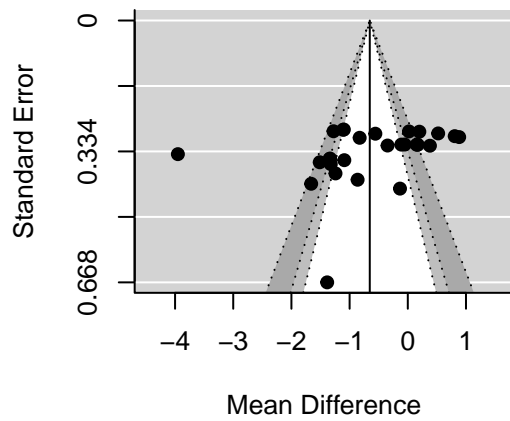
Heterogeneity: WM FA Right



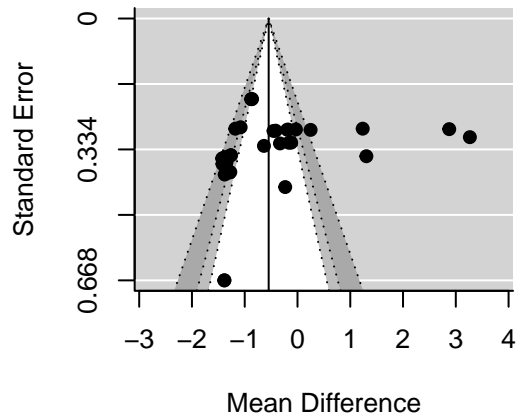
Heterogeneity: WM FA Left



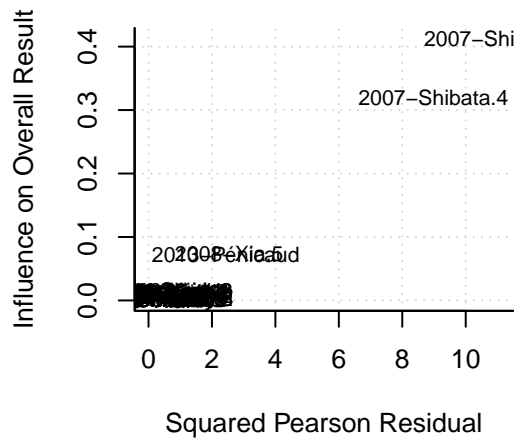
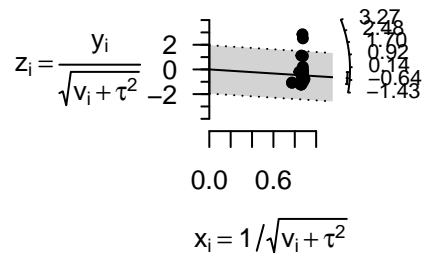
Heterogeneity: WM volume Right



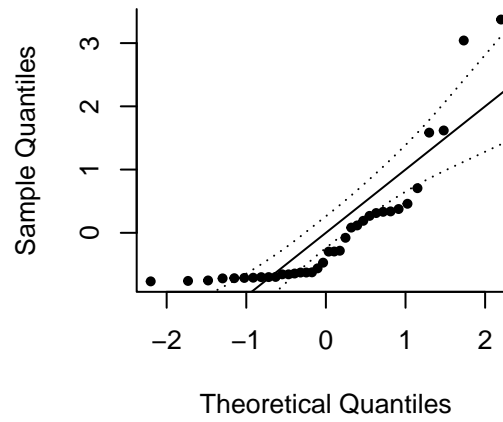
Heterogeneity: WM volume Left



WM volume Left

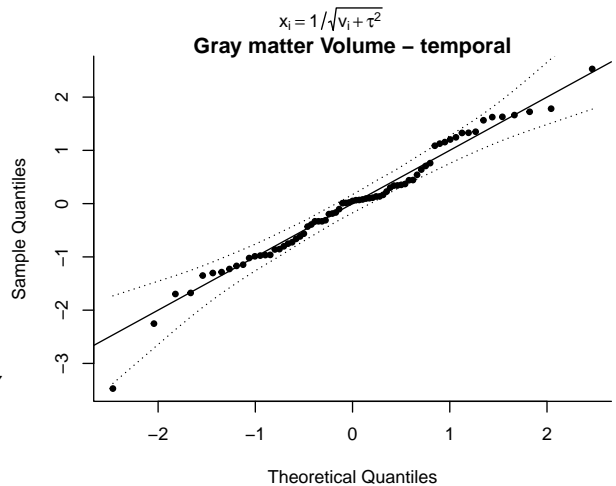
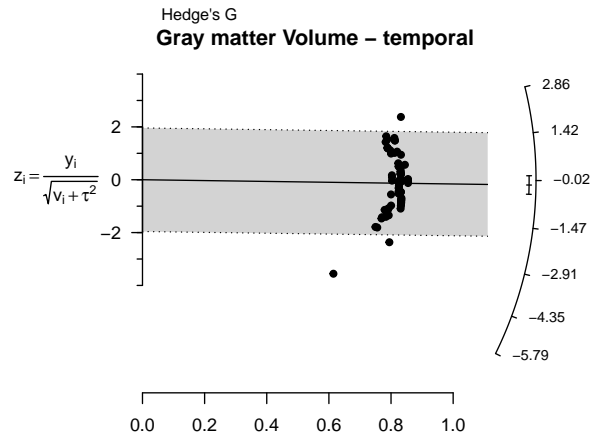


WM volume Left

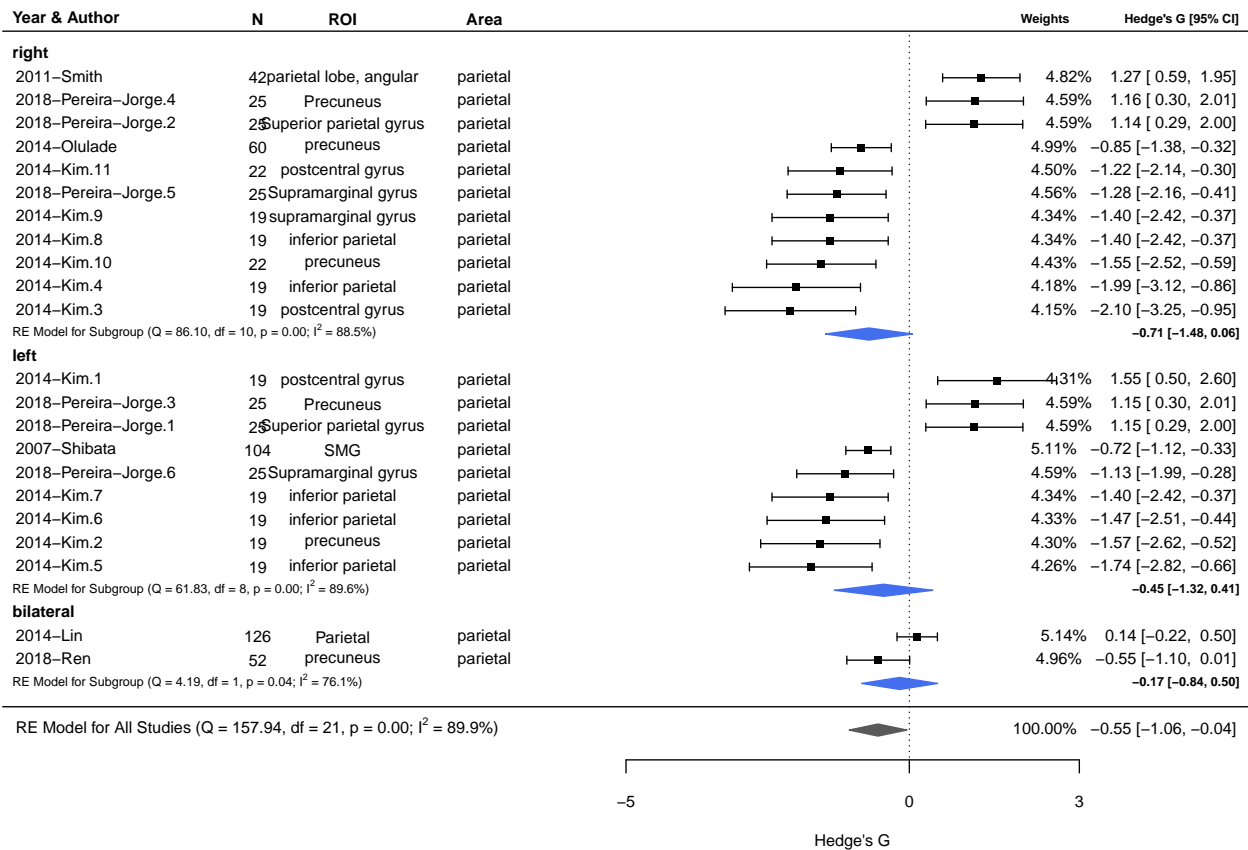


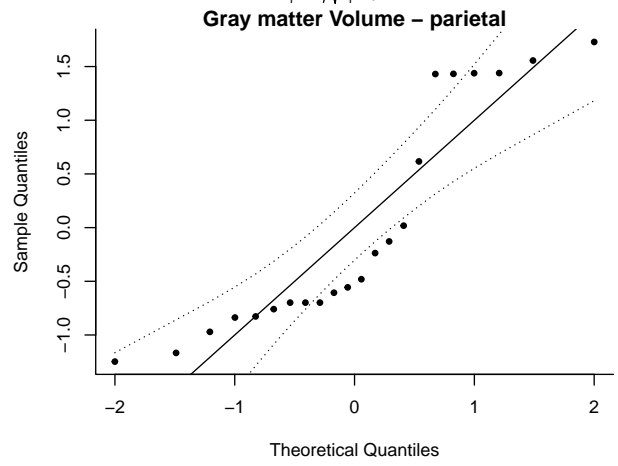
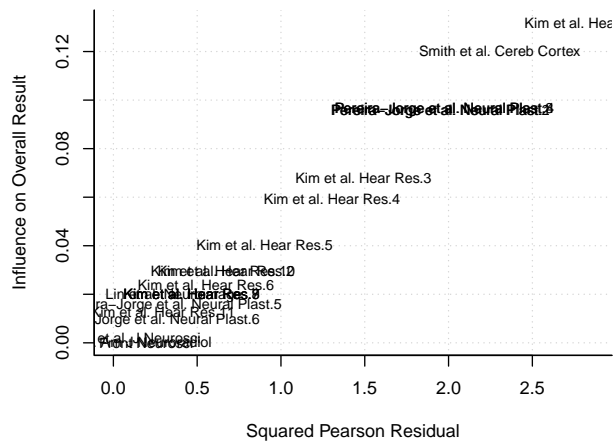
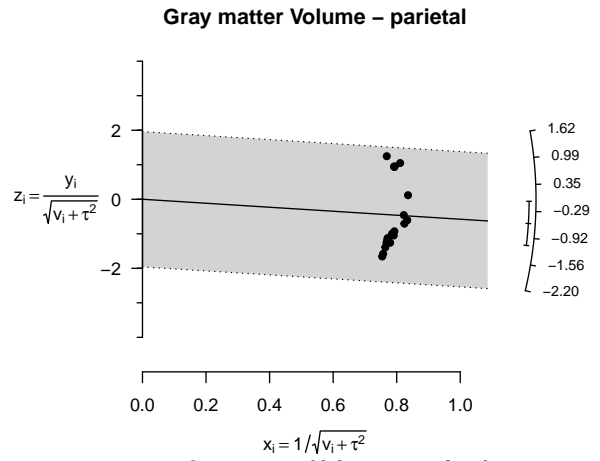
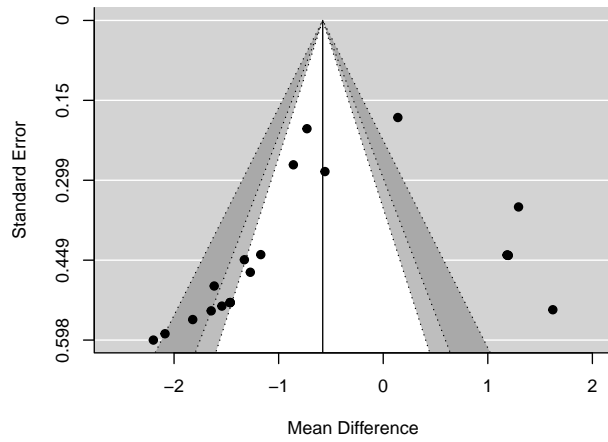
Gray matter Volume - temporal

Year & Author	N	ROI	Area	Weights	Hedge's G [95% CI]
total					
Smith	100	FG	temporal	1.41%	0.74 [0.10, 1.39]
Pereira-Jorge.1	25	Fusiform gyrus	temporal	1.27%	2.03 [1.04, 3.01]
Pereira-Jorge.3	25	FG	temporal	1.27%	1.99 [0.99, 2.99]
Pereira-Jorge.4	25	FG	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.4	20	temporal lobe	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.3	20	temporal lobe	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.2	20	temporal lobe	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.1	20	temporal lobe	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.5	20	transverse temporal sulcus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.6	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.7	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.8	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.9	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.10	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.11	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.12	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.13	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.14	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.15	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.16	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.17	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.18	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.19	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.20	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.21	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.22	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.23	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.24	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.25	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.26	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.27	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.28	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.29	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.30	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.31	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.32	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.33	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.34	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.35	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.36	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.37	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.38	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.39	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.40	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.41	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.42	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.43	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.44	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.45	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene.46	20	transverse temporal gyrus	temporal	1.27%	1.99 [0.99, 2.99]
Dehaene					

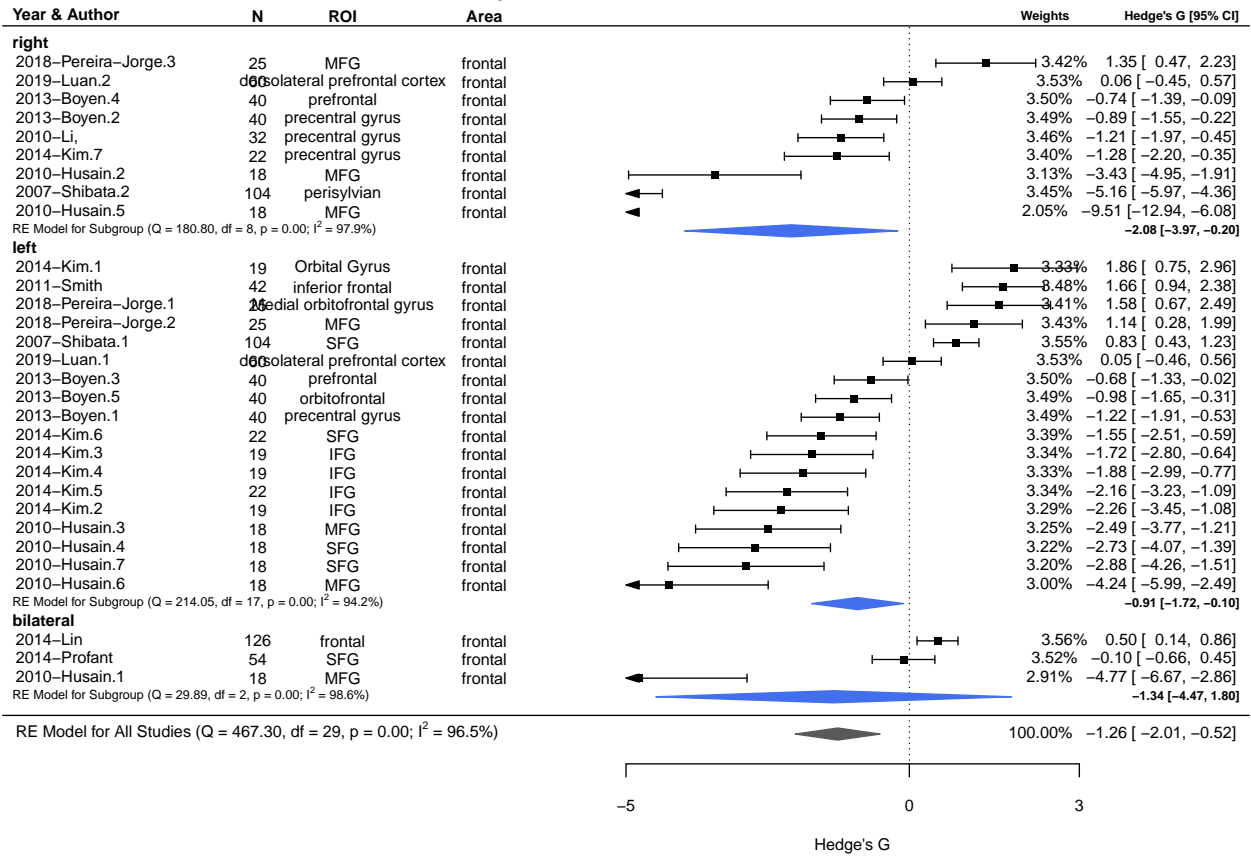


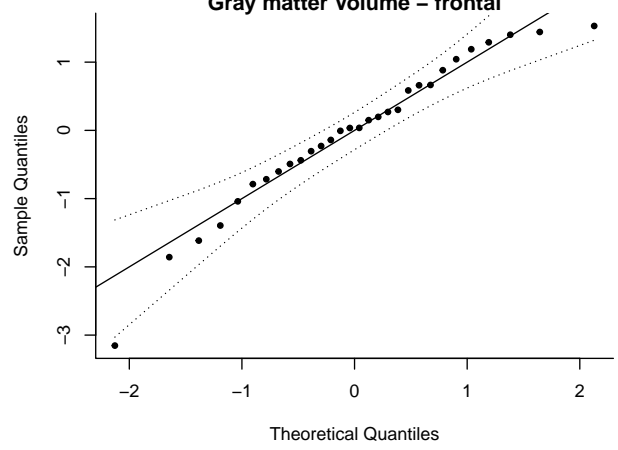
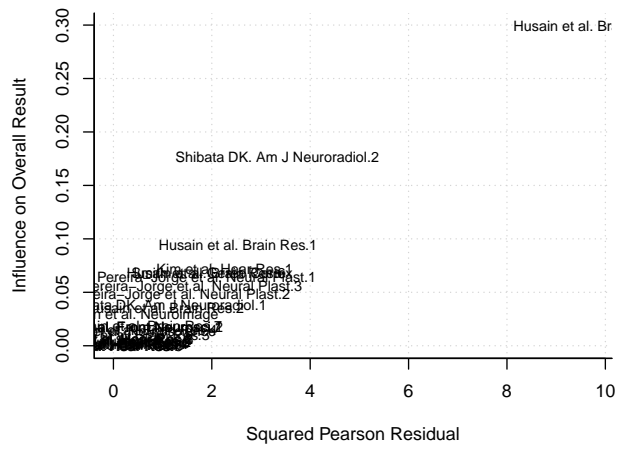
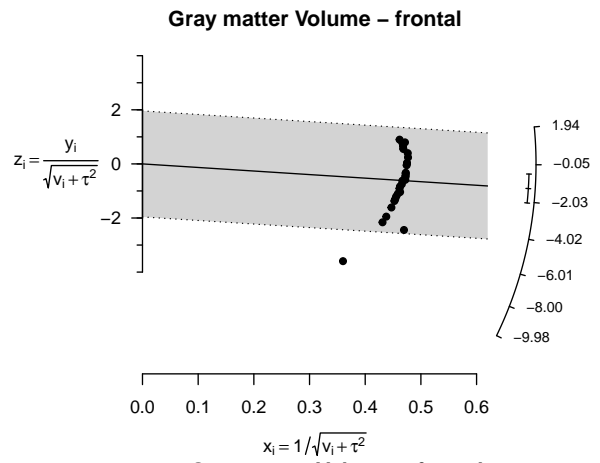
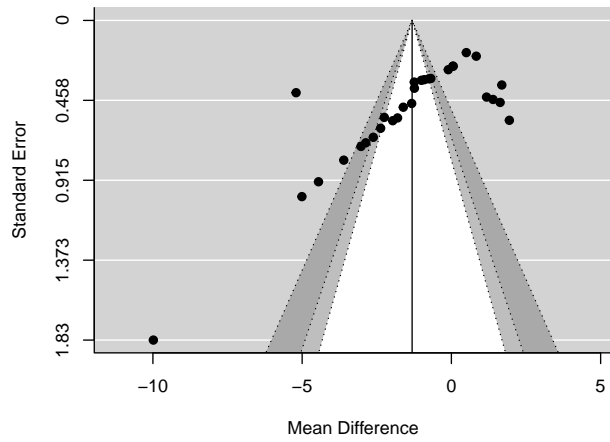
Gray matter Volume – parietal



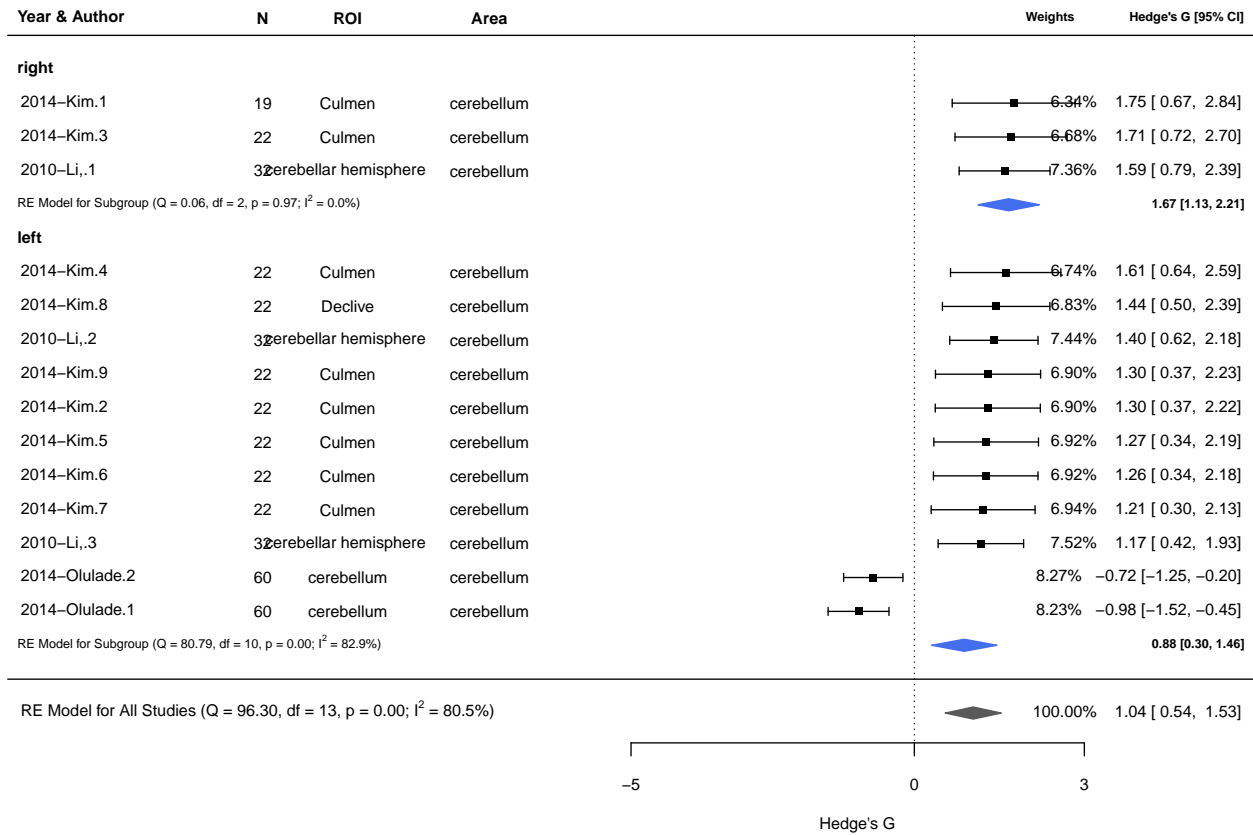


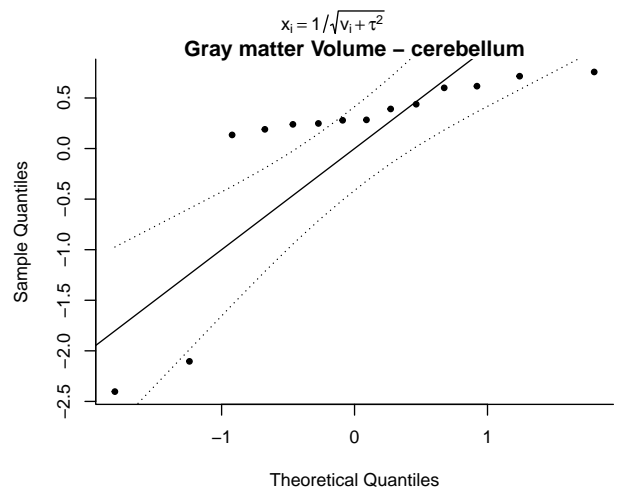
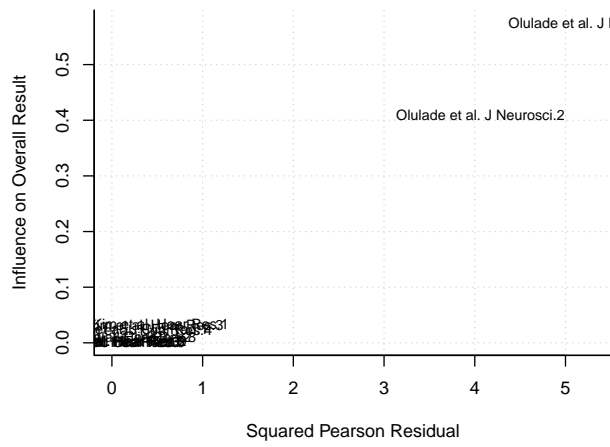
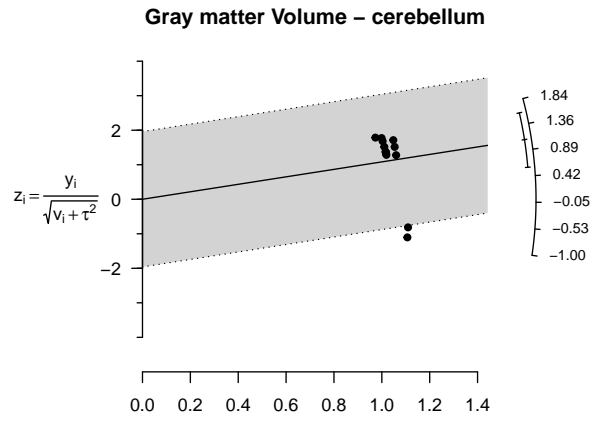
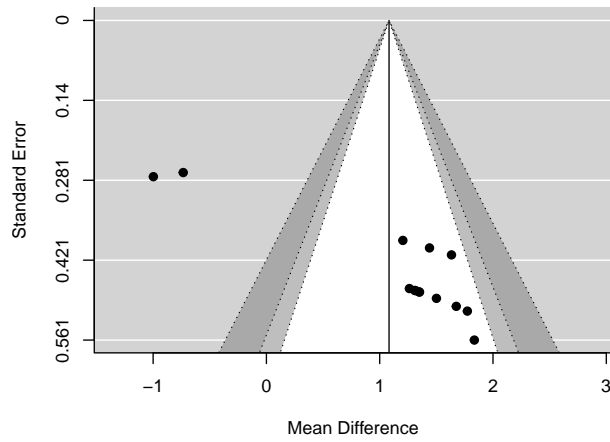
Gray matter Volume – frontal



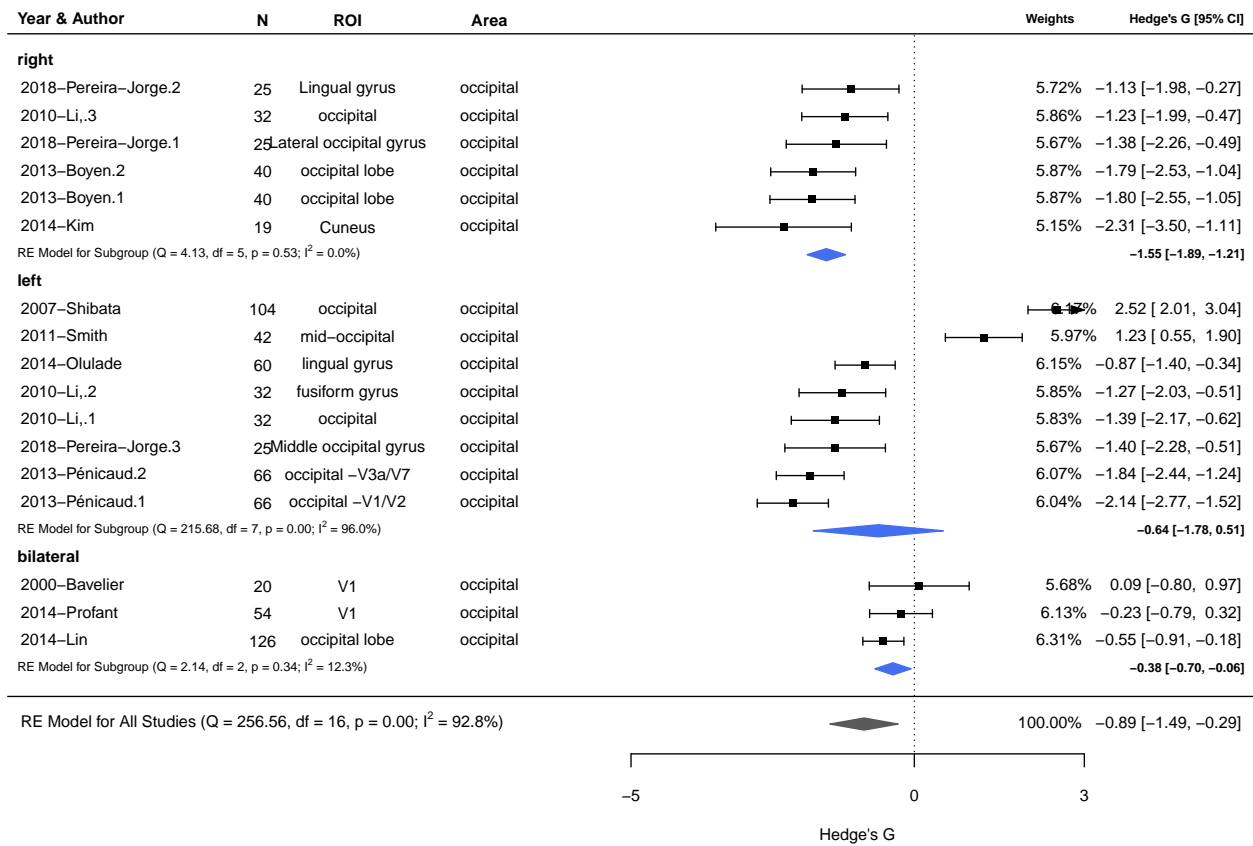


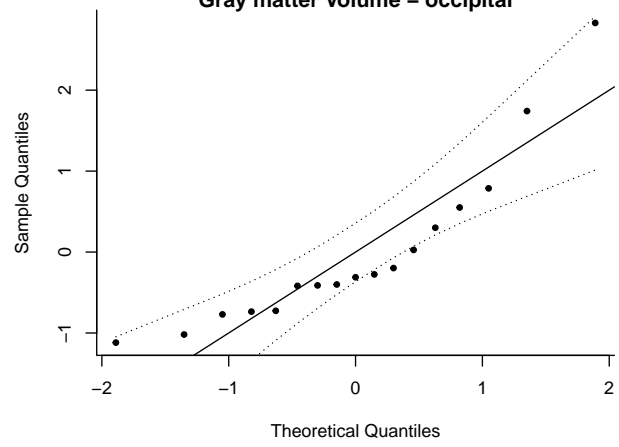
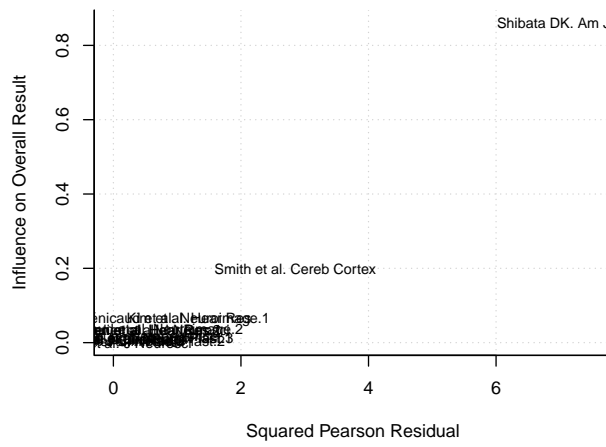
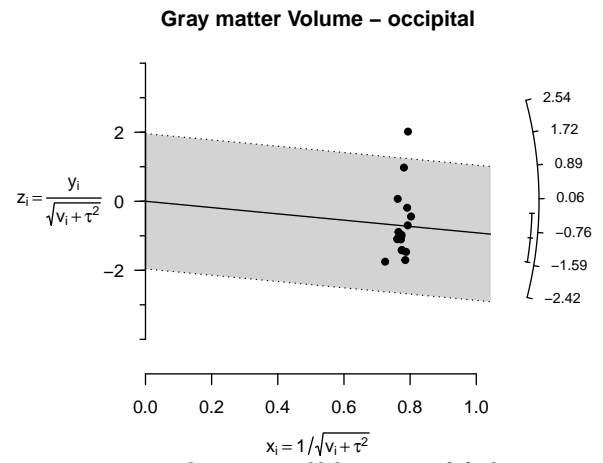
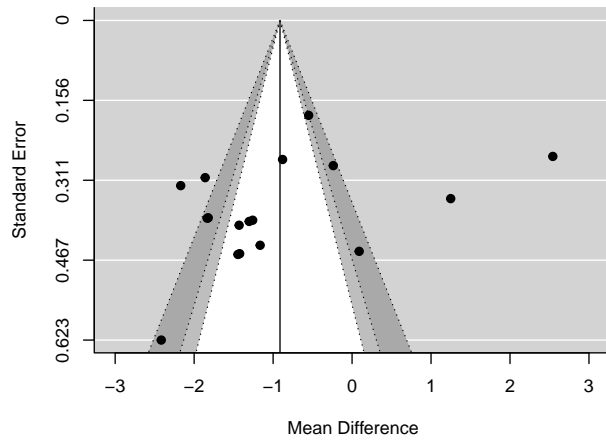
Gray matter Volume – cerebellum



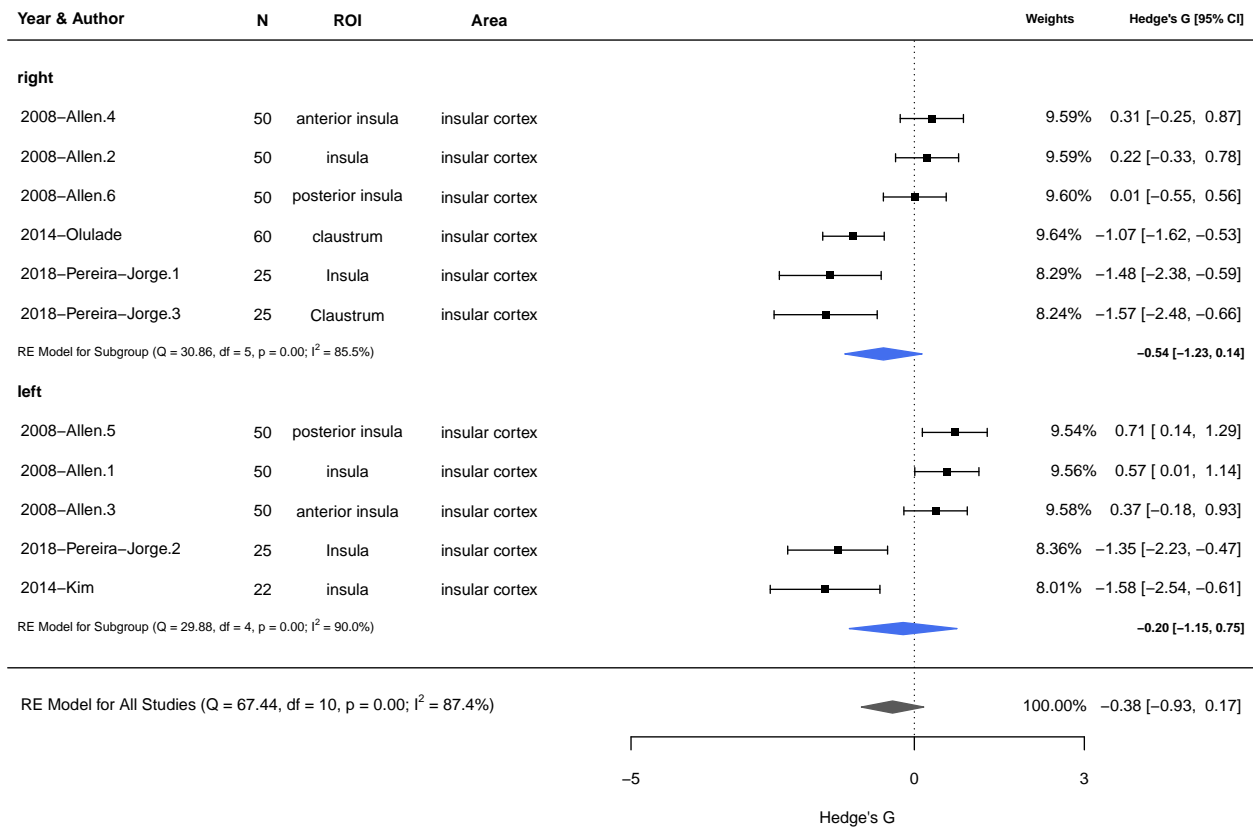


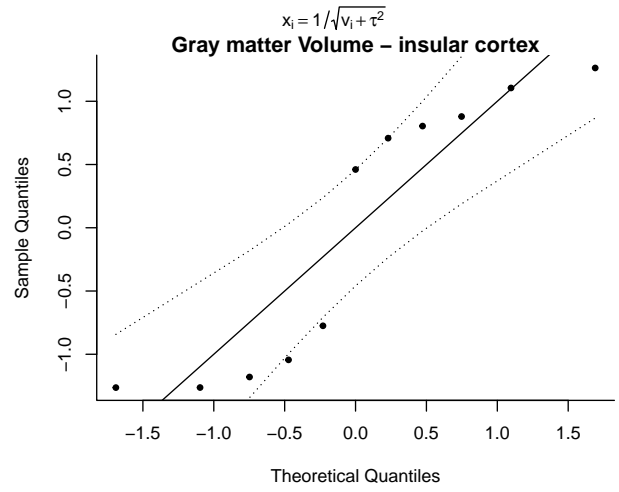
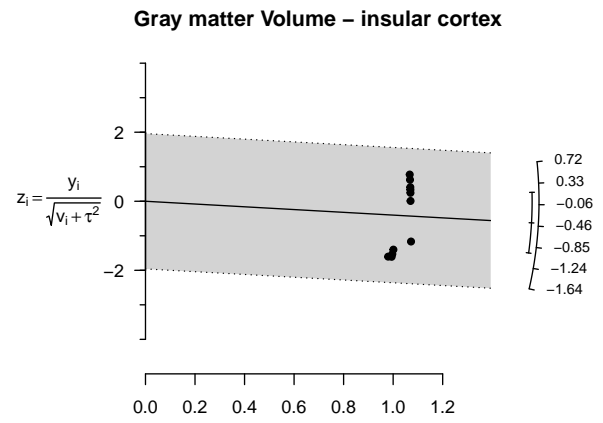
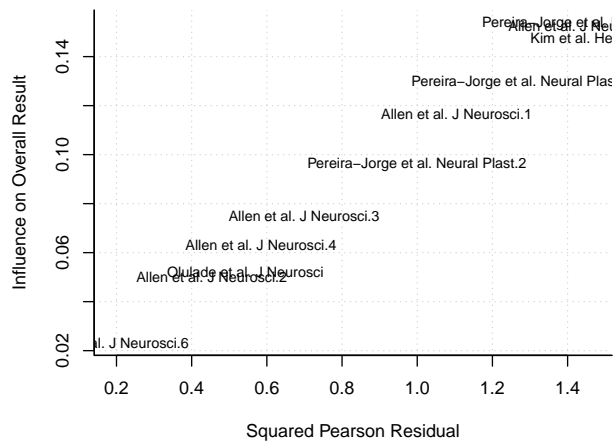
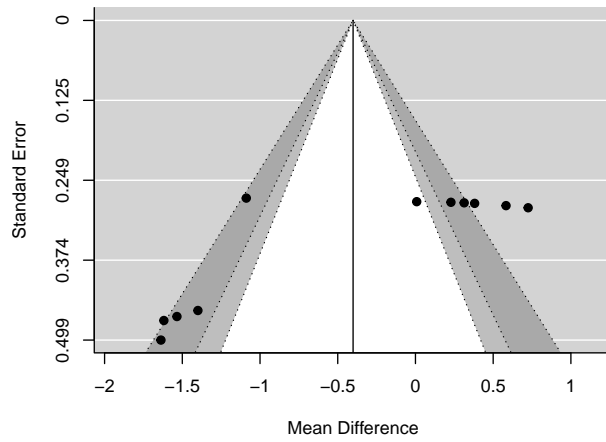
Gray matter Volume – occipital



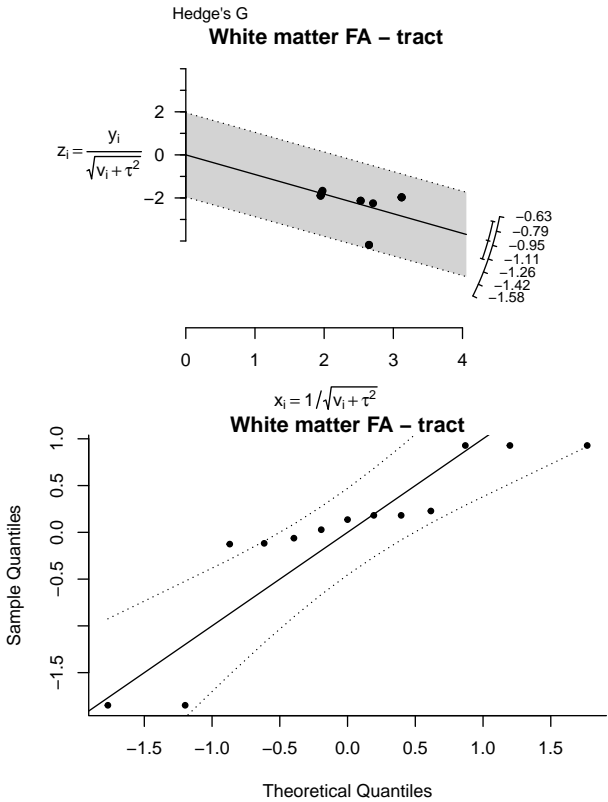
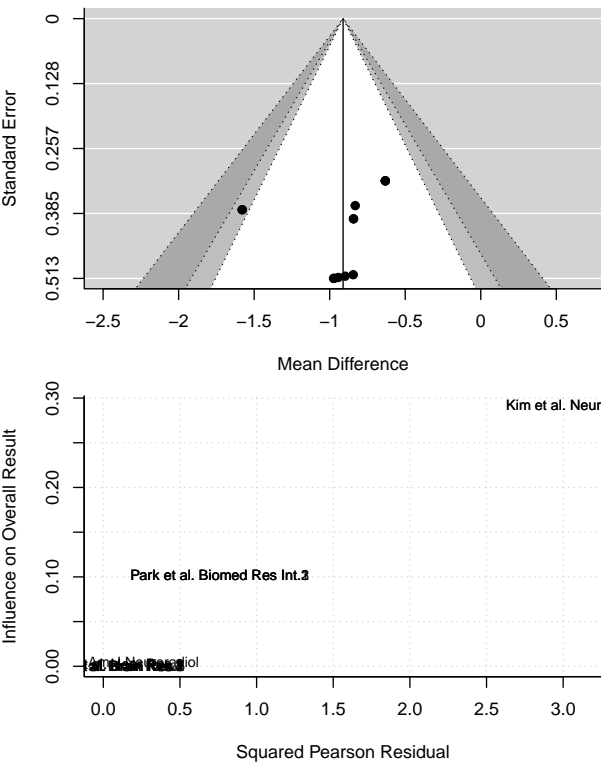
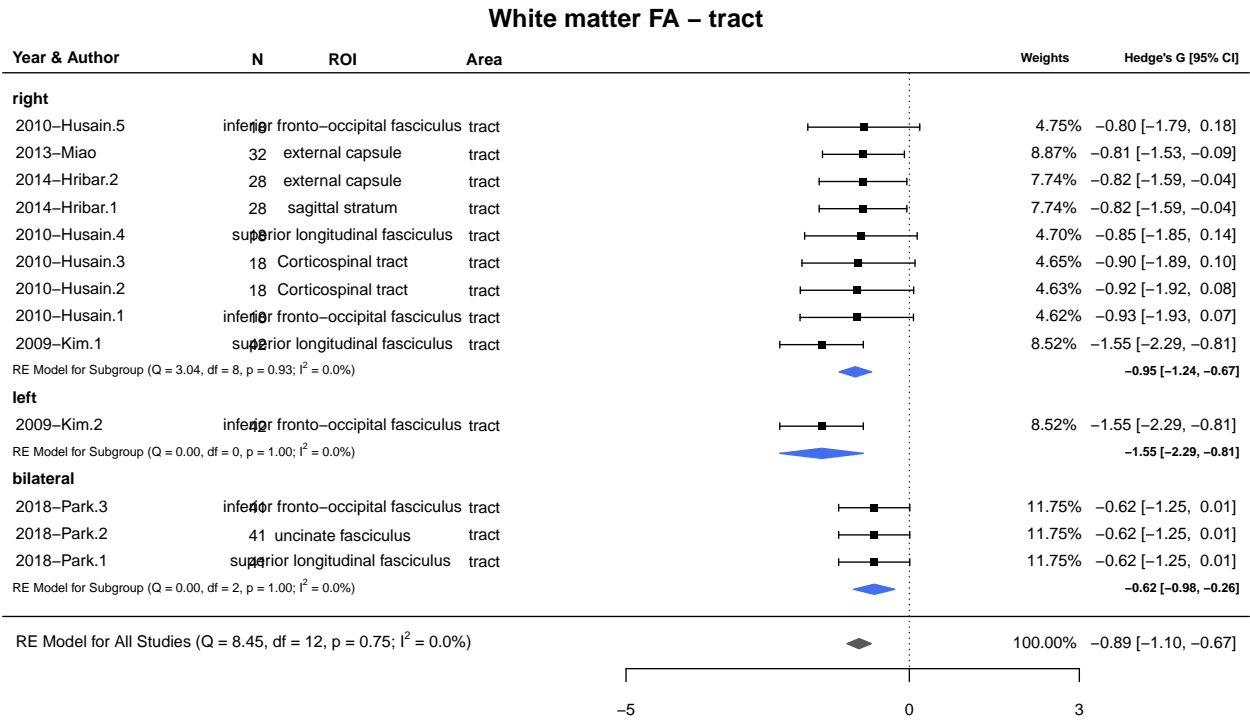


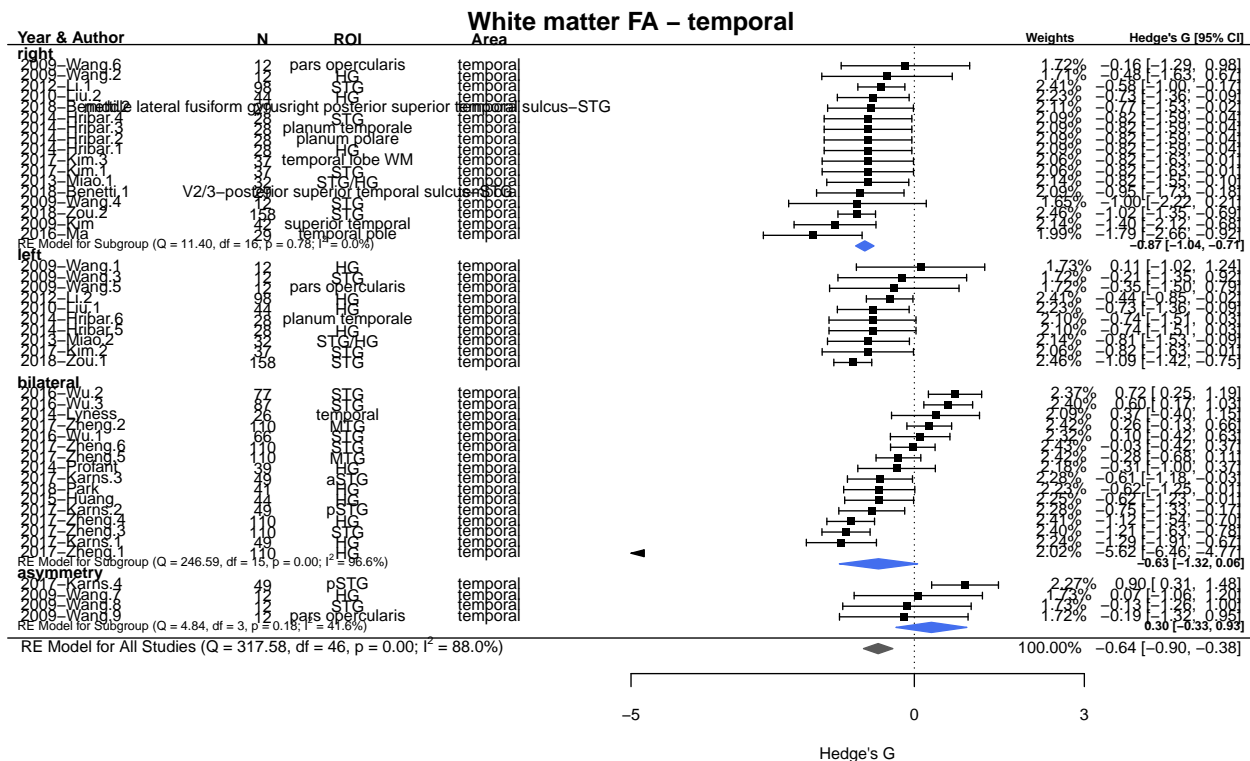
Gray matter Volume – insular cortex



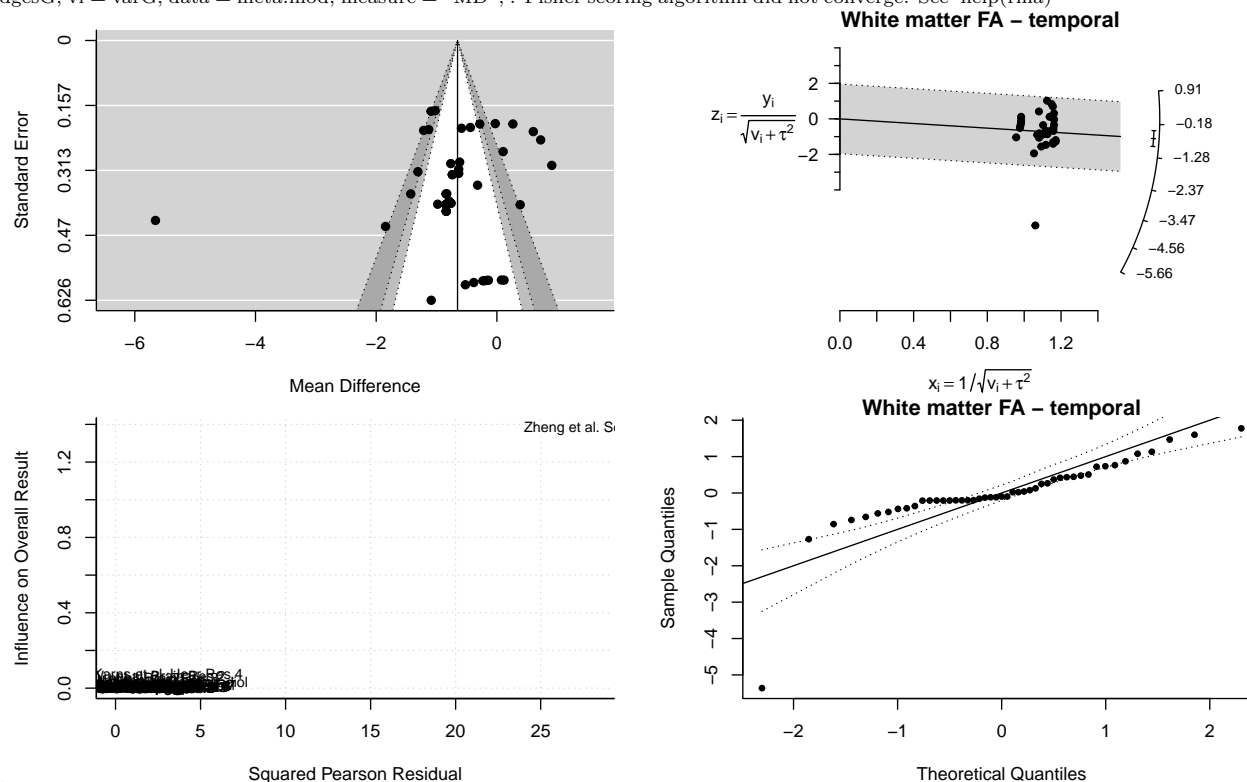


Meta-regressions of White Matter FA & Brain Areas: Random effects model no intercept covariated by Side



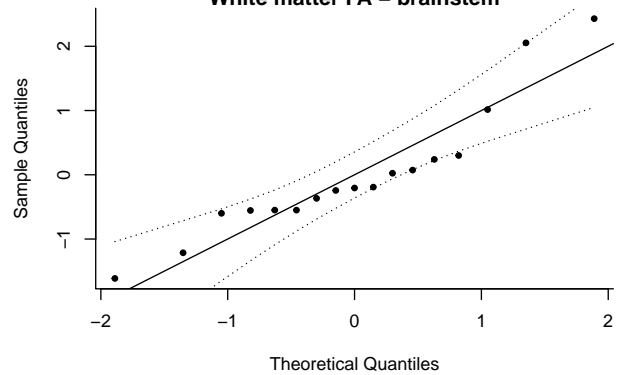
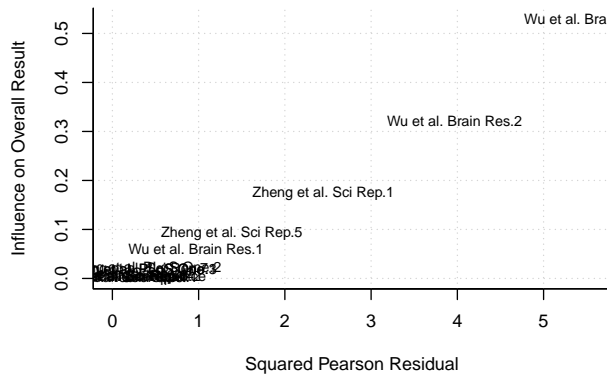
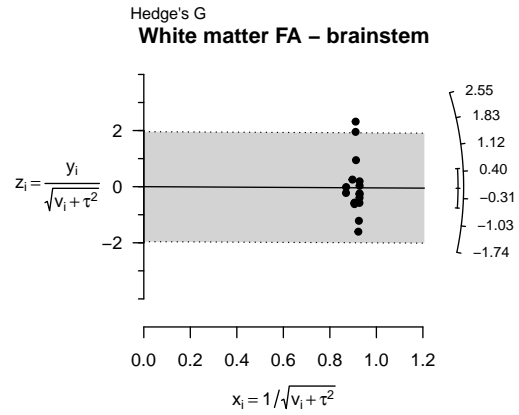
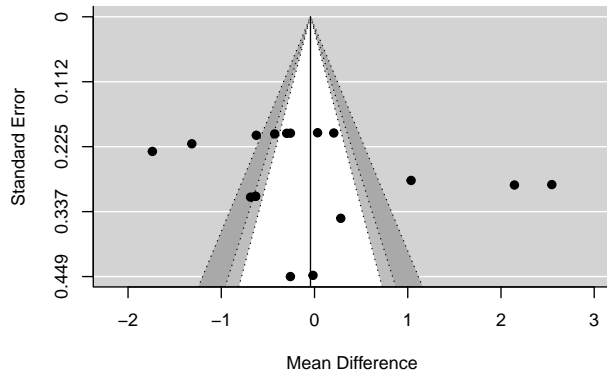
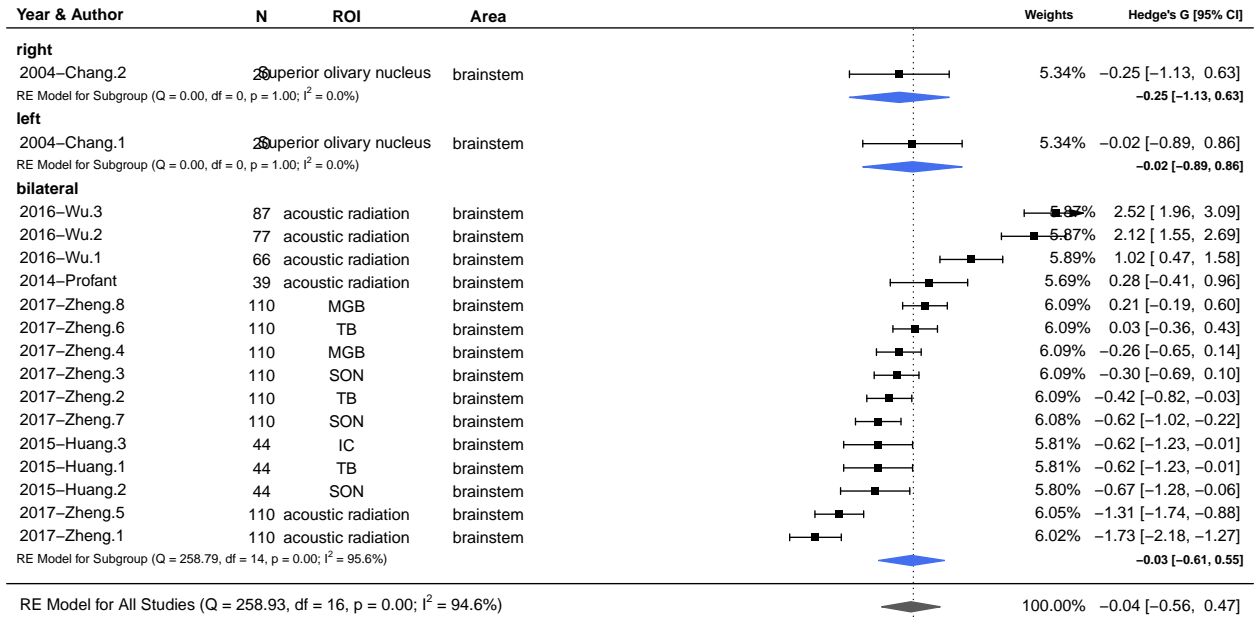


Error in rma(yi = hedgesG, vi = varG, data = meta.mod, measure = "MD", : Fisher scoring algorithm did not converge. See 'help(rma)'



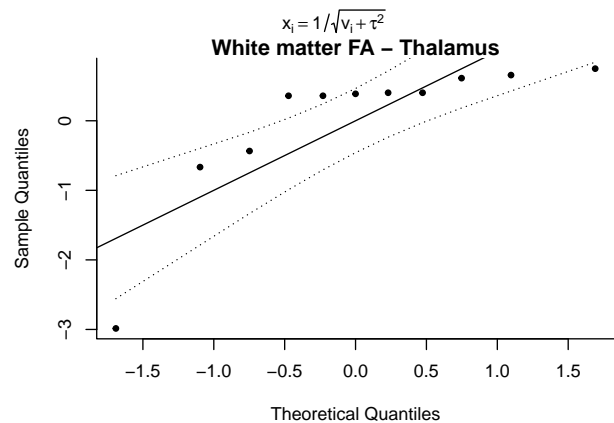
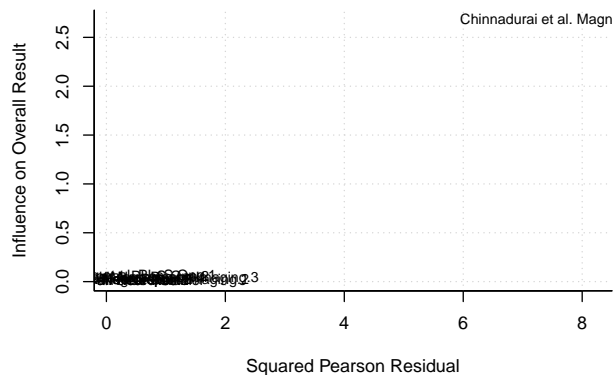
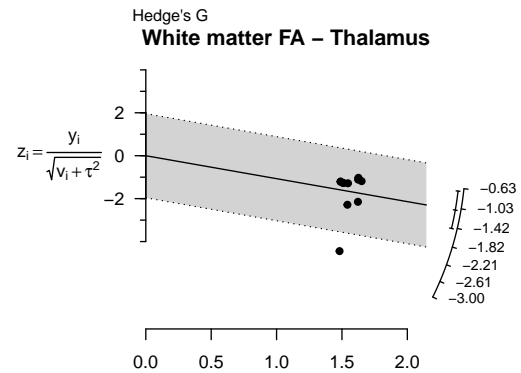
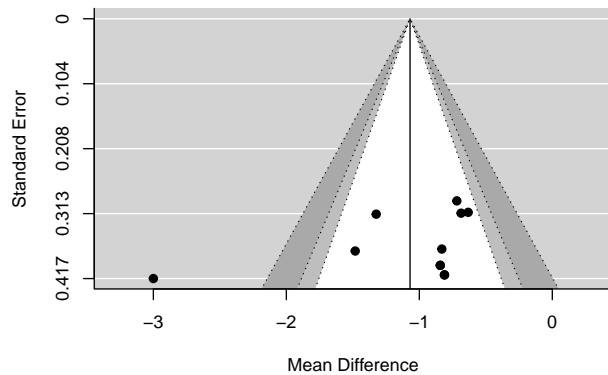
for possible remedies.

White matter FA – brainstem

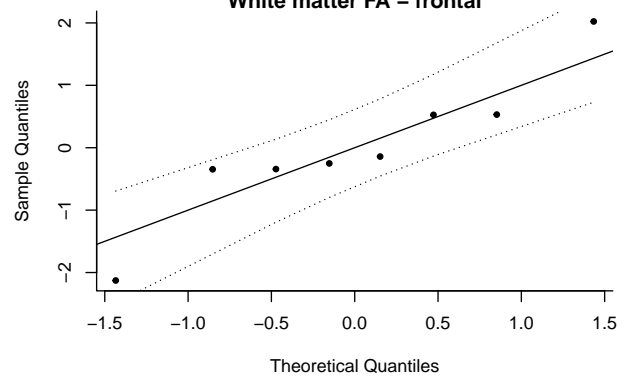
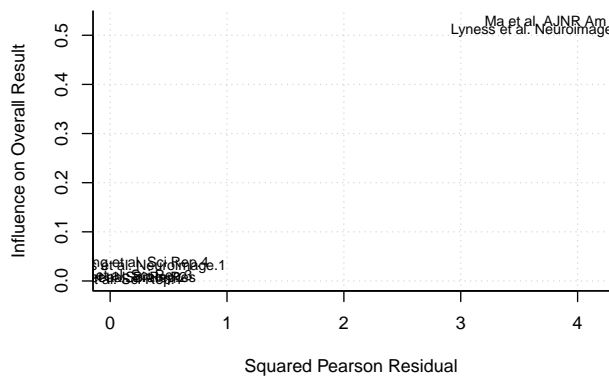
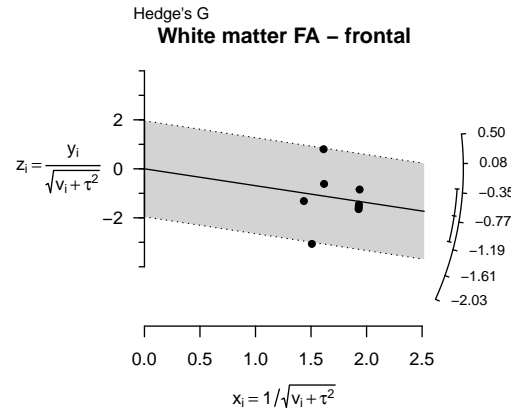
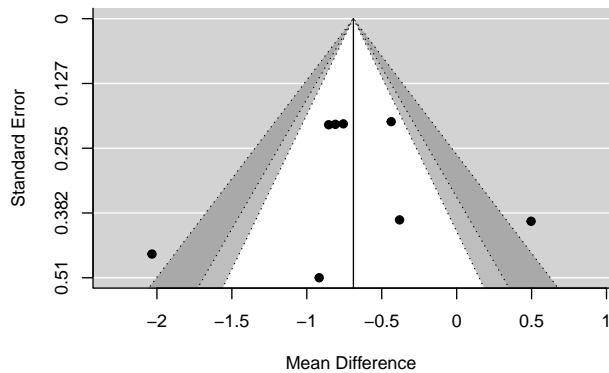
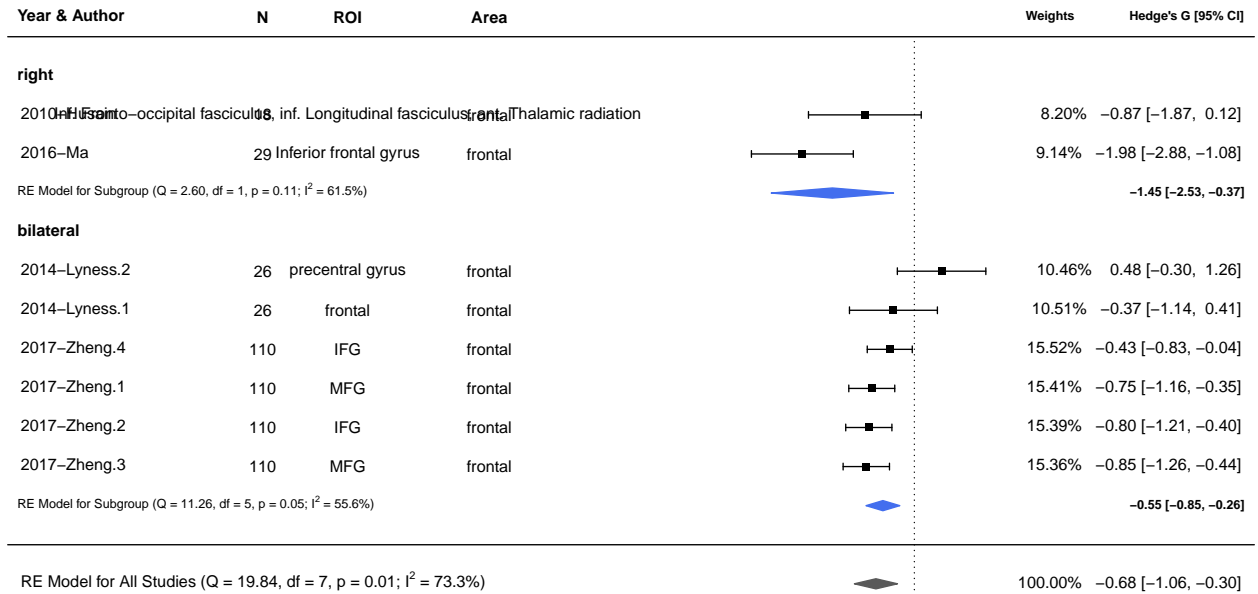


White matter FA – Thalamus

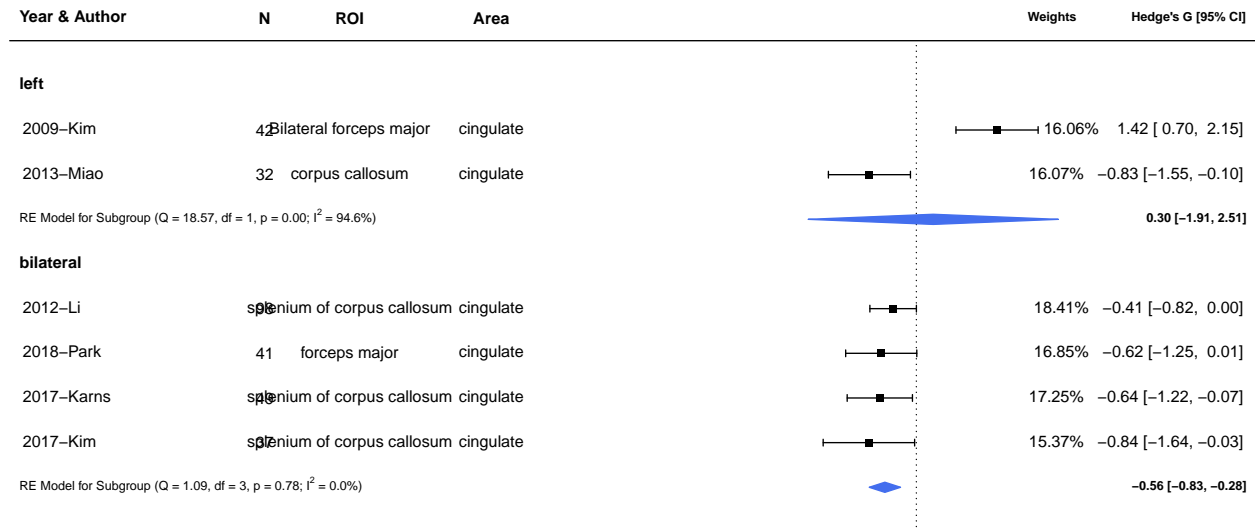
Year & Author	N	ROI	Area	Weights	Hedge's G [95% CI]
right					
2017–Kim.2	37	thalamus	Thalamus	8.32%	-0.79 [-1.60, 0.01]
2017–Kim.1	37	internal capsule	Thalamus	8.32%	-0.79 [-1.60, 0.01]
2013–Miao	32	thalamus	Thalamus	8.98%	-0.81 [-1.53, -0.09]
2014–Hribar.2	28	anterior thalamic radiation	Thalamus	8.57%	-0.82 [-1.59, -0.04]
2014–Hribar.1	28	retrolenticular part of internal capsule	Thalamus	8.57%	-0.82 [-1.59, -0.04]
2009–Kim	42	internal capsule	Thalamus	8.94%	-1.45 [-2.18, -0.73]
RE Model for Subgroup (Q = 2.48, df = 5, p = 0.78; I ² = 0.0%)					-0.93 [-1.24, -0.61]
bilateral					
2015–Huang.1	44	MGB	Thalamus	9.95%	-0.62 [-1.23, -0.01]
2015–Huang.2	44	AR	Thalamus	9.92%	-0.67 [-1.28, -0.06]
2016–Chinnadurai.3	50	LL	Thalamus	10.25%	-0.71 [-1.28, -0.13]
2016–Chinnadurai.2	50	IC	Thalamus	9.91%	-1.30 [-1.92, -0.69]
2016–Chinnadurai.1	50	IAC	Thalamus	8.27%	-2.95 [-3.76, -2.14]
RE Model for Subgroup (Q = 26.57, df = 4, p = 0.00; I ² = 88.3%)					-1.22 [-2.05, -0.39]
RE Model for All Studies (Q = 29.55, df = 10, p = 0.00; I ² = 68.4%)					100.00% -1.05 [-1.42, -0.67]



White matter FA – frontal



White matter FA – cingulate

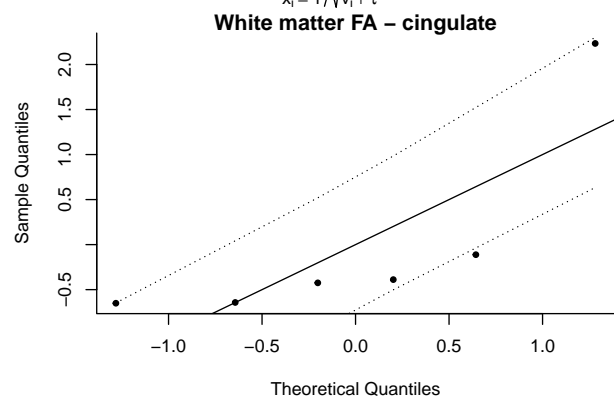
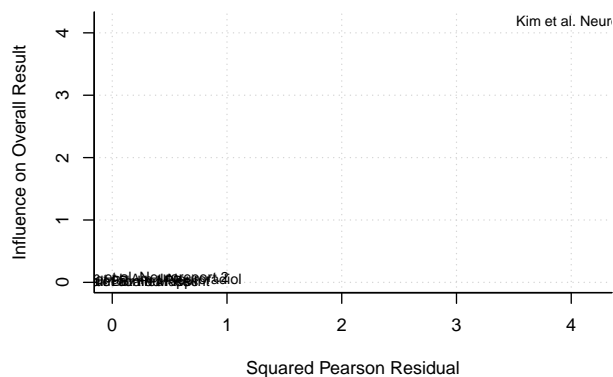
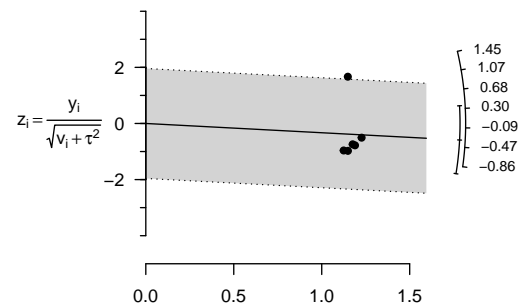
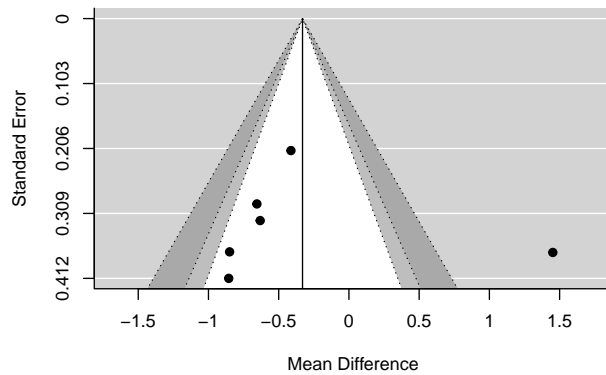


RE Model for All Studies (Q = 27.88, df = 5, p = 0.00; I² = 85.8%)

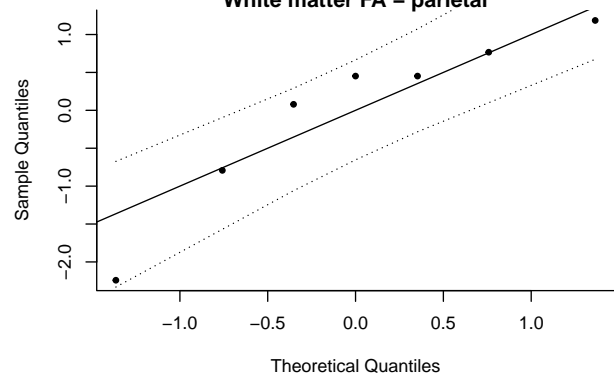
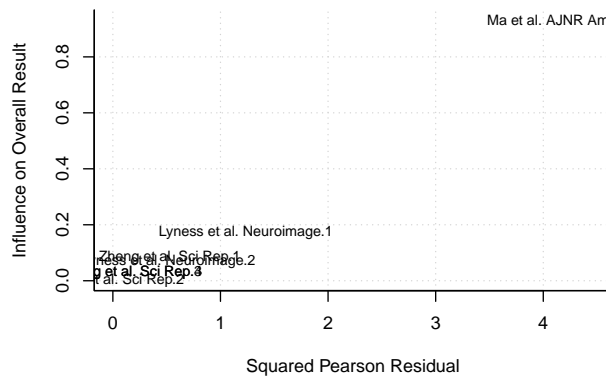
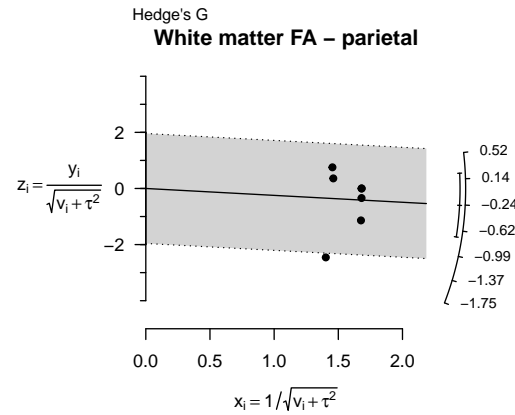
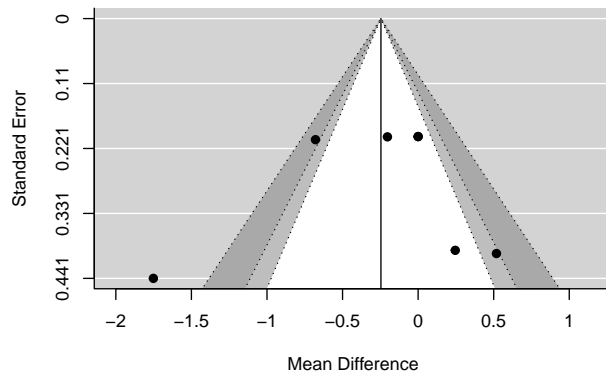
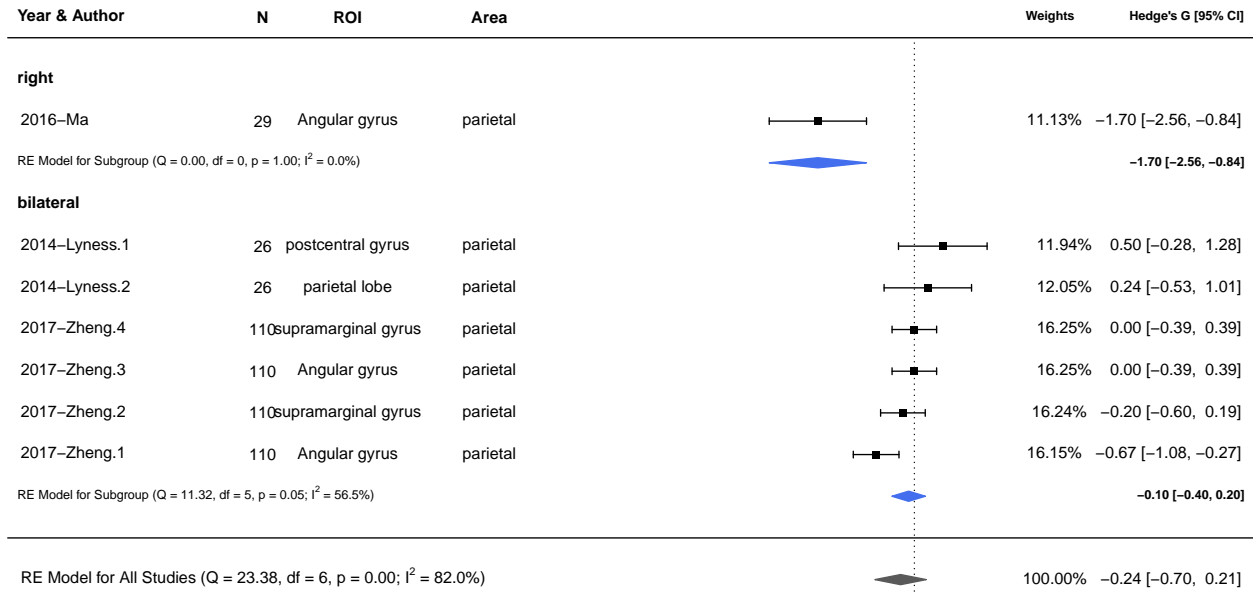
-5 0 3

Hedge's G

White matter FA – cingulate

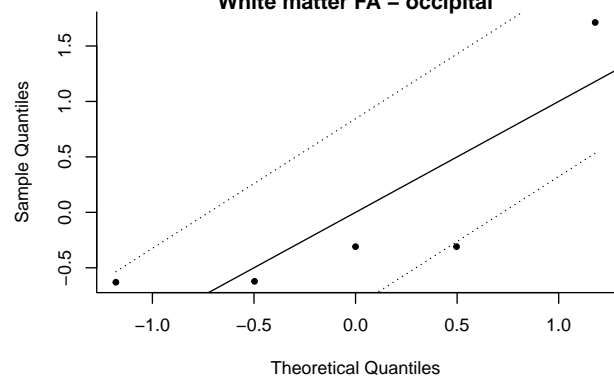
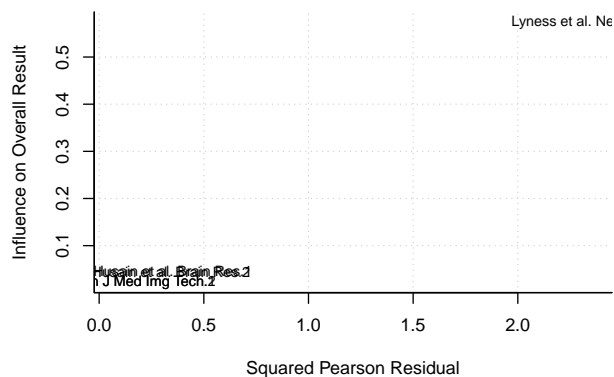
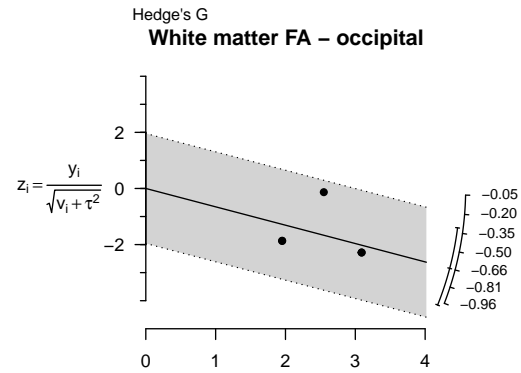
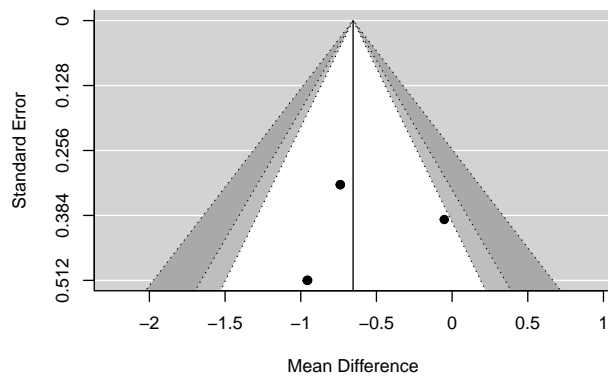
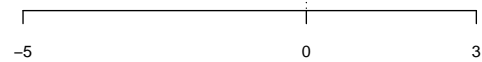


White matter FA – parietal

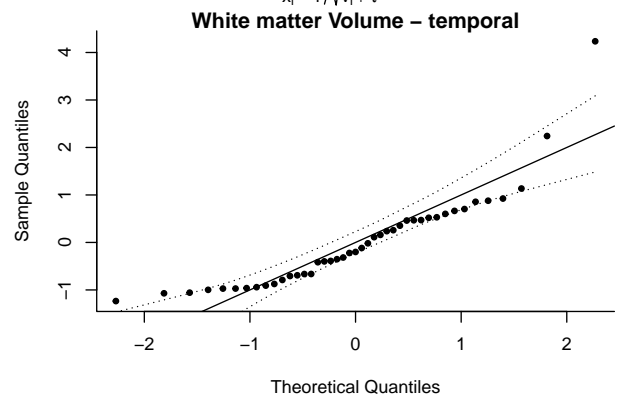
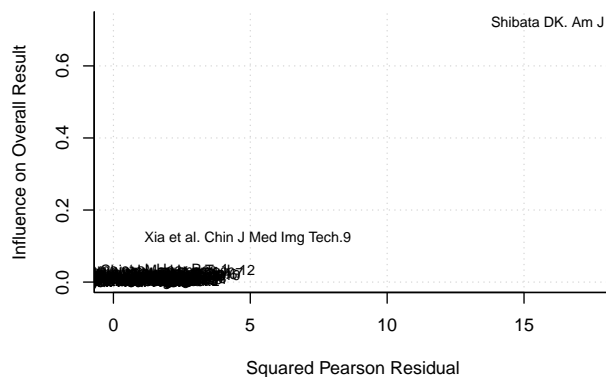
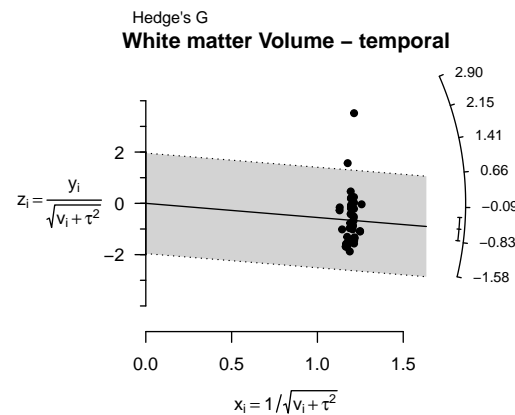
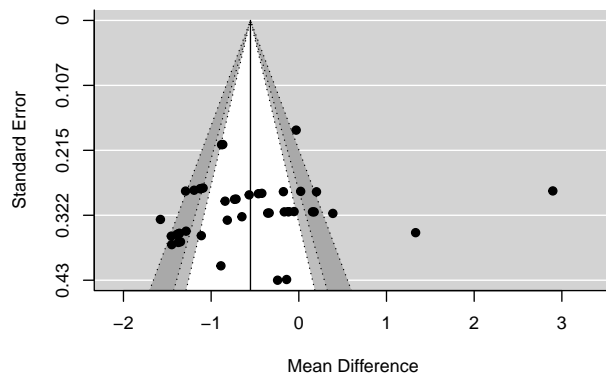
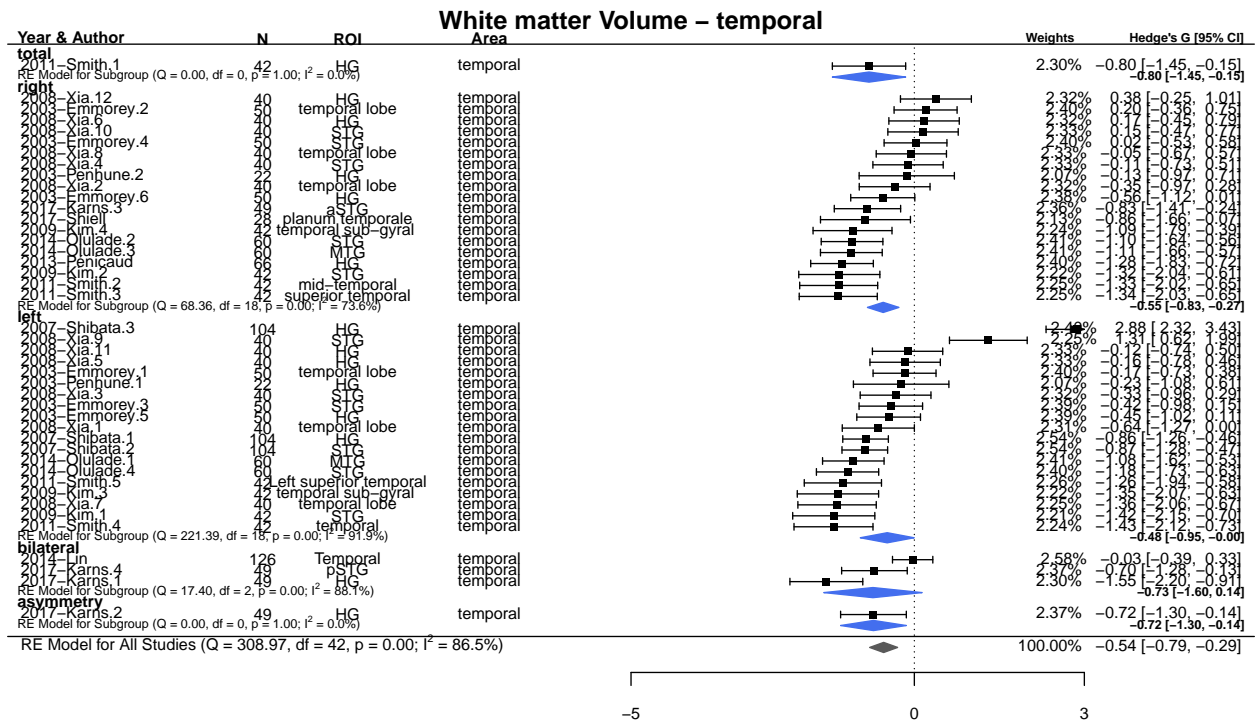


White matter FA – occipital

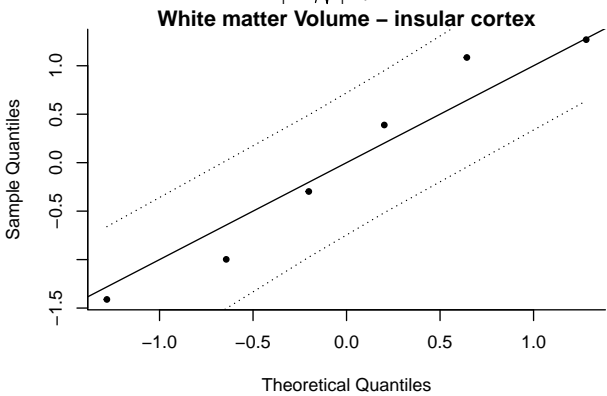
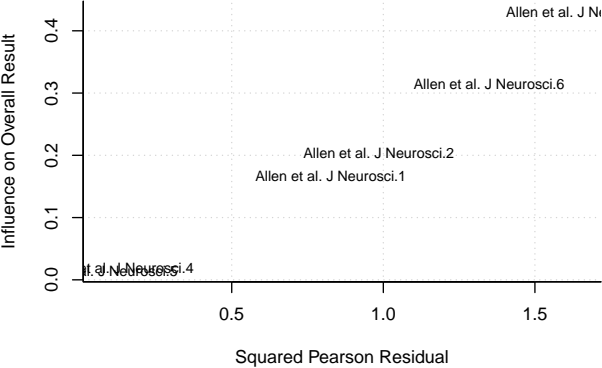
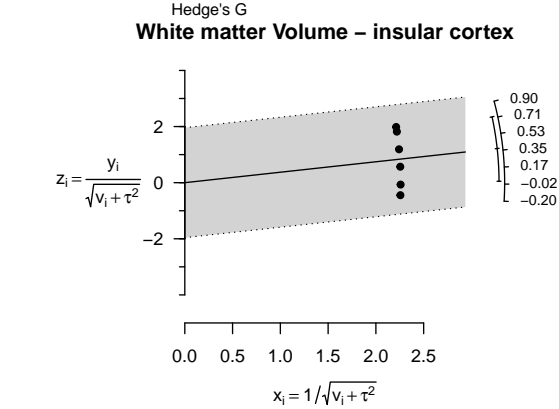
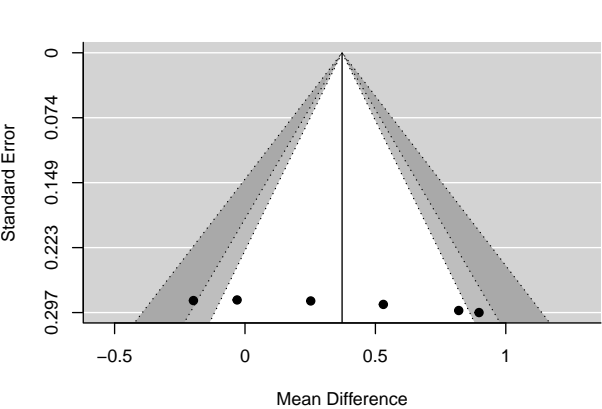
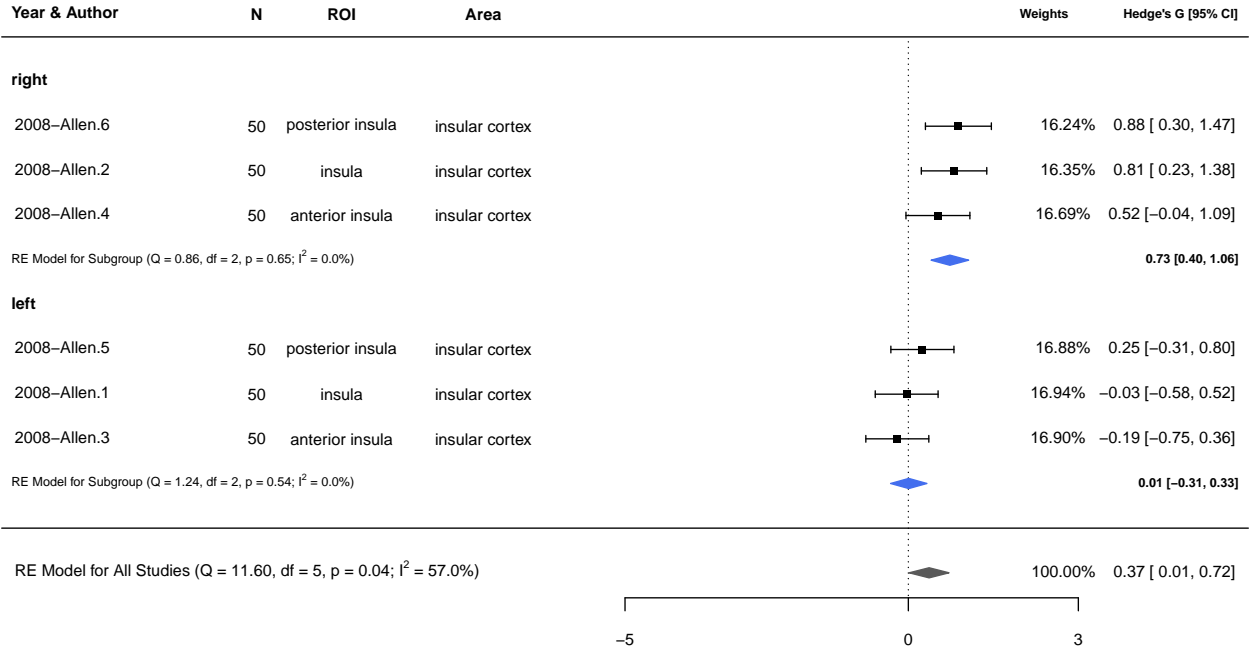
Year & Author	N	ROI	Area	Weights	Hedge's G [95% CI]
right					
2010–Liu.2	44	optic radiation	occipital	28.71%	-0.73 [-1.36, -0.09]
2010–Husain.2	18	Sup. Occipital Fasciculus	occipital	11.55%	-0.91 [-1.91, 0.09]
2010–Husain.1	18	Superior Occipital Fasciculus, Corticospinal tract	occipital	11.55%	-0.91 [-1.91, 0.09]
RE Model for Subgroup (Q = 0.15, df = 2, p = 0.93; I ² = 0.0%)					-0.81 [-1.28, -0.34]
left					
2010–Liu.1	44	optic radiation	occipital	28.71%	-0.73 [-1.36, -0.09]
RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I ² = 0.0%)					-0.73 [-1.36, -0.09]
bilateral					
2014–Lyness	26	occipital	occipital	19.49%	-0.05 [-0.82, 0.72]
RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I ² = 0.0%)					-0.05 [-0.82, 0.72]
RE Model for All Studies (Q = 2.96, df = 4, p = 0.56; I ² = 0.0%)					100.00% -0.64 [-0.98, -0.30]



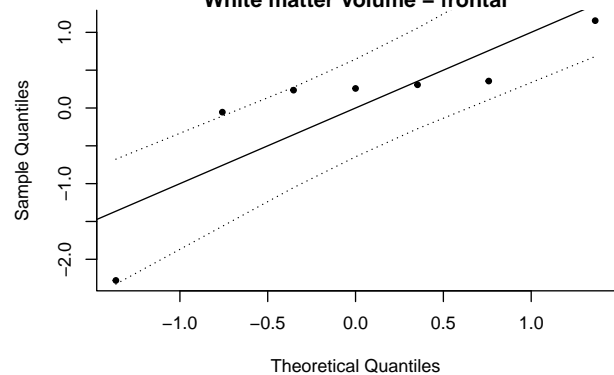
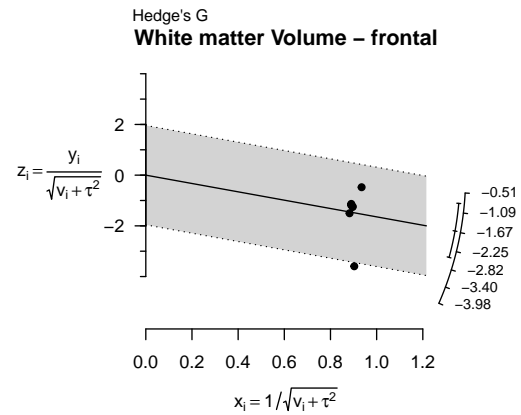
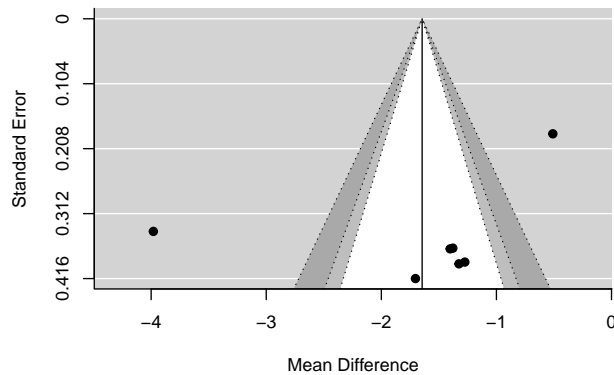
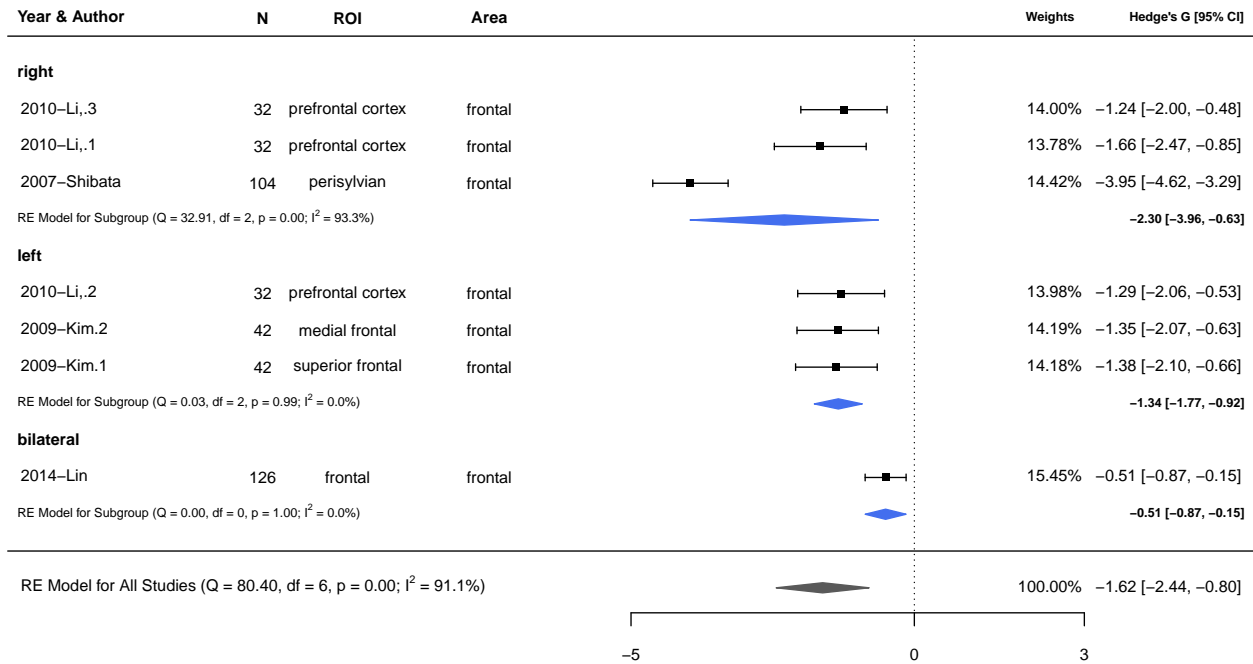
Meta-regressions of White Matter Volume & Brain Areas: Random effects model no intercept covariated by Side



White matter Volume – insular cortex



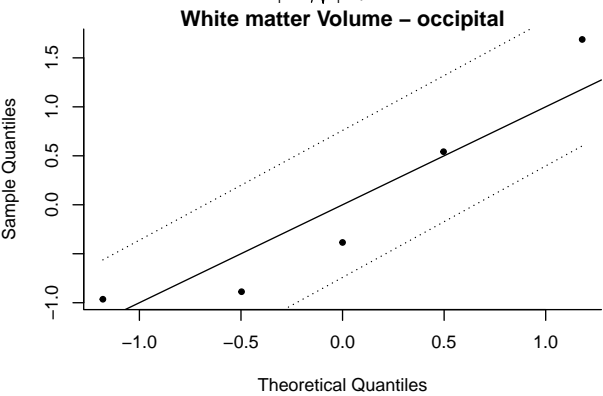
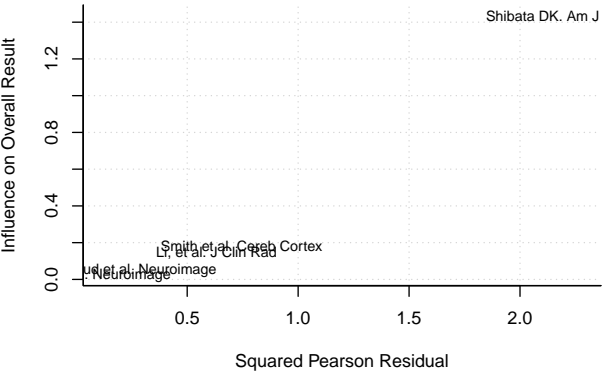
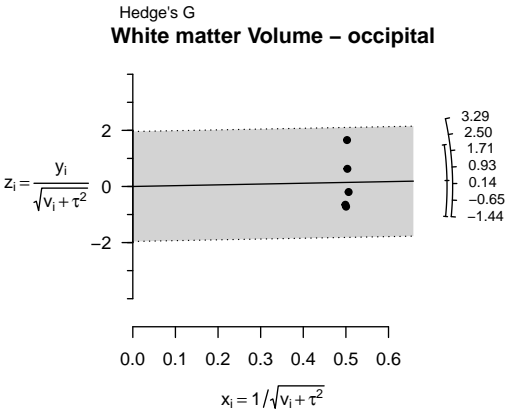
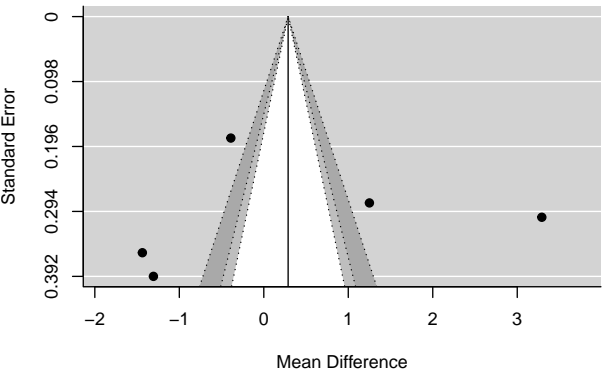
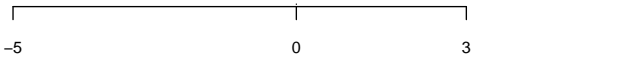
White matter Volume – frontal



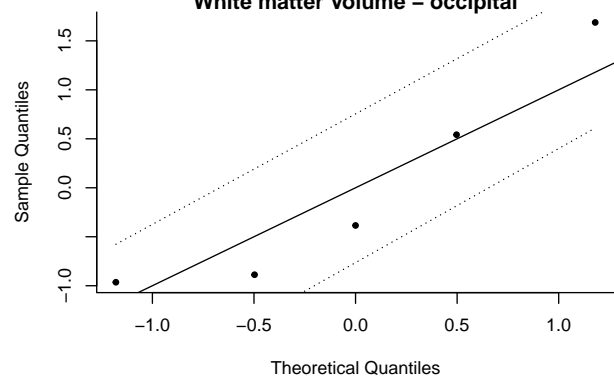
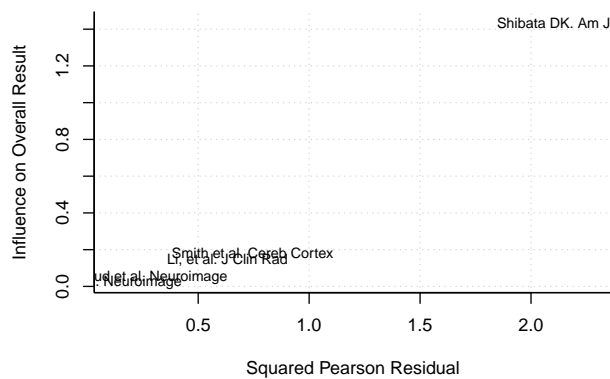
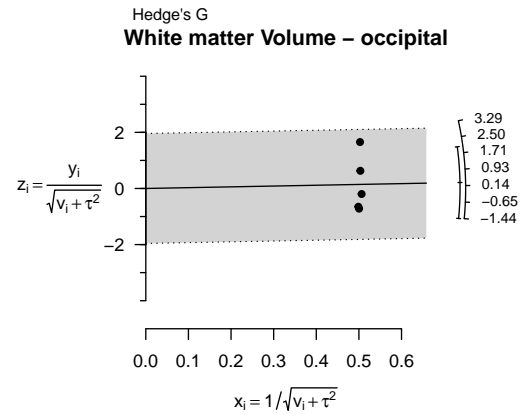
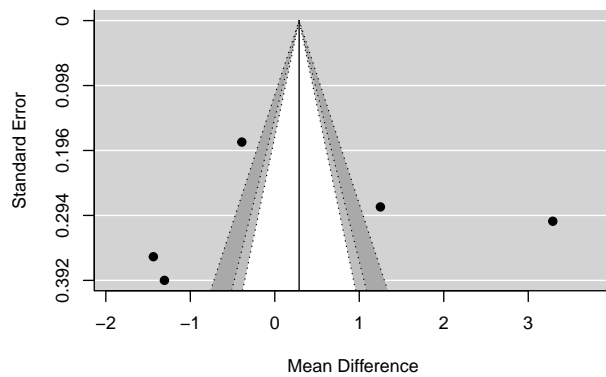
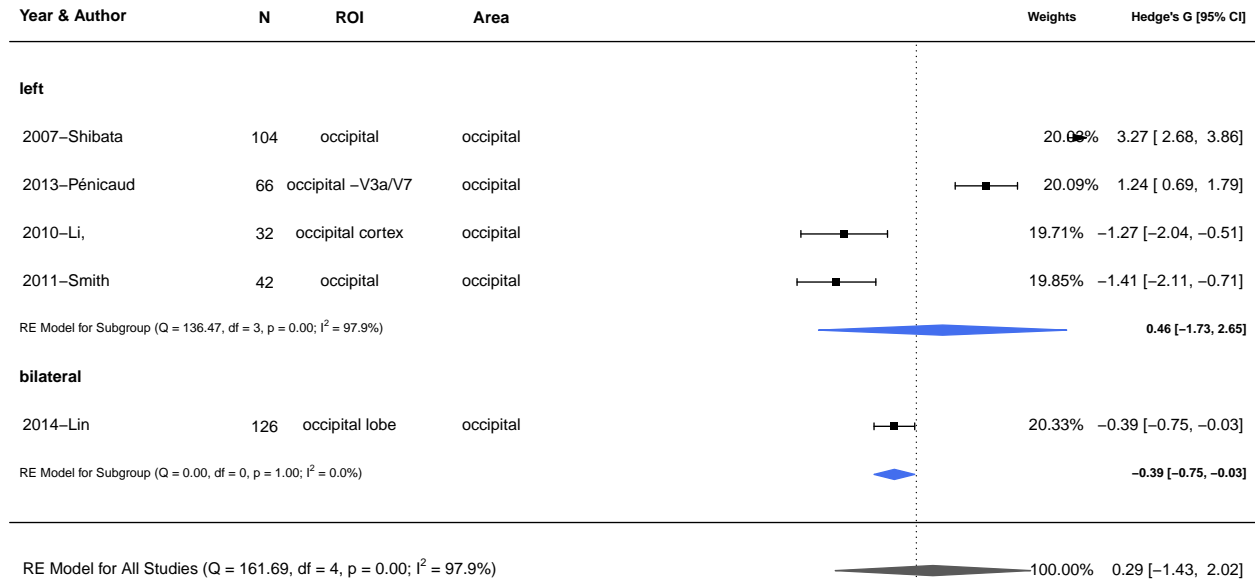
White matter Volume – occipital

Year & Author	N	ROI	Area	Weights	Hedge's G [95% CI]
left					
2007–Shibata	104	occipital	occipital	20.09%	3.27 [2.68, 3.86]
2013–Pénicaud	66	occipital –V3a/V7	occipital	20.09%	1.24 [0.69, 1.79]
2010–Li,	32	occipital cortex	occipital	19.71%	-1.27 [-2.04, -0.51]
2011–Smith	42	occipital	occipital	19.85%	-1.41 [-2.11, -0.71]
RE Model for Subgroup (Q = 136.47, df = 3, p = 0.00; I ² = 97.9%)					0.46 [-1.73, 2.65]
bilateral					
2014–Lin	126	occipital lobe	occipital	20.33%	-0.39 [-0.75, -0.03]
RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I ² = 0.0%)					-0.39 [-0.75, -0.03]

RE Model for All Studies (Q = 161.69, df = 4, p = 0.00; I² = 97.9%)

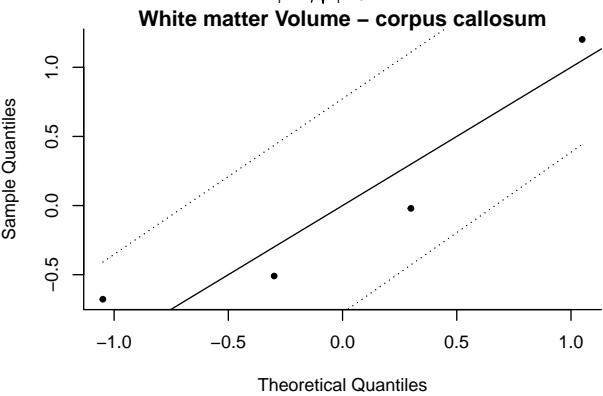
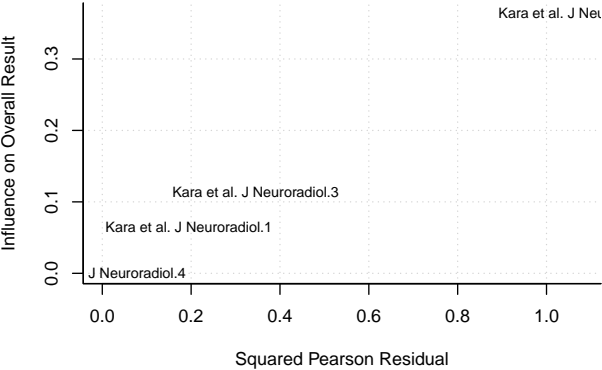
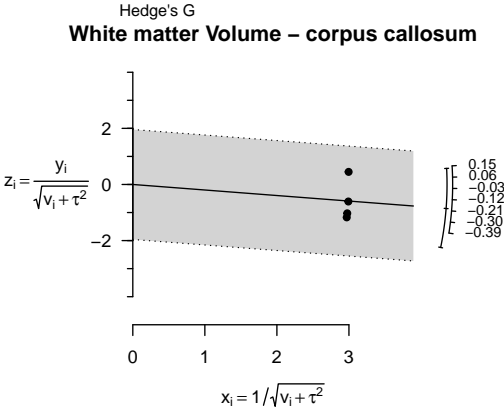
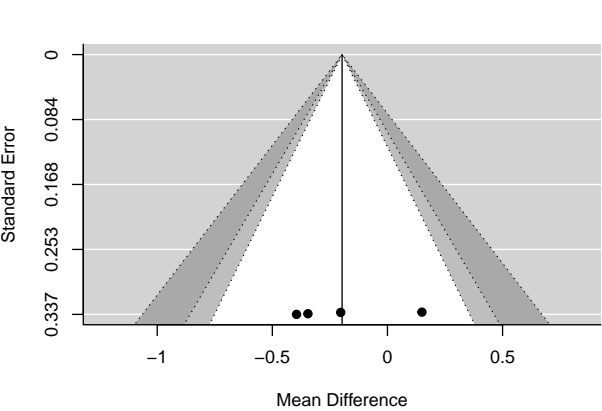
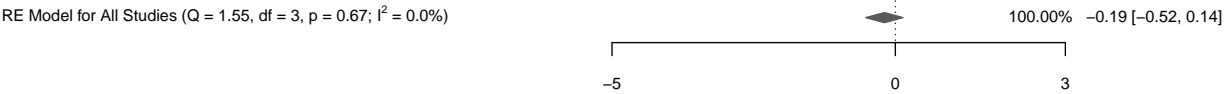


White matter Volume – occipital



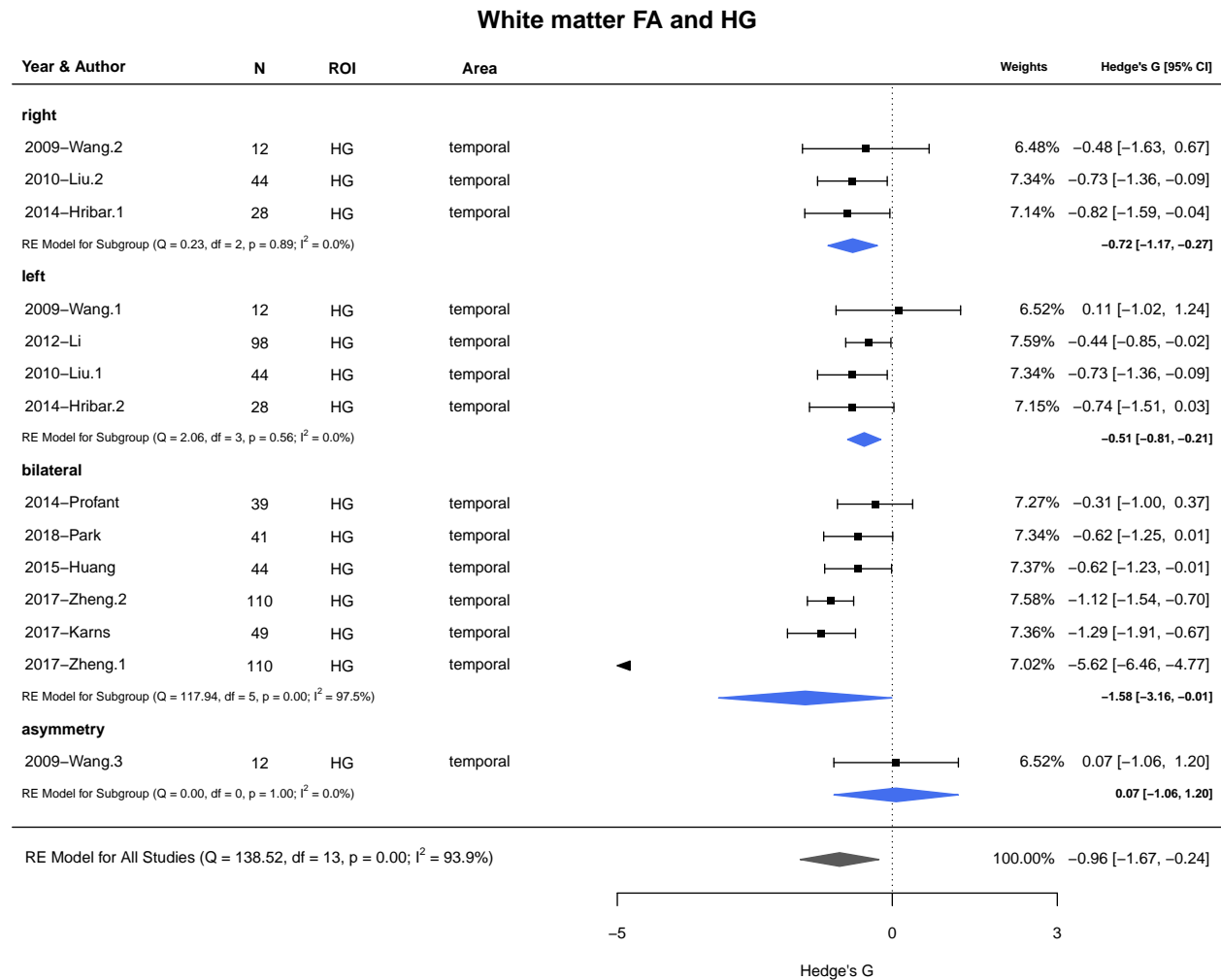
White matter Volume – corpus callosum

Year & Author	N	ROI	Area	Weights	Hedge's G [95% CI]
bilateral					
2006–Kara.2	38	corpus callosum (middle area)	corpus callosum	25.20%	0.15 [–0.51, 0.80]
2006–Kara.4	38	corpus callosum (total area)	corpus callosum	25.14%	–0.20 [–0.85, 0.46]
2006–Kara.1	38	corpus callosum (anterior area)	corpus callosum	24.89%	–0.34 [–1.00, 0.32]
2006–Kara.3	38	corpus callosum (posterior area)	corpus callosum	24.78%	–0.39 [–1.05, 0.27]
RE Model for Subgroup (Q = 1.55, df = 3, p = 0.67; I ² = 0.0%)					–0.19 [–0.52, 0.14]

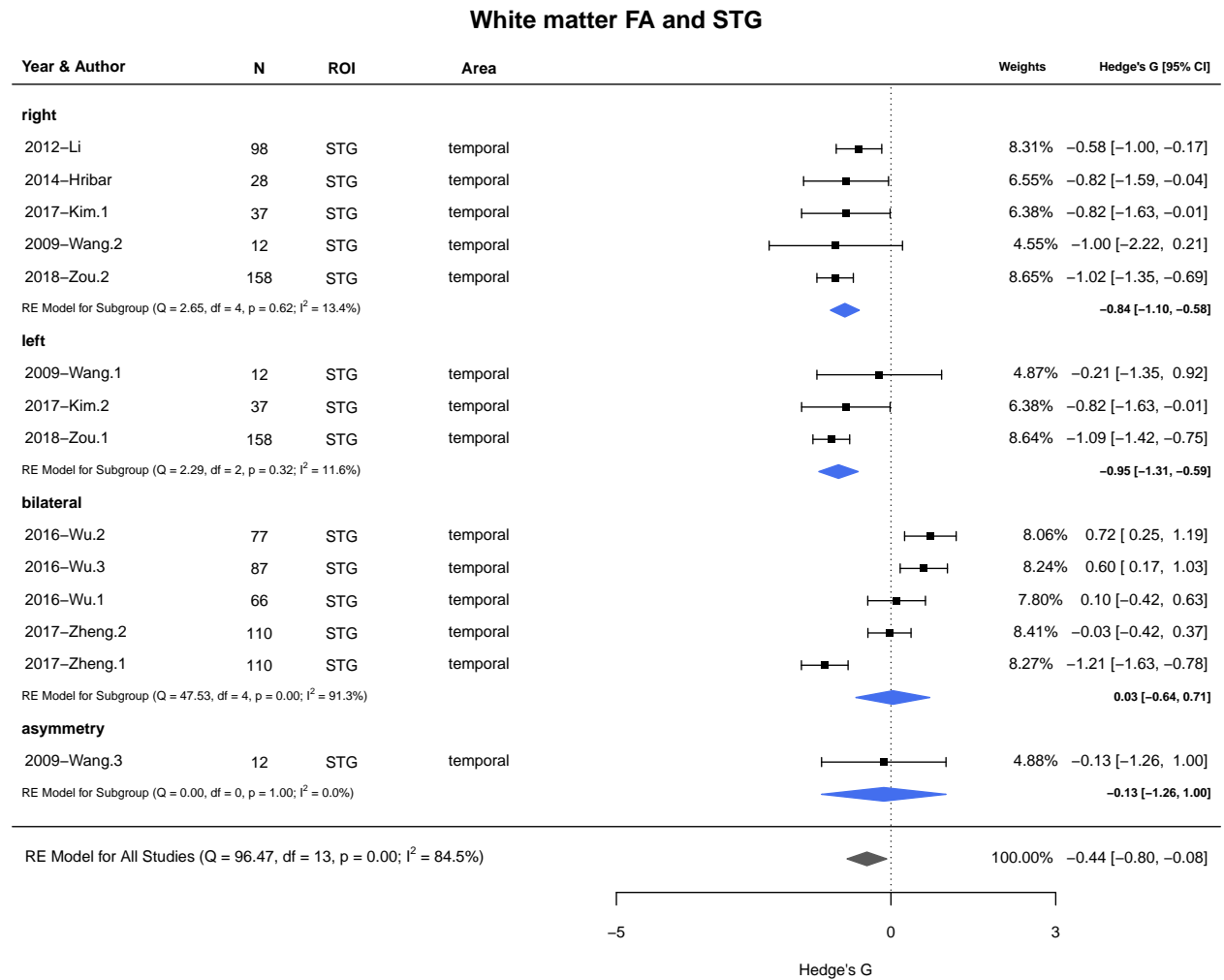


Supplementary material: Forest-plots of other Measures

Hesch gyrus FA white matter

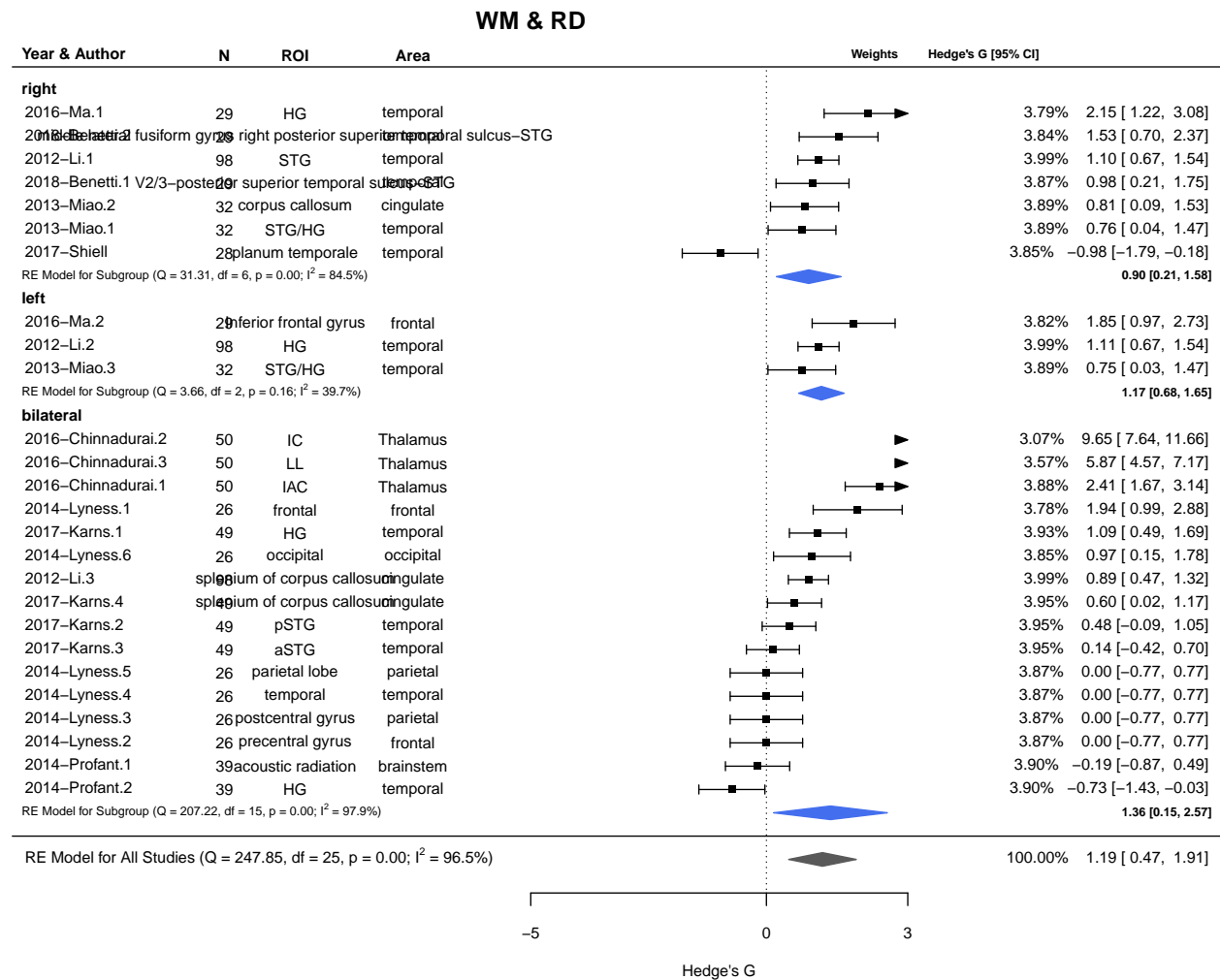


STG Volume White matter



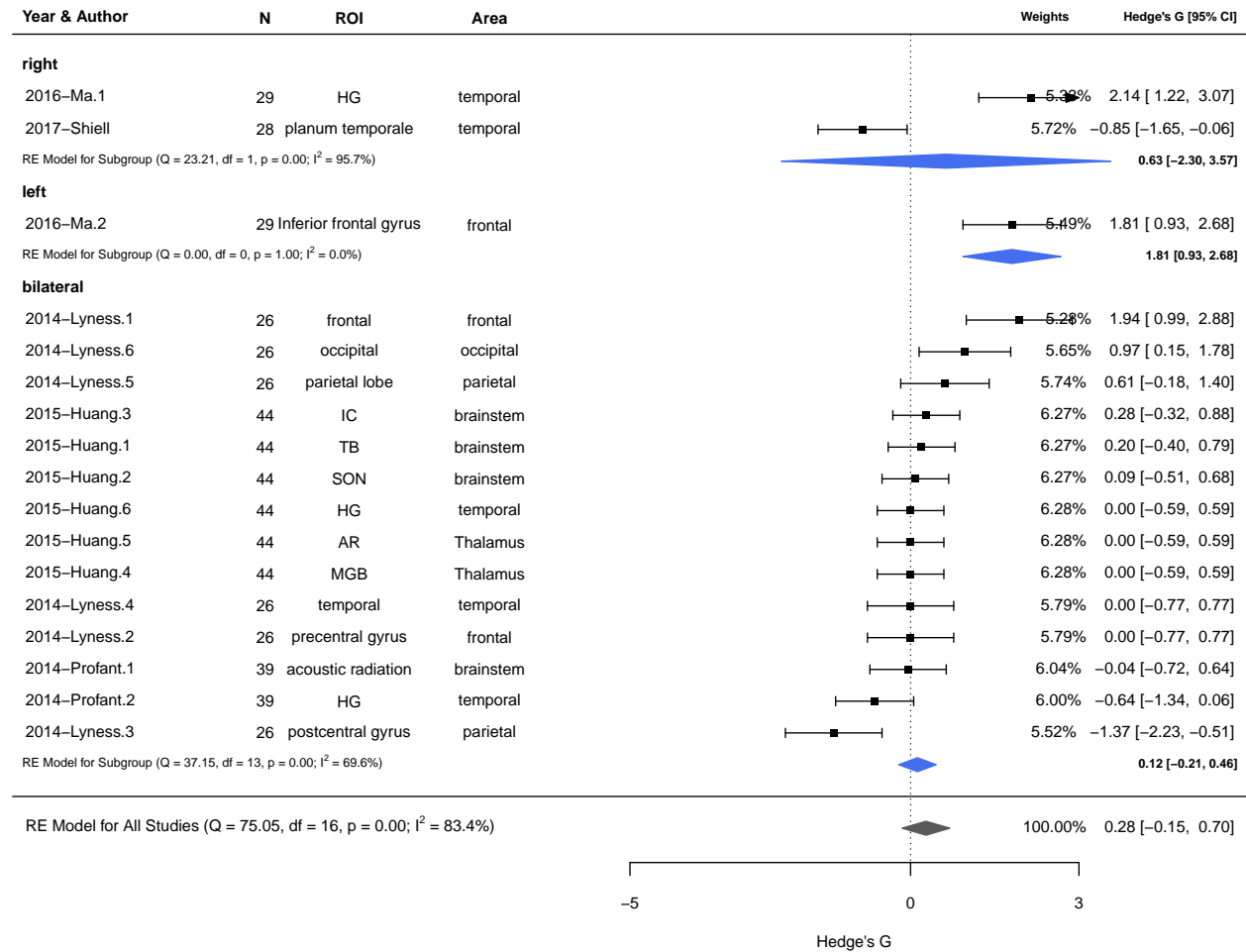
Measures of White matter Integrity

White matter: RD



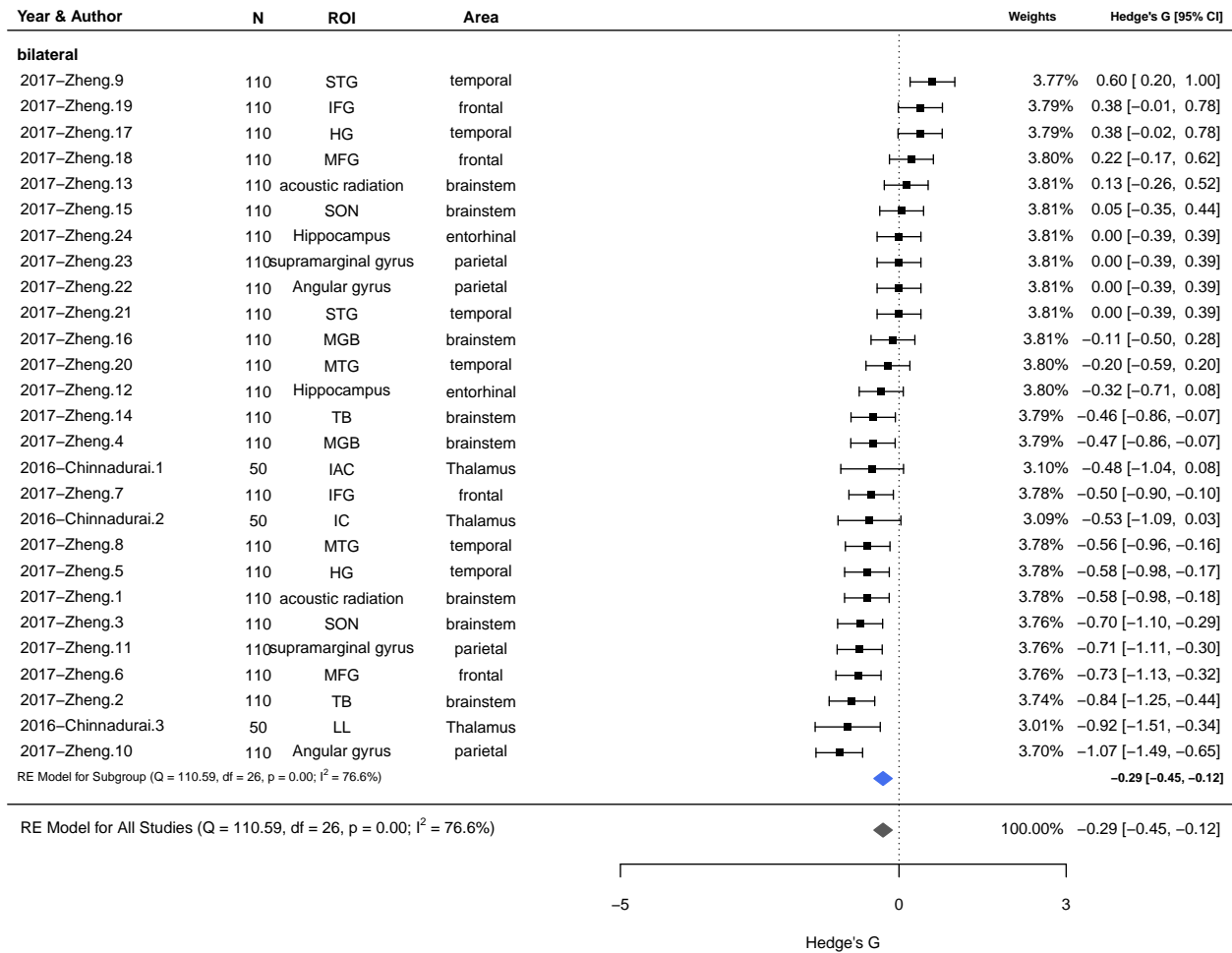
White matter: MD

WM & MD

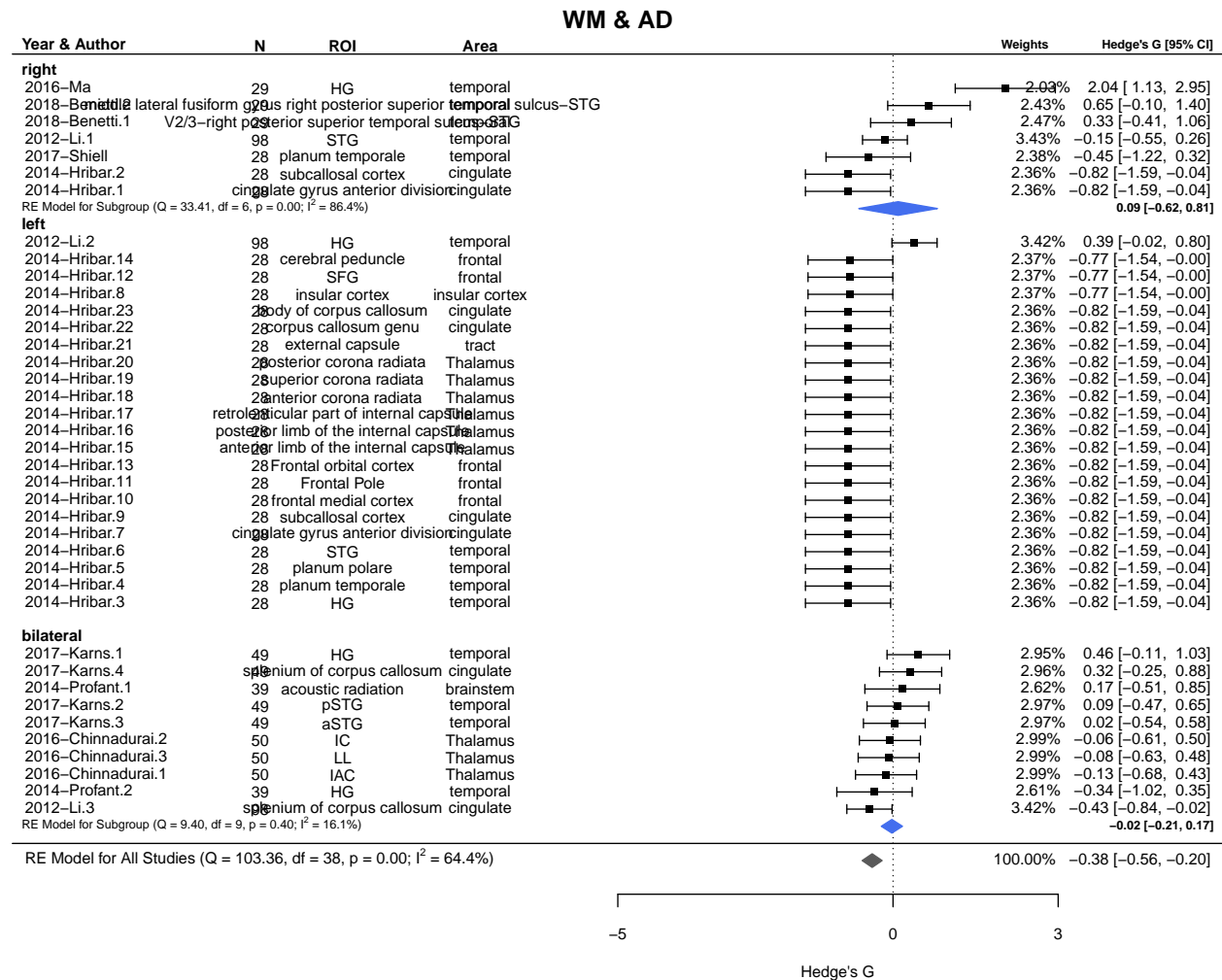


White matter: Mean Kurtosis

WM & Mean Kurtosis



White matter: AD

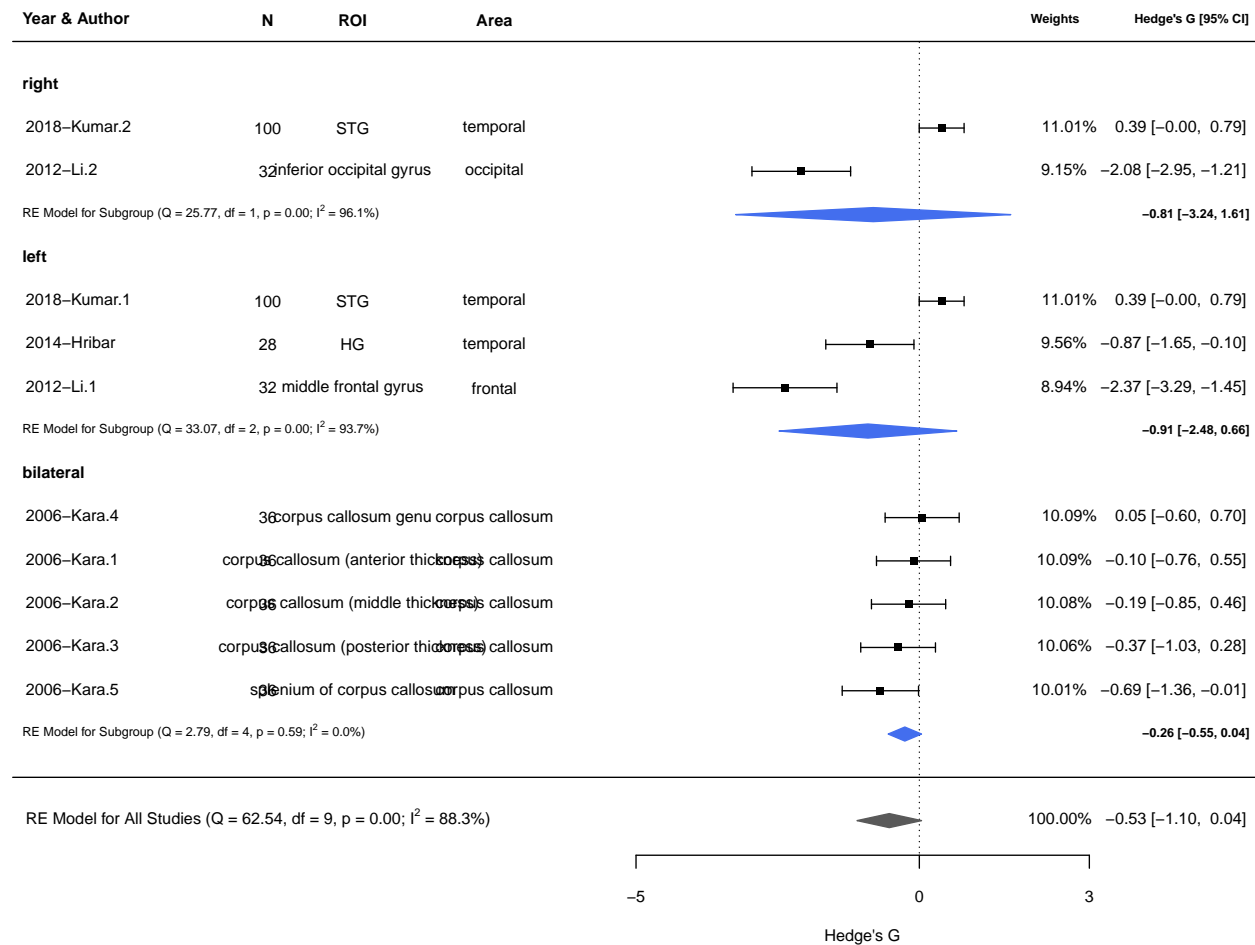


Error in rma(yi = hedgesG, vi = varG, data = meta.mod, measure = "MD", : Fisher scoring algorithm did not converge. See 'help(rma)' for possible remedies.

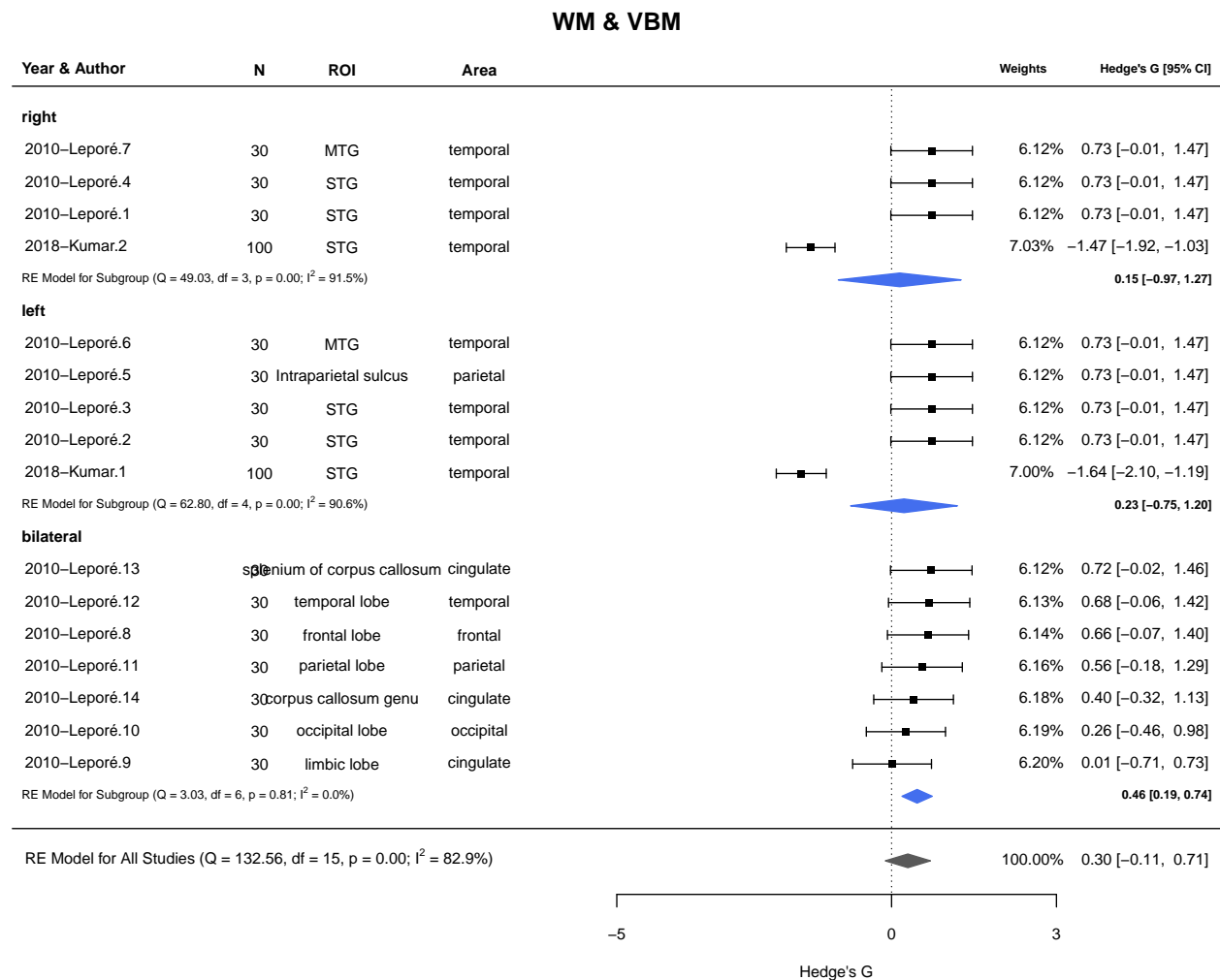
Other Measures of White Matter

White matter: Thickness

WM & Thickness



White matter: VBM



Meta Plots

The L'Abbé plot

In a L'Abbé plot (based on L'Abbé, Detsky, & O'Rourke, 1987), the arm-level outcomes for two experimental groups (e.g., treatment and control group) are plotted against each other. is treatment versus effect, since you have the cohen's d this should be relatively simple.

> WE DON'T HAVE TWO EXPERIMENTAL GROUPS

Baujat plot to identify studies contributing to heterogeneity

The plot shows the contribution of each study to the overall Q-test statistic for heterogeneity on the horizontal axis versus the influence of each study (defined as the standardized squared difference between the overall estimate based on a fixed-effects model with and without the ith study included in the model) on the vertical axis 2.17. Funnel plot to illustrate publication bias

Galbraith plot

Radial plot (radial) of variables and cohen's d - Galbraith, Rex (1988). "Graphical display of estimates having differing standard errors". Technometrics. Technometrics, Vol. 30, No. 3. 30 (3): 271–281.

2.18.2. We want to see this type of error plot over time for our patient cohorts by age. we want this for each measure WM and GM versus age on the x-axis so we can see GM and WM over time! Do a monte carlo simulation to connect different age population and create the error.

For a fixed-effects model, the plot shows the inverse of the standard errors on the horizontal axis against the individual observed effect sizes or outcomes standardized by their corresponding standard errors on the vertical axis. On the right hand side of the plot, an arc is drawn corresponding to the individual observed effect sizes or outcomes. A line projected from (0,0) through a particular point within the plot onto this arc indicates the value of the individual observed effect size or outcome for that point.

Resources

We are following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines: Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6:e1000097. doi: 10.1371/journal.pmed.1000097 AND <https://www.bmj.com/content/339/bmj.b2535>

- <https://stackoverflow.com/questions/14426637/how-to-do-bubble-plot>
- https://www.researchgate.net/publication/296680807_Menstrual_hygiene_management_among_adolescent_girls_in_India_A_Systematic_review_and_meta-analysis/figures?lo=1

Good explanation of some of the plots:

- https://ora.ox.ac.uk/objects/uuid:ff78831d-6f82-4187-97cc-349058e9abde/download_file?file_format=pdf&safe_filename=Rahimi%2Bet%2Bal%252C%2BData%2Bvisualisation%2Bfor%2Bmeta-analysis.pdf&type_of_work=Journal+article