

How hearing loss across the lifespan affects the brain: Structural correlates of hearing loss assessed by coordinate mapping using quantitative metrics of gray and white matter trajectories - Systematic review, meta-analysis and meta-regression

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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. Xia et al. Chin J Rad, 2008 was excluded because 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*, we used the average for the main table.
3. Xia et al. Chin J Med Img Tech, 2008 had 40 patients in total, in two groups 9-12 years and 19-22 years.
4. For some studies (eg. 2017, Ritgers et al. Front. Aging Neurosci) it was not possible to calculate the Hedges'G variance and were not include in some specific meta-regressions.
5. Studies with *Mixed etiology* were excluded, due to a non representative low number (n=3).
6. 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 mutiplied 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 and 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:

$$Variance = \frac{n_1 + n_2}{n_1 \times n_2} + \frac{Hedges'G^2}{2 \times (n_1 + n_2 - 2)}$$

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 withing 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 thure 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 diference of between groups was quantified in terms of Hedges'G and Cohen's D.

Total included studies

A total of **64** unique studies were included (19 acquires, 42 congenital and 3 mixed etiologies).

Table 1: Total unique studies 64

	Hearing Loss	Healthy
Total number of patients	7445	2924
Number mean	116.3	51.3
Number sd	479.3	204.3
Age mean	34.92	30.61
Age SD	23.08	19.45
%Female mean	50.41	54.97
%Female sd	12.2	12.64

Table 2: Acquired studies 19

	Hearing Loss	Healthy
Total number of patients	6469	1899
Number mean	340.5	146.1
Number sd	853.3	426.1
Age mean	65.31	56.44
Age SD	8.254	11.97
%Female mean	47.51	53.65
%Female sd	14.86	11.86

Table 3: Congenital studies 42

	Hearing Loss	Healthy
Total number of patients	927	976
Number mean	22.07	23.8
Number sd	17.06	14.63
Age mean	21.55	21.97
Age SD	12.21	12.68
%Female mean	51.16	55.23
%Female sd	10.95	13.2

Table 4: Mixed studies 3

	Hearing Loss	Healthy
Total number of patients	49	49
Number mean	16.33	16.33
Number sd	0.5774	0.5774
Age mean	25.26	25.13
Age SD	18.53	17.97
%Female mean	56.86	56.86
%Female sd	11.89	11.89

Table of included studies

Table 5: Studies without Hedges'G (n=7). These studies do not have control population (NA)

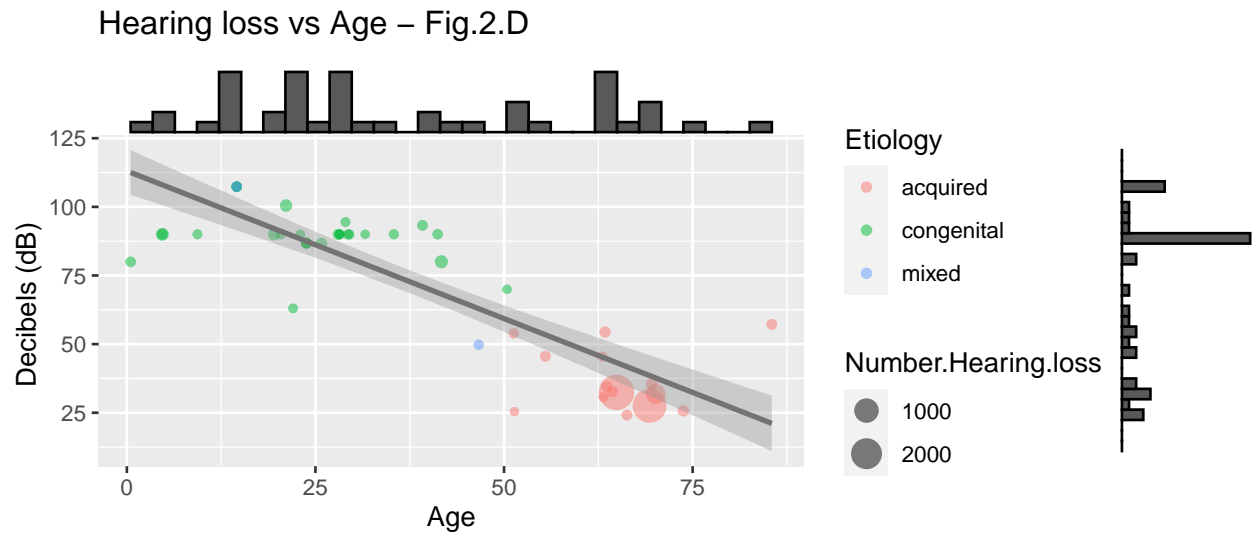
Source	Etiology	Number.Control
2011, Peelle et al. J Neurosci	acquired	NA
2012, Chang et al., Clin Exp Otorhinolaryngo	congenital	NA
2012, Eckert et al. J Assoc Res Otolaryngol	acquired	NA
2013, Eckert et al. J Assoc Res Otolaryngol	acquired	NA
2017, Qian et al. Neuroimage Clin	acquired	NA
2017, Ritgers et al. Front. Aging Neurosci	acquired	NA
2018, Ritgers et al. Neurobiol Aging	acquired	NA

Table 6: Studies with Hedges'G (n=57, mixed etiology=3)

Source	Etiology	all.techniques	all.measures
2000, Bavelier et al. J Neurosci	congenital	VBM	volume
2003, Emmorey et al. PNAS	congenital	VBM	asymmetry, GM+WM, ratio GM/WM, volume
2003, Penhune et al. Neuroimage	congenital	VBM	asymmetry, ratio GM/WM, volume
2004, Chang et al. Neuroreport	congenital	DTI	asymmetry, FA
2006, Kara et al. J Neuroradiol	congenital	VBM	length, Thickness, volume
2007, Meyer et al. Restor Neurol Neurosci	congenital	VBM	volume
2007, Shibata DK. Am J Neuroradiol	congenital	VBM	volume
2008, Allen et al. J Neurosci	congenital	VBM	asymmetry, ratio GM/WM, Vol proportion, volume
2008, Xia et al. Chin J Med Img Tech	congenital	VBM	volume
2009, Kim et al. Neuroreport	congenital	DTI, VBM	FA, volume
2009, Wang et al. Chin J Med Img Tech	congenital	DTI	FA
2010, Husain et al. Brain Res	acquired	DTI, VBM	FA, volume
2010, Leporé et al. Hum Brain Mapp	congenital	VBM	VBM
2010, Li, et al. J Clin Rad	congenital	VBM	volume
2010, Liu et al. Chin J Med Img Tech	congenital	CT	FA
2011, Smith et al. Cereb Cortex	congenital	VBM	asymmetry, ratio GM/WM, volume
2012, Li et al. Brain Res	congenital	CT	Thickness
2012, Li et al. Hum Brain Mapp	congenital	DTI	AD, FA, RD
2013, Allen et al. Front Neuroanat	congenital	VBM	asymmetry, volume
2013, Boyen et al. Hear Res	acquired	VBM	volume
2013, Li et al. Restor Neurol Neurosci	mixed	VBM	Thickness
2013, Miao et al. Am J Neuroradiol	congenital	DTI	FA, RD
2013, Pénicaud et al. Neuroimage	congenital	VBM	volume
2014, Hribar et al. Hear Res	congenital	DTI, VBM	AD, FA, Thickness
2014, Kim et al. Hear Res	congenital	VBM	volume
2014, Lin et al. Neuroimage	acquired	VBM	volume
2014, Lyness et al. Neuroimage	congenital	DTI	FA, MD, RD
2014, Olulade et al. J Neurosci	congenital	VBM	volume
2014, Profant et al. Neuroscience	acquired	DTI, VBM	AD, CT, FA, MD, RD, Surface, volume
2015, Huang et al. PLoS One	congenital	DTI	FA, MD
2015, Li et al. Restor Neurol Neurosci	mixed	CT	volume
2015, Tae Investig Magn Reson Imaging	congenital	VBM	VBM
2016, Amaral et al. Eur J Neurosci	congenital	VBM	asymmetry, Thickness
2016, Chinnadurai et al. Magn Reson Imaging	congenital	DTI	AD, Axial Kurtosis, FA, Mean Kurtosis, Radial Kurtosis, RD
2016, Ma et al. AJNR Am J Neuroradiol	acquired	DTI	AD, FA, MD, RD
2016, Shi et al. Neuroreport	congenital	VBM	volume
2016, Shiell et al. Neural Plasticity	congenital	CT	Thickness
2016, Smittenaar et al. Open Neuroimag J	congenital	CT	CT

Source	Etiology	all.techniques	all.measures
2016, Wu et al. Brain Res	congenital	VBM	ADC, FA
2017, Karns et al. Hear Res	congenital	DTI	AD, FA, RD, volume
2017, Kim et al. Neuroreport	congenital	DTI	FA
2017, Shiell & Zatorre. Hear Res	congenital	DTI	AD, MD, RD, volume
2017, Zheng et al. Sci Rep	congenital	DTI	FA, Mean Kurtosis
2018, Alfandari et al. Trends Hear	mixed	VBM	volume
2018, Benetti et al. Neuroimage	congenital	DTI	AD, FA, RD
2018, Chen et al. Behav Neurosci	acquired	VBM	volume
2018, Feng et al. PNAS	congenital	VBM	VBM
2018, Kumar U, Mishra M. Brain Res	congenital	VBM	Thickness, VBM
2018, Park et al. Biomed Res Int	congenital	DTI	FA
2018, Pereira-Jorge et al. Neural Plast	acquired	VBM	volume
2018, Ren et al. Front Neurosci	acquired	CT, VBM	Thickness, volume
2018, Uchida et al. Front Aging Neurosci	acquired	VBM	volume
2018, Zou et al. Otol Neurotol	congenital	DTI	AK, FA, MK, RK
2019, Belkhiria et al. Front. Aging Neurosci	acquired	VBM	CT, volume
2019, Luan et al. Front Neurosci	acquired	DTI, VBM	FA, MD, volume
2019, Ponticorvo et al. Hum Brain Mapp	acquired	VBM	volume
2019, Xu et al. J Magn Reson Imaging	acquired	VBM	volume

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



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



Fig.2.E – Severity

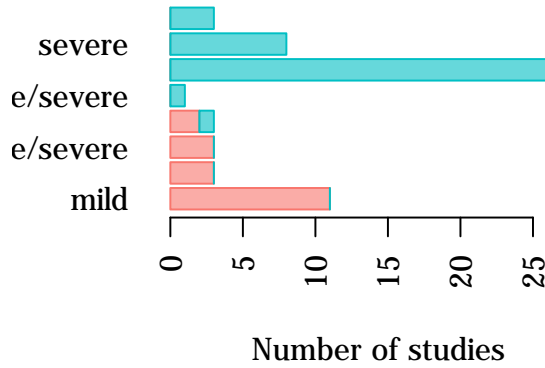
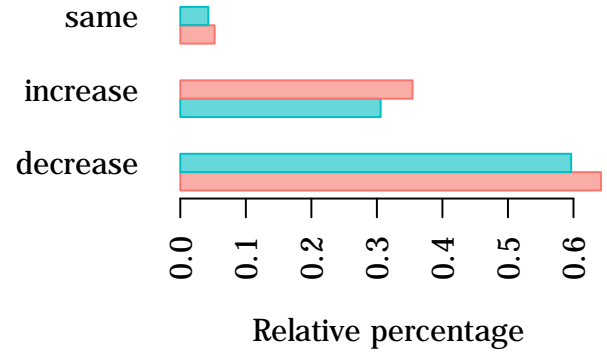


Fig.2.F – Effect direction



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 7: 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 8: 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

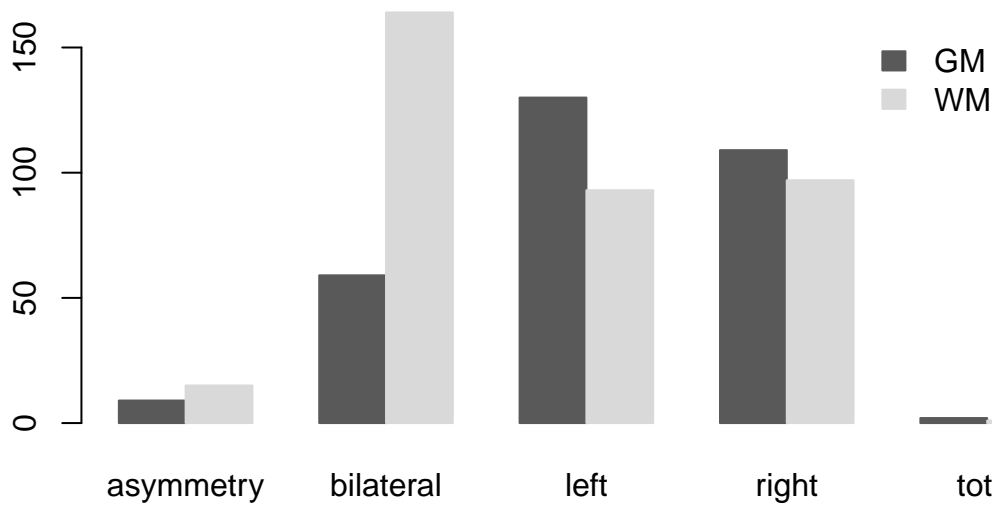
	RK	Surface	Thickness	VBM	Vol proportion	volume
GM	2	4	14	43	6	194
WM	2	0	10	16	6	79

Table 10: Matter vs Side

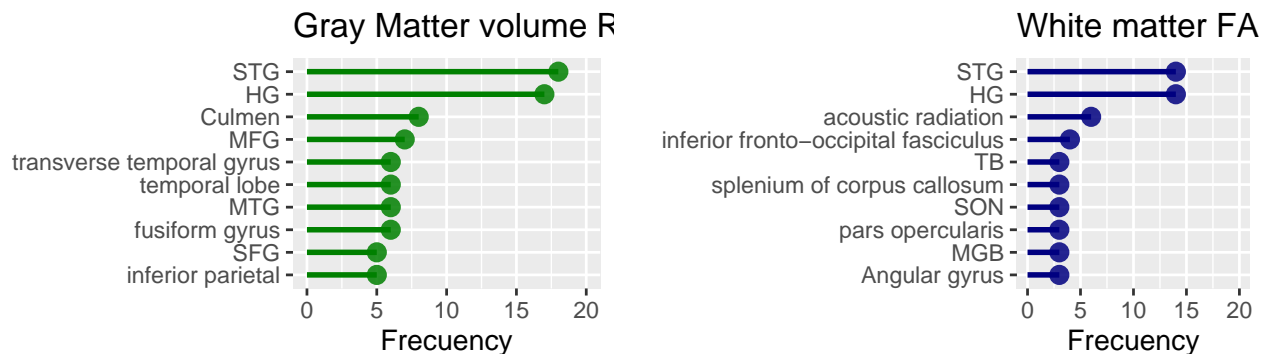
	asymmetry	bilateral	left	right	total
GM	9	59	130	109	2
WM	15	164	93	97	1

Brain structure (GM, WM) and side

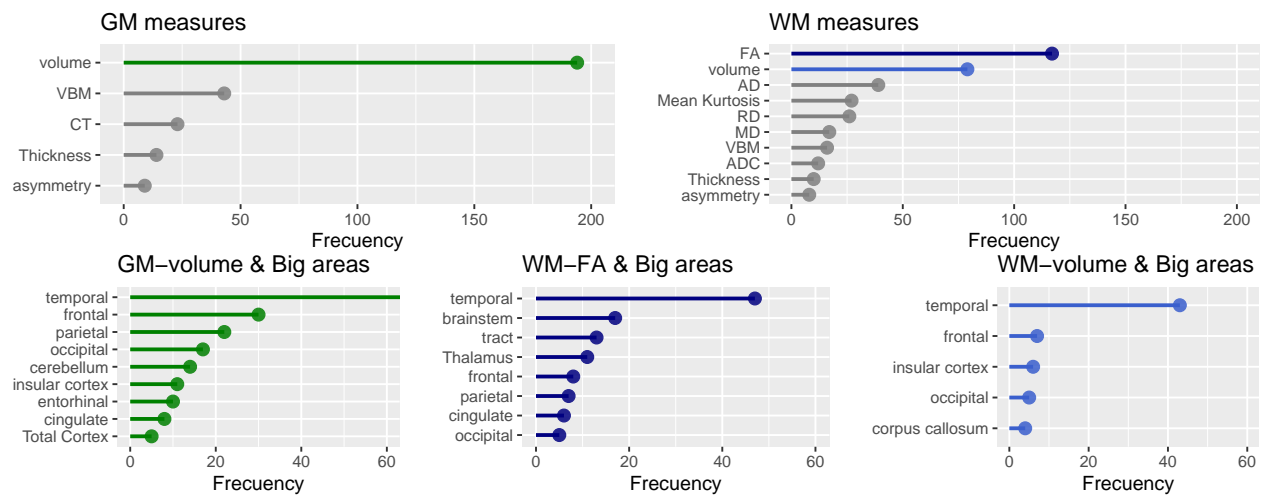
Matter vs Side



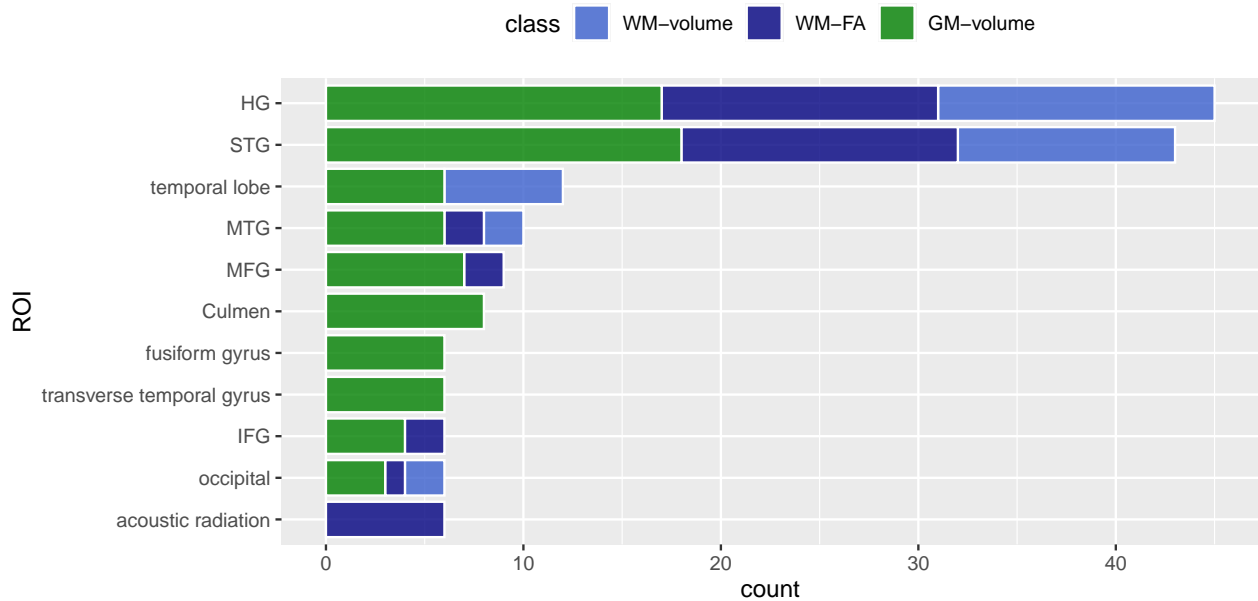
Brain structure (GM, WM) by MRI measure (volume) and ROI



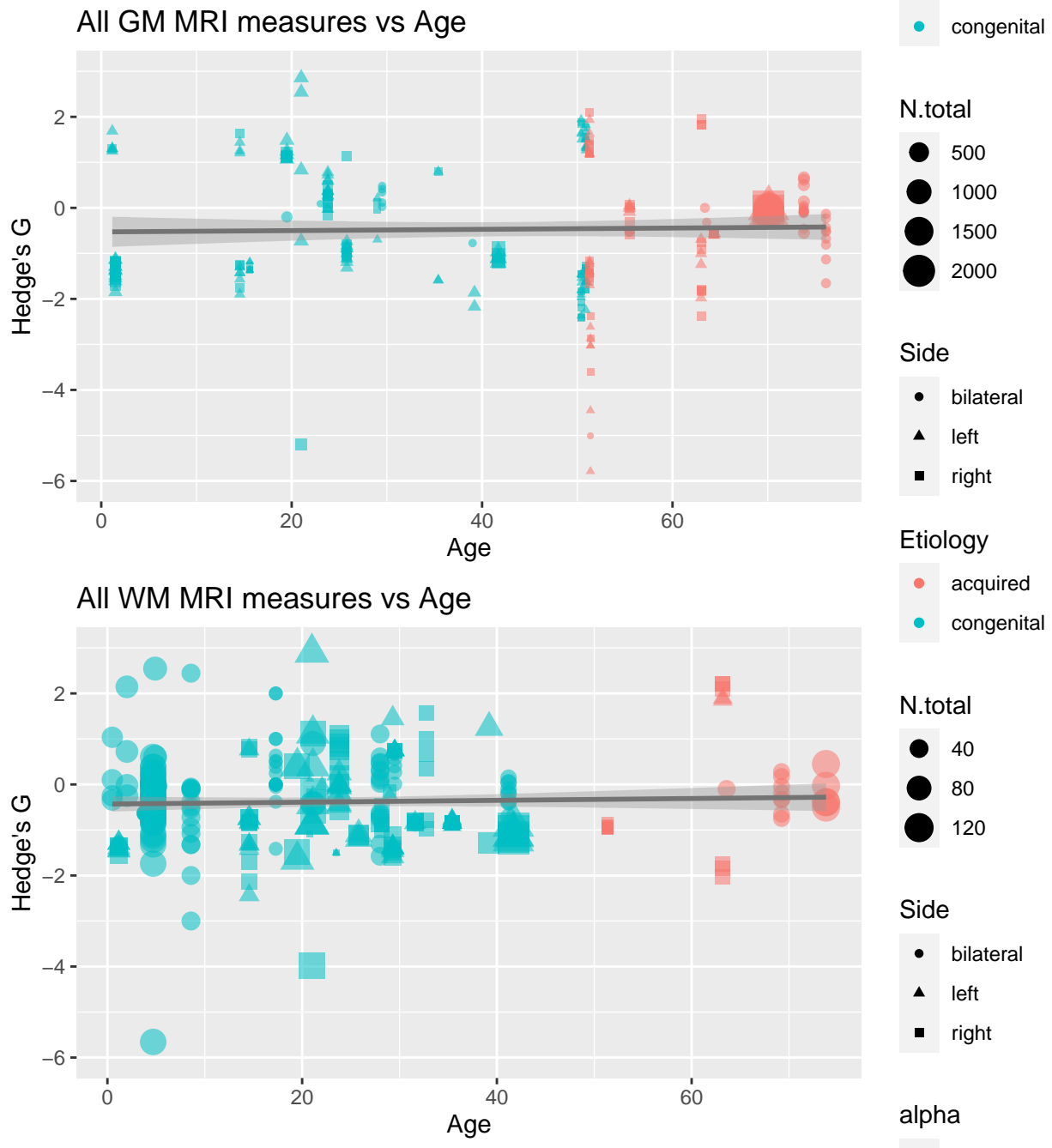
Studies characteristics (Figure 2.A, 2.B): Brain structure (GM, WM) by MRI measure (volume and FA)



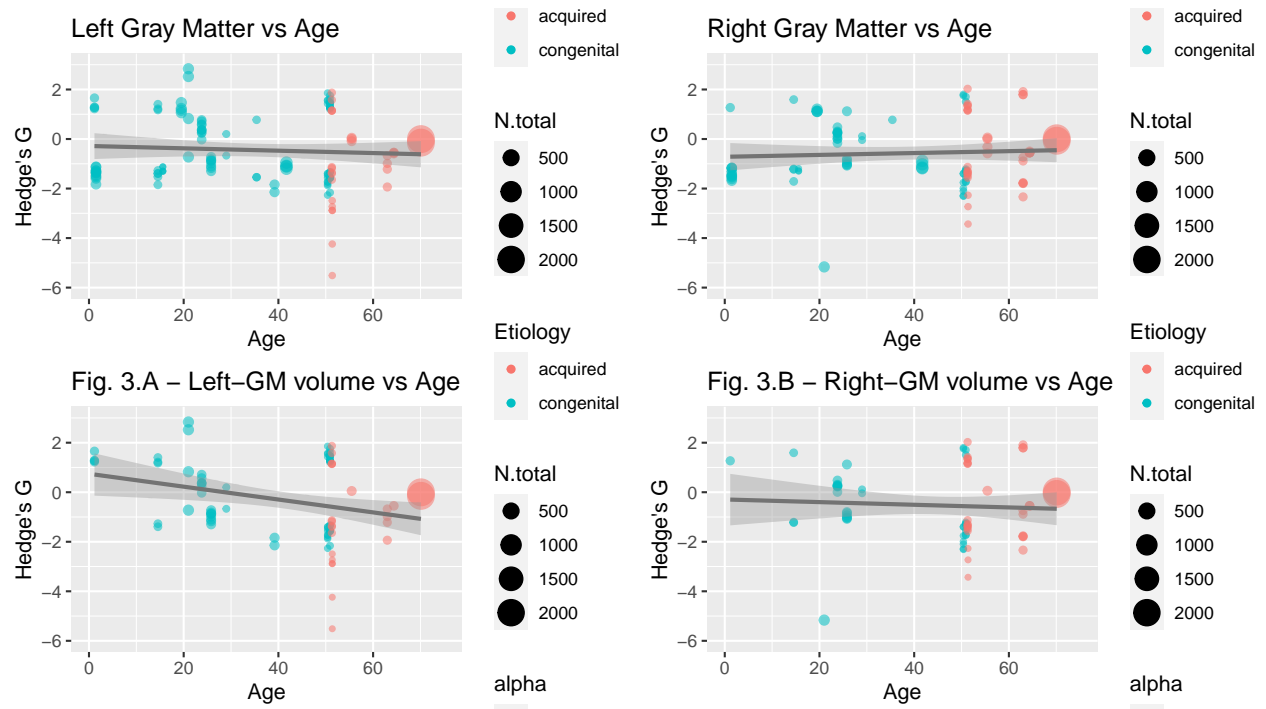
MRI measures by ROI (Figure 2.C)



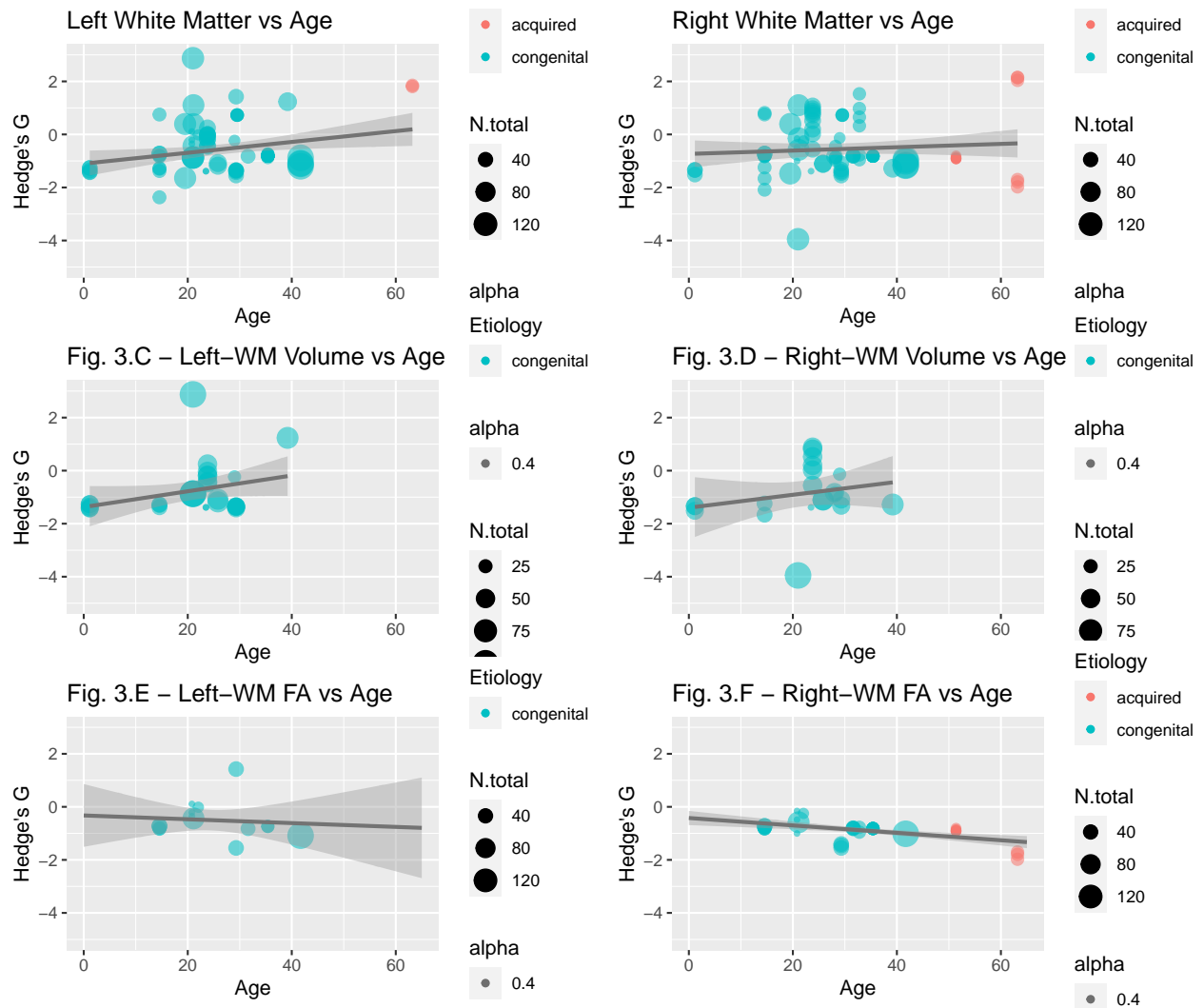
Relations of all MRI measurements of GM and WM with age



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

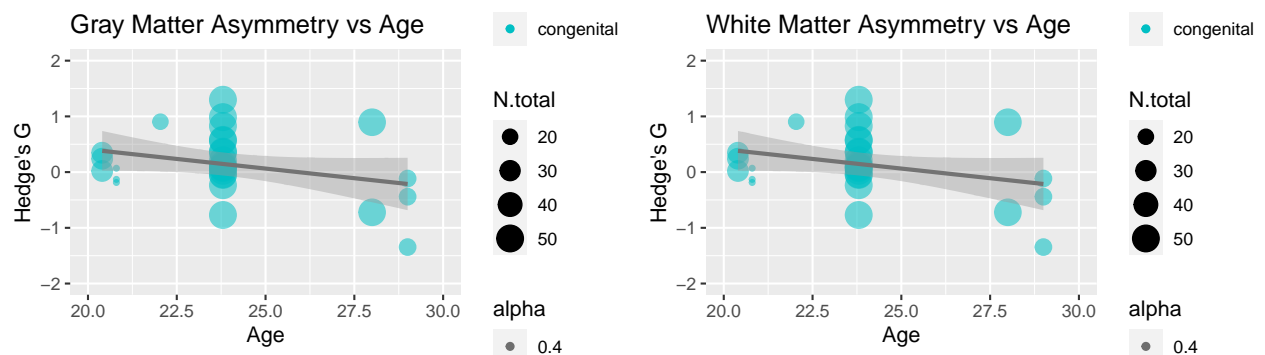
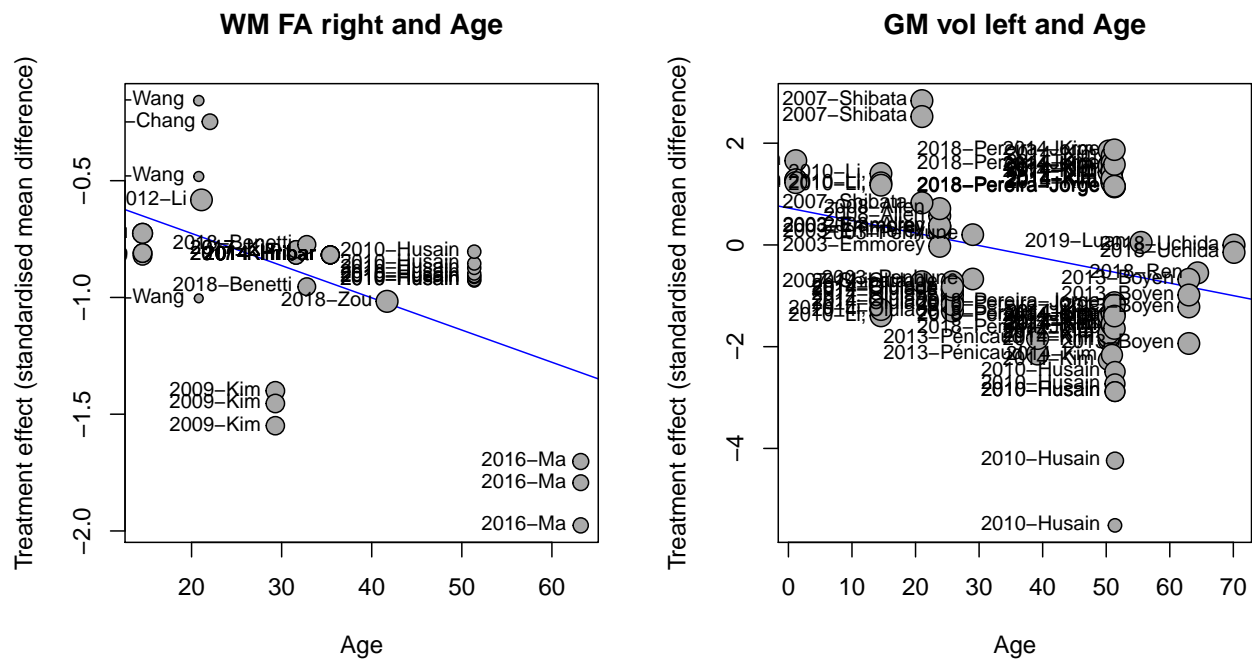
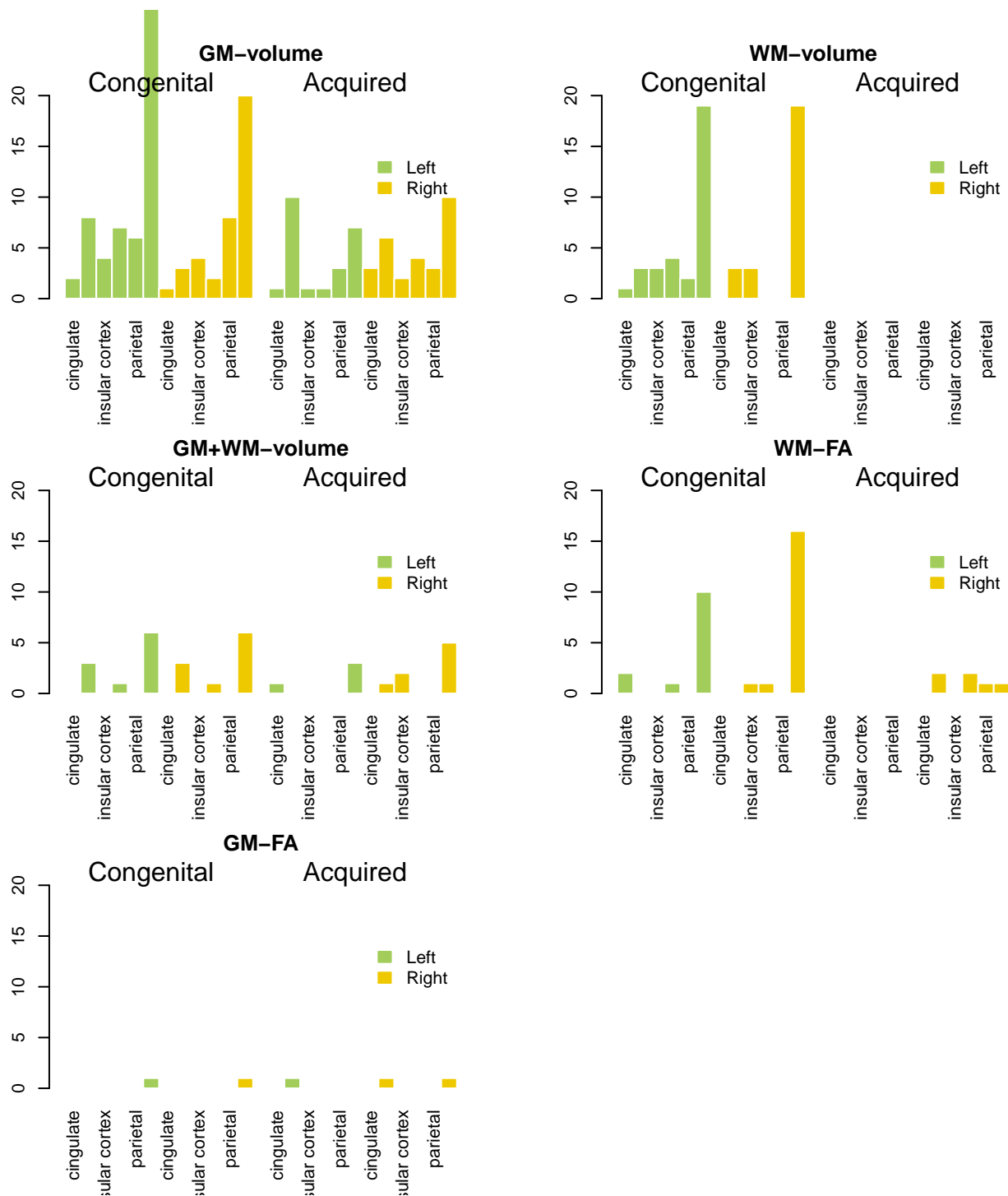


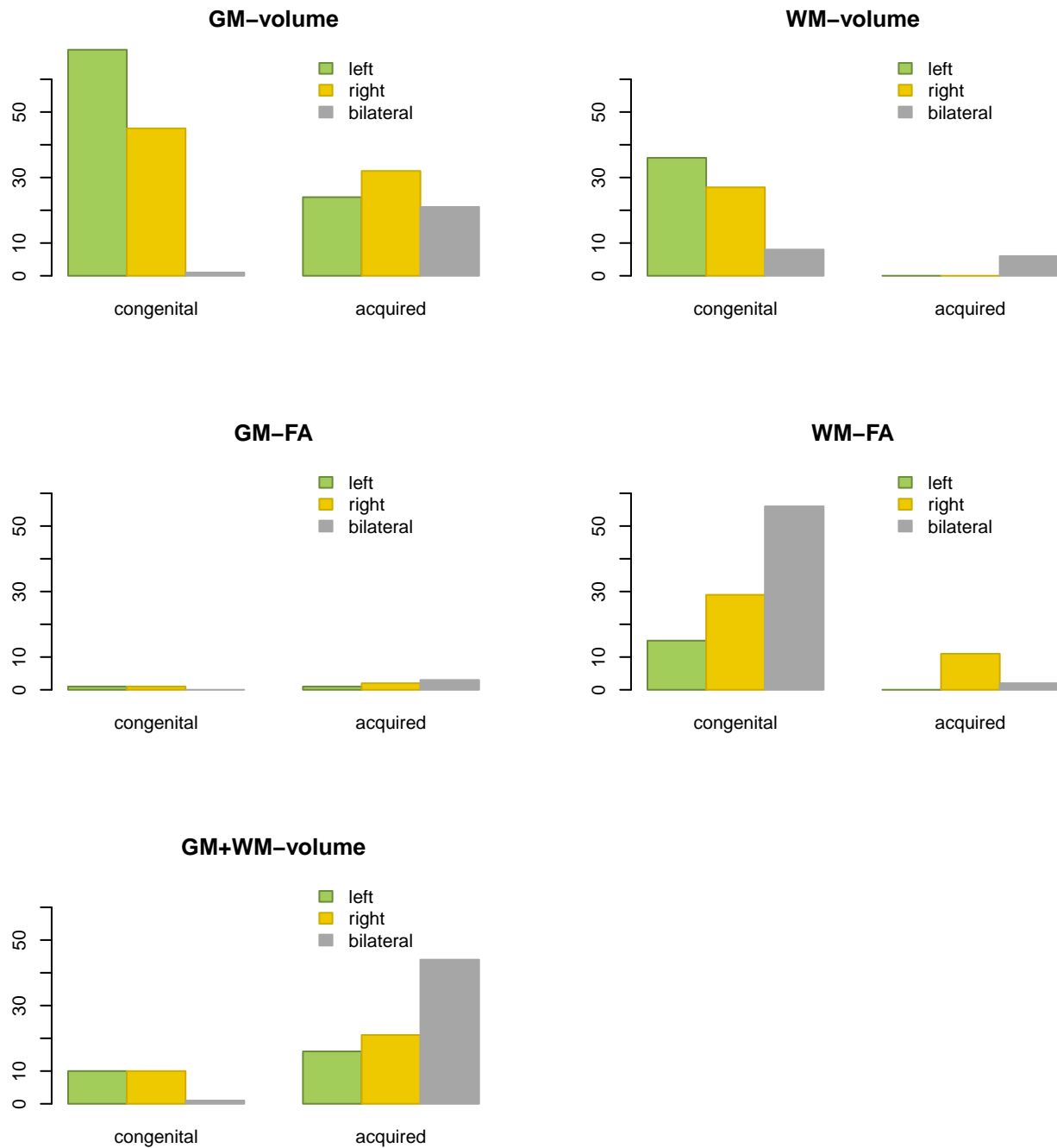
Table of estimates and meta-regression: WM and GM relation with age by MRI measures (volume and FA)

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



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





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

Table 12: Congenital - Gray Matter Volume

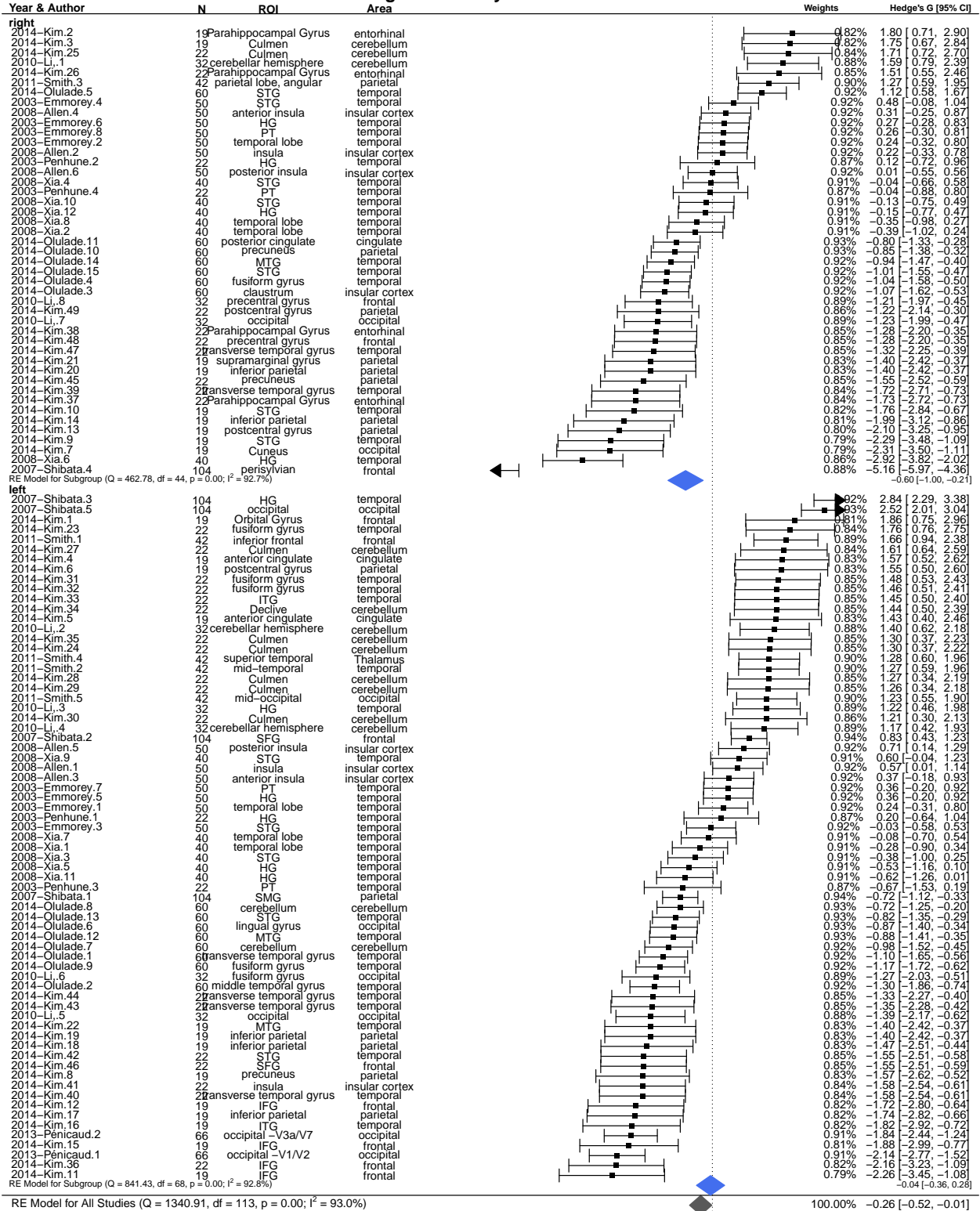
Mixed-effect model: $k = 114$: $\tau^2 = 1.35$ (SE = 0.22)
 $I^2 = 91.08\%$, $H^2 = 11.21$
 Residual heterogeneity: $QE(df = 98) = 1048.28$, $p.val = 7.08528565862191e-159$
 Test of moderators (big areas): $QM(df = 16) = 48.63$
 $p.val = 3.78635028624703e-05$

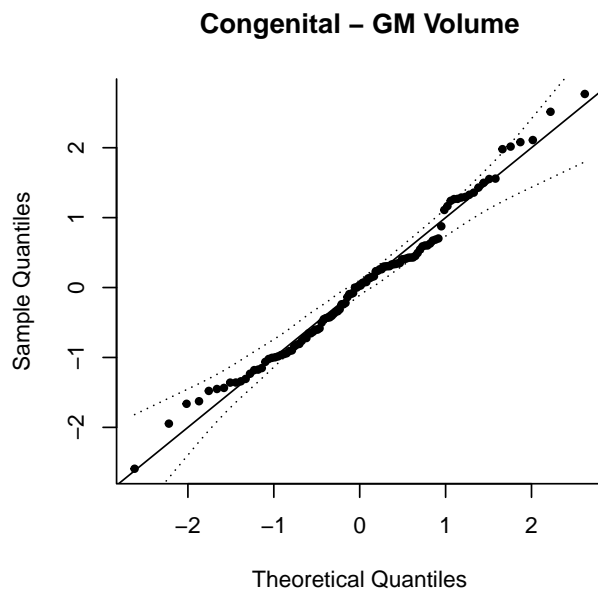
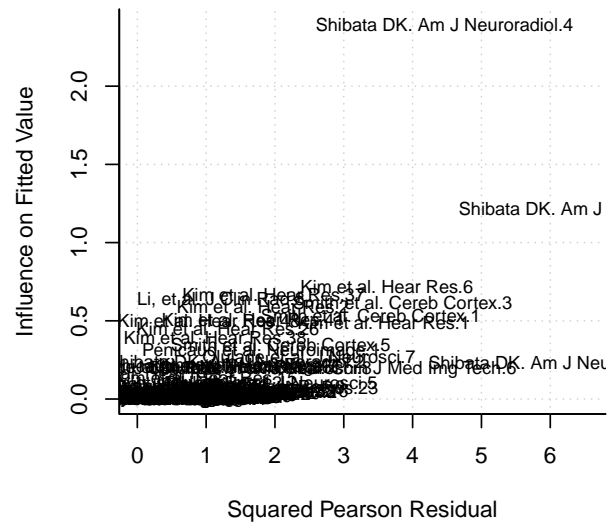
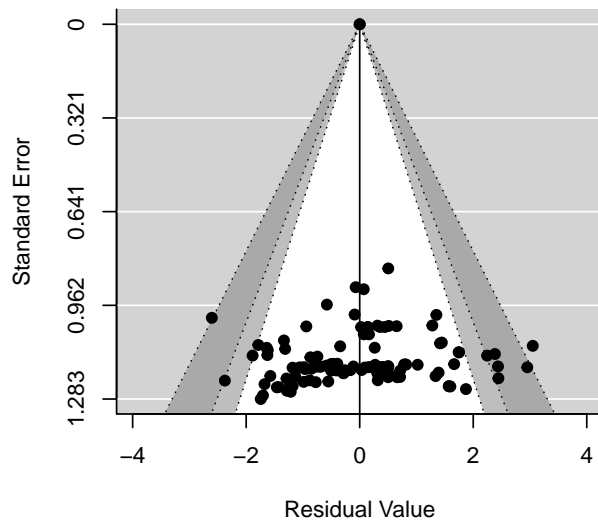
Table 13: Table continues below

	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
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 15: Acquired - Gray Matter Volume

Mixed-effect model: $k = 56$; $\tau^2 = 2.49$ (SE= 0.6) $I^2 = 98.57\%$, $H^2 = 70.1$
 Residual heterogeneity: $QE(df = 41) = 412.31$, $p.val = 8.01499990705428e-63$
 Test of moderators (big areas): $QM(df = 15) = 29.35$
 $p.val = 0.014479351188099$

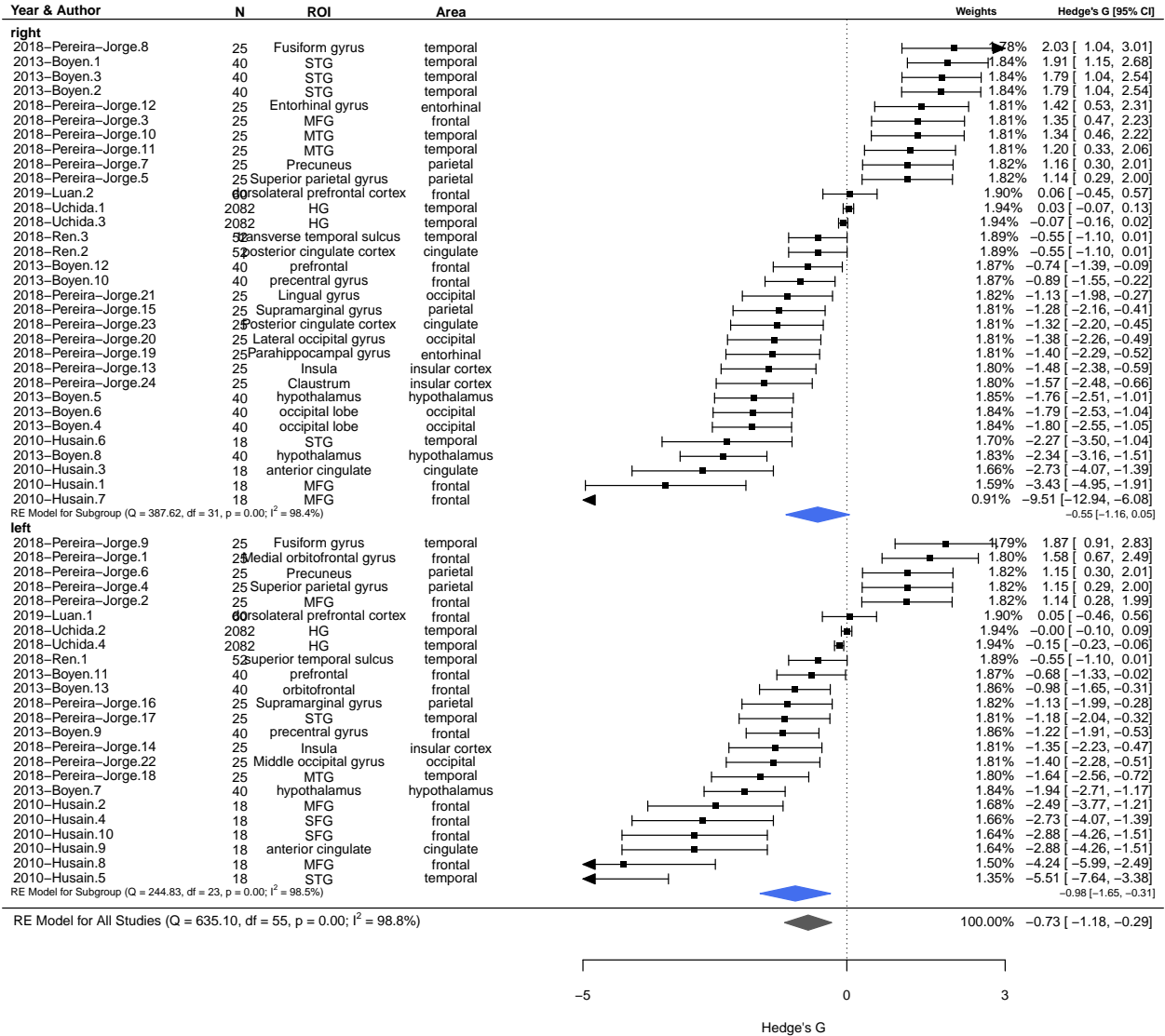
Table 16: Table continues below

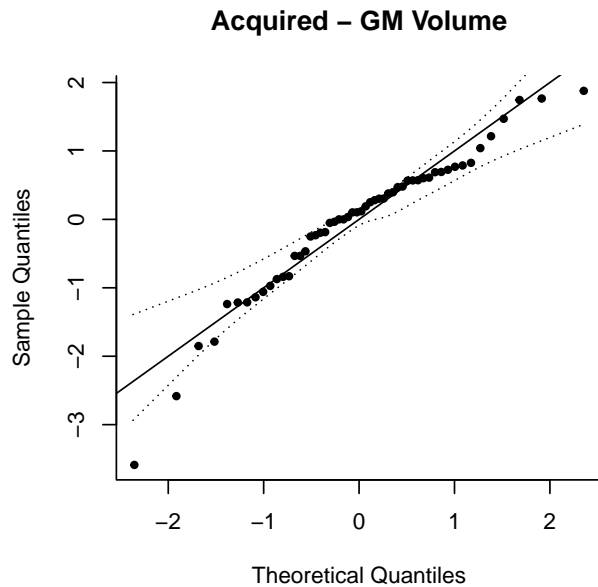
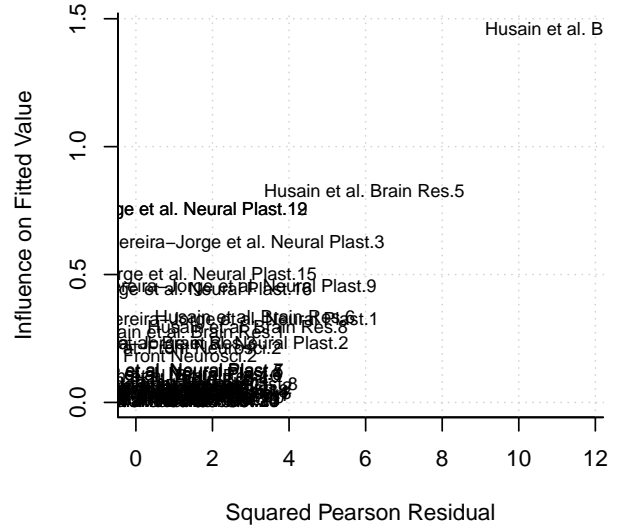
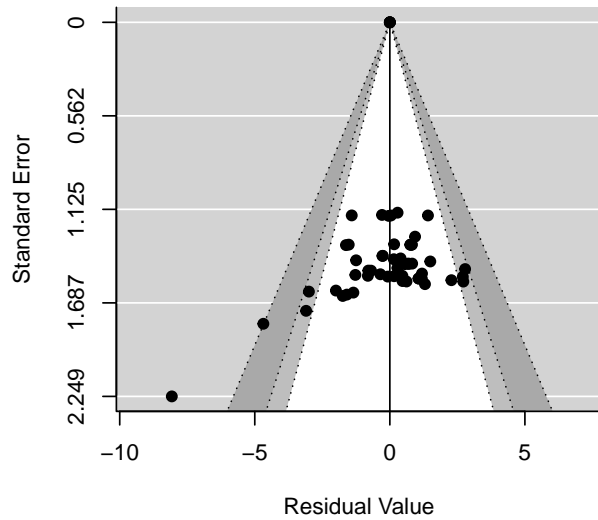
	HedgeG	se	zval	ci.lo	ci.up
left cingulate	-2.883	1.728	-1.669	-6.269	0.5024
left frontal	-1.14	0.5268	-2.164	-2.173	-0.1076
left hypothalamus	-1.937	1.626	-1.191	-5.124	1.25

	HedgeG	se	zval	ci.lo	ci.up
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

Acquired – Gray Matter Volume





CONGENITAL - White Matter by VOLUME

Random effects model no intercept covariated by Big area

Table 18: Congenital White Matter Volume

Mixed-effect model: $k = 63$: $\tau^2 = 0.83$ (SE= 0.19)
 $I^2 = 89.36\%$, $H^2 = 9.4$
 Residual heterogeneity: $QE(df = 50) = 462.69$, $p.val = 3.35220276992225e-68$
 Test of moderators (big areas): $QM(df = 13) = 50.92$
 $p.val = 2.07007590853841e-06$

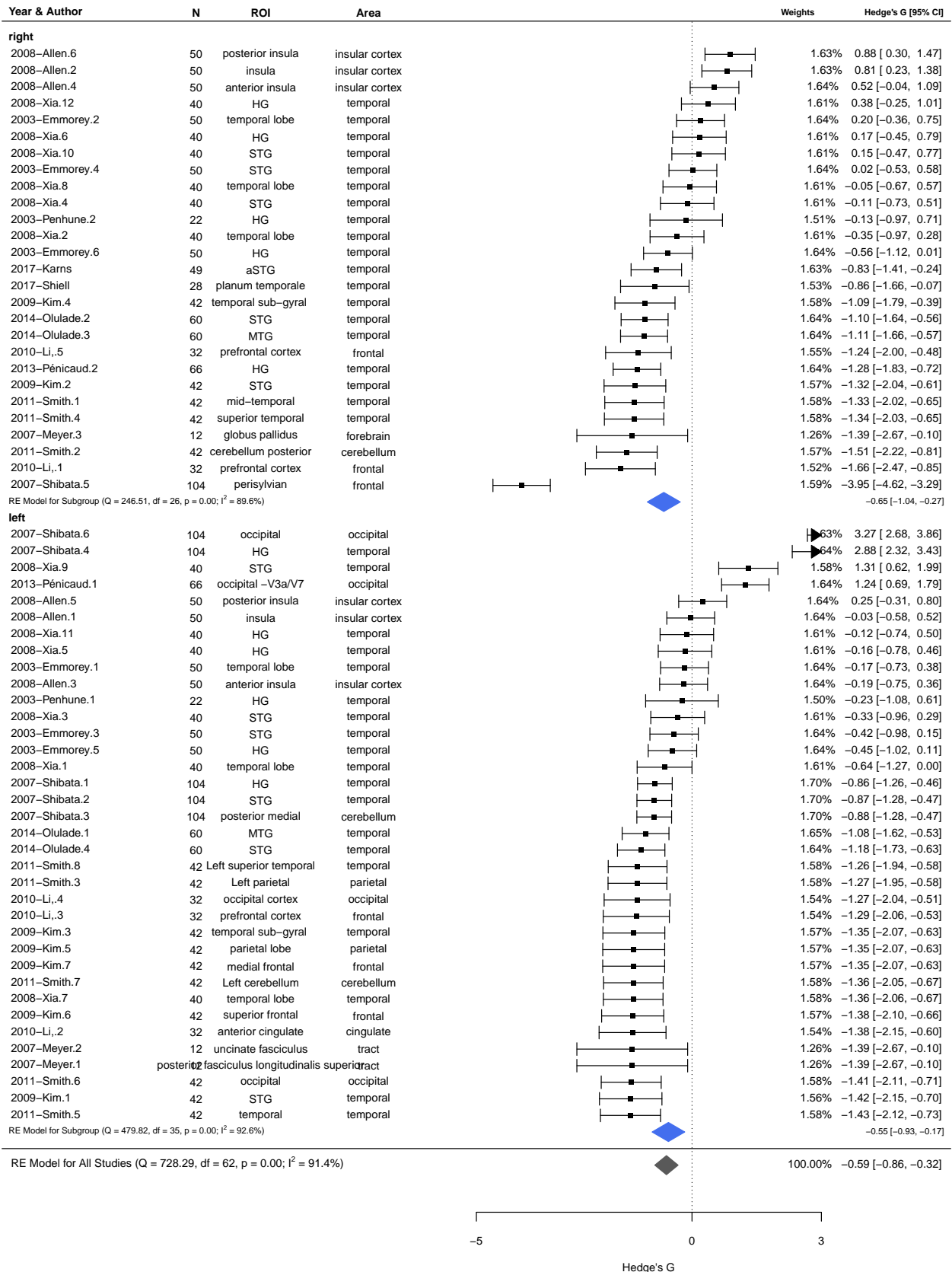
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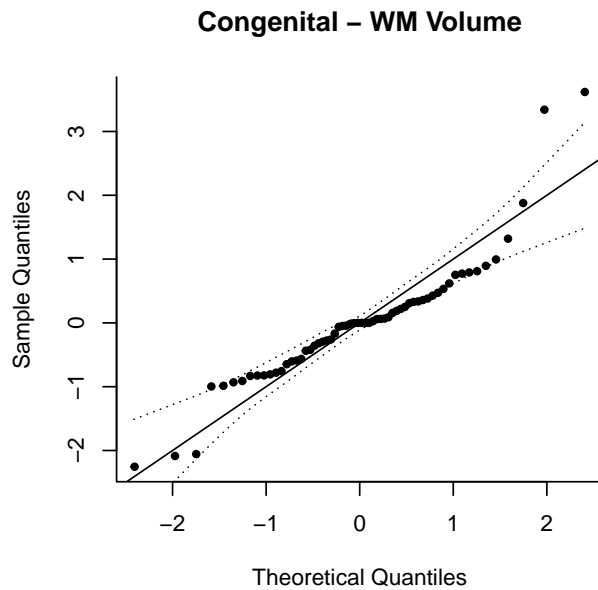
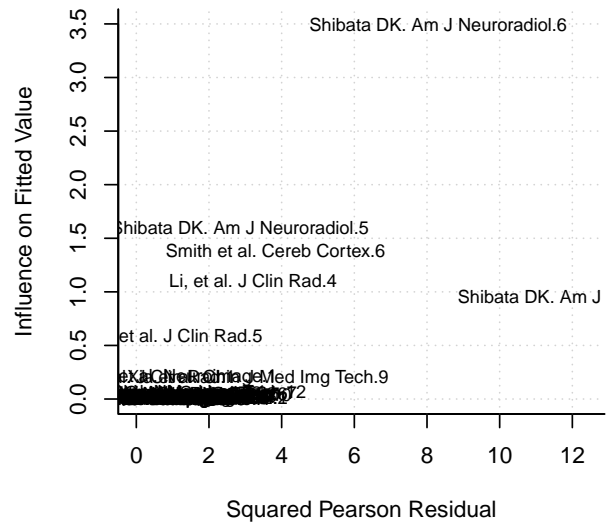
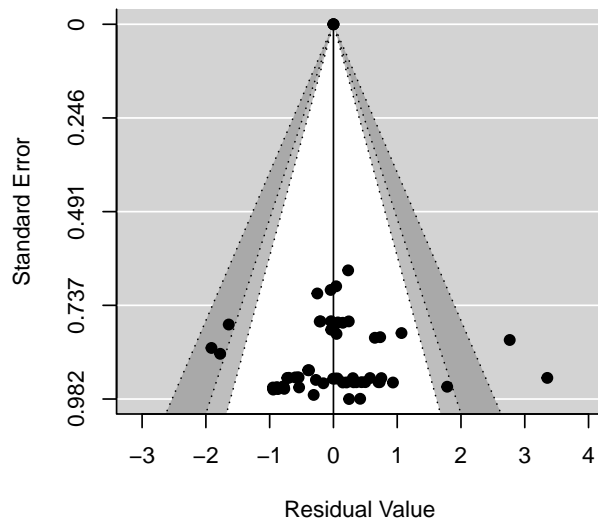
	HedgeG	se	zval	ci.lo	ci.up
left cerebellum	-1.107	0.6745	-1.641	-2.429	0.2149
left cingulate	-1.379	0.9926	-1.389	-3.324	0.5668
left frontal	-1.34	0.5684	-2.358	-2.454	-0.2262

	HedgeG	se	zval	ci.lo	ci.up
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)

Table 21: acquired White Matter Volume

Mixed-effect model: $k = 6$: $\tau^2 = 0.09$ (SE= 0.21) $I^2 = 59.05\%$, $H^2 = 2.44$
 Residual heterogeneity: $QE(df = 1) = 2.44$, $p.val = 0.118106312179678$
 Test of moderators (big areas): $QM(df = 5) = 5.26$ $p.val = 0.385192885534552$

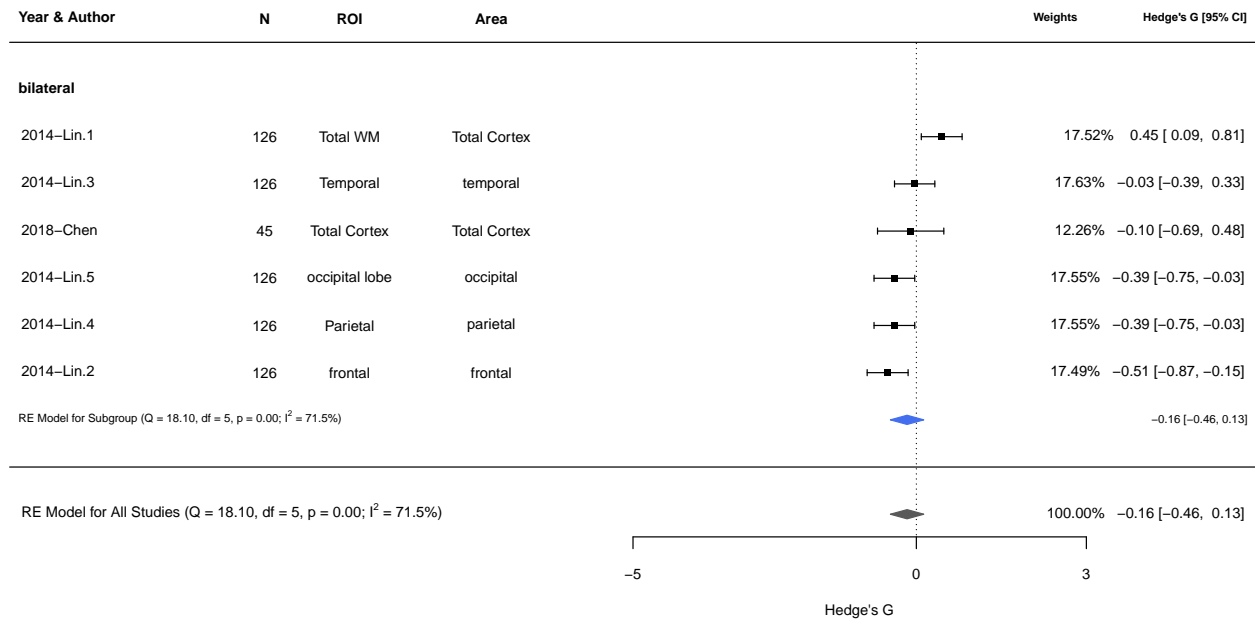
Table 22: Table continues below

	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

	HedgeG	se	zval	ci.lo	ci.up
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

	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

acquired White Matter Volume



Nothing is significant

CONGENITAL - White Matter by FA fractional anisotropy

Random effects model no intercept covariated by Big area

Table 24: Congenital White Matter FA

Mixed-effect model: k= 44 : tau²= 0.04 (SE= 0.04)
I²= 24.12 %, H²= 1.32
Residual heterogeneity: QE(df= 33)= 40.58 , p.val= 0.17085782139714
Test of moderators (big areas): QM(df= 11)= 168.31
p.val= 2.63258401967927e-30

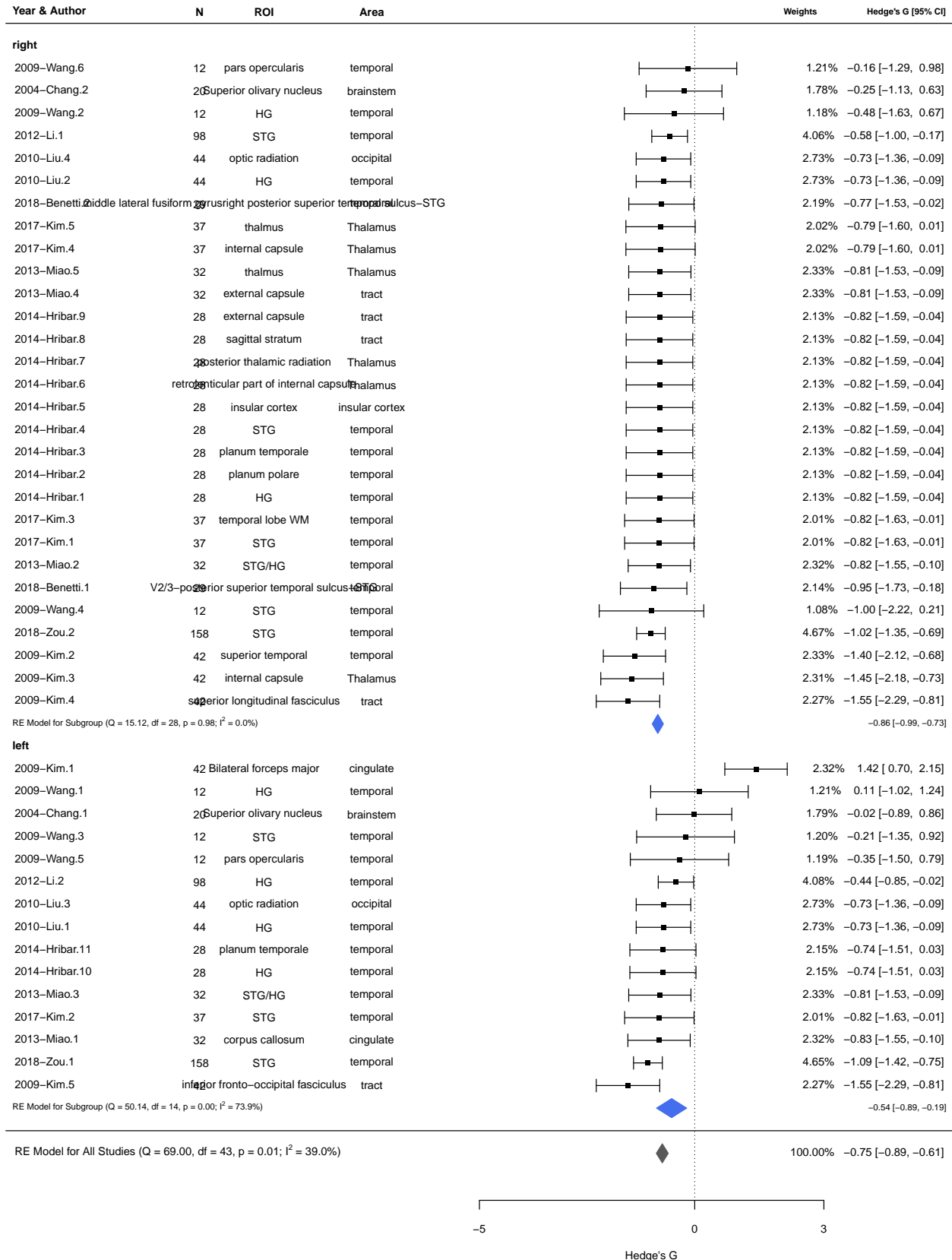
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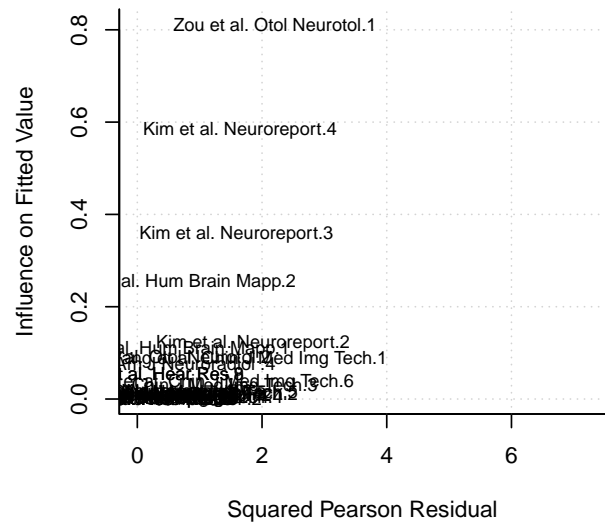
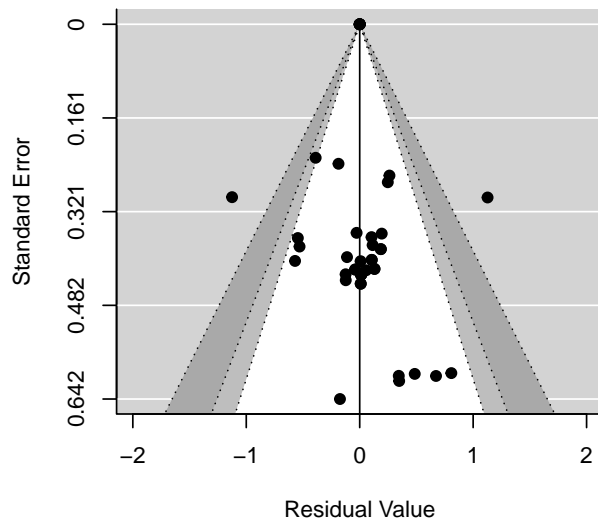
	HedgeG	se	zval	ci.lo	ci.up
left brainstem	-0.01557	0.4891	-0.03183	-0.9742	0.9431
left cingulate	0.297	0.2965	1.002	-0.2841	0.8781
left occipital	-0.7254	0.3791	-1.914	-1.468	0.01755
left temporal	-0.698	0.1265	-5.518	-0.946	-0.4501
left tract	-1.549	0.425	-3.645	-2.382	-0.7163
right brainstem	-0.2476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

	HedgeG	se	zval	ci.lo	ci.up
right occipital	-0.7254	0.3791	-1.914	-1.468	0.01755
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

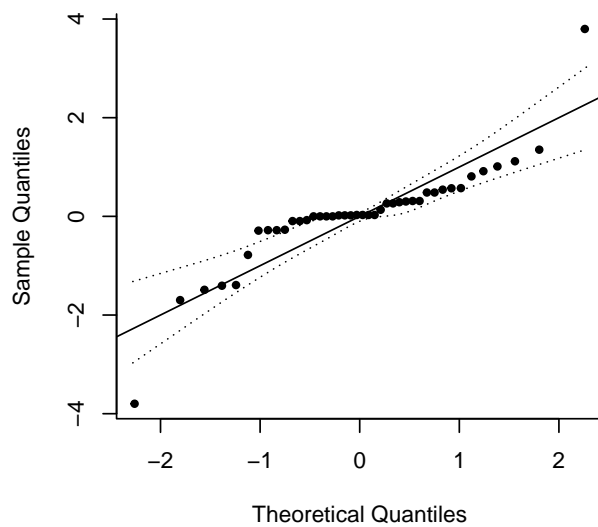
	pval	N
left brainstem	0.9746	1
left cingulate	0.3165	2
left occipital	0.05566	1
left temporal	3.421e-08	10
left tract	0.000267	1
right brainstem	0.614	1
right insular cortex	0.064	1
right occipital	0.05566	1
right temporal	1.121e-15	16
right Thalamus	2.416e-07	6
right tract	3.226e-06	4

Congenital White Matter FA





Congenital White Matter FA



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

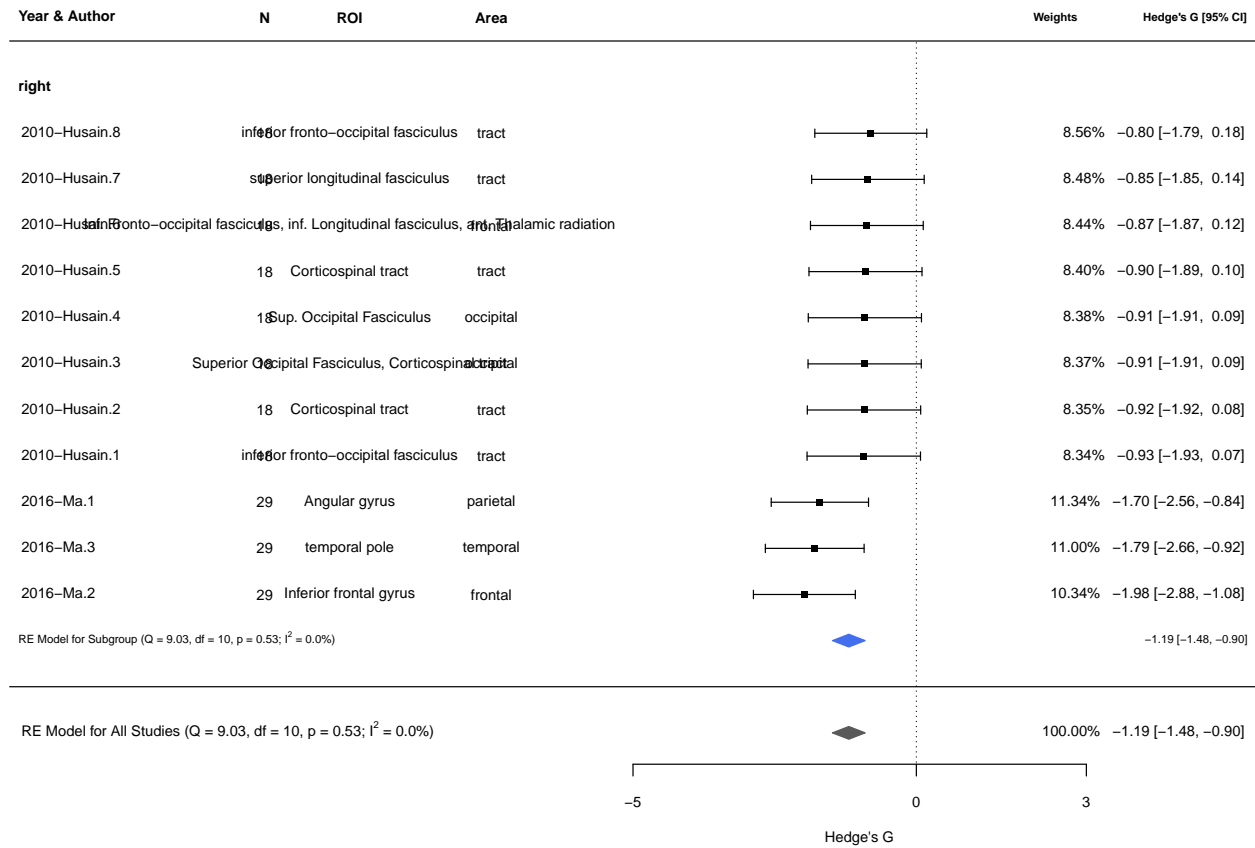
Random effects model no intercept covariated by Big area

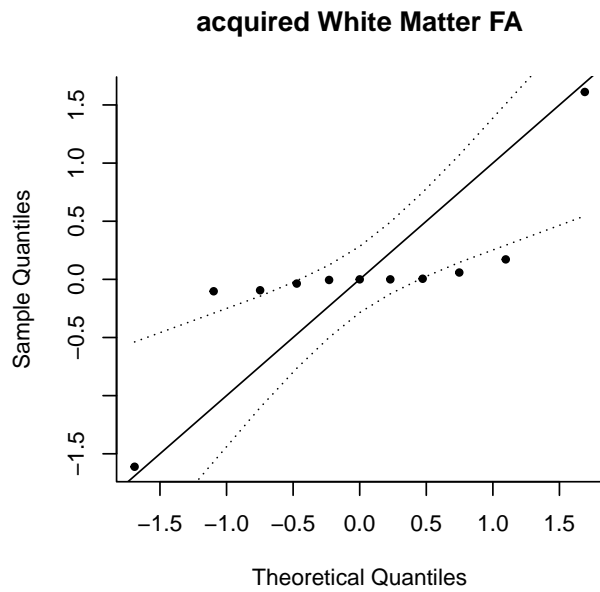
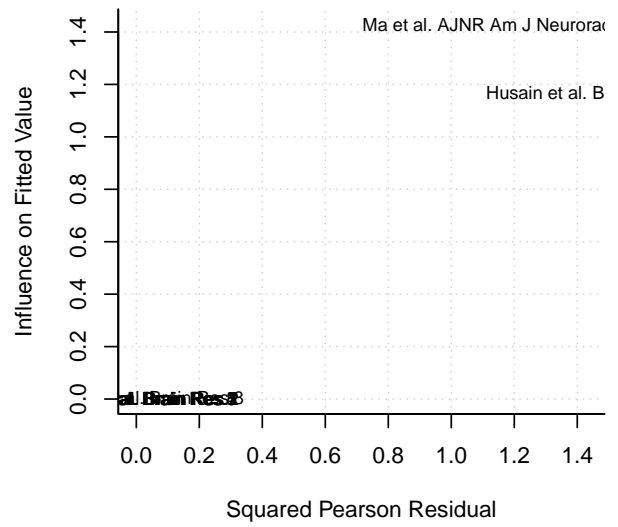
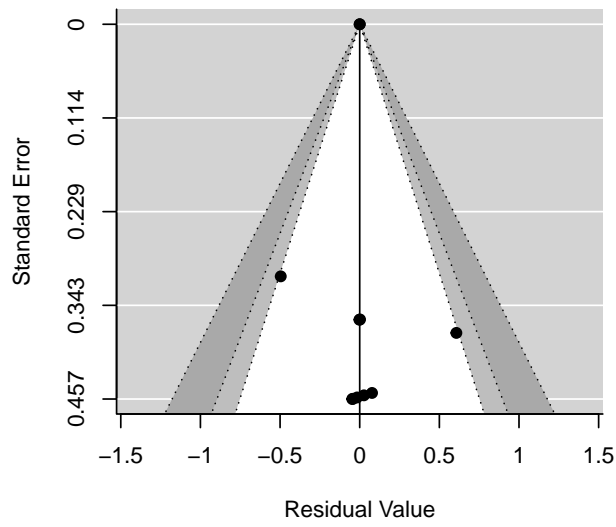
Table 27: acquired White Matter FA

Mixed-effect model: $k = 11$: $\tau^2 = 0$ (SE= 0.15) $I^2 = 0\%$, $H^2 = 1$
 Residual heterogeneity: $QE(df = 6) = 2.64$, $p.val = 0.852507484101014$
 Test of moderators (big areas): $QM(df = 5) = 71.74$ $p.val = 4.45450158997401e-14$

	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

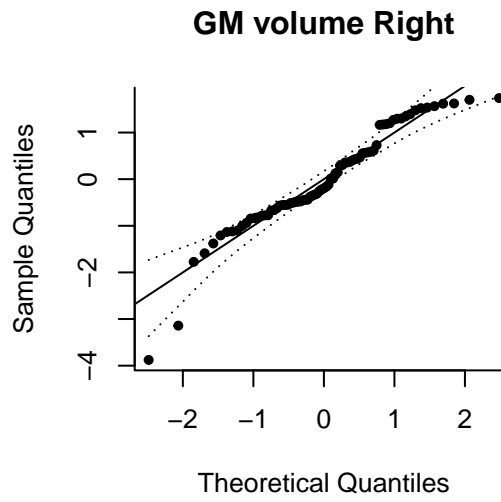
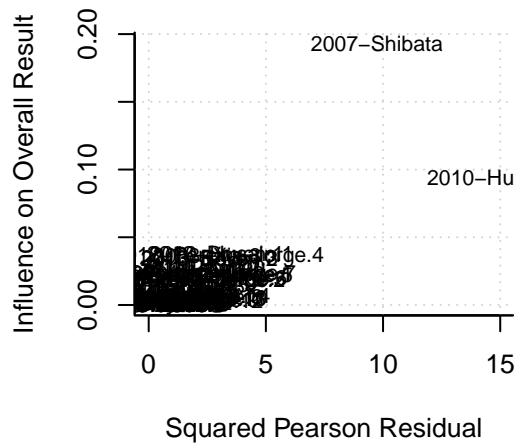
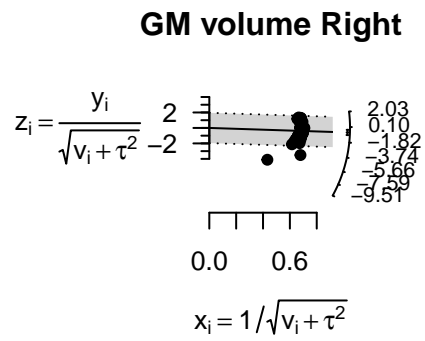
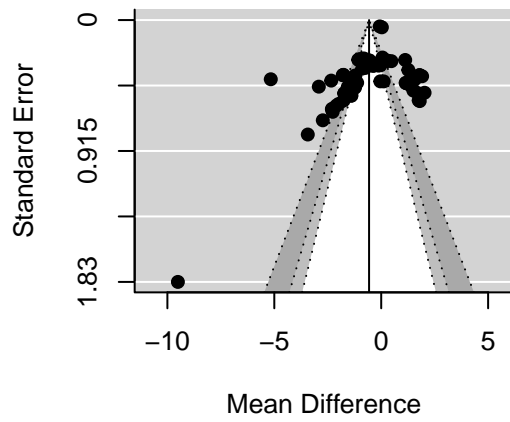
acquired White Matter FA



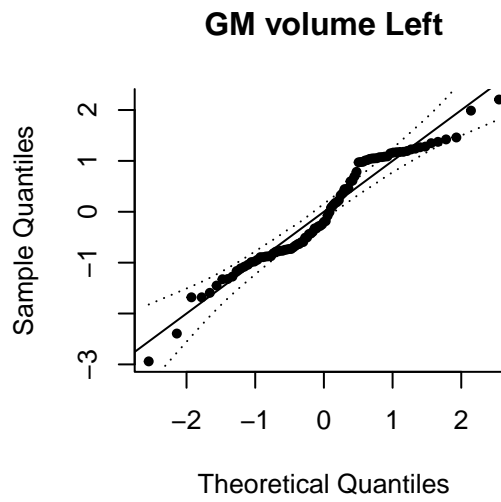
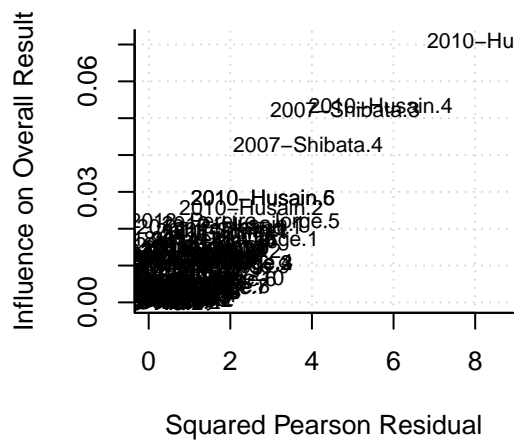
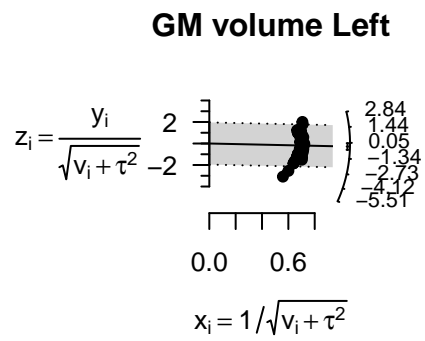
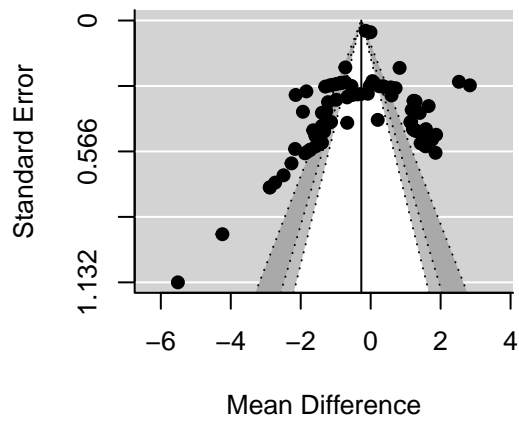


Supplementary material: heterogeneity per model

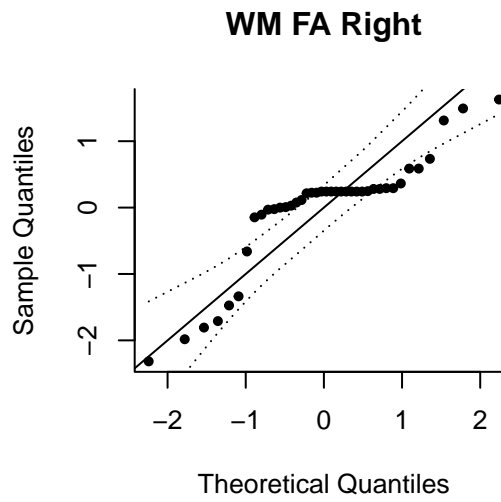
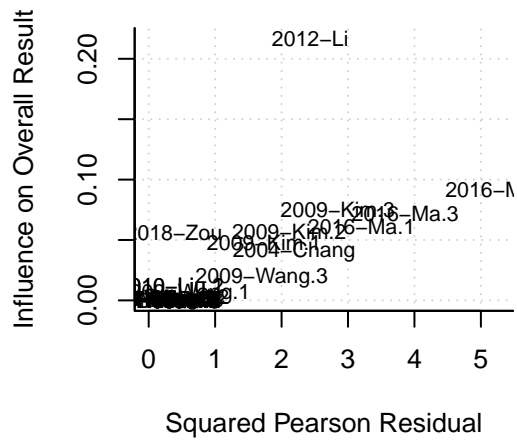
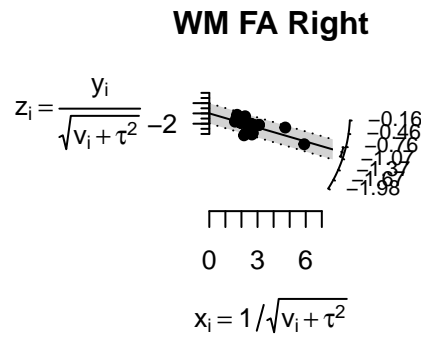
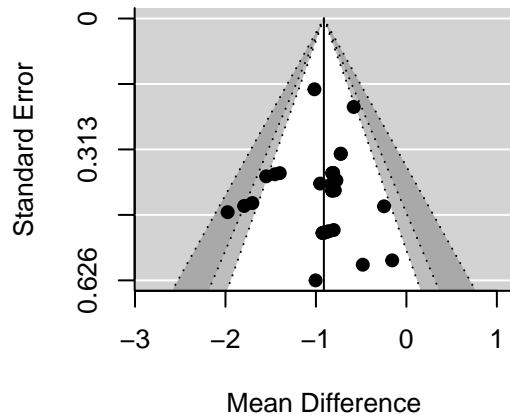
Heterogeneity: GM volume Right



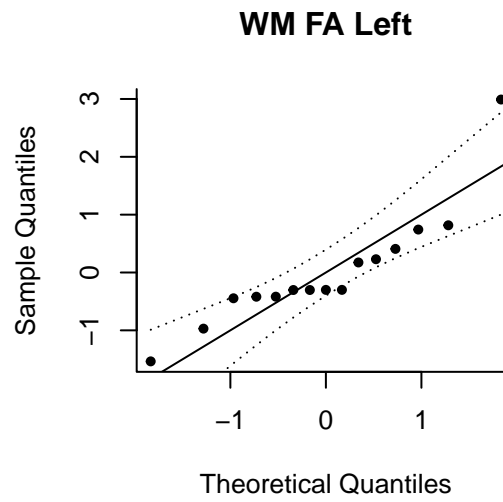
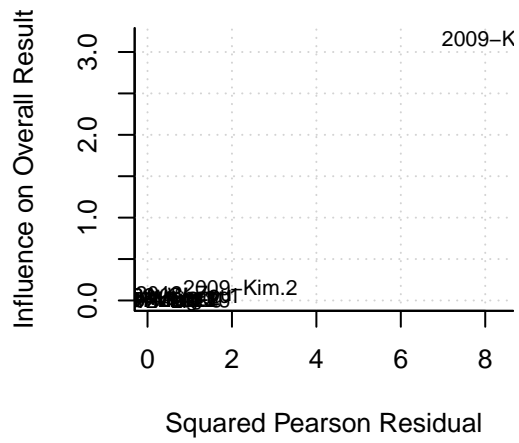
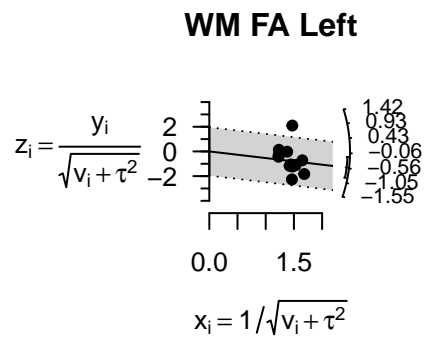
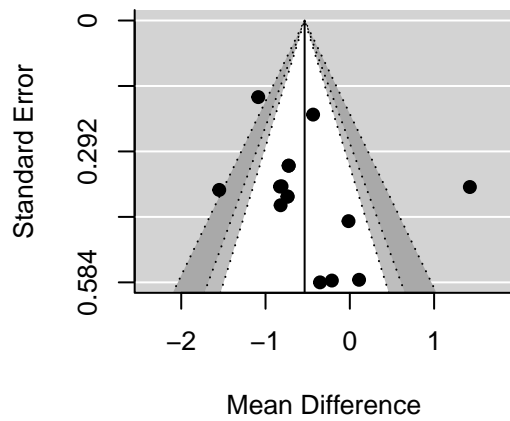
Heterogeneity: GM volume Left



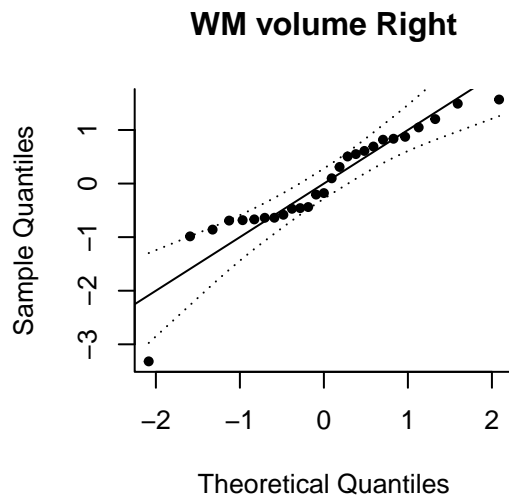
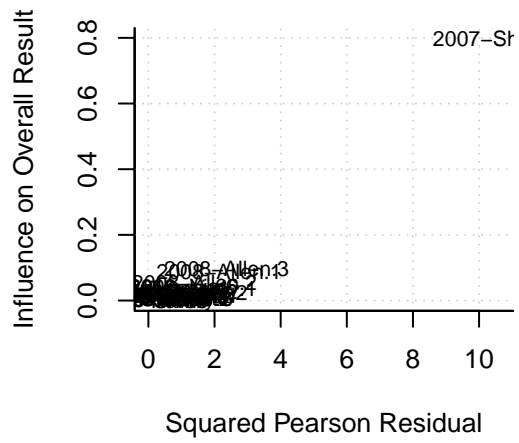
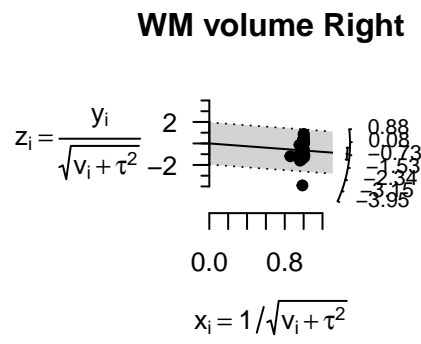
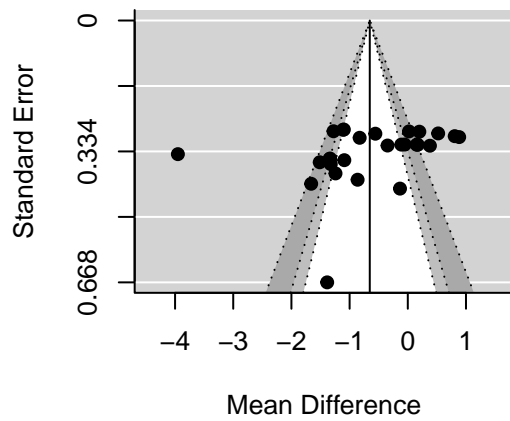
Heterogeneity: WM FA Right



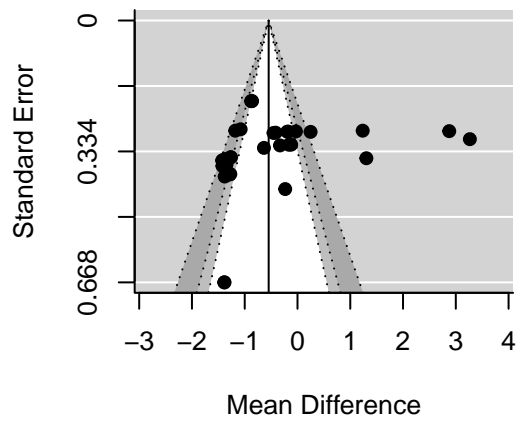
Heterogeneity: WM FA Left



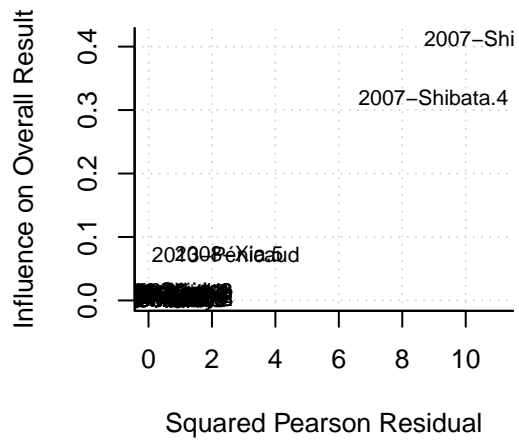
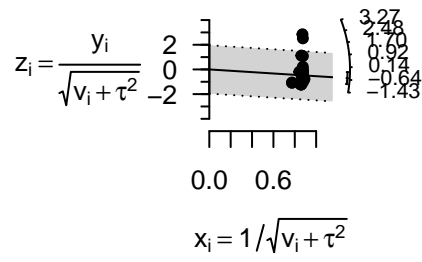
Heterogeneity: WM volume Right



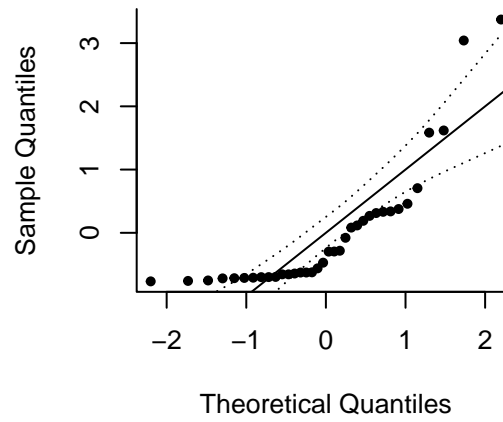
Heterogeneity: WM volume Left

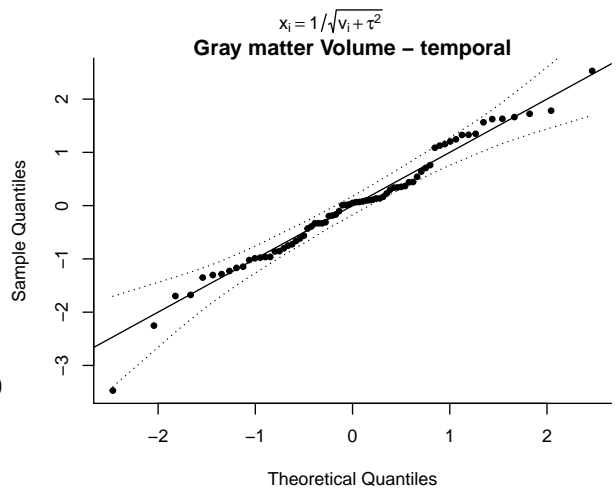
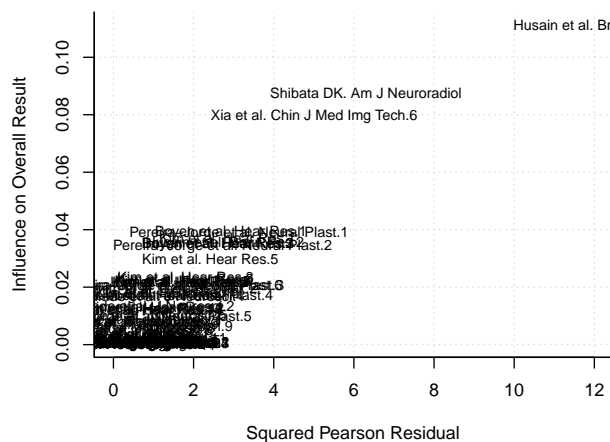
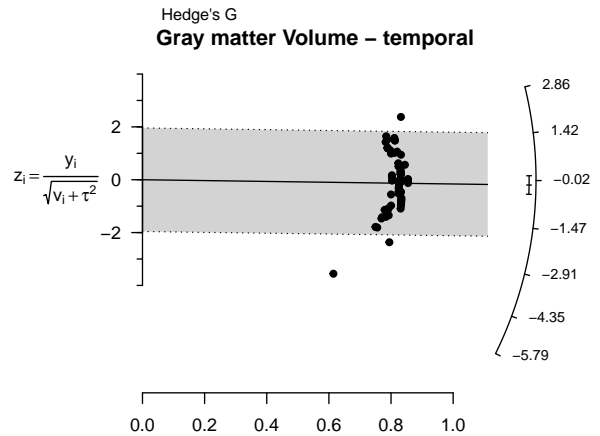
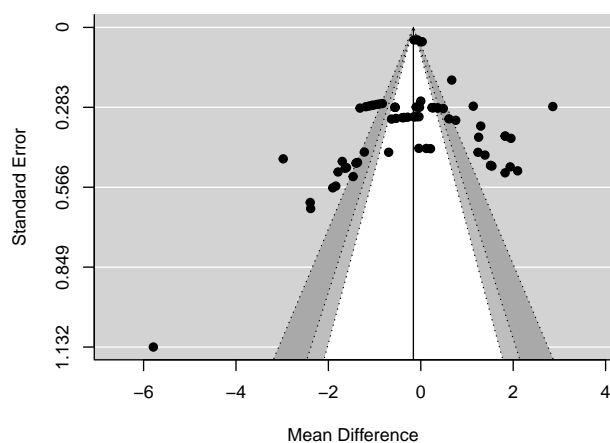


WM volume Left

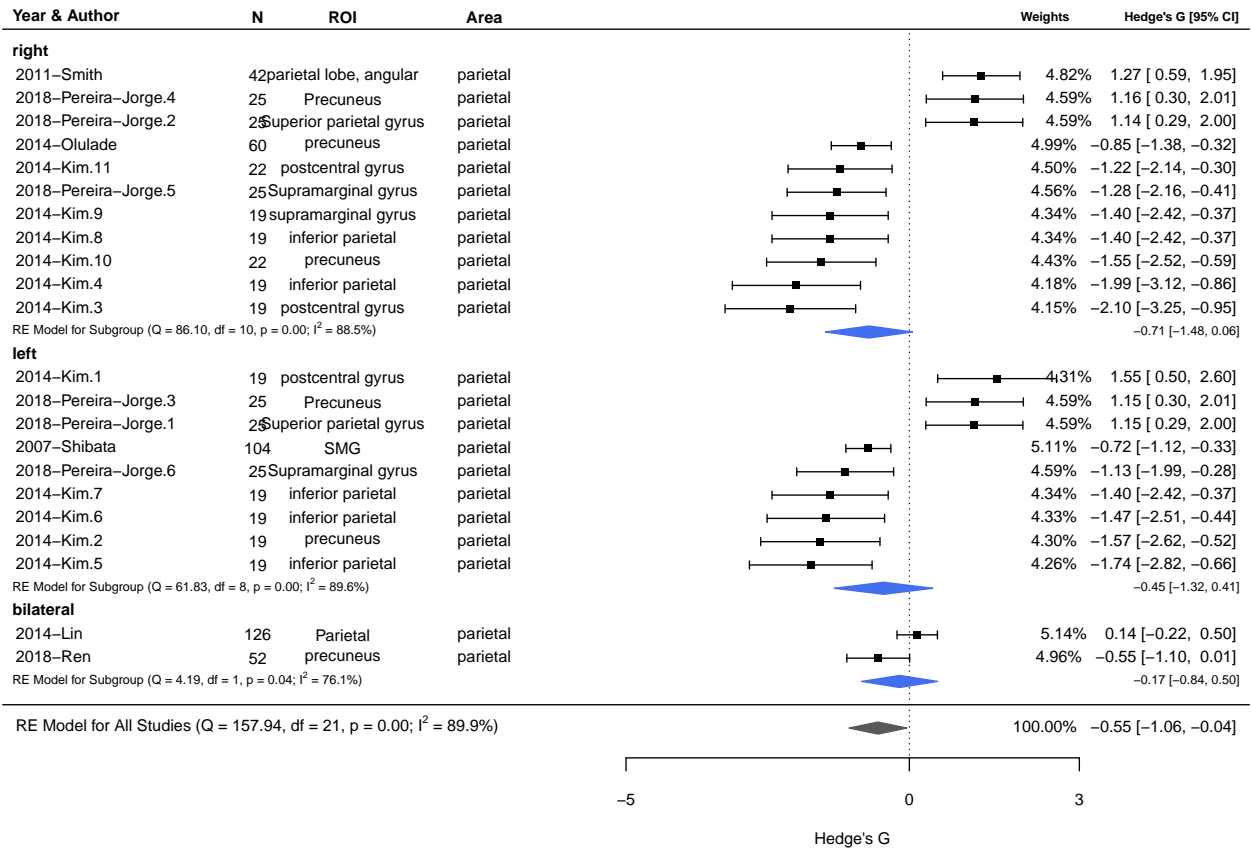


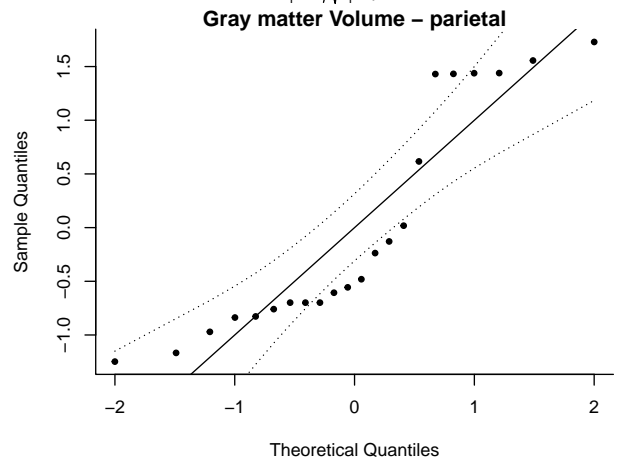
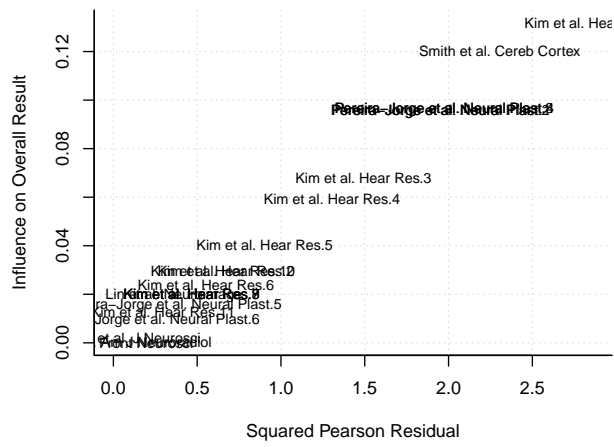
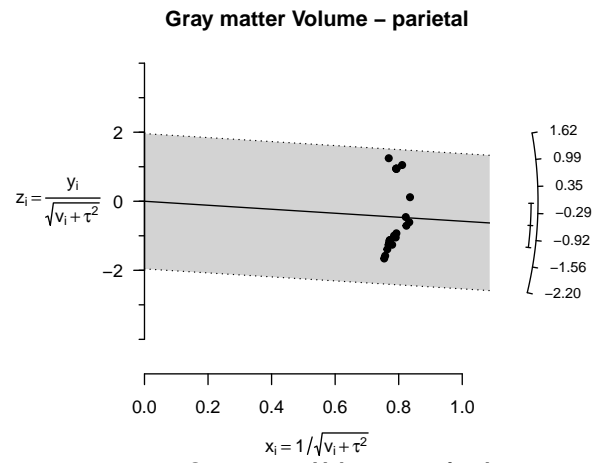
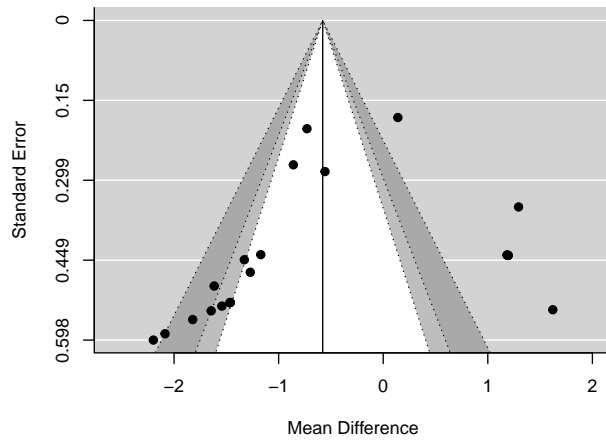
WM volume Left



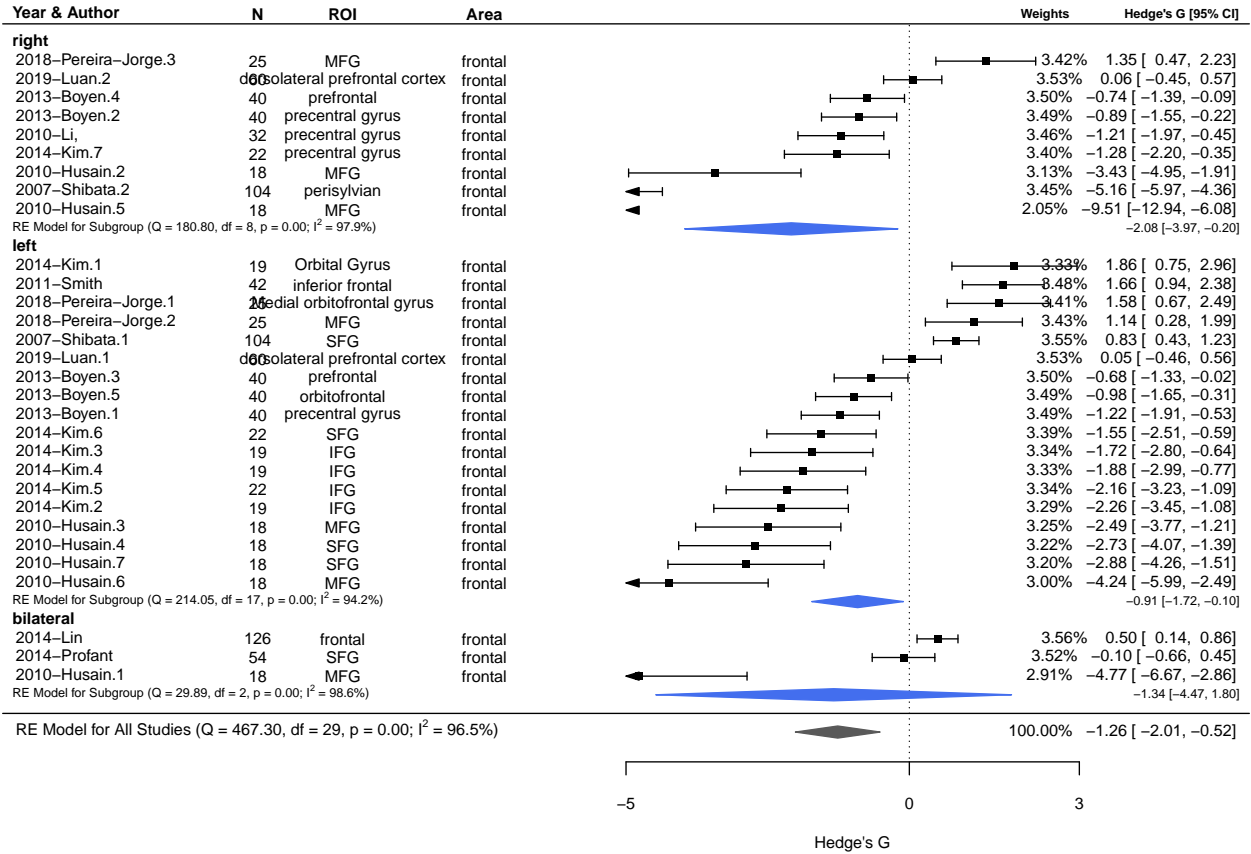
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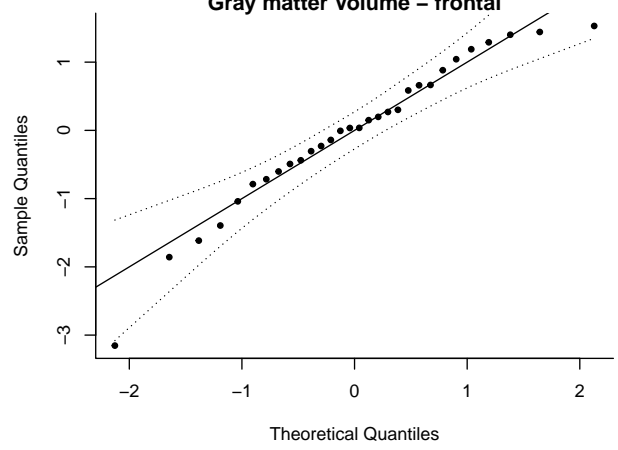
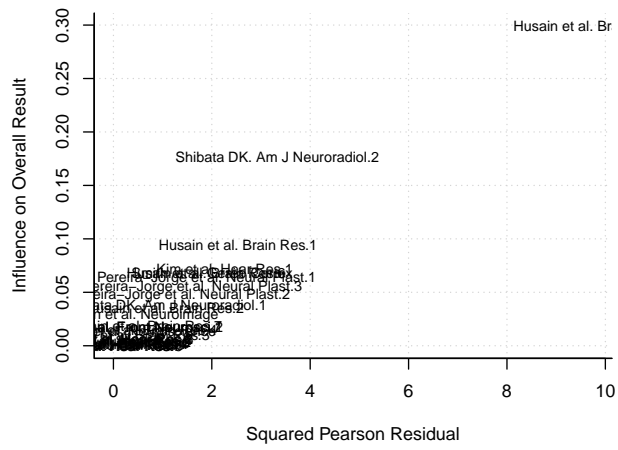
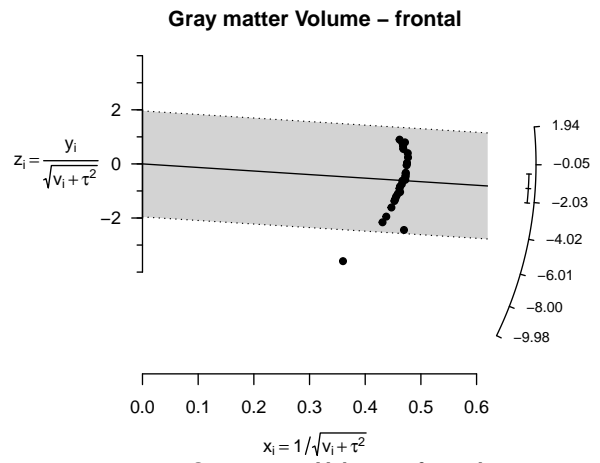
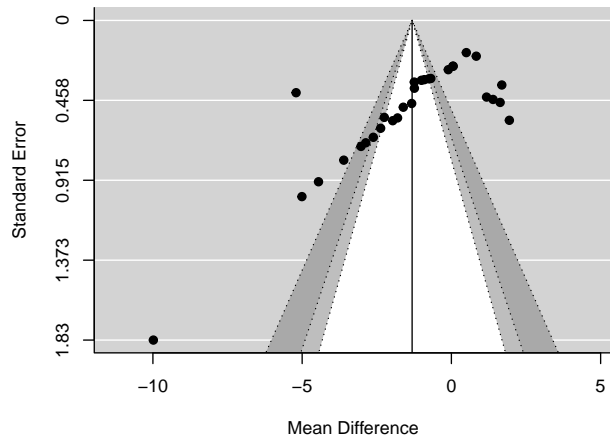
Gray matter Volume – parietal



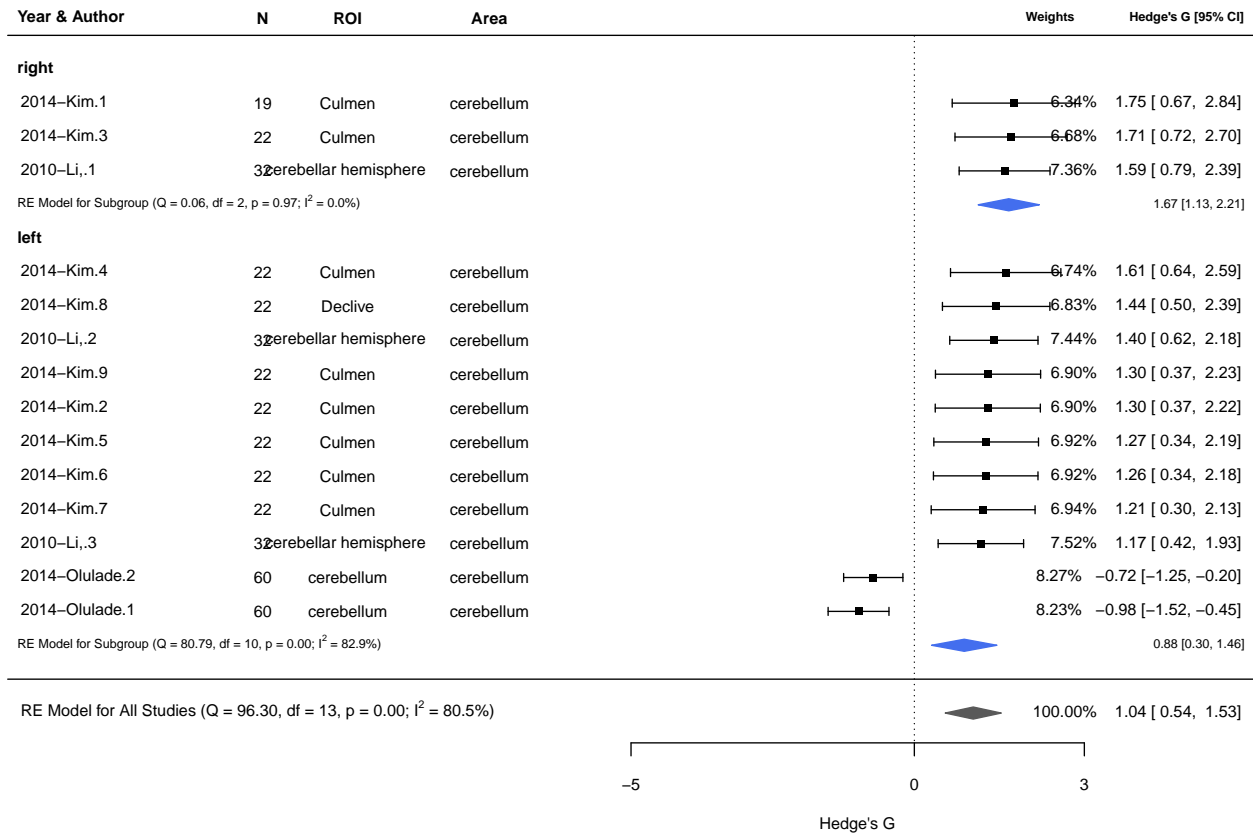


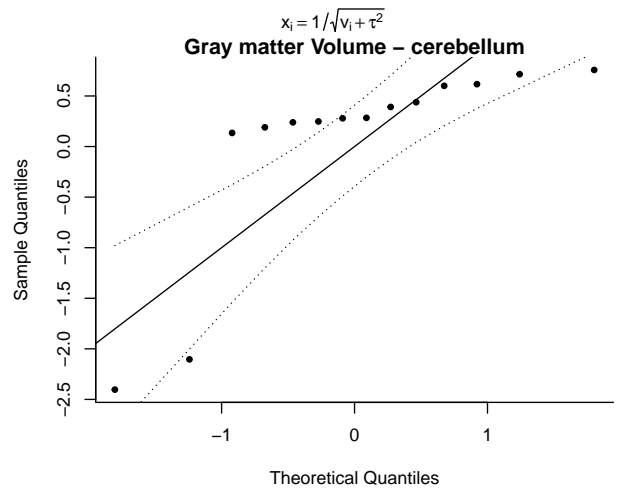
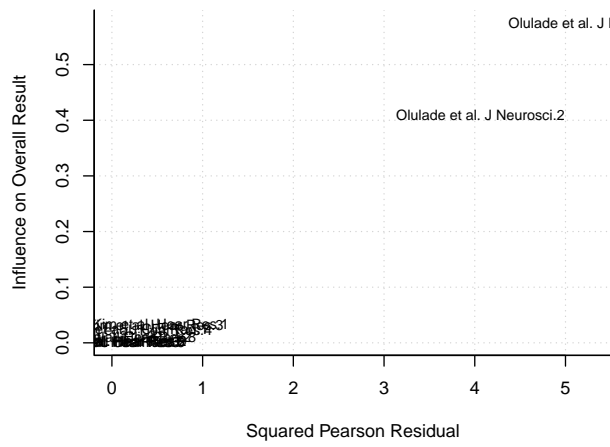
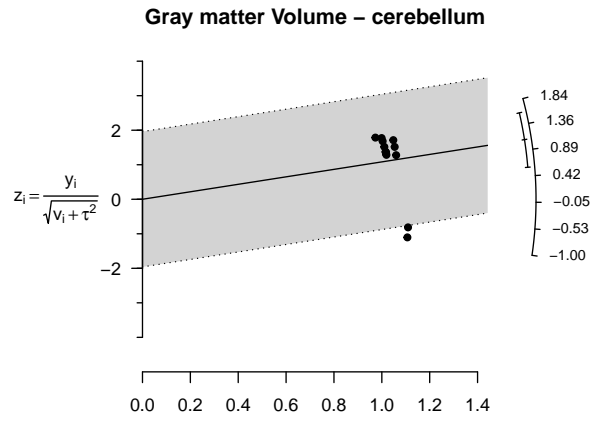
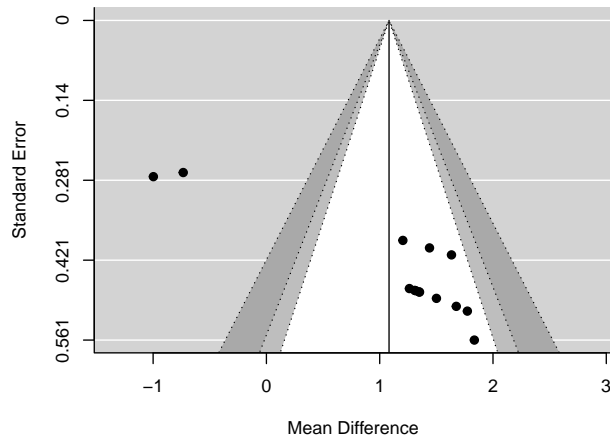
Gray matter Volume – frontal



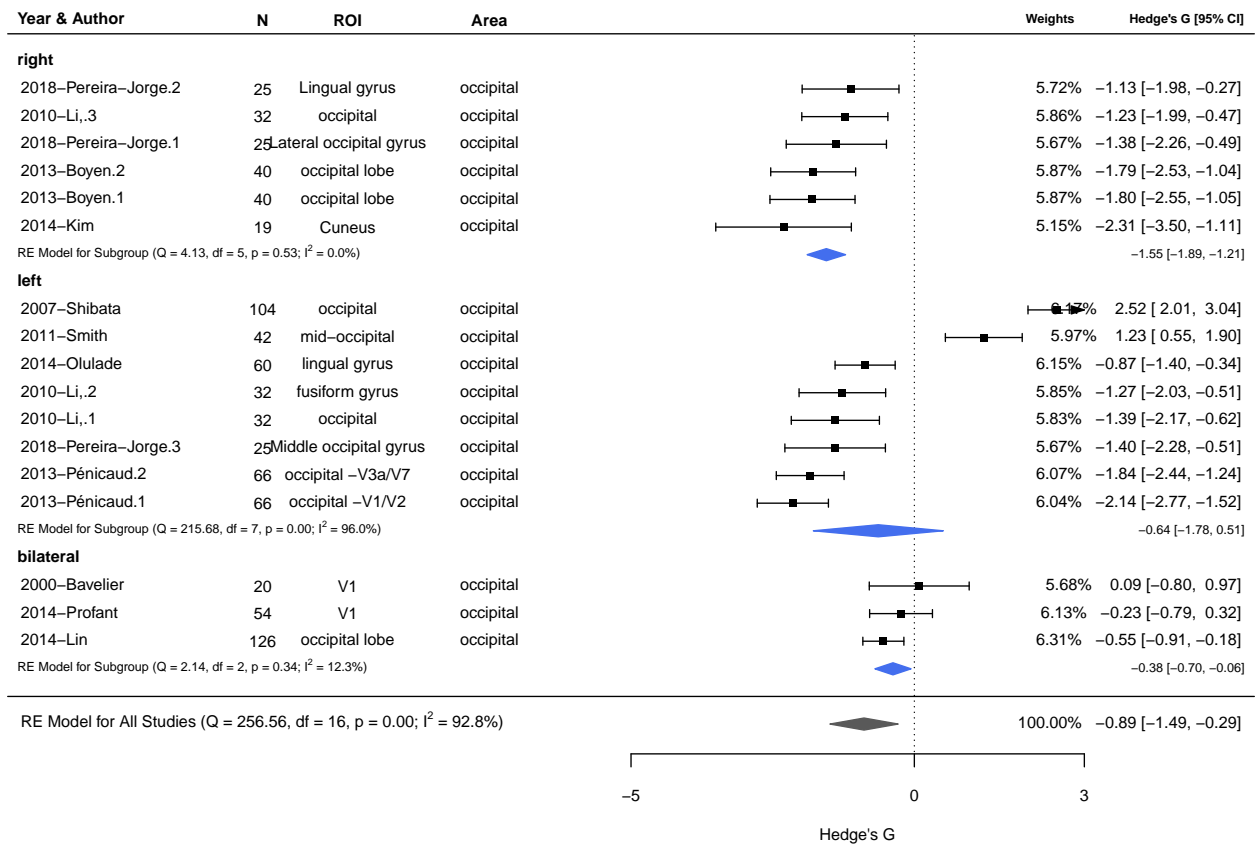


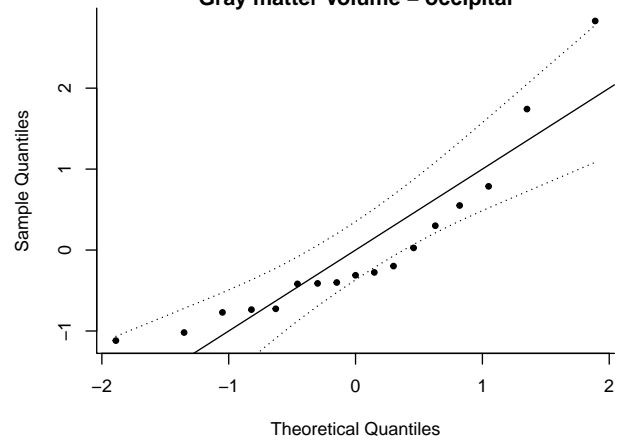
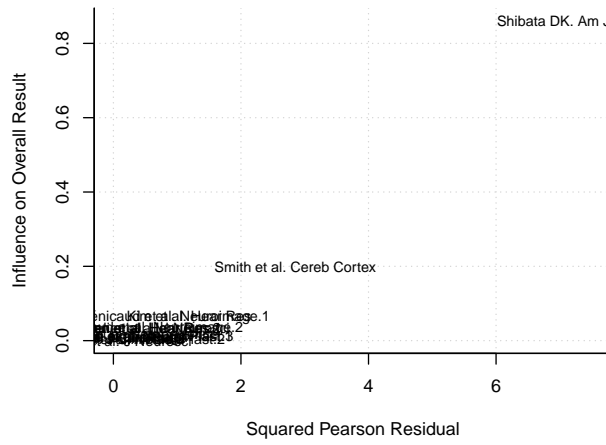
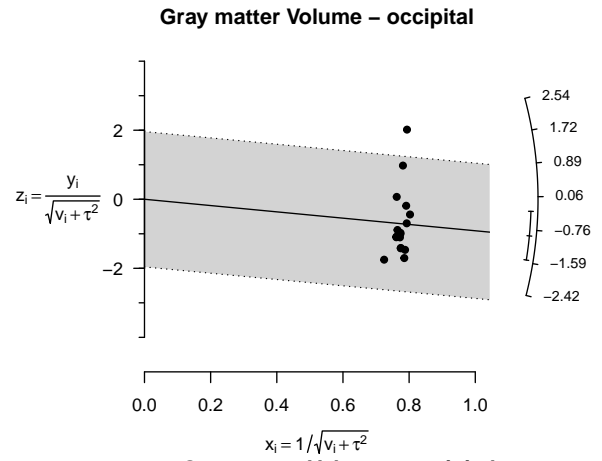
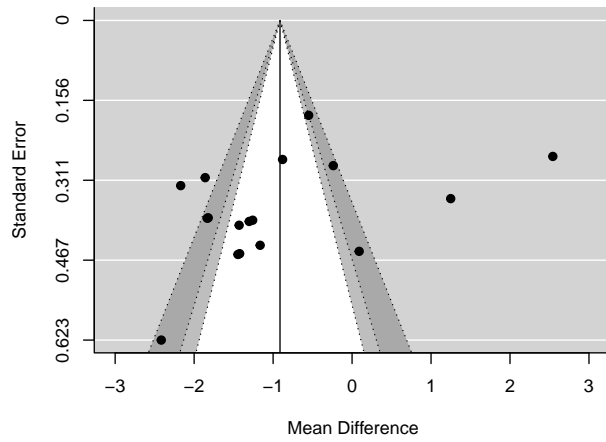
Gray matter Volume – cerebellum



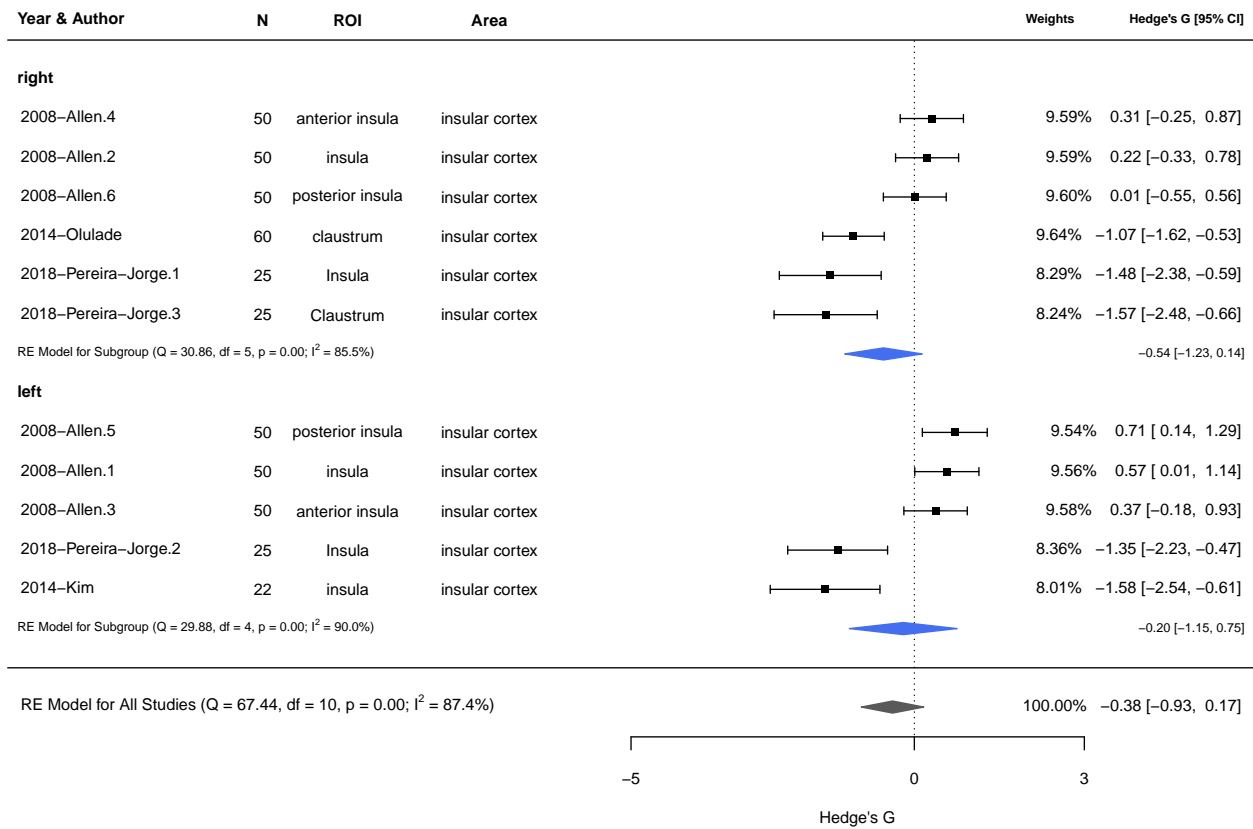


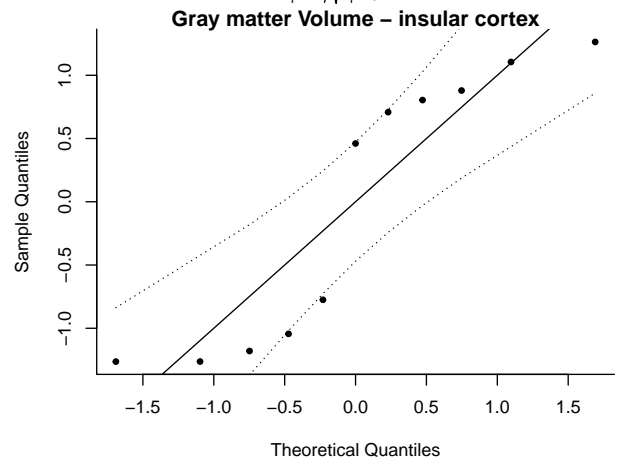
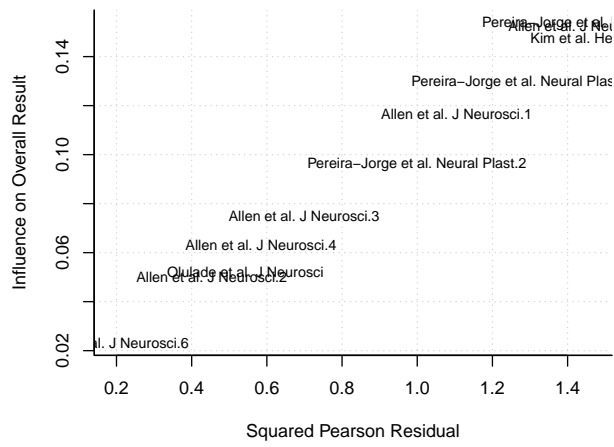
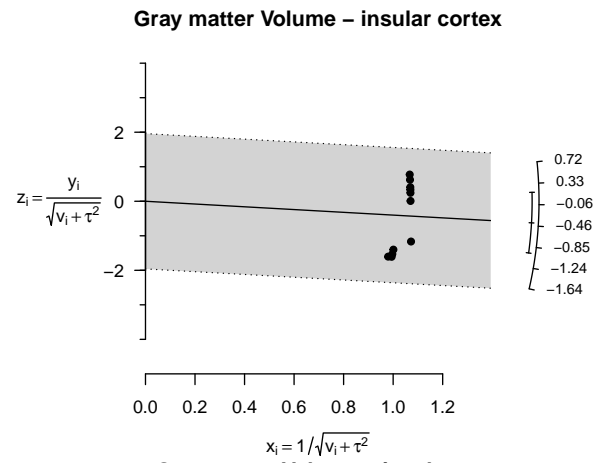
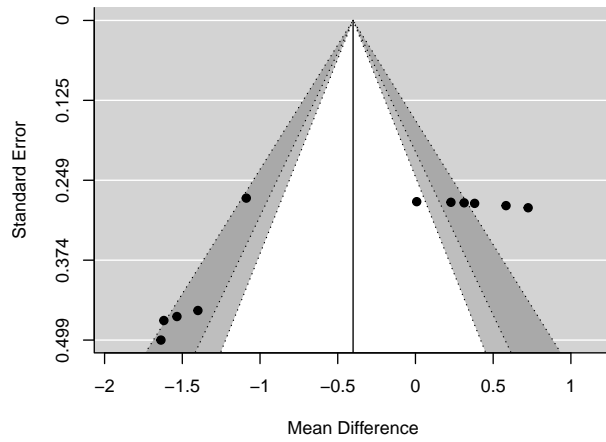
Gray matter Volume – occipital



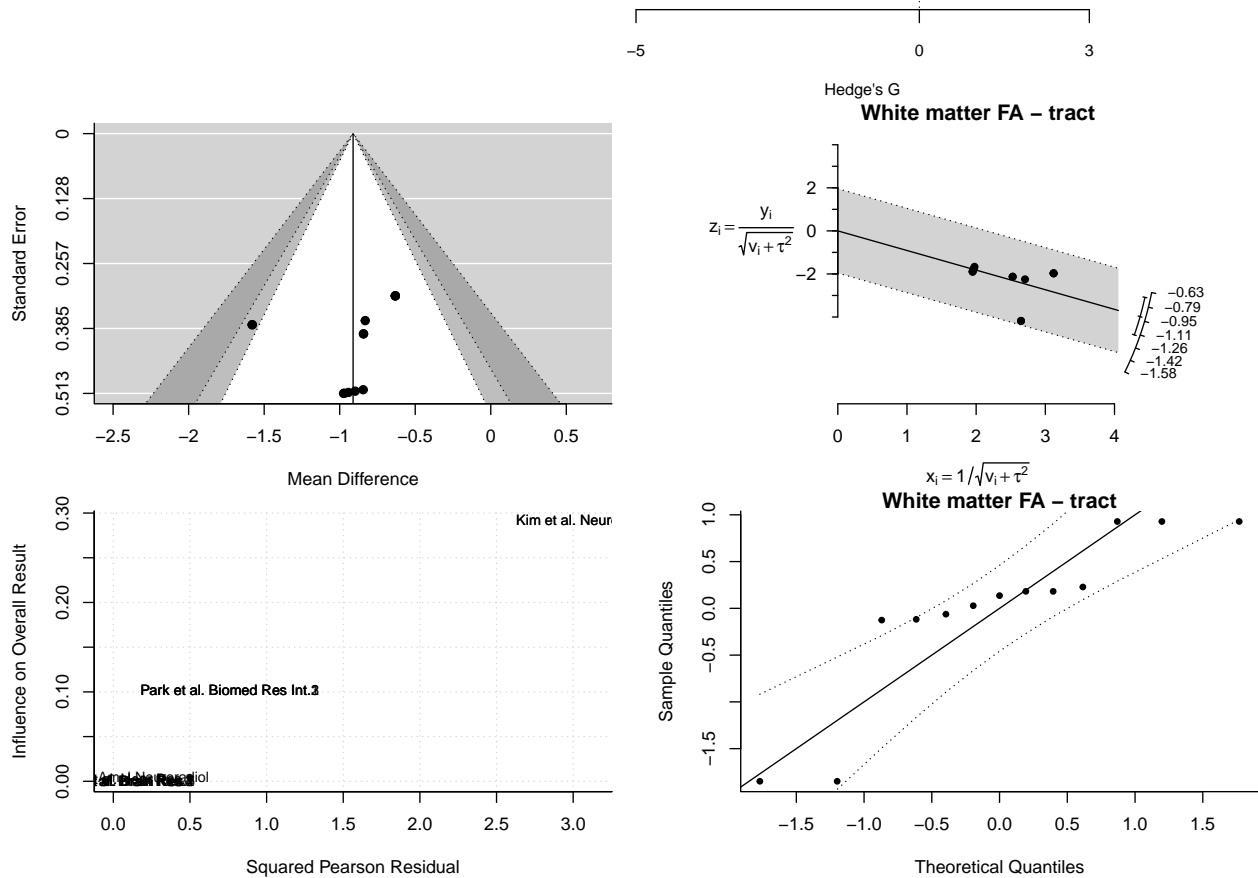
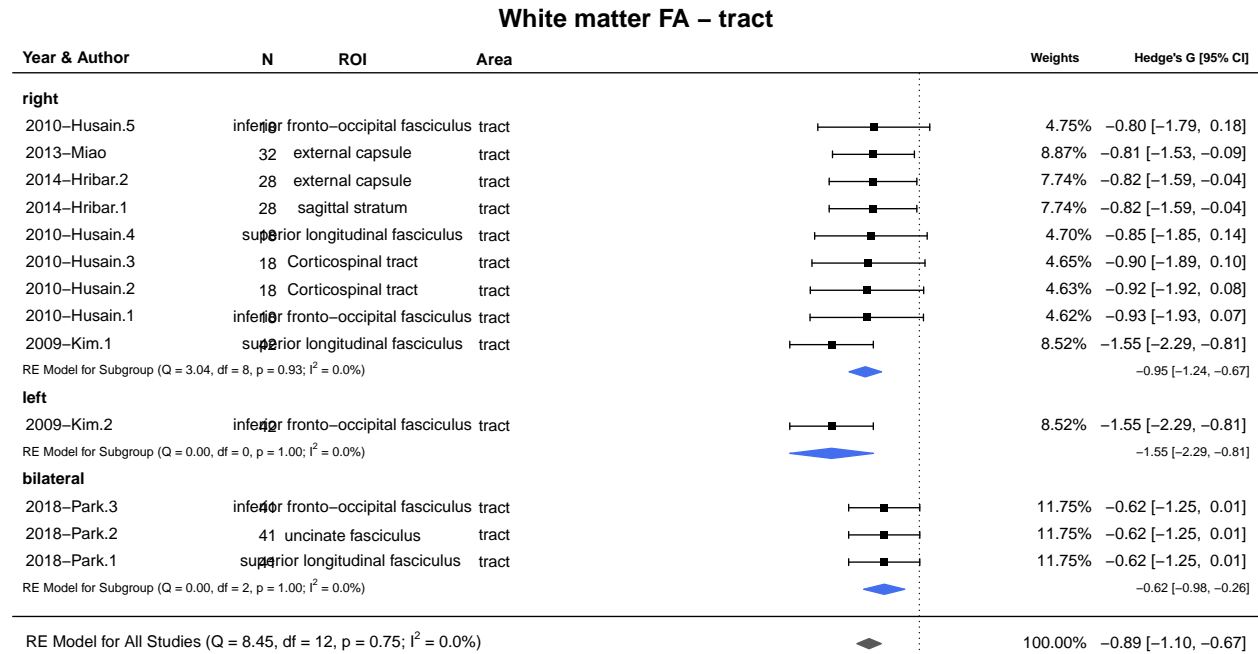


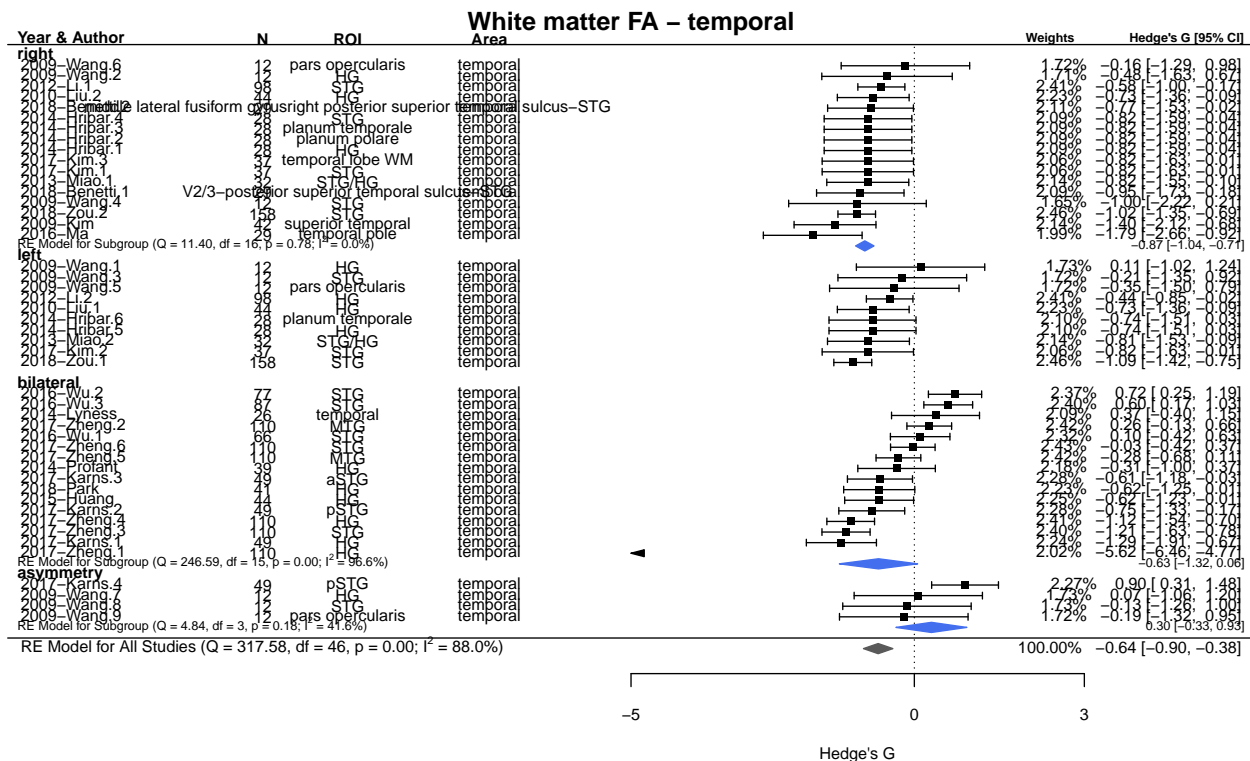
Gray matter Volume – insular cortex



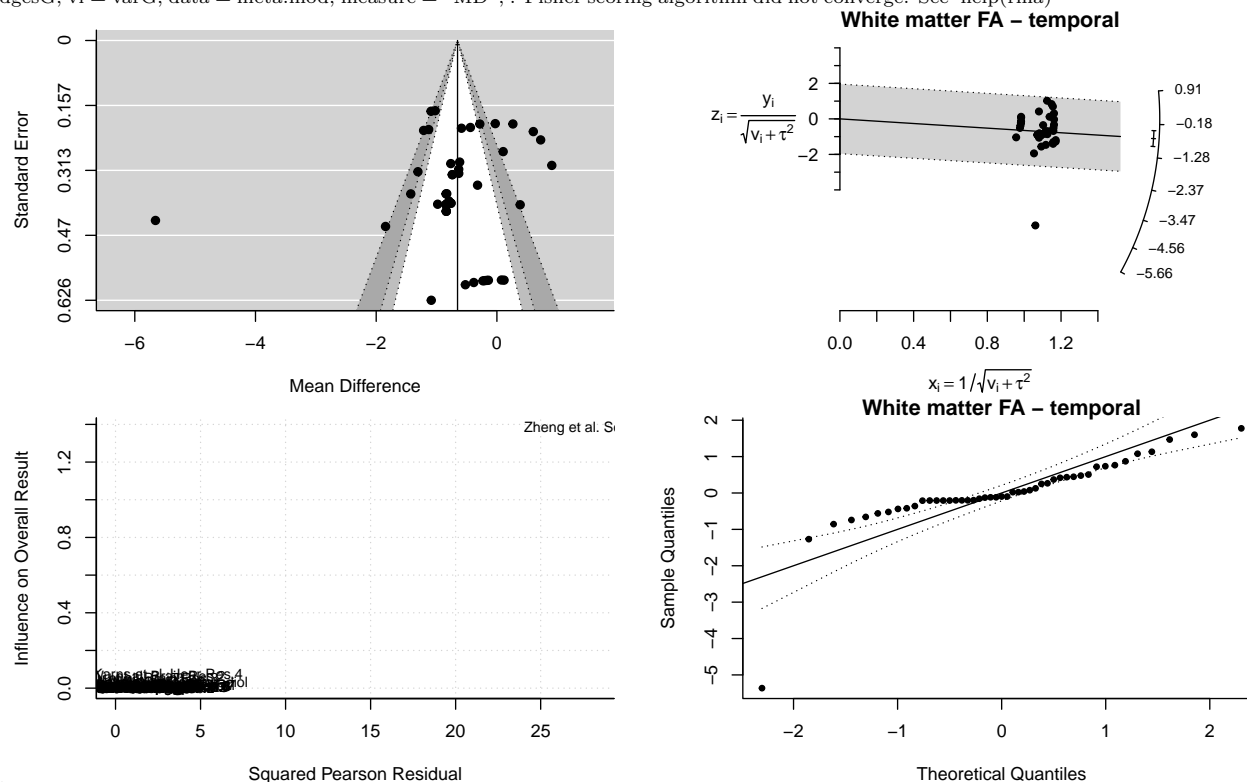


Meta-regressions of White Matter FA & Brain Areas: Random effects model no intercept covariated by Side



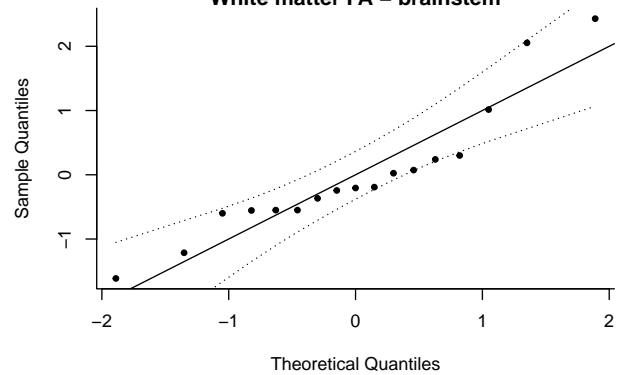
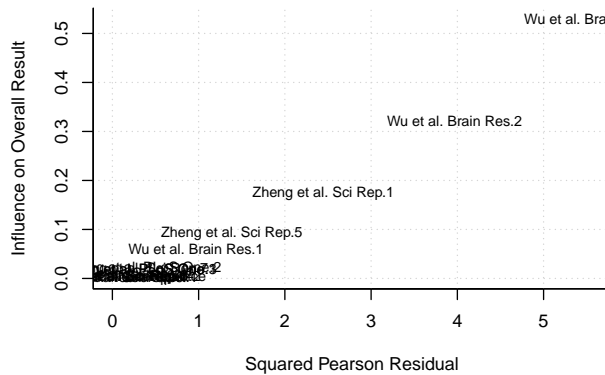
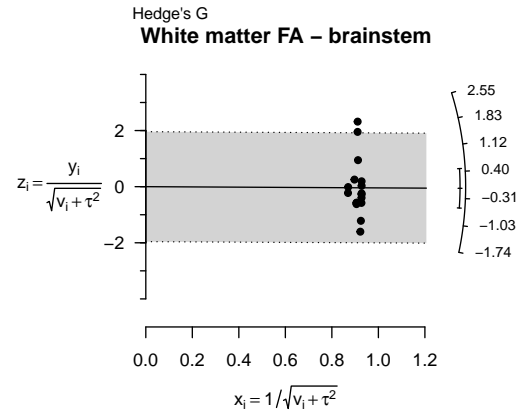
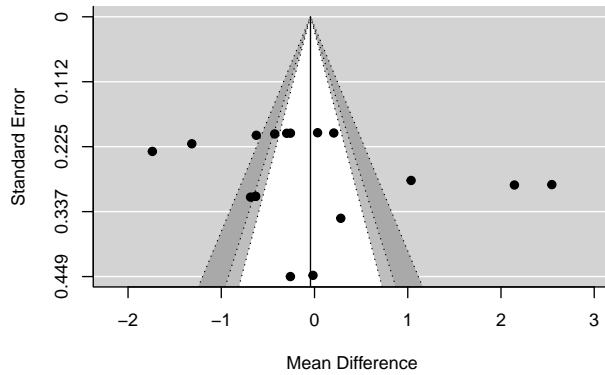
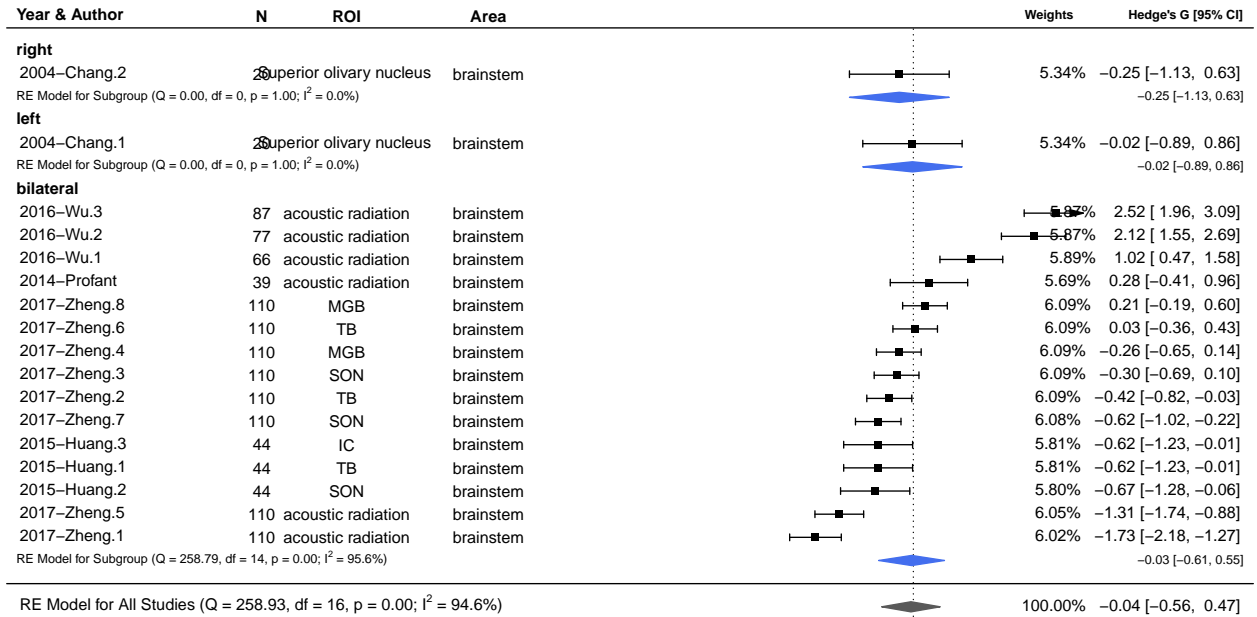


Error in rma(yi = hedgesG, vi = varG, data = meta.mod, measure = "MD", : Fisher scoring algorithm did not converge. See 'help(rma)'



for possible remedies.

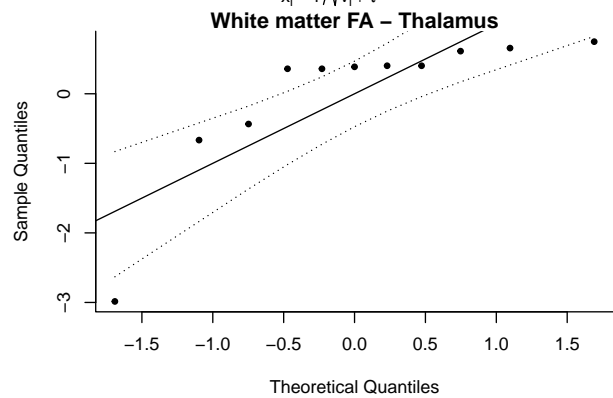
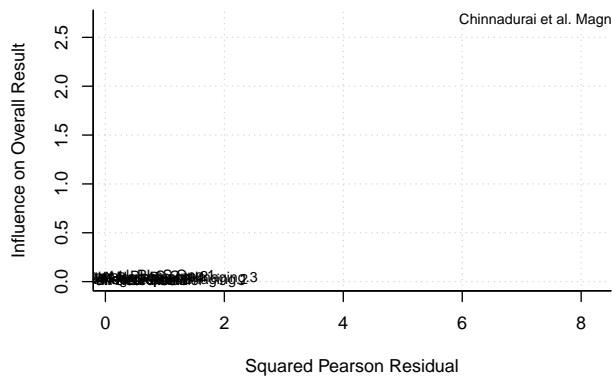
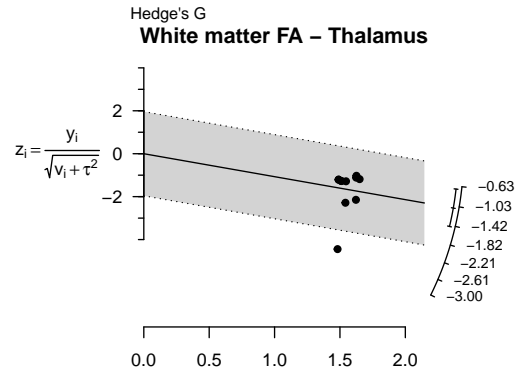
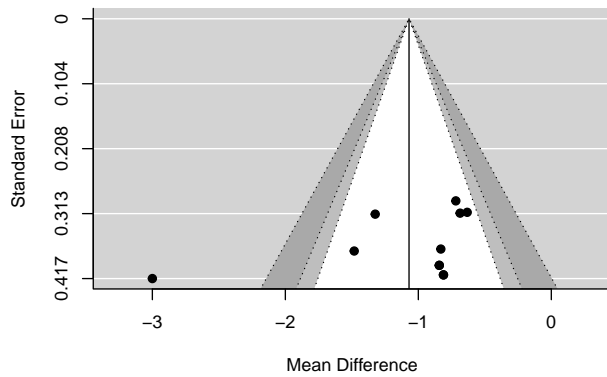
White matter FA – brainstem



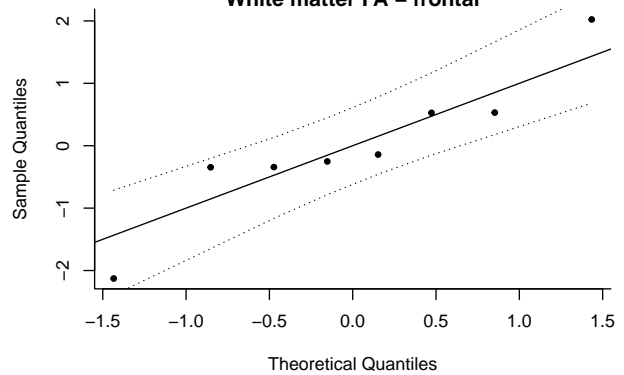
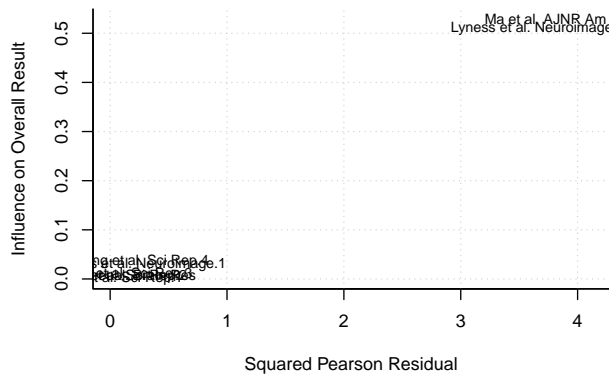
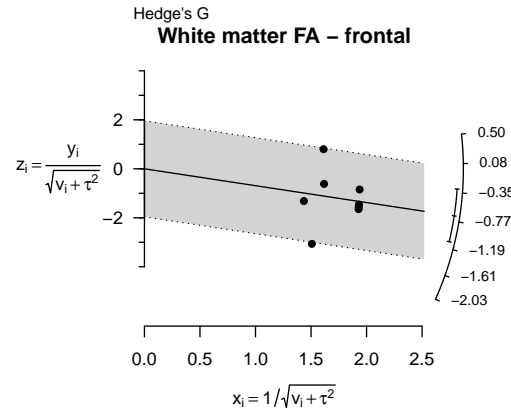
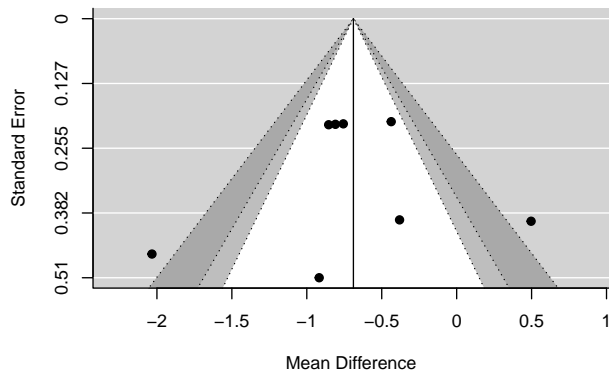
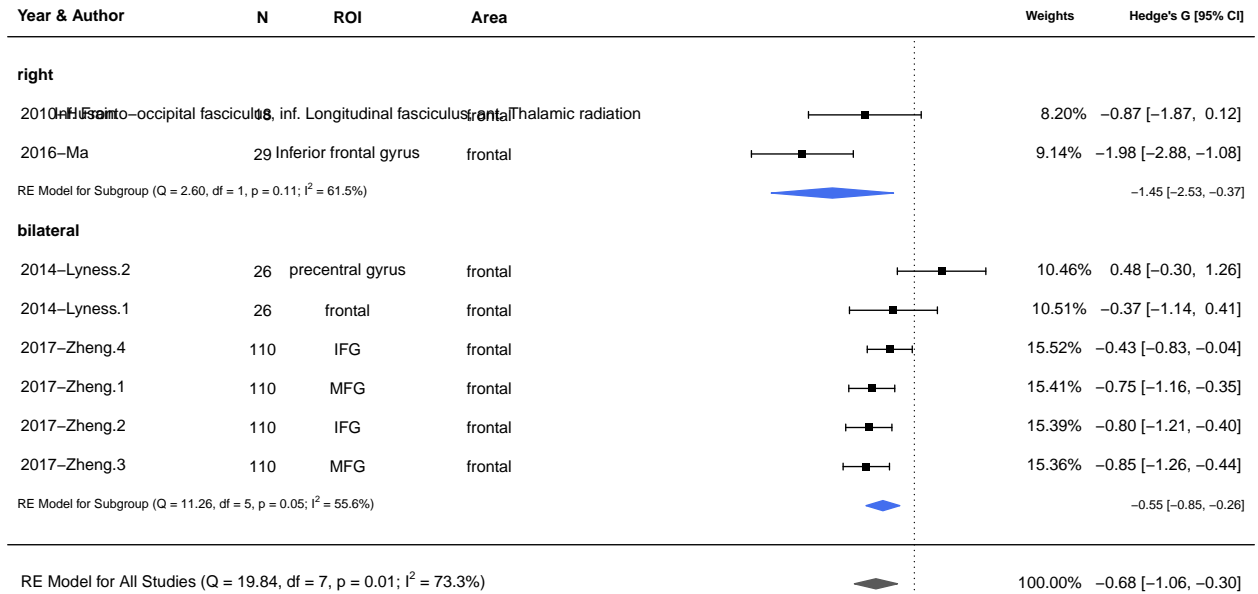
White matter FA – Thalamus

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]

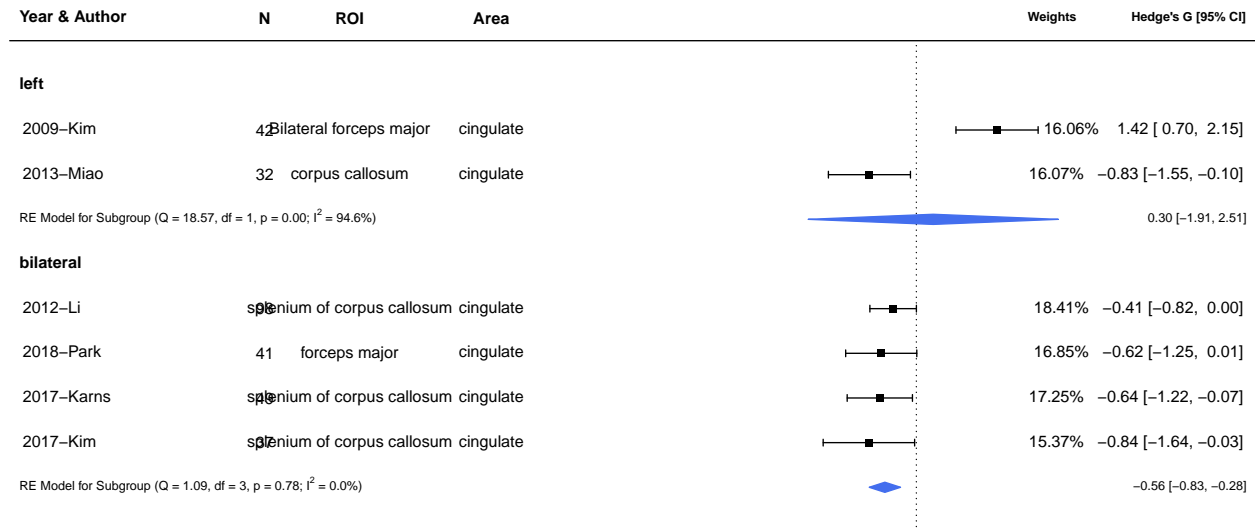
-5 0 3



White matter FA – frontal

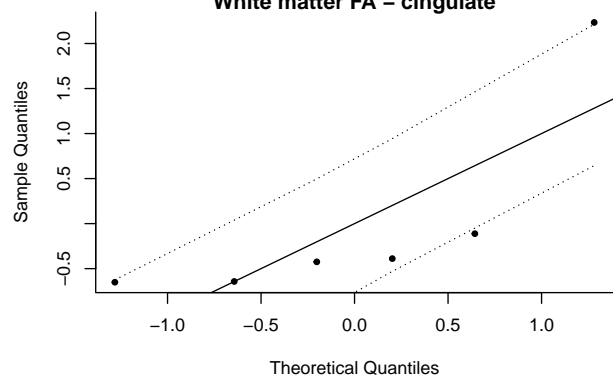
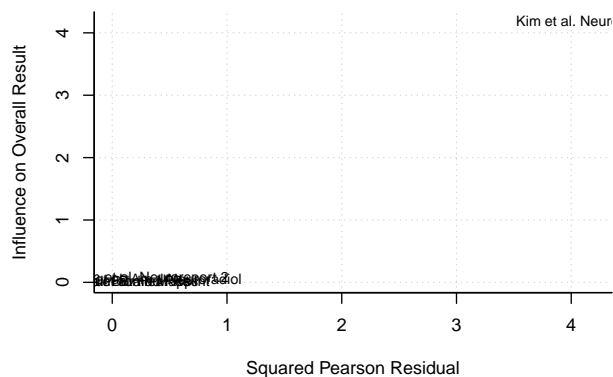
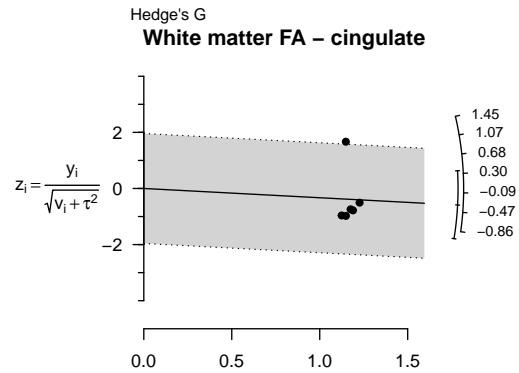
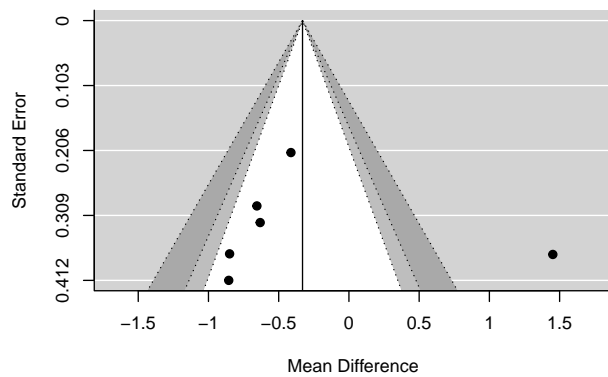


White matter FA – cingulate

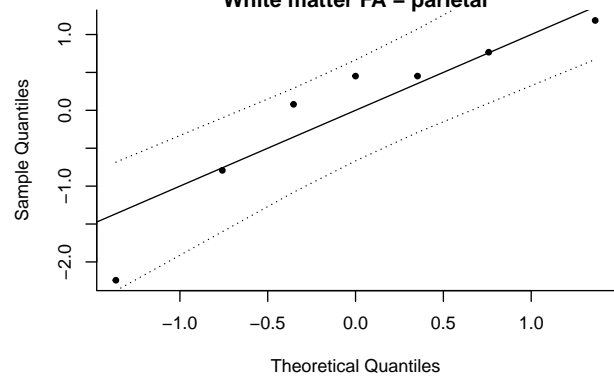
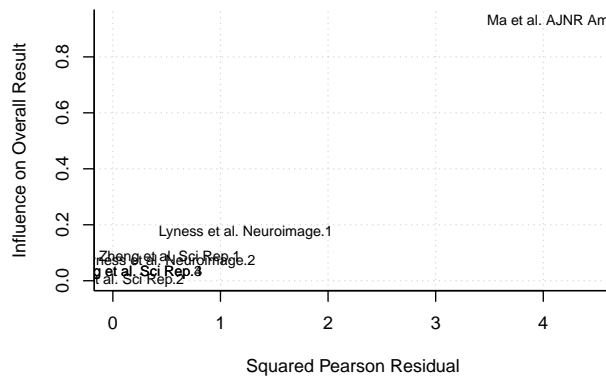
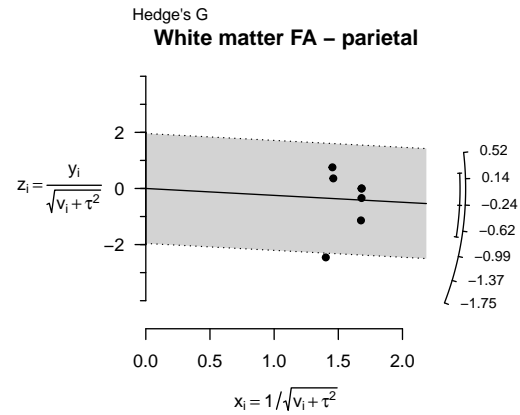
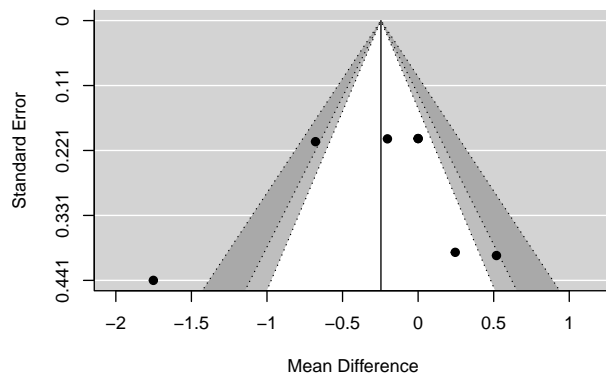
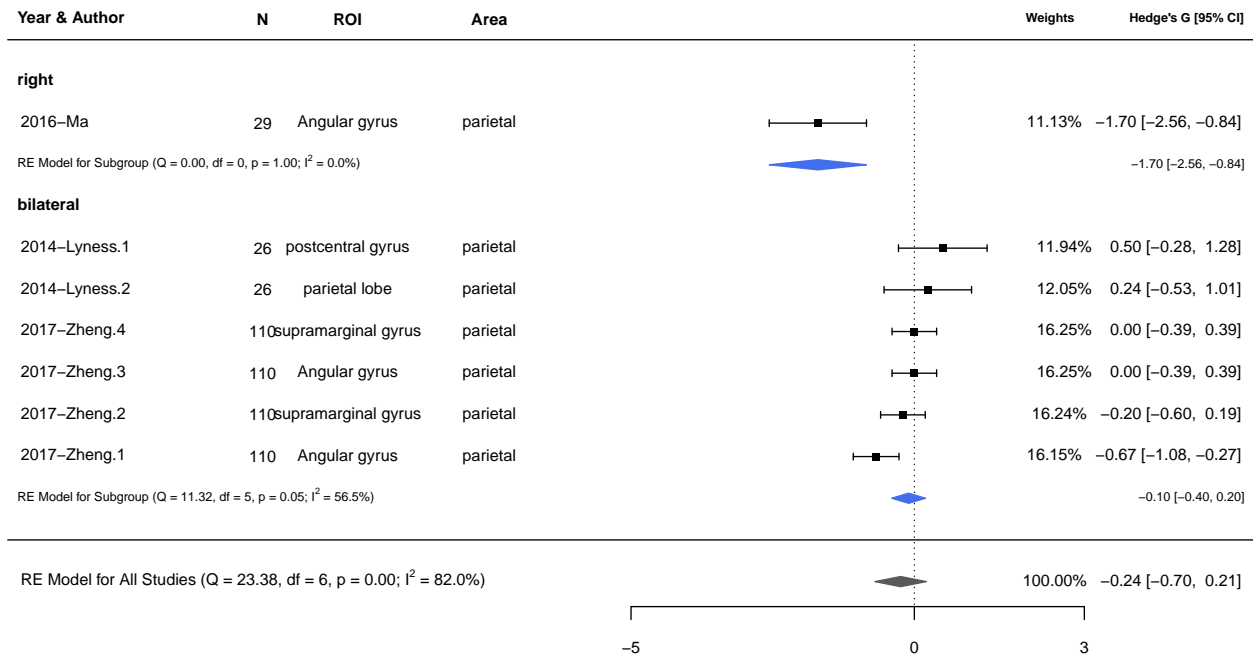


RE Model for All Studies (Q = 27.88, df = 5, p = 0.00; I² = 85.8%)

-5 0 3

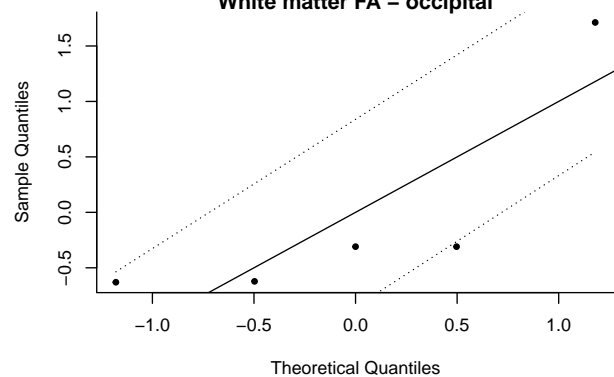
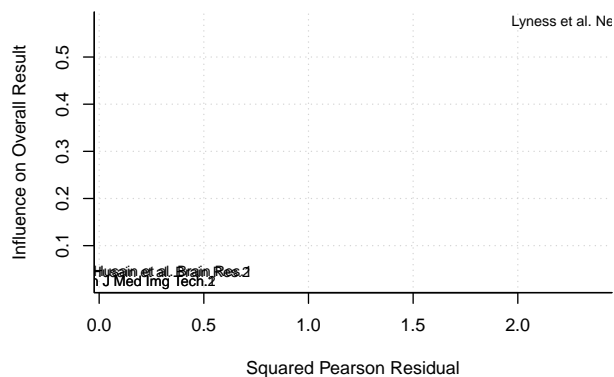
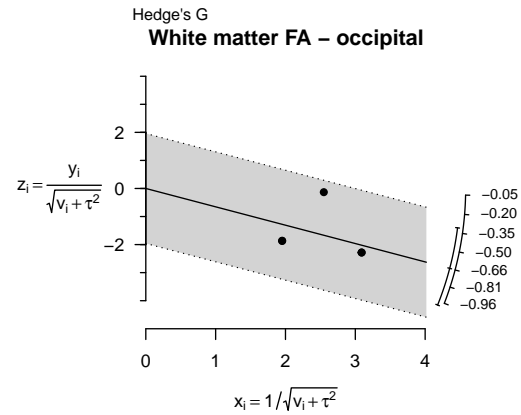
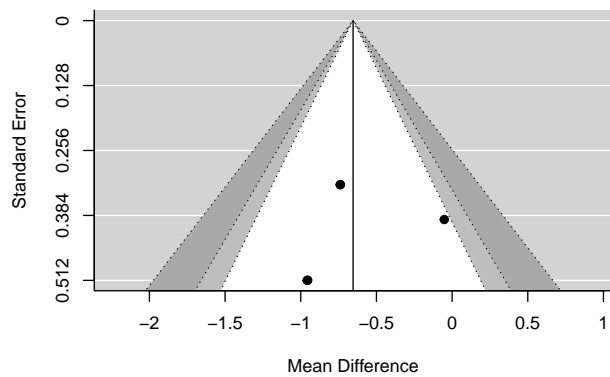
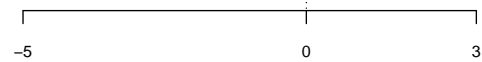


White matter FA – parietal

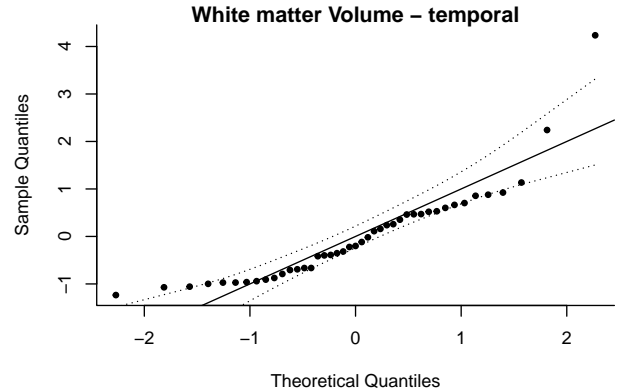
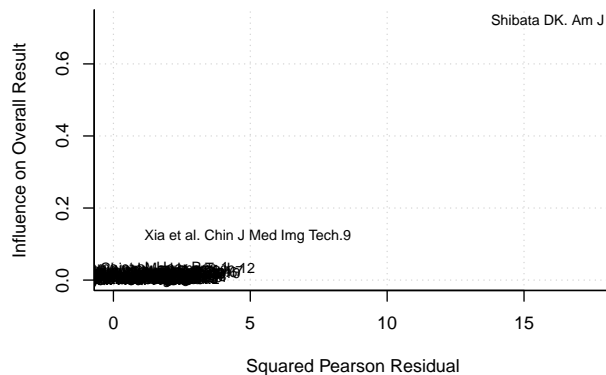
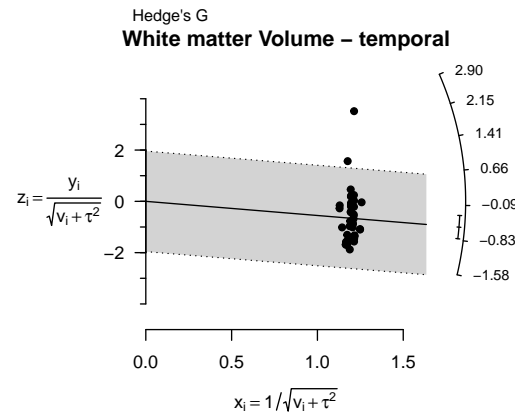
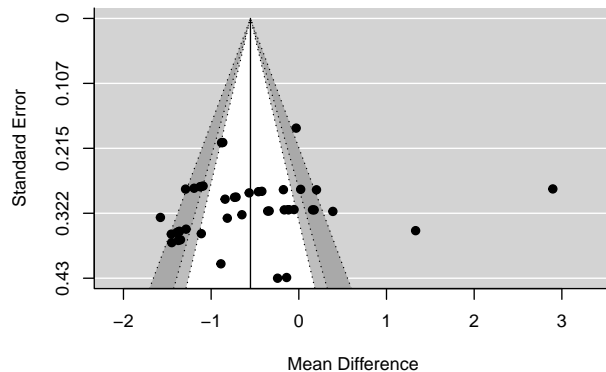
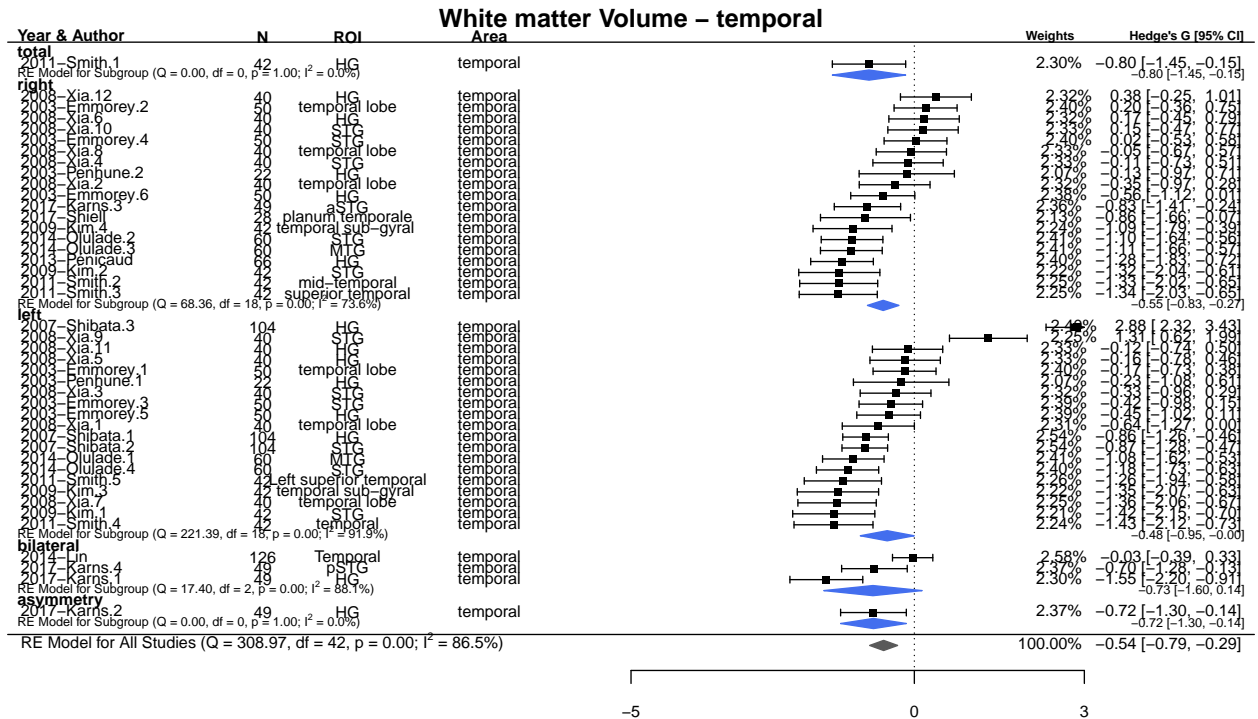


White matter FA – occipital

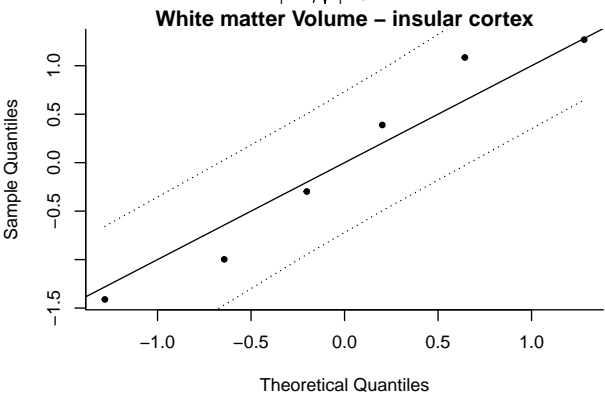
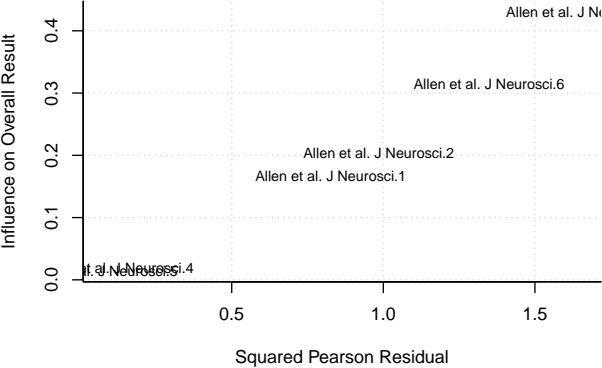
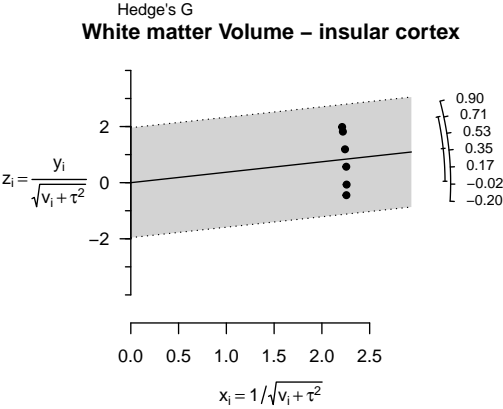
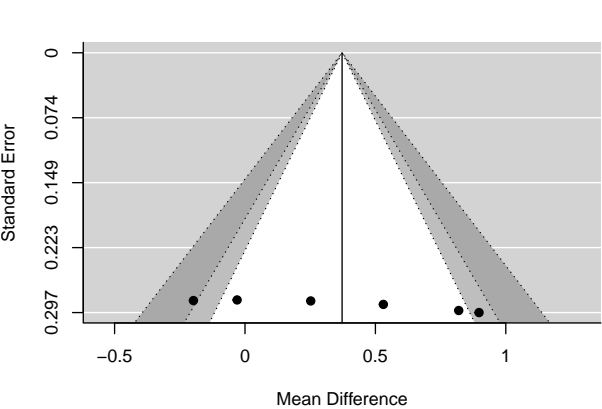
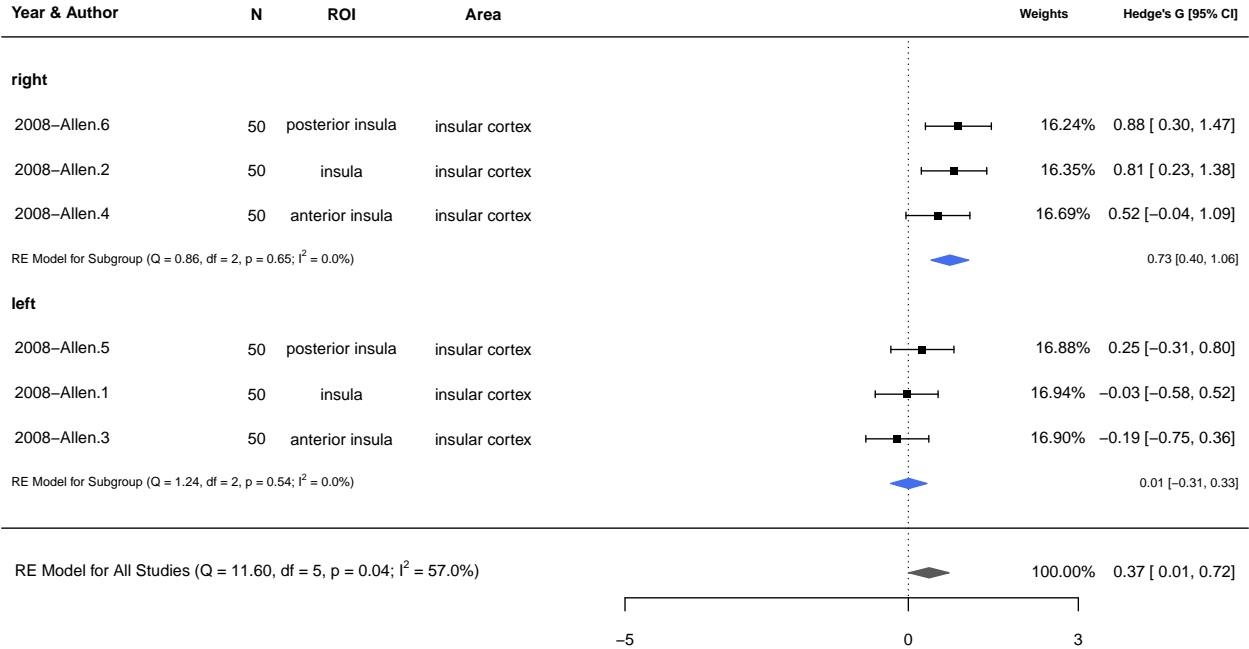
Year & Author	N	ROI	Area	Weights	Hedge's G [95% CI]
right					
2010–Liu.2	44	optic radiation	occipital	28.71%	-0.73 [-1.36, -0.09]
2010–Husain.2	18	Sup. Occipital Fasciculus	occipital	11.55%	-0.91 [-1.91, 0.09]
2010–Husain.1	18	Superior Occipital Fasciculus, Corticospinal tract	occipital	11.55%	-0.91 [-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]



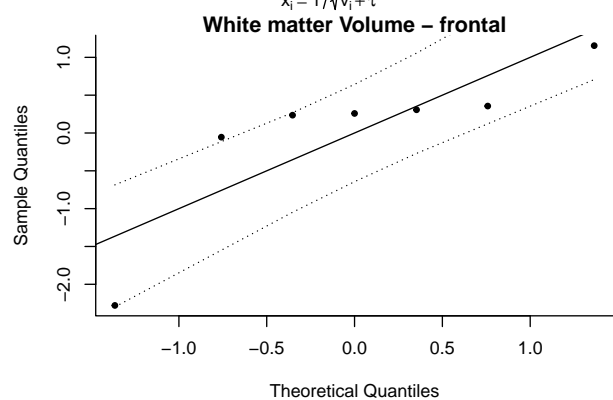
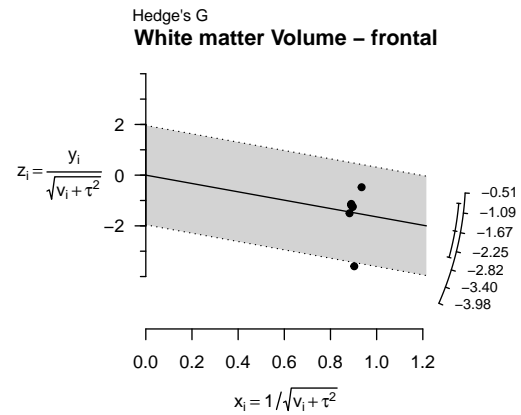
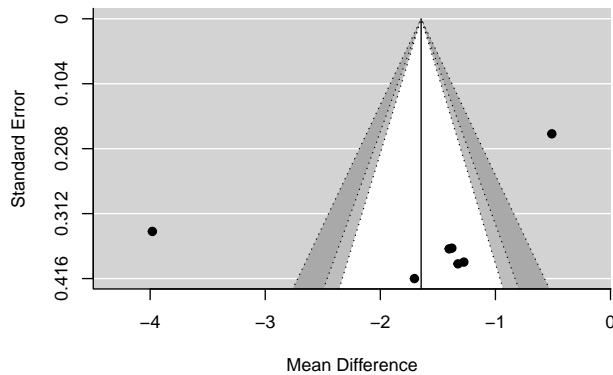
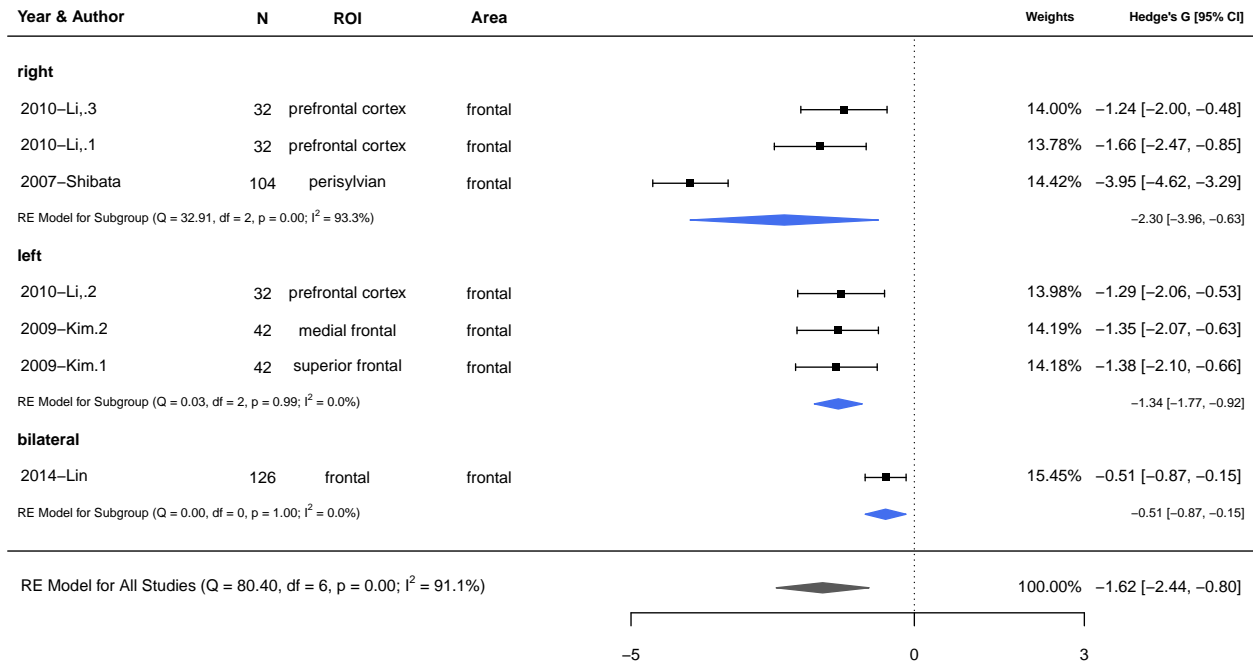
Meta-regressions of White Matter Volume & Brain Areas: Random effects model no intercept covariated by Side



White matter Volume – insular cortex



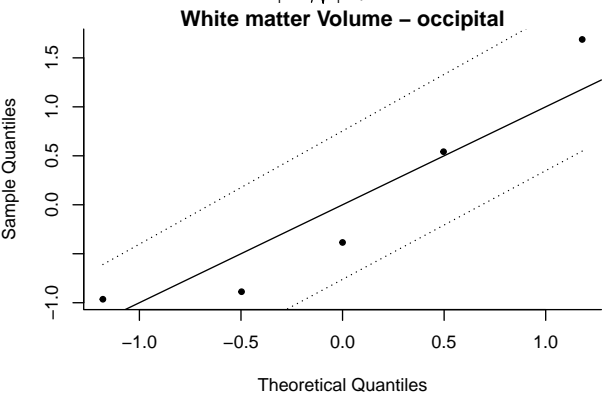
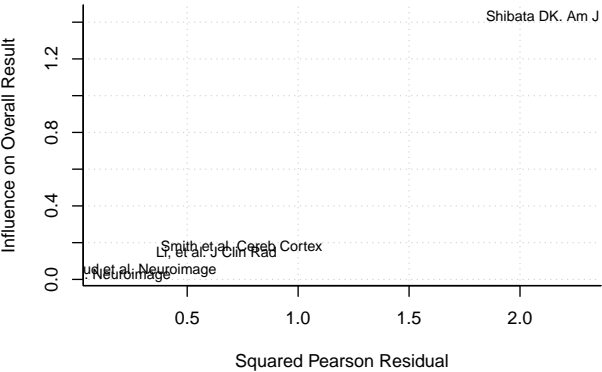
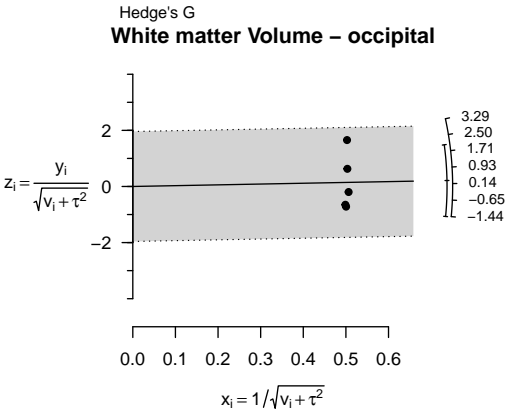
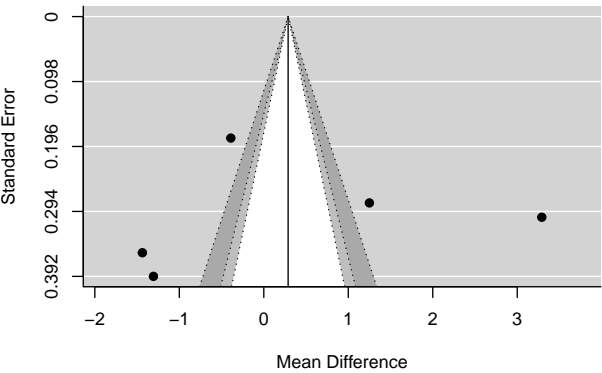
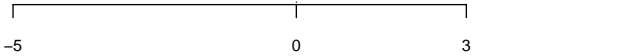
White matter Volume – frontal



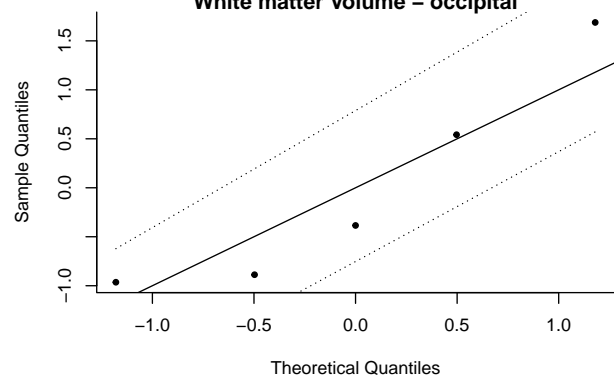
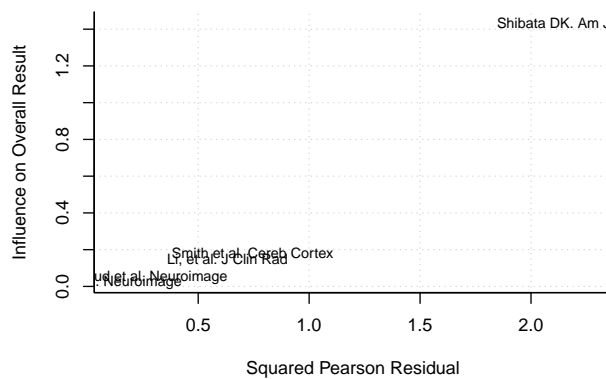
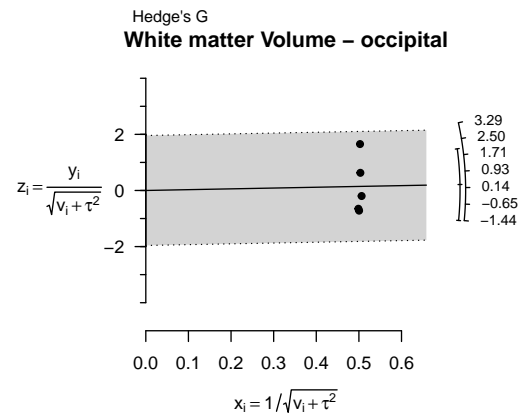
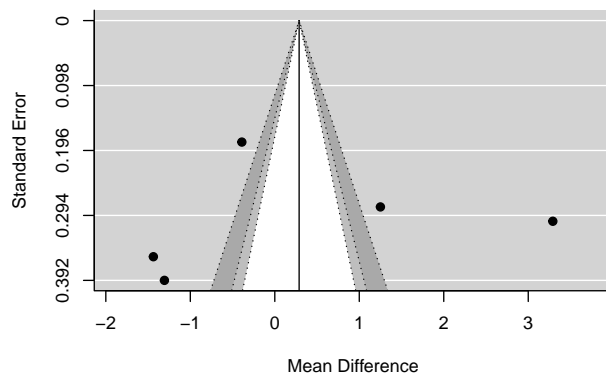
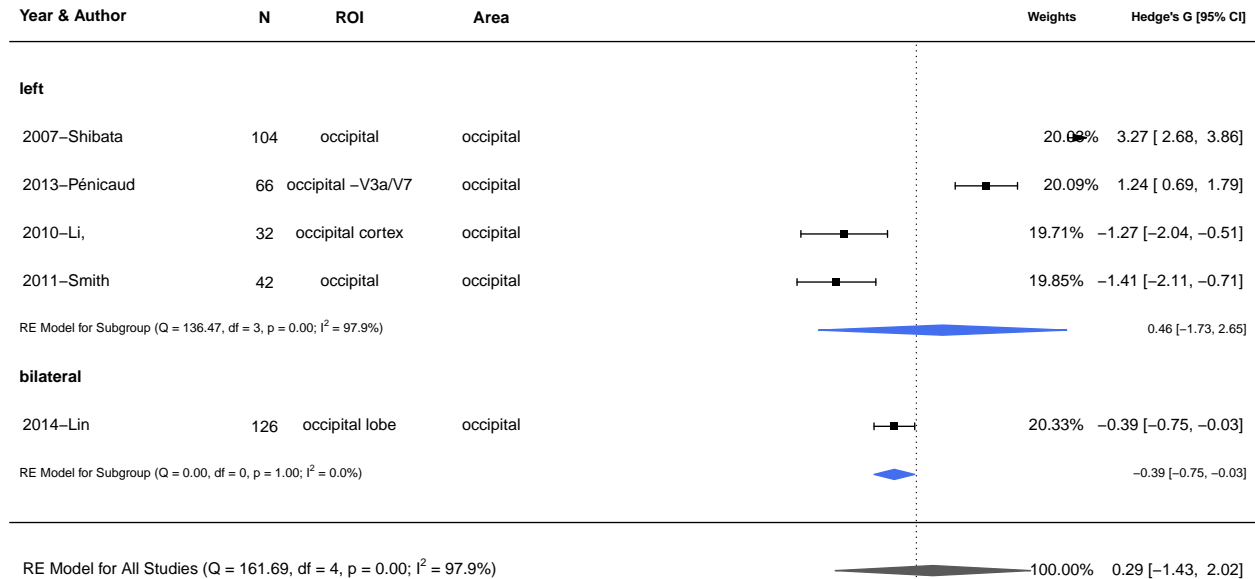
White matter Volume – occipital

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%)

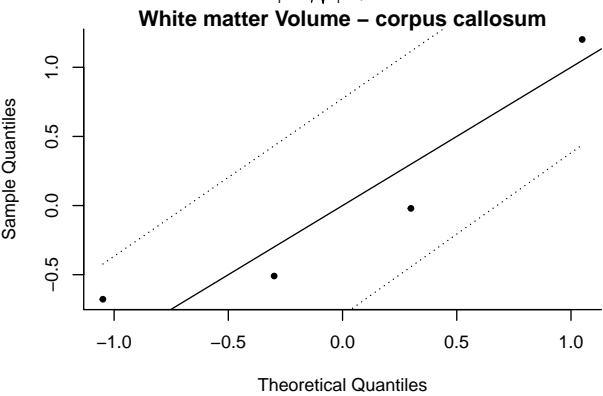
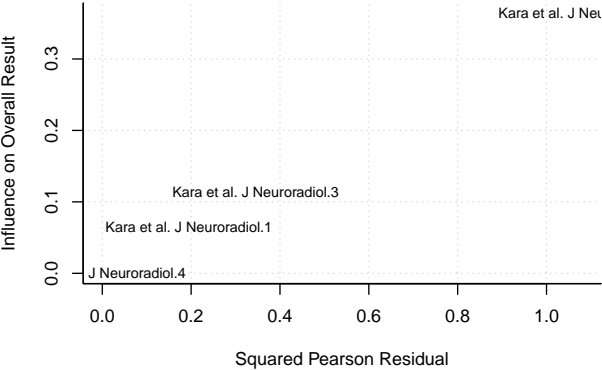
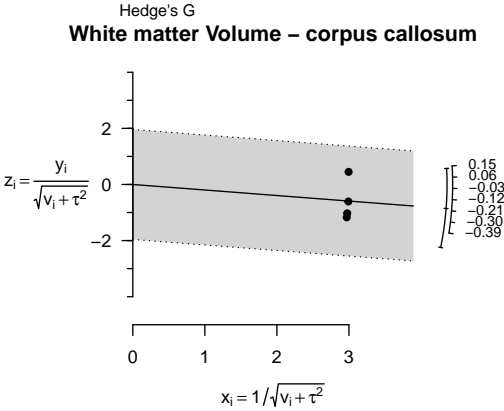
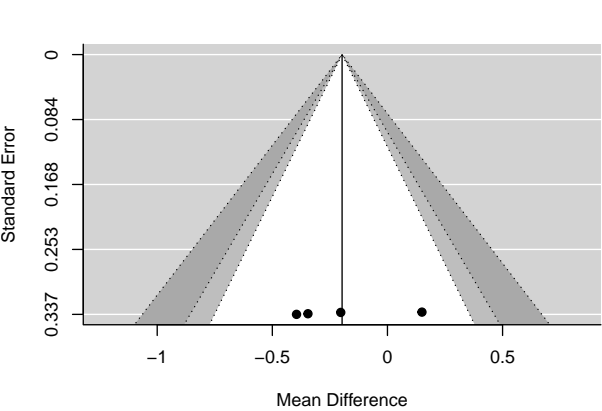
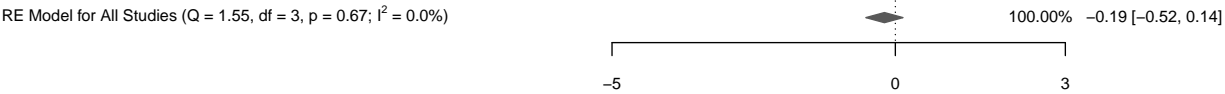


White matter Volume – occipital



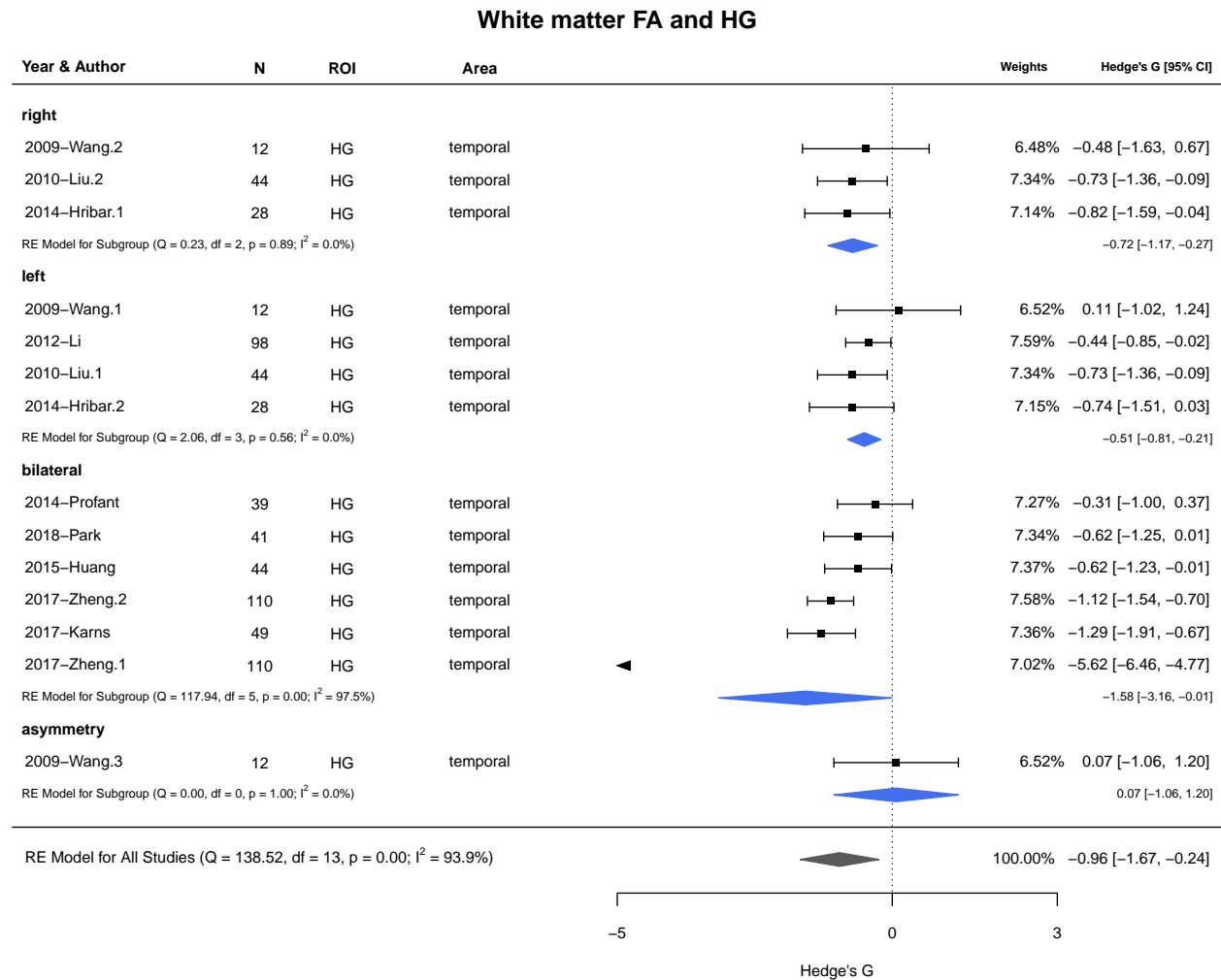
White matter Volume – corpus callosum

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]

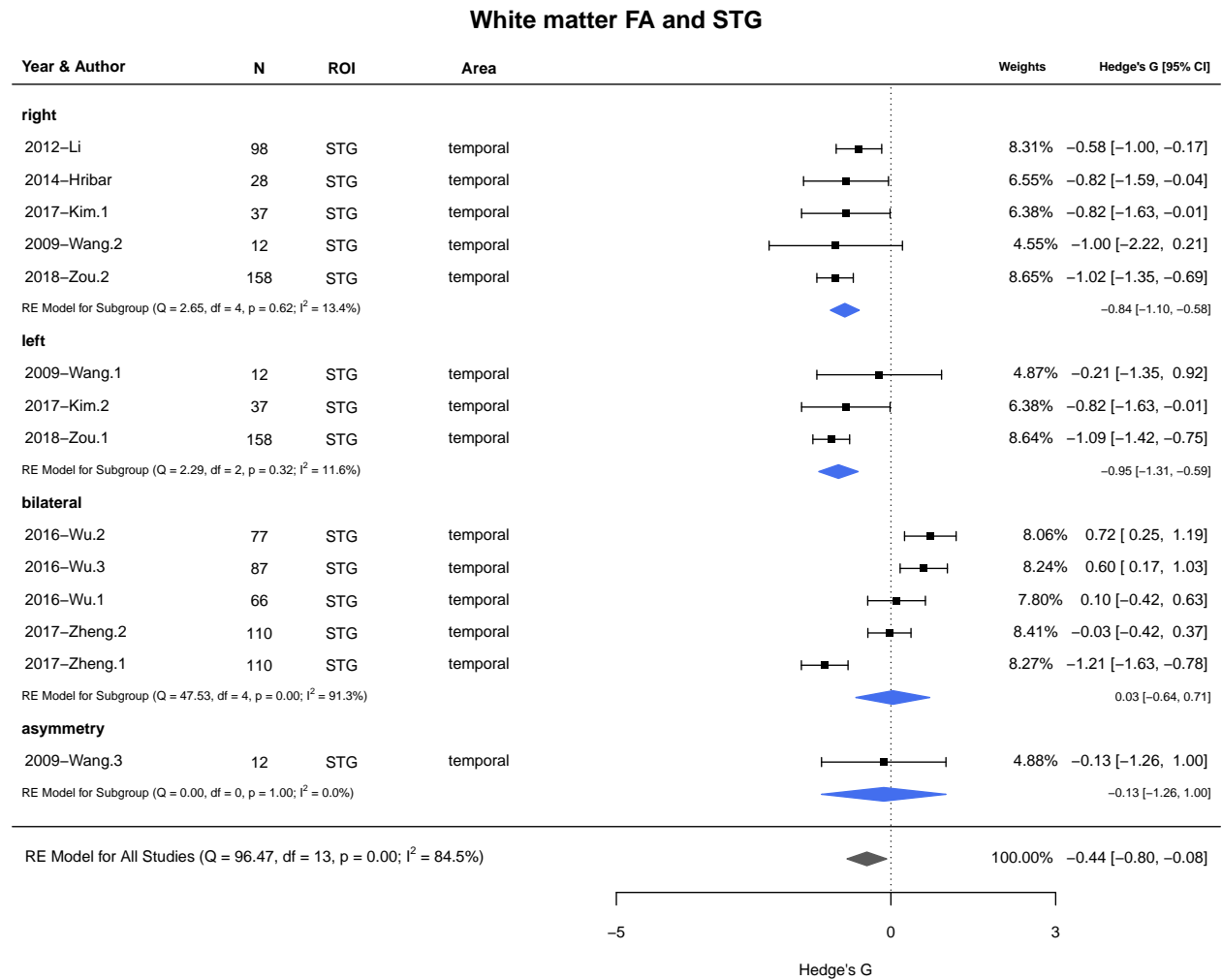


Supplementary material: Forest-plots of other Measures

Hesch gyrus FA white matter

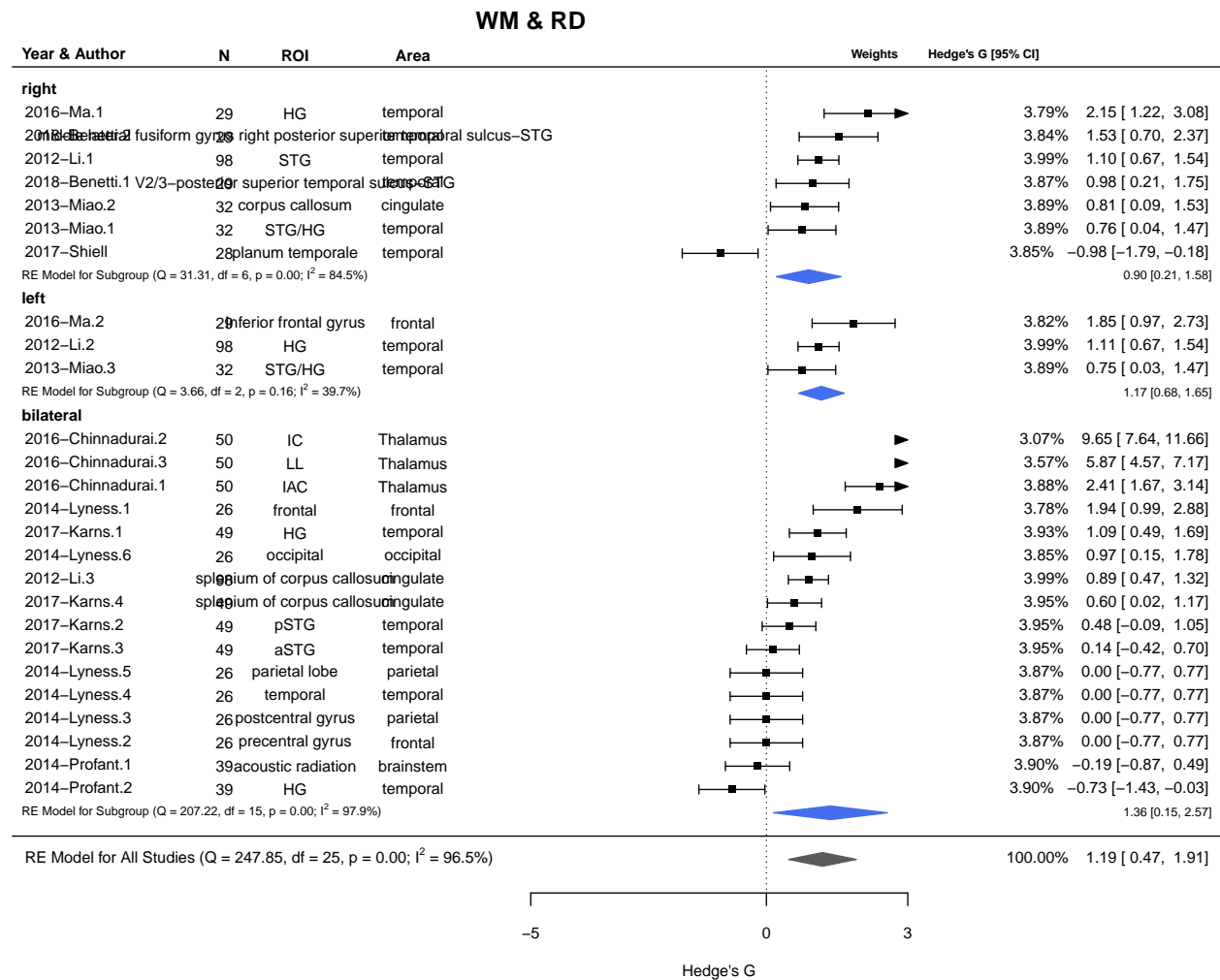


STG Volume White matter



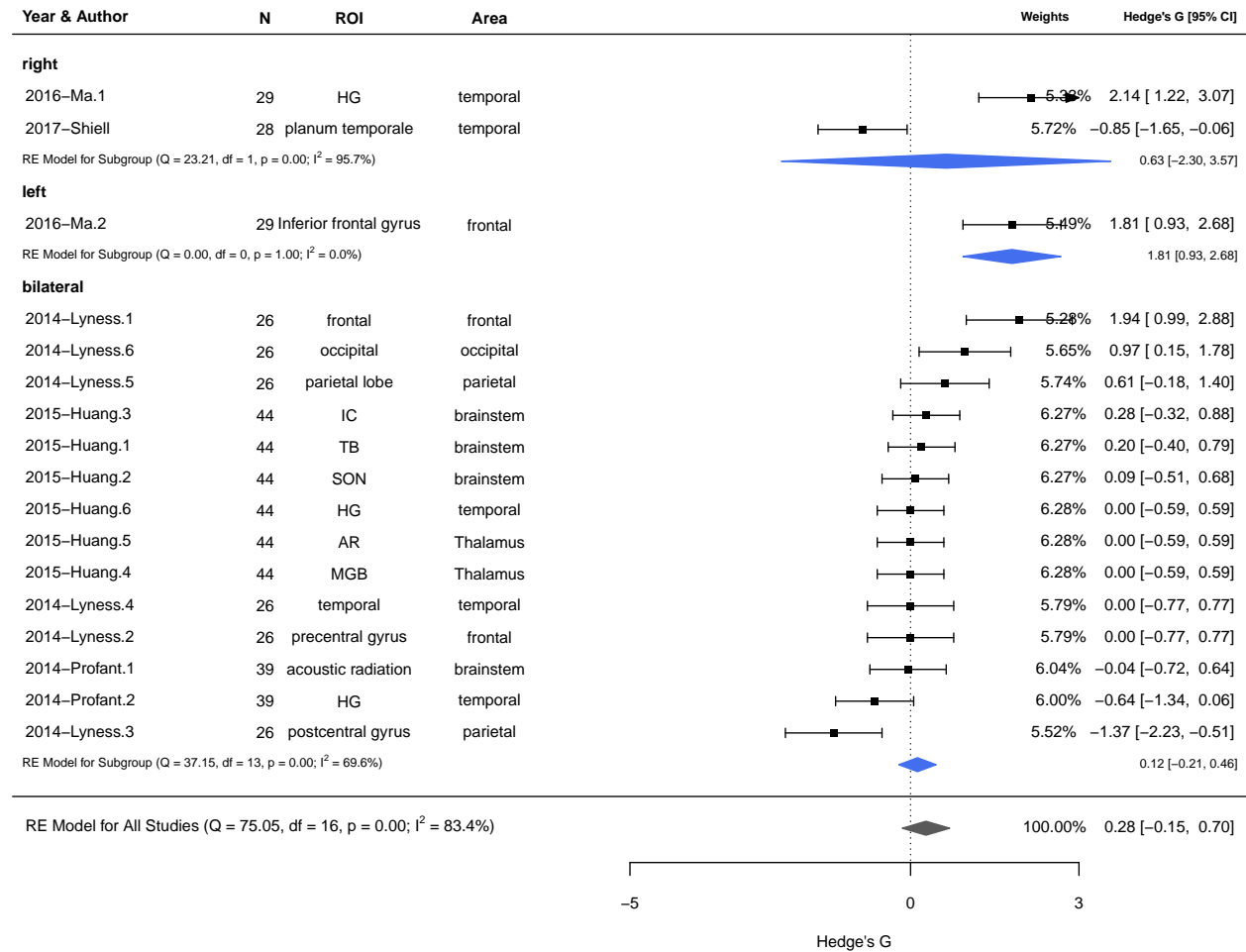
Measures of White matter Integrity

White matter: RD



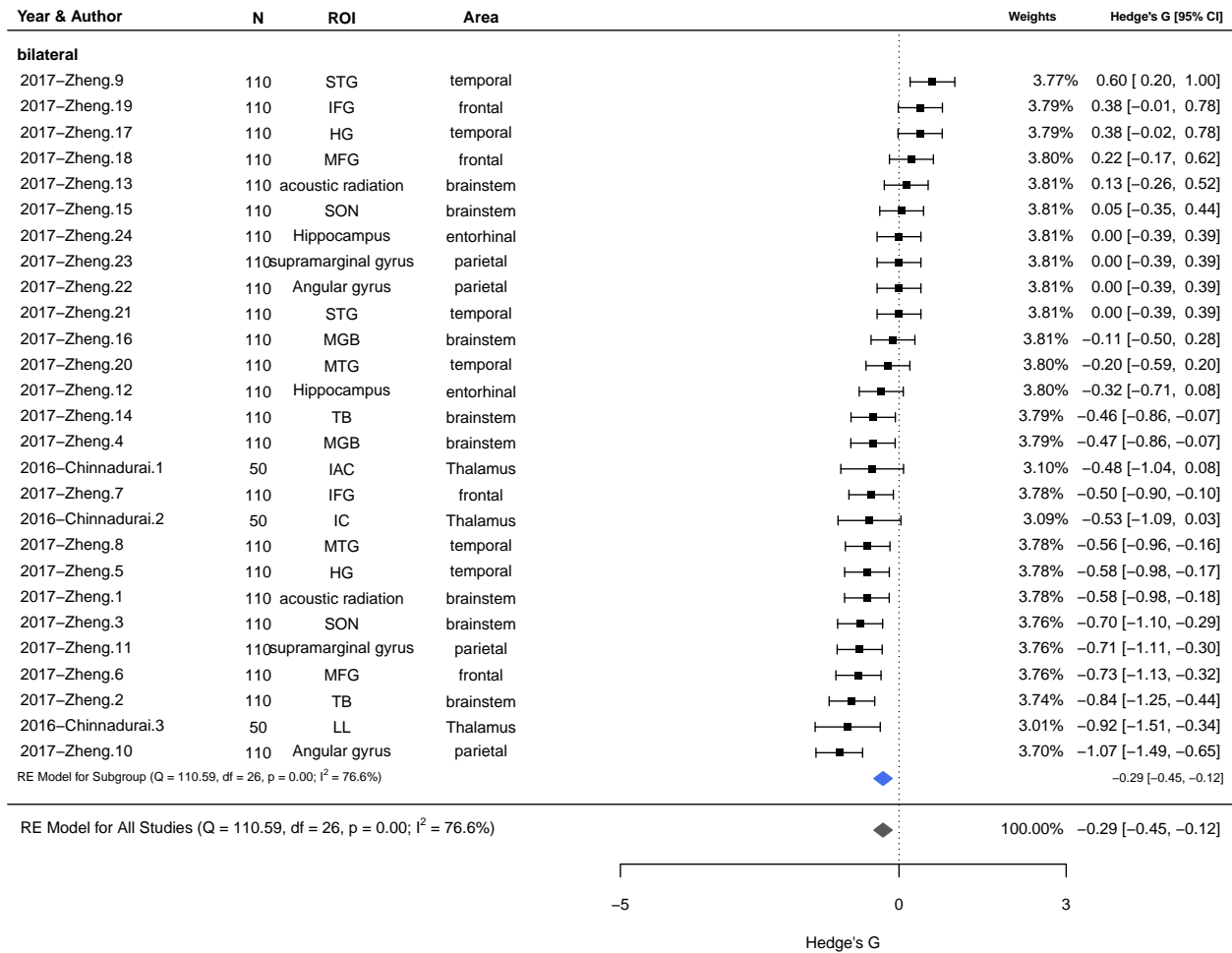
White matter: MD

WM & MD

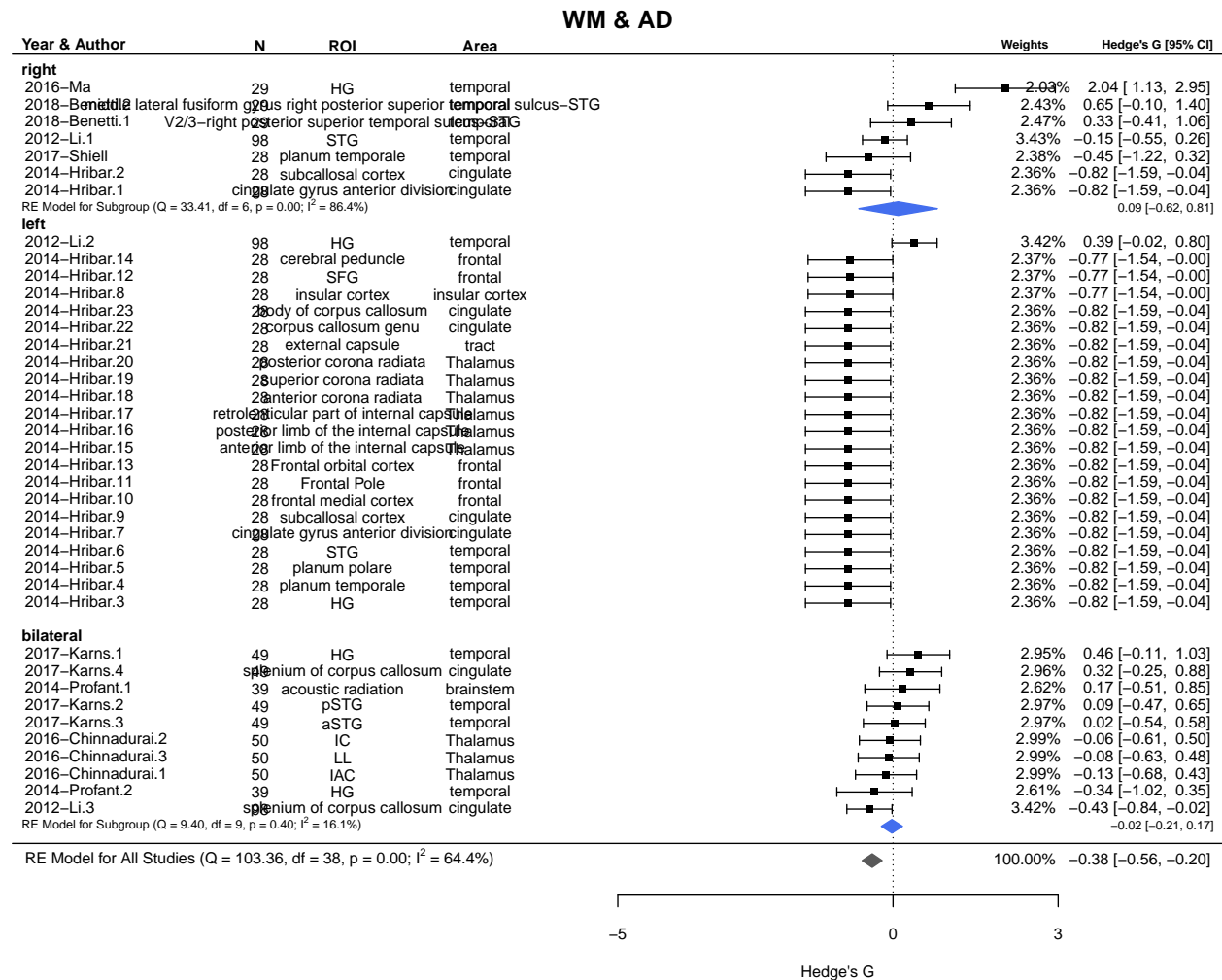


White matter: Mean Kurtosis

WM & Mean Kurtosis



White matter: AD

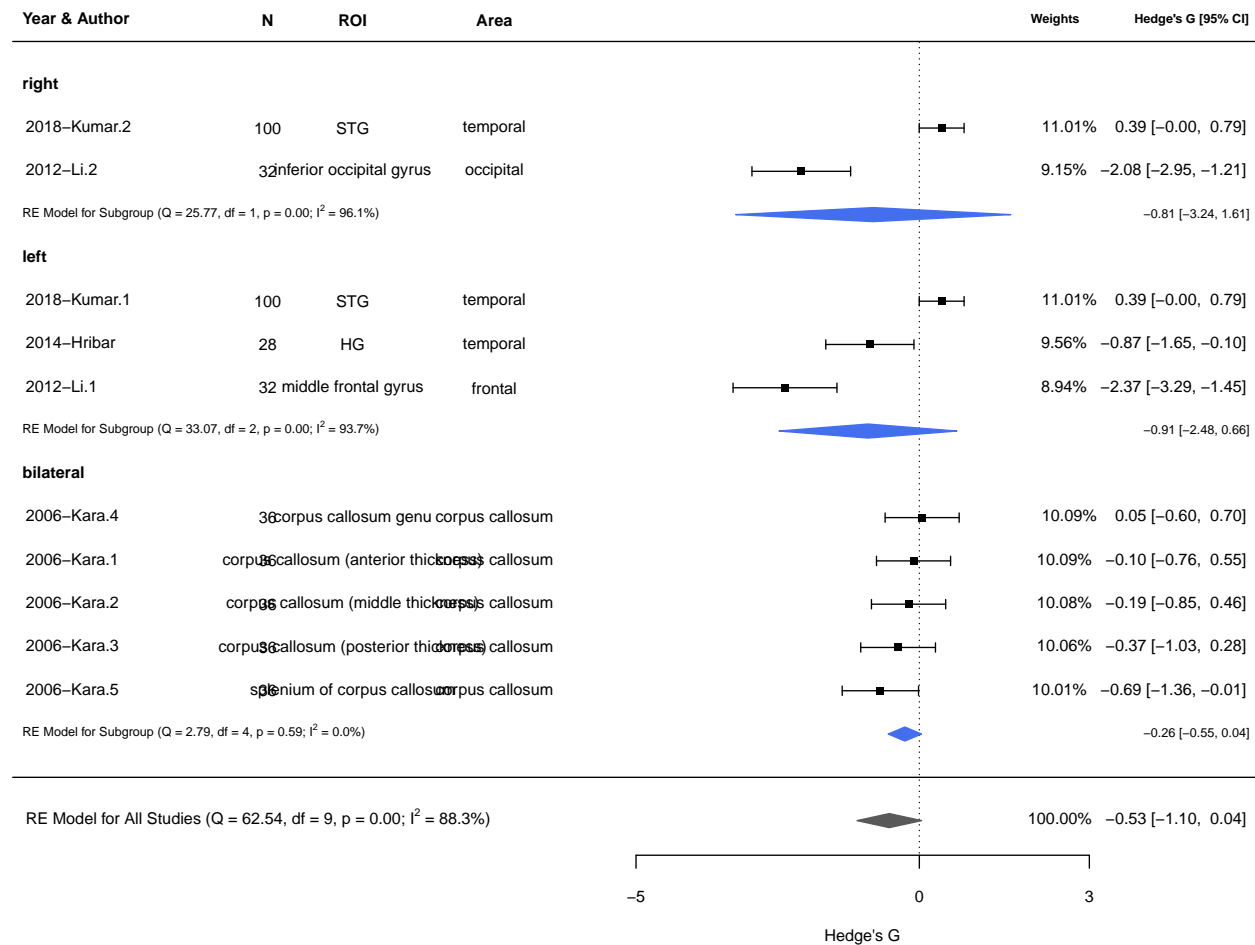


Error in rma(yi = hedgesG, vi = varG, data = meta.mod, measure = "MD", : Fisher scoring algorithm did not converge. See 'help(rma)' for possible remedies.

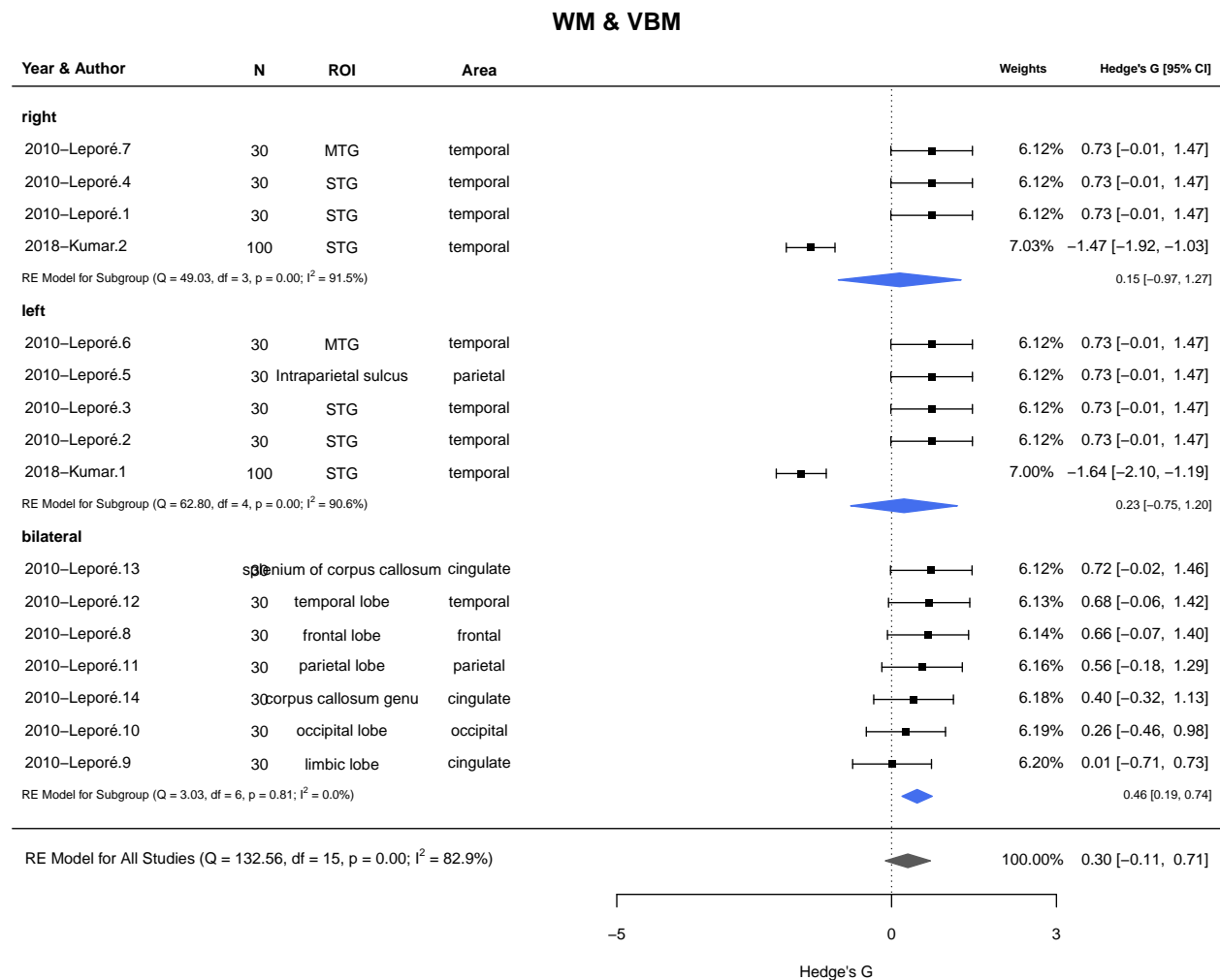
Other Measures of White Matter

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