Data In brief: Hearing loss impacts gray and white matter across the lifespan: systematic review, meta-analysis and meta-regression

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Abstract

Importance. Hearing loss is a heterogeneous disorder thought to affect brain reorganization across the lifespan. The exact structural endophenotype of hearing loss is not known, although it is assumed to affect the auditory regions of the temporal lobe such as Heschl’s gyrus.

Objective. Here we assessed the structural alterations of hearing loss by using a meta-analysis of effect size measures based on MNI coordinate mapping of MRI studies. Unique effect size metrics based on Cohen’s d and Hedges’ g were created to map coordinates of gray matter (GM) and white matter (WM) alterations from bilateral congenital and acquired hearing loss populations. Three coordinate mapping techniques were used and compared: coordinate-based anatomic likelihood estimation (ALE), multi-level kernel density analysis (mKDA), and seed-based d Mapping (SDM). Using a meta-regression, GM and WM trajectories were mapped to visualize the progression of congenital and acquired hearing loss throughout the lifespan. Heterogeneity in effect size metrics was determined using the forest, Baujat, Funnel, Galbraith and bubble plots to discern dispersion and spread of datapoints. Lastly, we displayed an endophenotype map of hearing loss alterations in GM and WM obtained from a multivariable meta-regression of the effect size.

Data Sources. PubMed, Google Scholar and Scopus primary and secondary literature was searched from inception to May 2020, augmented by expert recommendations, grey searchers, and primary literature citation inclusions.

Study Selection. Any peer-reviewed publication irrespective of language that involved the structural neuroimaging of the human brain in participants with hearing loss at any age.

Data Extraction and Synthesis. Data was collected on 1) October 10th, 2012 through November 1st, 2012, 2) June 6th through July 20th 2018, 3) directly prior to publication following the Preferred Reporting Items for Systematic Review and Meta-Analyses. Results were summarized across studies in a random-effects model.

Main Outcomes and Measures. Effect sizes for GM and WM metrics associated with hearing loss in structural MNI coordinates were used for the outcome measure.

Results. The systematic review and meta-analysis revealed n = 72 studies with structural alterations measured by MRI (bilateral=64, unilateral=8). The bilateral studies contained more than 66,545 variable datapoint metrics broadly categorizing hearing loss into congenital and acquired cases from mild to profound impact (n = 7445) and control cases (n = 2924) with ages of 34.92 ± 23.08 and 30.61 ± 19.45 years, respectively. We found hearing loss affects GM and underlying WM in nearly every region of the brain. In congenital hearing loss, GM decreased most in the frontal lobe. Acquired hearing loss similarly had a decrease in frontal lobe GM, albeit the insula was most decreased. Congenital white matter underlying the frontal lobe GM was most decreased. The temporal lobe had different GM alterations in congenital and acquired, decreasing in the former and increasing in the latter, possibly due to age-dependent compensation. The WM alterations most frequently underlined GM alterations in congenital hearing loss, while acquired hearing loss studies did not assess the WM metric frequently.

Limitations. There were several limitations of neuroimaging studies in the hearing loss field with manuscripts many for example not reporting mean and SD for GM or WM metrics, lack of MNI coordinates, and some not reporting sufficient control populations. These factors could have contributed to heterogeneity as underlying explanatory variables.

Conclusions and Relevance. Although temporal lobe auditory regions are most commonly thought to be affected in hearing loss, the present analysis found the frontal lobe gray matter and underlying white matter most decreased in both congenital and acquired hearing loss. The present study demonstrates hearing loss across the lifespan and the compensatory adaptations which occur to the brain due to lack of auditory input. This meta-analysis review presents a novel ‘hit-enter’ repeatability format for assessing hearing loss, providing all data, scripts and analysis from data curation to visualization available for reproducibility. Future studies should use the endophenotype of hearing loss as a prognostic template for discerning impact and clinical outcomes.
Truncated Abstract

Hearing loss is a heterogeneous disorder thought to affect brain reorganization across the lifespan. The exact structural endophenotype of hearing loss is not known, although it is assumed to affect the auditory regions of the temporal lobe such as Heschl’s gyrus. Here we assessed the structural alterations of hearing loss by using a meta-analysis of effect size measures based on MNI coordinate mapping of MRI studies. Unique effect size metrics based on Cohen’s d and Hedges’ g were created to map coordinates of gray matter (GM) and white matter (WM) alterations from bilateral congenital and acquired hearing loss populations. Three mapping techniques were used and compared: coordinate-based anatomic likelihood estimation (ALE), multi-level kernel density analysis (mKDA), and seed-based d Mapping (SDM). Using a meta-regression, GM and WM trajectories were mapped to visualize the progression of hearing loss throughout the lifespan. Heterogeneity in effect size metrics was determined using the forest, Baujat, Funnel, Galbraith and bubble plots to discern dispersion and spread of datapoints. Lastly, we displayed an endophenotype map of hearing loss alterations in GM and WM obtained from a multivariable meta-regression of the effect size. The systematic review and meta-analysis revealed n = 72 studies with structural alterations measured with MRI (bilateral=64, unilateral=8). The bilateral studies contained more than 28000 variable datapoint metrics broadly categorizing hearing loss into congenital and acquired cases (n = 7445) and control cases (n = 2924) with ages of 34.92 ± 23.08 and 30.61 ± 19.45 years, respectively. We found hearing loss affects GM and underlying WM in nearly every region of the brain. In congenital hearing loss, GM decreased most in the frontal lobe. Acquired hearing loss similarly had a decrease in frontal lobe GM, albeit the insula was most decreased. Congenital white matter underlying the frontal lobe GM was most decreased. The temporal lobe had different GM alterations in congenital and acquired, decreasing in the former and increasing in the latter. The WM alterations most frequently underlined GM alterations in congenital hearing loss, while acquired hearing loss studies did not assess the WM metric frequently. There were several limitations of studies in the hearing loss field with manuscripts for example not reporting mean and SD for GM or WM metrics, lack of MNI coordinates, and some not reporting sufficient control populations. These factors could have contributed to heterogeneity as underlying explanatory variables. The present article presents a novel ‘hit-enter’ repeatability format for assessing hearing loss, providing all data, scripts and analysis from data curation to visualization available for reproducibility. Future studies should use the endophenotype of hearing loss as a prognostic template for discerning impact and clinical outcomes.
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1. Supplemental information

An extensive amount of data associated with the MNI coordinate mapping is presented in the supplemental information to support our conclusions for ALE, mKDA, SDM. Tables and figures outline ROI of interest and significance. Additionally, sub-analyses associated with the heterogeneity plots (Forest plot, Baujat plot, Funnel plot, Galbraith plot, and bubble plot) in the meta-analysis are presented for all assessments. All supplemental information is additive in nature and bolsters our results.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA Guidelines). The study was registered in 2018 and supplementary information, code, csv files, and extended analyses can be found at OSF (https://osf.io/7y59j/). Detailed, annotated, expanded, and updated code can be found at GitHub (https://github.com/FrancisManno/MetaHearingLoss or www.fmanno.com). The literature review had been initiated by two authors nearly 6 years prior to registration (FAMM, JTR). The review followed the checklist enumerations as outlined by the Organization for Human Brain Mapping (OHBM) Committee on Best Practices in Data Analysis and Sharing (COBIDAS; http://www.humanbrainmapping.org/cobidas). All analyses for the present study used custom Matlab scripts (2017a: The Mathworks, Natick, USA) and R version 3.6.3, specifically the packages meta and metafor. The manuscript is completely reproducible, replicable, and amendable for future iterations, with a ‘hit-enter’ repeatability, considered the gold-standard.

2.1. Eligibility criteria and study search

Criteria for study eligibility were peer-reviewed publications in any language of an original investigation involving human participants who underwent structural MRI neuroimaging of the brain due to hearing loss. The search was performed in English, Chinese, Spanish and French and had no language restriction. Bilateral hearing loss (BHL) and unilateral hearing loss (UHL) of any degree (mild, moderate, severe and profound) were included in the literature search. For the quantitative portions of the analysis UHL was excluded, due to the small number of studies (n ≈ 10; See Supplementary Information) and not to bias the results due to side of hearing. Therefore, the final inclusion criteria were any MRI studies of BHL (Figure 1a and Supplementary Figure SI.1 Flow Diagram). We identified potentially eligible studies using PubMed, Google Scholar, and Scopus. The literature search was performed at 3 timepoints: 1) Wednesday October 10th, 2012 through November 1st, 2012, 2) June 6th through July 20th 2018 and 3) directly prior to publication to ensure capture of all relevant articles. On all three instances, the search was first performed in PubMed to identify primary literature with follow-up searching using Google Scholar. Once primary literature was identified, a Scopus search of citing literature was performed (secondary and grey). These secondary literature sources were screened similarly as primary literature sources. Primary and secondary sources were then-cross-checked for citing sources and additional references. In the Supplementary Information, the Scopus citations are listed as of July 2019. The Medical Subject Headings (MeSH) search terms were: (deafness OR “hearing loss” OR “bilateral hearing loss” OR “unilateral hearing loss” OR “conductive hearing loss” OR “sensory neural hearing loss”) AND (“magnetic resonance imaging” OR MRI OR “diffusion tensor imaging” OR DTI) NOT (Review[Filter] OR Editorial[Filter] OR Comment[Filter]). Additionally, the search was augmented by correspondence with a distributed network of scientists with hearing loss who are familiar with the field (JTR). To our knowledge this is the first systematic, meta-analytic, or quantitative review of effect sizes of structural neuroimaging in hearing loss. Two authors (FAMM and JTR) screened the titles and abstracts of all records retrieved. Of those articles retrieved, studies that provisionally met eligibility criteria were assessed for eligibility by examining the full text and following the data acquisition protocol (Details appear in the Methods and Table 1 in the Supplementary Information). All information was tabulated into ISA-tab formatted CSV data descriptors by manual data entry (meta_sideDeaf.csv; Checked by two authors FAMM and JTR). The ISA format http://isa-tools.org/) is built around the Investigation
(I: the project context), Study (S: a unit of research) and Assay (A: analytical measurement) data model serializations (tabular). The unit of analysis for the present manuscript was the study in addition to region of interest and GM and WM metric information tabulated from the study as described in the Data Acquisition section.

2.2. Data acquisition, metrics and outcome measures

All eligible studies were included to contribute basic structural neuroimaging data (GM, WM, volume, etc.), audiometric data (hearing loss degree in dB), demographic data (age, sex, etc.), and MRI scanning characteristics (FOV, voxel size in $mm^3$, slices, etc) which were used as the sub-unit of analysis (see Figure 1b; meta_sideDeaf.csv). The variables extracted from the studies can be found in meta_sideDeaf.csv, as columns: 1) study, 2) etiology (i.e. congenital acquired), 3) side deaf (i.e. bilateral in the present review), 4) severity (i.e., mild, moderate, severe, profound), 5) number hearing loss (i.e. experiment group size), 6) HL and control male and female number (i.e. hearing loss males and females), 7) HL and control age (i.e. hearing loss cohort age with SD), 8) HL and control age range low and high categories, 9) average dB HL and SD, 10) left and right ear average dB HL and SD, 11) sign language (i.e. French, American), 12) MRI strength (1T, 1.5T, 3T), 13) acquisition matrix size in $mm^2$, 14) slices in scan sequence, 15) slice thickness (mm), 15) field of view (FOV in cm), 16) scan sequence (i.e. T1), 17) technique (i.e., DTI, VBM), 18) system of analysis (i.e. SPM, FMRIB, Freesurfer, etc), 19) for the region of interest, MNI coordinates in MNI-x, MNI-y, MNI-z, 20) Brodmann location, 21) lobar region of interest (general ROI, i.e. temporal lobe, frontal lobe), 22) specific ROI (i.e. Heschl’s gyrus), 23) hemispheric side (i.e. left or right or bilateral), 24) measure (i.e. cortical thickness, volume, asymmetry, fractional anisotropy, etc), 25) matter (i.e. gray matter or white matter), 26) effect (i.e. increase, decrease, same), 27) Cohen’s d, and 28) effect correlation r. Cohen’s d and effect correlation r were derived measures. Cohen’s d and Hedges’ g were used for assessing the ROI meta-regression (Figure 1a and 1d). When available, experimental group (i.e. HL) and control group sample size, degrees of freedom, raw values for the measure (i.e. volume $mm^3$ and sd), Z score, F test, t-value, or P-value were used for creating the effect size metrics, as not all studies reported identical variables of input for effect size measure calculations. Converting between values given by a study was done with standard formula. As an example, a study might report sample size, t value and a p-value for a measure of Heschl’s gyrus volume between hearing loss and control, but not the actual group volume in $mm^3$. Cohen’s d, outcome measures and variables of the studies are reported in the meta_sideDeaf.csv, as columns as described above. A variability score was estimated for those studies that did not provide standard deviation or error of the mean distribution. The variability was calculated based on the effect size and under the assumption of a normal distribution (see SI variance estimation formula).

3.2. Creating the standardized metric Cohen’s d and Hedges’ g

Effect size Cohen’s d was used to compare values between studies. Cohen’s d uses the means and standard deviations of two groups (HL and control), where $M = \text{mean}$, $SD = \text{standard deviation}$, $n = \text{samplesize}$, $df = \text{degrees freedom}$:

$$Cohen's \, d = (M1 - M2)/SDpooled$$

where $SDpooled = \sqrt{(SD1^2 + SD2^2)/2}$. Hedges’ g uses the means and standard deviations of two groups (HL and control), and the sample size weighted pooled standard deviation for correction. Hedges’ g was used for most analyses to avoid scaling issues. Cohen’s d and Hedges’ g were used for assessing the ROI meta-regression (Figure 1a and 1d). When available, experimental group (i.e. HL) and control group sample size, degrees of freedom, raw values for the measure (i.e. volume $mm^3$ and sd), Z score, F test, t-value, or P-value were used for creating the effect size metrics, as not all studies reported identical variables of input for effect size measure calculations. coinverting between values given by a study was done with standard formula. As an example, a study might report sample size, t value and a p-value for a measure of Heschl’s gyrus volume between hearing loss and control, but not the actual group volume in $mm^3$. Cohen’s d, outcome measures and variables of the studies are reported in the meta_sideDeaf.csv, as columns as described above. A variability score was estimated for those studies that did not provide standard deviation or error of the mean distribution. The variability was calculated based on the effect size and under the assumption of a normal distribution (see SI variance estimation formula).
2.4. Regions of interest in hearing loss

A central interest in neuroscience is determining how different brain regions are modified due to changes in sensory experience over developmental periods. More specifically, sensory deprivation due to hearing loss is known to elicit cross-modal plasticity, were the primary auditory cortex is more than likely to be recruited by visual inputs. The longitudinal processes associated with structural cortical reorganization in the brain due to hearing loss in humans is currently unknown. Here we map specific ROI from MNI coordinates in hearing loss throughout the human lifespan to ascertain the longitudinal progression of changes in GM and WM. Because hearing loss affects the brain in a widespread nature, we are interested in the general and specific areas and thus performed untheshelof and thresholded analyses. The MNI coordinate mapping is divided into general coordinate-based anatomic likelihood estimation (ALE), multi-level kernel density analysis (mKDA), and Seed-based Differential Mapping (SDM). ALE investigates where location probabilities reflect spatial uncertainty associated with the foci of each experiment overlap and mKDA tests how many foci are reported close to any individual voxel. These theoretical differences, that ALE evaluates probabilities of activity localization, where mKDA uses experimental foci counts, allow two different and precise interpretations of the resultant MNI coordinate maps. The SDM analysis is a combination of the methodology and assumptions of ALE and mKDA, using effect sizes and a representation of both positive and negative differences in the same structural brain map. Two levels of structure were assessed: 1) ROIs grouped under a cortical region (i.e. Lobar region: temporal (Heschl’s’ gyrus and superior temporal gyrus) and 2) areas spatially distant Heschl’s gyrus and occipital pole.

2.4.1. Coordinate-based anatomic likelihood estimation

The specific question for this procedure is: where is foci convergence across experiments higher than would be expected by chance if their results were independently distributed? GingerALE version 2.3.6. from BrainMap was used which performs coordinate-based anatomic likelihood estimation (ALE) meta-analytic random effects analyses on MNI coordinates (performed in C+). For the present study, MNI coordinates were used and all figures are presented in MNI space. Structural data from the studies was registered with and entered into Scribe (http://www.brainmap.org/scribe/) for ease of future replication (meta_sideDeaf.csv; https://osf.io/7y59j/). The ALE plots estimate the clustering between foci in hearing loss (Figure 1c). The convergence of foci reported from different experiments is modelled as probability distributions (blobs in Figure 1c) which width is based on empirical estimates of the spatial uncertainty due to the between-subject and between template variability of neuroimaging data. The ALE was assessed against a null-distribution of random special association between experiments using a false discovery rate (FDR) for correcting the family-wise error rate (FWER) and cluster-level inference. Input variables were sample size = N and MNI in x/y/z. The settings were cluster-level FWER = 0.01, FDR corrected threshold of P < 0.05 for cluster-level inference, threshold permutations = 10,000, and cluster forming threshold level of P < 0.001, chosen minimum cluster size = 50mm^3 for analysis and reported only cluster size > 200mm^3. The output was the ALE modelled activation map (MA map) in MNI space, a significant peaks list which detailed up to 10 ROI, based on cluster statistics including volume (mm^3), bounds, weighted center (x/y/z), and the locations and values at peaks within the region. The final ALE output (after union of voxel-wise Gaussians of all foci from ALE MA maps) is a ALE image map at a given α value. The ALE image map is a construction of reported MNI foci spatial probability distributions at the coordinates associated with hearing loss. The conclusion and interpretation of the ALE image map based on the body of literature in hearing loss is the generalization of ROI peaks in the brain most affected by hearing loss. The mKDA precedes in a similar manner, assessing MNI coordinate localization significance, and creating clustering of MNI coordinates (Figure 1c).

2.4.2. Multi-Level Kernel Density Analysis

The specific question for this procedure is: how many foci are reported close to any individual voxel among experiments? The mKDA procedure evaluates consistency and specificity of regional structural alterations...
based on previous studies reported MNI coordinates (performed in Matlab 2017a). The mKDA represents activation focus as a sphere given arbitrary weights based on sample size = N. Peaks from each comparison study map are separately convolved with the kernel to generate comparison indicator maps (CIMs). Subsequently, the summary density map resulting in the proportion of activated comparisons is subjected to statistical thresholding by a Monte Carlo iteration procedure where locations of the centers of each blob are selected at random and uniformly distributed. Here, the null hypothesis is rejected in voxels where the number of nearby peaks is greater than expected by chance. Lastly, the final mKDA montage map is created by FWER control utilizing extent thresholding. Input variables were sample size = N and MNI in x/y/z, sphere size 10 mm (Figure 1c – MNI input). The output was a series CIMs (blobs on Figure 1c). The CIMs were used for determining significance by: 1) height-based thresholding used the center of a 10 mm sphere (yellow in figures, representing P < 0.05) for identifying the number of contiguous voxels needed to say that a cluster was significant and 2) extent-based thresholding was used to estimate which individual voxels show greater activation at different \( \alpha \) levels, \( P < 0.001 \) clusters (orange – stringent), \( P < 0.01 \) clusters (red – medium), and \( P < 0.05 \) clusters (purple – lenient). The aforementioned coloring scheme is applicable to all mKDA maps. The final output was a mKDA montage union map based on height and extent thresholding. Further output was significant region location (x/y/z), voxels, cluster sizes range, volume (\( mm^3 \)), and maxstat (maximum of the z field) for extent-based thresholding at stringent, medium and lenient \( \alpha \) levels. The conclusion and interpretation of the mKDA montage map based on the body of literature in hearing loss is the generalizability of particular regions being structurally altered at a specific \( \alpha \) level.

2.4.3. Seed-based d Mapping (SDM)

The specific question for this procedure is: how do increases and decreases in GM and WM relate among groups (congenital and acquired versus control) of experimental subjects. The SDM analysis examines regions of increased and decreased grey matter volume accounting for ‘peaks’ effect-size in experimental dataset and signing a positive and negative difference. SDM calculates effect sizes from given p-values or t-values to determine lower and upper bounds of possible effect sizes for each voxel using an anisotropic unnormalized kernel, with the resultant effect size and error estimated using MetaNSUE. A meta-analysis of the effect size metrics from the imputed datasets is then computed using Rubin’s rules to combine effect sizes in these datasets into a singular set of parameters that can be used for the final analysis (i.e. image derivation). Lastly, a permutation test is used to determine the distribution of possible maxima activations/deactivations found and this distribution is used to correct for multiple comparisons. Parameters were kept consistent with the above, with the exception of “modality,” which was changed to “other” to account for the heterogeneity of modalities employed in the studies selected. For example, in each group (GM, WM, adult, aged adult, and pediatric), SDM reported a specific set of MNI coordinates found to be statistically significant compared to the null hypothesis that there was no significant difference at that coordinate at various thresholds (including \( p < 0.05 \)) and the direction of the difference (positive or negative). Output was provided in the form of coordinates that contributed to a peak coordinate exhibiting significance, the size of the region found to be significant (in voxels), and a general description of the region based on a standard atlas (i.e., right superior temporal gyrus, BA 42). The conclusion and interpretation of the SDM map are increases or decreases in GM or WM represented by p-values on brain coordinates.

2.5. Meta-regression longitudinal progression of GM and WM trajectories in hearing loss

To determine the longitudinal GM and WM trajectories associated with hearing loss, a random effects meta-regression was performed using Cohen’s d or Hedges’ g and the variability estimated with the standard deviation. The specific question for this procedure is: how does GM and WM alterations change in hearing loss over the lifespan? The multivariate meta-regression covaried age, sample size = n with GM or WM metrics by ROI.
2.6. Heterogeneity of gray matter and white matter

To determine heterogeneity among measures (GM and WM metrics) between experiments, heterogeneity plots (forest plot, Baujat plot, Funnel plot, Galbraith plot and bubble plot), were constructed using R packages meta27,28 and metafor.29,30 Heterogeneity allows determining the dispersion of a particular measure due to variability or uncertainty. The question for these procedures is: how does heterogeneity in a particular GM or WM metric effect generalizability to the ROI in hearing loss. The forest plot used Hedges’ g to demonstrate effect size by measure (GM or WM) and included a summary estimate (centre of diamond) with 95% confidence intervals.30 The reported metrics were Test for Heterogeneity χ², Cochran’s Q (computed by summing the squared deviations of each study’s estimate from the overall meta-analytic estimate, weighting the contribution of each study by its inverse variance),51 and the value I² (the consistency of the results of studies in meta-analyses: I² = 100, where Q is Cochran’s heterogeneity statistic).52,53 Cochran’s Q is distributed as a chi-square statistic χ² with a P value.52 I² is scaled from 0% to 100% and interpreted as a value of 0% indicating no heterogeneity, and larger values show increasing heterogeneity.52,53 Effects were summarized across studies using the generic inverse-variance weighting method (DerSimonian and Laird random effects weighted by 1/SE² – standarderror). Heterogeneity in results was estimated using the τ² statistic (standard deviation of effect sizes between studies).24,25 The Baujat plot was used to identify studies contributing to heterogeneity.54 The X-axis represents the contribution of the measure (GM and WM) to the overall Cochran Q-test for heterogeneity. The Y-axis represents the influence of the measure (GM and WM), defined as the standardized squared difference between the treatment effects (acquired/congenital) estimated with and without the ith study.54 The Baujat plot is interpreted as heterogeneous when influential measures (GM or WM) appear in the upper right quadrant of the graph.54 The Funnel plot was used to illustrate ‘bias’, based on effect size estimates of GM and WM against sample size (plots have 95% CI in light grey and bias exists on P < 0.1).55–57 The Y-axis represents standard error (of the GM or WM metric, normalized across values [0 since we have not added mean and SD]) and the X-axis the residual value of the effect size. The degree of funnel plot asymmetry was measured by the intercept from regression of the standard normal deviates (odds ratio divided by its standard error) against the estimates precision.55–57 The funnel plot precision in estimating the underlying effect of the measure will increase as sample size increases and in the absence of bias the plotted effect size estimates will be scattered in the white region, resembling a symmetrical inverted funnel.55–57 To interpret the Funnel plot, bias is represented as asymmetry where GM or WM measures skew the results and therefore, are found outside of funnel CI area. The Galbraith plot (radial plot) was used to estimate metric (GM or WM) error.58–60 The Y-axis represents a transformed scale of standardized effect size estimates, centered at the reference value and having the unit standard error.58–60 The Y-axis for effect size has ± 2 standard error (shaded in grey) for any point estimate.58–60 The X-axis indicates precision (defined as reciprocal of standard error), where points with large error fall near the origin and points with small error are further away near the arc.58–60 On the right-hand side of the plot, an arc is drawn corresponding to the individual observed effect sizes (Hedges’ g)58–60 A line projected from the origin (0,0) through a particular point within the plot onto this arc indicates the value of the individual observed effect size for that point.58–60 The interpretation of the Galbraith plot is made based on effect size scattering for GM and WM. If a set of effect size estimates agree with one another, in addition to having precision correctly assessed, they will scatter homoscedastically (with unit standard deviations on the y-scale) about a line through the origin.58–60 If the effect size estimates disagree with one another, they will vary heteroscedastically, resulting in statistical dispersion.58–60 Said another way, consistent effect size estimates are grouped closely together, while those that are uncertain are found as outliers. The bubble plot was used to display the results of the meta-regression of GM or WM with the bubble extent representing effect size and the regression dependent on the corresponding variable (ROI). The quantile-quantile (QQ) plot is used for testing normality of the data.61 Interpretation of the QQ plot is made by datapoints circumscribing the diagonal line within the confidence boundaries whereas data not normally distributed lies outside the 95% CI.61 The graphical display of study heterogeneity (GOSH) plots62 is a method to visualize the effect of study-level heterogeneity using a fixed-effects model between subset variable characteristics. The X-axis is the logs ratio of the GM or WM metric and the Y-Axis is Cochran Q-statistic. The interpretation of GOSH plots is based on the model estimates forming a symmetric, contiguous, and unimodal distribution whereas a multimodal distribution suggests heterogeneity in GM or WM metrics.62 The bubble plot is interpreted by size of bubble having larger effect on the regression line for the metric (GM or WM). The heterogeneity
plot analyses will allow the determination of metric (GM or WM) variability or uncertainty.

2.7. Surface visualization of ROI mapping to create hearing loss endophenotype

Acquired and congenital multivariate meta-regression models by brain area where calculated. Random effects models covaried by main brain area were fitted to obtain the weights of left and right ROIs with GM or WM metrics. The resultant effect size estimates were backprojected to the respective brain area to create a meta-analytic endophenotype of hearing loss of GM and WM. Here the effect size is visualized on the cortical surface with the meta-regression estimate per ROI derived from the meta-analysis. Interpretation of the surface visualization is done with a cold-hot color bar which represents negative to positive effect sizes, respectively. Brain surface visualization and surface projection was done using Freesurfer and SurfStat merging lobe mapping with an annotation file. A mixed effects model was used to account for the variation in GM or WM effect size metrics for a particular ROI within the congenital or acquired hearing loss groups. The meta-analytic test of moderators in the model determines whether we can reject the null hypothesis of no effect of GM or WM by ROI for congenital or acquired hearing loss in the constructed endophenotype.

2.8. Research statistical strategy: Analysis overview, hypothesis, assumptions, and interpretation

Our main research question was what are the structural manifestations of hearing loss? The research strategy followed a four-pronged approach. First, we assessed general and specific GM and WM alterations associated with where alterations occur in hearing loss. Second, we assessed general and specific ROI GM and WM longitudinal trends in hearing loss. Third, we wanted to understand the heterogeneity attributed to GM or WM by general and specific ROI. Lastly, we created a novel effect size meta-regression backploting of the alterations in hearing loss to a cortical surface, in order to visualize the endophenotype of hearing loss. Studies were not excluded for any analysis, but discussed if considered biased (the Methods and SI Table 1 in the Supplemental Information). The overall null hypothesis for the analyses was no effect due to hearing loss for GM or WM. The effect size measure was used as the outcome variable. The alternative hypothesis was accepted if hearing loss effected GM or WM was \( P < 0.05 \), indicating the ROI was significantly altered. The assumptions underlying the statistics were normal distribution and datapoint effect size errors were independent and identically distributed. Nevertheless, a few studies contributed pseudoreplicated data by assessing the same patient population, albeit different GM and WM metrics. We did not note these metrics altering the results for any analysis. The unit of analysis was GM or WM metrics or effect size metrics such as Hedges' \( g \).

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Literature research

• Literature Search Methodology (eFigure PRISMA)
  1. PubMed searches were performed to acquire the requisite background information for this review. The searches had the purpose of identifying all sources concerning structural MRI assessments of unilateral or bilateral hearing loss. All studies must have utilized MRI as a structural assessment for hearing loss.
  2. Search Terminology: "Unilateral hearing loss OR single-sided deafness, "Bilateral hearing loss OR deafness", "AND MRI OR magnetic resonance imaging"

• First Search Oct/Nov 2012
  1. A literature search in PubMed using MeSH and truncated (wildcard) terms was performed for studies pertaining to “unilateral hearing loss” or “bilateral hearing loss on Wed October 10, 2012 through Thurs November 1, 2012. The literature search returned precisely 3,057 results. All abstracts returned were read for descriptions of congenital unilateral/bilateral hearing loss using MRI. Approximately, 905 studies meet the following inclusion criteria. These studies were surveyed to ascertain whether they were relevant for inclusion based on the ‘Review inclusion criteria.’
  2. The primary inclusion and exclusion criteria were predetermined by following recommendations on meta-analysis (Sutton, et al., 2000)

• Inclusion criteria
  1. Structural MRI study of bilateral or unilateral hearing loss
  2. Study had at least one cohort of participants whom had congenital unilateral/bilateral hearing loss
  3. The study, with a cohort of hearing impaired participants, had an adequate hearing control
  4. The normal hearing controls were sufficiently matched to the hearing impaired cohort (i.e age, gender, education, etc.)
  5. An experiment comparing the two cohorts was performed consisting of, but not limited to, MRI structural assessment

• Exclusion criteria
1. All studies were first included in the review and then given an asterisk if deemed inappropriate for inclusion.
2. Case studies (i.e., reports with only one patient)
3. Manuscripts with insufficient power of replication (i.e., manuscript with 2 patients)
4. Manuscripts with an inadequate or absent normal hearing control cohort (i.e., no control cohort was reported) – indicated in table.
5. Normal hearing control cohort lacked matching demographic characteristics (i.e. the study had a group of hearing loss pediatric children and the normal hearing control group was adults)
6. Manuscripts without an experiment comparing the hearing loss and normal cohort (i.e., bilateral hearing loss was not compared to hearing controls).

- Second Search June/July 2018
  1. Searches from first search and second search were combined along with personal correspondences of articles from JTR.
  2. Pubmed: (deafness OR "hearing loss" OR "bilateral hearing loss" OR “unilateral hearing loss” OR “conductive hearing loss” OR “sensorineural hearing Loss”) AND ("magnetic resonance imaging" OR MRI OR DTI OR "diffusion tensor imaging") NOT (Review[Filter] OR Editorial[Filter] OR Comment[Filter])
  3. Returned 4,179 articles. Articles were checked again throughout June/July 2018. Final article list was checked through Scopus.
  4. All references we checked at date indicated in table.
  5. Approximately 911 studies meet inclusion criteria
  6. Approximately 178 studies were screened from both periods and invited
  7. Approximately 118 were excluded based on exclusion criteria or not pertaining to inclusion criteria
  8. A total of 51 studies were analyzed

- Controls
  - Our requirements for duplicated studies were studies which used the identical participants but had different methodology, participants age was identical, or it was stated participants were used by authors in two studies
  - Only included original statistics here from the studies. All derived effect sizes were from study information. Asymmetry statistics were created if a study included a left and a right side for an identical ROI. Statistics from our analysis could be derived from, example asymmetry as indicated above.
  - Asymmetry if included was converted to: only for asymmetry (check asymmetry) (L - R) /[(L+R)/2], where positive result = LEFT, negative result = RIGHT
  - If studies included acquired and congenital we only used congenital metrics.

Figure SI.1 Flow diagram

Eligibility Criteria for the meta-regression

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.
Figure 1: Flowchart of data-acquisition* All available bilateral/unilateral studies were analyzed.
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 Hegdes’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.

**Tables of included studies**

A total of 64 unique bilateral 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 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 Otorhinolaryngology | 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. Neurobiology Aging | acquired | NA |

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

| Source | Etiology  | all.techniques | all.measures |
|--------|-----------|----------------|--------------|
| 2010, Liu et al. Chin J Med Img Tech | congenital | CT | FA |
| 2012, Li et al. Brain Res | congenital | CT | Thickness |
| 2015, Li et al. Restor Neurol Neurosci | mixed | CT | volume |
| 2016, Shiell et al. Neural Plasticity | congenital | CT | Thickness |
| 2016, Smittenauer et al. Open Neuroimag J | congenital | CT | |
| 2018, Ren et al. Front Neurosci | acquired | CT, VBM | Thickness, volume |
| 2004, Chang et al. Neureport | congenital | DTI | asymmetry, FA |
| 2009, Wang et al. Chin J Med Img Tech | congenital | DTI | FA |
| 2012, Li et al. Hum Brain Mapp | congenital | DTI | AD, FA, RD |
| 2013, Miao et al. Am J Neuroladiol | congenital | DTI | FA, RD |
| 2014, Lyness et al. Neuroimage | congenital | DTI | FA, MD, RD |
| 2015, Huang et al. PLoS One | congenital | DTI | FA, MD |
| 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 |
| 2017, Karns et al. Hear Res | congenital | DTI | AD, FA, RD, volume |
| 2017, Kim et al. Neureport | congenital | DTI | FA |
| 2017, Shiel & Zatorre. Hear Res | congenital | DTI | AD, MD, RD, volume |
| 2017, Zheng et al. Sci Rep | congenital | DTI | FA, Mean Kurtosis |
| 2018, Benetti et al. Neuroimage | congenital | DTI | AD, FA, RD |
| 2018, Park et al. Biomed Res Int | congenital | DTI | FA |
| 2018, Zou et al. Otol Neurotol | congenital | DTI | AK, FA, MK, RK |
| 2009, Kim et al. Neureport | congenital | DTI, VBM | FA, volume |
| 2010, Husain et al. Brain Res | acquired | DTI, VBM | FA, volume |
| 2014, Hribar et al. Hear Res | congenital | DTI, VBM | AD, FA, Thickness |
| 2014, Profant et al. Neuroscience | acquired | DTI, VBM | AD, CT, FA, MD, RD, Surface, volume |
| 2019, Luan et al. Front Neurosci | acquired | DTI, VBM | FA, MD, volume |
| 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 |
| 2006, Kara et al. J Neuroladiol | congenital | VBM | length, Thickness, volume |
| 2007, Meyer et al. Restor Neurol Neurosci | congenital | VBM | volume |
| 2007, Shibata DK. Am J Neuroladiol | 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 |
| 2010, Leporé et al. Hum Brain Mapp | congenital | VBM | VBM |
| 2010, Li et al. J Clin Rad | congenital | VBM | volume |
| 2011, Smith et al. Cereb Cortex | congenital | VBM | asymmetry, ratio GM/WM, volume |
| 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, Pénicaud et al. Neuroimage | congenital | VBM | volume |
| 2014, Kim et al. Hear Res | congenital | VBM | volume |
Table 7: Studies Measuring White Matter Thickness (n=4)

| Source                                   | MRI measure | Matter | Brain area      | Side  | ROI                            |
|------------------------------------------|-------------|--------|-----------------|-------|--------------------------------|
| 2012, Li et al. Brain Res                | Thickness   | WM     | frontal         | left  | middle frontal gyrus           |
| 2012, Li et al. Brain Res                | Thickness   | WM     | occipital       | right | inferior occipital gyrus       |
| 2014, Hribar et al. Hear Res             | Thickness   | WM     | temporal        | left  | HG                             |
| 2006, Kara et al. J Neuroradiol          | Thickness   | WM     | corpus callosum | bilateral | corpus callosum (anterior thickness) |
| 2006, Kara et al. J Neuroradiol          | Thickness   | WM     | corpus callosum | bilateral | corpus callosum (middle thickness) |
| 2006, Kara et al. J Neuroradiol          | Thickness   | WM     | corpus callosum | bilateral | corpus callosum (posterior thickness) |
| 2006, Kara et al. J Neuroradiol          | Thickness   | WM     | corpus callosum | bilateral | splenium of corpus callosum    |
| 2018, Kumar U, Mishra M. Brain Res       | Thickness   | WM     | temporal        | left  | STG                            |
| 2018, Kumar U, Mishra M. Brain Res       | Thickness   | WM     | temporal        | right | STG                            |

Table 8: Studies Measuring Gray Matter FA (n=2)

| Source                                   | MRI measure | Matter | Brain area | Side  | ROI                                    |
|------------------------------------------|-------------|--------|------------|-------|----------------------------------------|
| 2019, Luan et al. Front Neurosci         | FA          | GM     | frontal    | left  | dorsolateral prefrontal cortex         |
| 2019, Luan et al. Front Neurosci         | FA          | GM     | frontal    | right | dorsolateral prefrontal cortex         |
| 2019, Luan et al. Front Neurosci         | FA          | GM     | occipital  | bilateral | inferior fronto-occipital fasciculus   |
| 2019, Luan et al. Front Neurosci         | FA          | GM     | temporal   | bilateral | inferior longitudinal fasciculus       |
| 2019, Luan et al. Front Neurosci         | FA          | GM     | parietal   | bilateral | superior longitudinal fasciculus       |
### Formulas

Effect size direction was directly included in the Cohen’s D value by multiplying by -1 if the effect was decrease and by 1 if it was none of increased. The value of Cohen’s D $r_{Y1}$, was calculated using the means and standard deviations of two groups ($M_1$=treatment and $M_2$=control):

$$Cohen's\ D = \frac{M_1 - M_2}{S_{pooled}}$$

where

$$S_{pooled} = \sqrt{\frac{(n_1 - 1) \times s_1^2 + (n_2 - 1) \times s_2^2}{n_1 + n_2 - 2}}$$

and the effect-size correlation is:

$$r_{Y1} = \frac{d}{\sqrt{d^2 + 4}}$$

We calculate the value of Cohen’s d and the effect size correlation, $r_{Y1}$, using the t test value for a between subjects $t-test$ and the degrees of freedom, the following formula was used:

$$Cohen's\ D = \frac{2t}{\sqrt{df}} \text{ and } r_{Y1} = \sqrt{\frac{t^2}{t^2 + df}}$$

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

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

Finally, the 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:

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

### Estimation of heterogeneity per model

We estimated heterogeneity in results using the $\tau$ 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 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.

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Unilateral hearing loss (total n=8)

- VBM studies
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- DTI
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  2. Lin et al. J Magn Reson Imaging. 2008 Sep;28(3):598-603. (Bilateral and unilateral SNHL Adult) - DTI-Studio
  3. Rachakonda et al. Front Syst Neurosci. 2014 May 26:8:87. (Unilateral left and right, adolescent) – Not indicated
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  5. Vos et al. Hear Res. 2015 May;323:1-8. (Unilateral mixed left and right SNHL adult) – DTI Tractography - ExploreDTI

Signed differential mapping (SDM)

Seed-based d Mapping (formerly “Signed Differential Mapping”): > https://www.sdmproject.com/

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| MNI coordinate | SDM.Z | P       | Voxels | Description | Direction |
|----------------|-------|---------|--------|-------------|-----------|
| -8.52,-20      | 4.350 | 0.00000698 | 916    | Left gyrus rectus, BA 11 | positive |
| -16,-100,-6    | 3.835 | 0.0000628 | 950    | Left calcarine fissure / surrounding cortex, BA 17 | positive |
| -22,-38,60     | 3.621 | 0.001470 | 755    | (undefined), BA 3 | positive |
| 26,-76,38      | 3.187 | 0.0007187 | 508    | Right superior occipital gyrus, BA 19 | positive |
| 30,-32,56      | 3.494 | 0.002378 | 457    | Right postcentral gyrus, BA 3 | positive |
| -8,8,312       | 3.387 | 0.0003530 | 419    | Left anterior cingulate / paracingulate gyr, BA 32 | positive |
| -4,-28,32      | 2.901 | 0.018615 | 399    | Left median cingulate / paracingulate gyr, BA 23 | positive |
| 62,2,10        | 2.817 | 0.024230 | 319    | Right rolandic operculum, BA 6 | positive |
| 14,-44,-10     | 3.679 | 0.001172 | 259    | Right cerebellum, hemispheric lobule IV / V, BA 30 | positive |
| -8,-52,-8      | 2.704 | 0.0034276 | 287    | Left cerebellum, hemispheric lobule IV / V, BA 18 | positive |
| -26,-92,20     | 3.424 | 0.0030909 | 240    | Left middle occipital gyrus, BA 18 | positive |
| 8,-72,22       | 2.994 | 0.013756 | 102    | Corpus callosum | positive |
| -42,-36,22     | 2.463 | 0.0058921 | 70     | Left superior temporal gyrus, BA 48 | positive |
| -56,10,30      | 2.664 | 0.038628 | 52     | Left precentral gyrus, BA 44 | positive |
| -18,40,30      | 2.625 | 0.043344 | 36     | Corpus callosum | positive |
| 44,-4,-10      | 1.938 | 0.0263297 | 39     | Right superior temporal gyrus | positive |
| -32,-16,-12    | 2.134 | 0.0164014 | 35     | Corpus callosum | positive |
| 62,-32,-6      | 2.029 | 0.0212226 | 33     | Right middle temporal gyrus, BA 21 | positive |
| 36,-22,-14     | 2.677 | 0.037128 | 24     | Right hippocampus, BA 20 | positive |
| 6,-34,56       | 1.959 | 0.0250691 | 21     | Right paracentral lobule | positive |
| -26,20,-16     | 2.194 | 0.0141032 | 19     | Left frontal orbito-polar tract | positive |
| -22,40,36      | 1.988 | 0.0234269 | 8      | Left superior frontal gyrus, dorsolateral, BA 9 | positive |
| 34,-68,-46     | 1.865 | 0.0311240 | 7      | Right cerebellum, hemispheric lobule VIIIB | positive |
| -30,-10,-42    | 1.762 | 0.030477 | 2      | Left inferior temporal gyrus, BA 20 | positive |
| -18,42,40      | 1.660 | 0.0484373 | 2      | Left superior frontal gyrus, dorsolateral, BA 9 | positive |
| 52,2,-4        | 1.673 | 0.0471951 | 1      | Right superior temporal gyrus, BA 38 | positive |
| -20,40,36      | 1.670 | 0.0475018 | 1      | Left superior frontal gyrus, dorsolateral, BA 9 | positive |
| 52,-14,-10     | 1.655 | 0.0498883 | 1      | Right superior temporal gyrus, BA 22 | positive |
| 8,-54,-38      | -2.751 | 0.0029747 | 714    | Right cerebellum, hemispheric lobule IX | negative |
| -50,-16,-14    | -3.099 | 0.000463 | 521    | Left middle temporal gyrus, BA 20 | negative |
| 42,12,-34      | -3.013 | 0.0012935 | 323    | Right temporal pole, middle temporal gyrus, BA 20 | negative |
| -6,26,44       | -3.092 | 0.000937 | 214    | Left superior frontal gyrus, medial, BA 8 | negative |
| -48,-52,40     | -2.485 | 0.0064724 | 223    | Left inferior parietal (excluding supramarginal and angular) gyr, BA 40 | negative |
| -44,8,-30      | -2.333 | 0.0039195 | 190    | Left temporal pole, middle temporal gyrus, BA 20 | negative |
| 16,-12,-10     | -2.861 | 0.0121141 | 164    | Right cortico-spinal projections | negative |
| 38,-22,36      | -3.305 | 0.004744 | 149    | Right superior longitudinal fasciculus III | negative |
| 46,-58,42      | -3.349 | 0.000456 | 141    | Right angular gyrus, BA 39 | negative |
| -20,-54,12     | -3.587 | 0.0001674 | 109    | Corpus callosum | negative |
| -36,32,18      | -3.168 | 0.0007666 | 123    | Left inferior frontal gyrus, triangular part, BA 48 | negative |
| 22,36,48       | -4.063 | 0.000243 | 103    | Right superior frontal gyrus, dorsolateral, BA 9 | negative |
| -46,-6,-26     | -2.997 | 0.0031640 | 97     | Left inferior network, inferior longitudinal fasciculus | negative |
| -4,-32,22      | -2.655 | 0.0039663 | 100    | Corpus callosum | negative |
| -14,-66,-32    | -2.564 | 0.0051706 | 68     | (undefined) | negative |
| -30,-58,-58    | -2.242 | 0.0124691 | 60     | Left cerebellum, hemispheric lobule VIII | negative |
| 28,42,28       | -2.263 | 0.0118076 | 52     | Right middle frontal gyrus, BA 46 | negative |
| -40,-70,-46    | -2.622 | 0.0036985 | 37     | Left cerebellum, crus II | negative |
| 26,-12,-2      | -2.269 | 0.016403 | 42     | Right cortico-spinal projections | negative |
| -4,-54,18      | -2.683 | 0.0036455 | 31     | Right precuneus, BA 30 | negative |
| -54,26,-26     | -2.386 | 0.005091 | 28     | Left superior longitudinal fasciculus III | negative |
| 44,12,54       | -2.203 | 0.0137867 | 25     | Right middle frontal gyrus, BA 9 | negative |
| 44,6,20        | -2.171 | 0.0149726 | 24     | Right superior longitudinal fasciculus III | negative |
| 10,-70,40      | -1.972 | 0.0242994 | 23     | Right precuneus, BA 7 | negative |
| -40,-48,58     | -2.064 | 0.0195199 | 17     | Left inferior parietal (excluding supramarginal and angular) gyr, BA 40 | negative |
| -30,-66,-48    | -1.896 | 0.0289586 | 18     | Left cerebellum, hemispheric lobule VIII | negative |
| 0,-66,-10      | -1.927 | 0.026926 | 11     | Cerebellum, vermic lobule VI | negative |
| 34,-10,50      | -1.989 | 0.0233668 | 10     | Right superior longitudinal fasciculus II | negative |
| -2,26,-10      | -1.831 | 0.0352533 | 9      | Left anterior cingulate / paracingulate gyr, BA 11 | negative |
| 12,-80,48      | -1.879 | 0.030139 | 7      | Right precuneus, BA 7 | negative |
| 60,-44,32      | -1.917 | 0.0275989 | 7      | Right supramarginal gyrus, BA 40 | negative |
Table 10: SDM: congenital... continuation

| MNI.coordinate | SDM.Z  | P       | Voxels | Description                                      | Direction     |
|----------------|--------|---------|--------|--------------------------------------------------|---------------|
| 24,-26,4       | -1.898 | 0.0288799 | 7      | Corpus callosum                                 | negative      |
| 18,-32,28      | -1.950 | 0.0255769 | 4      | Corpus callosum                                 | negative      |
| -26,-4,-16     | -1.954 | 0.0253757 | 4      | Left amygdala, BA 34                            | negative      |
| -44,-6,28      | -1.778 | 0.0377381 | 4      | Left inferior frontal gyrus, opercular part, BA 44 | negative      |
| 40,-18,24      | -1.931 | 0.0287345 | 3      | Right superior longitudinal fasciculus III      | negative      |
| 4,-66,-16      | -1.760 | 0.0392402 | 3      | Cerebellum, vermic lobule VI                    | negative      |
| 56,-38,24      | -1.950 | 0.0255769 | 4      | Corpus callosum                                 | negative      |
| -42,-4,22      | -1.716 | 0.0430821 | 3      | Left superior longitudinal fasciculus III       | negative      |
| -10,-32,-10    | -1.785 | 0.0371247 | 2      | Left anterior cingulate / paracingulate gyri, BA 11 | negative      |
| -56,-46,38     | -1.738 | 0.0412244 | 2      | Left inferior parietal (excluding supramarginal and angular) gyri, BA 40 | negative      |
| 42,-16,-10     | -1.696 | 0.049376  | 2      | Right inferior network, inferior longitudinal fasciculus | negative      |
| 10,-80,38      | -1.674 | 0.0471222 | 2      | Right cuneus cortex, BA 19                      | negative      |
| -32,-8,-28     | -1.870 | 0.0307359 | 1      | Left inferior network, inferior longitudinal fasciculus | negative      |
| -18,-42,8      | -1.828 | 0.0338045 | 1      | Corpus callosum                                 | negative      |
| -24,-2,-28     | -1.803 | 0.0357051 | 1      | Left amygdala, BA 28                            | negative      |
| -30,-52,8      | -1.784 | 0.0372359 | 1      | Left fusiform gyrus, BA 37                      | negative      |
| -18,-36,-8     | -1.782 | 0.0373835 | 1      | Left median network, cingulum                   | negative      |
| -30,-64,10     | -1.738 | 0.0410686 | 1      | Corpus callosum                                 | negative      |
| -24,-32,14     | -1.723 | 0.0424798 | 1      | Left median network, cingulum                   | negative      |
| 10,-82,44      | -1.679 | 0.0466105 | 1      | Right cuneus cortex, BA 19                      | negative      |
| 20,-6,-20      | -1.666 | 0.0478409 | 1      | Right hippocampus, BA 28                        | negative      |
| 34,-28,40      | -1.654 | 0.0490536 | 1      | Right middle frontal gyrus, BA 9                | negative      |

Table 11: SDM: acquired

| MNI.coordinate | SDM.Z  | P       | Voxels | Description                                      | Direction     |
|----------------|--------|---------|--------|--------------------------------------------------|---------------|
| 60,-24,16      | 3.668  | 0.0001223 | 651    | Right superior temporal gyrus, BA 42            | positive      |
| 52,-60,4       | 2.650  | 0.0040274 | 109    | Right middle temporal gyrus, BA 37              | positive      |
| -44,-10,6      | -2.782 | 0.0027017 | 858    | Left rolandic operculum, BA 48                  | negative      |
| 6,-34,34       | -1.853 | 0.0319374 | 65     | Right median network, cingulum                  | negative      |
| -54,-30,16     | -1.663 | 0.0481477 | 1      | Left superior temporal gyrus, BA 42            | negative      |

Table 12: SDM: pediatric

| MNI.coordinate | SDM.Z  | P       | Voxels | Description                                      | Direction     |
|----------------|--------|---------|--------|--------------------------------------------------|---------------|
| -6,-32,32      | 3.238  | 0.0006011 | 586    | Left median network, cingulum                   | positive      |
| 26,-78,36      | 3.087  | 0.0010125 | 471    | Right superior occipital gyrus, BA 19           | positive      |
| -10,-52,2      | 2.958  | 0.0015398 | 144    | Left superior frontal gyrus, medial orbital, BA 10 | positive      |
| -18,-98,6      | 2.835  | 0.0029947 | 131    | Left calcarine fissure / surrounding cortex, BA 18 | positive      |
| 6,-36,56       | 2.455  | 0.0070484 | 138    | Right paracentral lobule                        | positive      |
| -2,-42,8       | 2.298  | 0.0107808 | 90     | Left anterior cingulate / paracingulate gyri, BA 32 | positive      |
| -2,-42,-22     | 2.094  | 0.0181222 | 26     | Left gyrus rectus, BA 11                        | positive      |
| -2,-46,-26     | 1.726  | 0.0421527 | 1      | Left gyrus rectus, BA 11                        | positive      |
| 10,-52,16      | 1.645  | 0.0049967 | 1      | Corpus callosum                                 | positive      |
| 46,-54,42      | -3.111 | 0.0009324 | 269    | Right inferior parietal (excluding supramarginal and angular) gyri, BA 40 | negative      |
| -48,-22,0      | -3.096 | 0.0009681 | 211    | Corpus callosum                                 | negative      |
| 52,-24,2       | -1.825 | 0.0340229 | 9      | Corpus callosum                                 | negative      |
| -44,-16,-16    | -1.789 | 0.0368080 | 6      | Left inferior network, inferior longitudinal fasciculus | negative      |
### Table 13: SDM: adult

| MNI coordinate | SDM.Z | P       | Voxels | Description                                      | Direction |
|----------------|-------|---------|--------|--------------------------------------------------|-----------|
| 58,-2,-10      | 2.524 | 0.0057985 | 301    | Right superior temporal gyrus, BA 21             | positive  |
| -22,-36,60     | 2.706 | 0.0025855 | 288    | Left postcentral gyrus, BA 3                     | positive  |
| 44,12,-34      | -2.342| 0.0095819 | 84     | Right temporal pole, middle temporal gyrus, BA 20| negative  |
| -38,34,18      | -2.212| 0.0134751 | 30     | Left inferior frontal gyrus, triangular part, BA 45| negative  |
| -44,6,-30      | -1.906| 0.0283524 | 23     | Left middle temporal gyrus, BA 20                | negative  |
| -58,-20,-14    | -1.773| 0.0380803 | 6      | Left middle temporal gyrus, BA 21                | negative  |

### Table 14: SDM: AgedAdult

| MNI coordinate | SDM.Z | P       | Voxels | Description                                      | Direction |
|----------------|-------|---------|--------|--------------------------------------------------|-----------|
| 58,-16,6       | 3.210 | 0.0006627 | 1782   | Right superior temporal gyrus, BA 48             | positive  |
| 54,-60,4       | 3.121 | 0.0000015 | 461    | Right middle temporal gyrus                      | positive  |
| 16,-74,40      | 2.492 | 0.0063471 | 198    | Right precuneus, BA 19                          | positive  |
| 14,-8,-8       | 2.328 | 0.0099603 | 36     | Right cortico-spinal projections                 | positive  |
| -10,42,-20     | 2.097 | 0.0180048 | 29     | Left gyrus rectus, BA 11                         | positive  |
| 36,-44,14      | 1.823 | 0.0341623 | 7      | Right inferior network, inferior longitudinal fasciculus | positive  |
| 42,16,30       | 1.828 | 0.0337837 | 6      | Right inferior frontal gyrus, opercular part, BA 44| positive  |
| -4,-60,38      | 1.683 | 0.0462278 | 2      | Left precuneus                                  | positive  |
| 48,-10,-12     | 1.677 | 0.046785  | 1      | Right superior temporal gyrus, BA 48             | positive  |
| 38,14,28       | 1.659 | 0.0458649 | 1      | Right inferior frontal gyrus, opercular part, BA 48| positive  |
| 50,-16,-10     | 1.646 | 0.0498625 | 1      | Right middle temporal gyrus, BA 48               | positive  |
| -32,-6,12      | -1.738| 0.0411015 | 6      | Left insula, BA 48                              | negative  |
| -32,-10,6      | -1.736| 0.0412629 | 4      | (undefined), BA 48                              | negative  |
| -34,-10,16     | -1.717| 0.0430003 | 3      | Left insula, BA 48                              | negative  |
| -28,-14,10     | -1.691| 0.0454556 | 3      | Left striatum                                   | negative  |

### Table 15: SDM: GM

| MNI coordinate | SDM.Z | P       | Voxels | Description                                      | Direction |
|----------------|-------|---------|--------|--------------------------------------------------|-----------|
| 62,-12,8       | 3.709 | 0.0001041 | 1093   | Right superior temporal gyrus, BA 22             | positive  |
| -4,-90,8       | 2.378 | 0.0087125 | 198    | Left calcarine fissure / surrounding cortex, BA 18| positive  |
| 22,-74,40      | 2.735 | 0.0031158 | 127    | Right superior occipital gyrus, BA 7             | positive  |
| -10,-32,36     | 2.402 | 0.0081576 | 123    | Left median network, cingulum                    | positive  |
| -6,42,-20      | 2.746 | 0.0030164 | 100    | Corpus callosum                                  | positive  |
| 54,-62,4       | 2.426 | 0.0076259 | 58     | Right middle temporal gyrus, BA 37               | positive  |
| 0,-36,54       | 1.807 | 0.0353866 | 5      | Left paracentral lobule                          | positive  |
| -8,-96,2       | 1.655 | 0.0489485 | 1      | Left calcarine fissure / surrounding cortex, BA 17| positive  |
| -4,24,44       | -2.476| 0.0066513 | 41     | Left superior frontal gyrus, medial, BA 8        | negative  |
### Table 16: SDM: WM

| MNI coordinate | SDM.Z | P | Voxels | Description                        | Direction |
|----------------|-------|---|--------|------------------------------------|-----------|
| 62,-14,-18     | 2.769 | 0.0028142 | 586 | Right middle temporal gyrus, BA 21 | positive  |
| -22,-36,60     | 2.695 | 0.0035164 | 258 | Left postcentral gyrus, BA 3       | positive  |
| 10,38,10       | 2.847 | 0.002033  | 142 | Right median network, cingulum     | positive  |
| -14,56,-2      | 2.255 | 0.0120670 | 19  | Corpus callosum                    | positive  |
| 44,-4,-10      | 1.788 | 0.0369088 | 6   | Right superior temporal gyrus      | positive  |
| -50,-16,-14    | -2.681| 0.003704  | 456 | Left middle temporal gyrus, BA 20  | negative  |
| 6,-64,-33      | -2.665| 0.0038518 | 240 | Cerebellum, vermic lobule VIII     | negative  |
| -14,-64,-30    | -3.205| 0.0006742 | 176 | Left inferior frontal gyrus        | negative  |
| 10,38,10       | 2.847 | 0.0022033 | 142 | Right median network, cingulum     | positive  |
| -14,56,-2      | 2.255 | 0.0120670 | 19  | Corpus callosum                    | positive  |
| 44,-4,-10      | 1.788 | 0.0369088 | 6   | Right superior temporal gyrus      | positive  |

### Table 17: ALE report of first 10 clusters

| Cluster Number | Volume mm³ | WC.x | WC.y | WC.z | Extrema value x | y | z | Label                                      |
|----------------|------------|------|------|------|-----------------|---|---|--------------------------------------------|
| 1              | 592        | -43.2| -22.8| 8.1  | 0.007556        | -50.0| -20.0| 8.0 Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 13 |
| 2              | 584        | 44.9 | -21.6| 5.3  | 0.007556        | 44.7 | -22.0| 3.3 Right Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13 |
| 3              | 272        | 41.1 | -25.6| 12.9 | 0.007556        | 42.0 | -25.5| 12.5 Right Cerebrum.Temporal.Lobe.Transverse Temporal Gyrus.Gray Matter.Brodmann area 41 |
| 4              | 256        | 25.1 | -14.7| 4.4  | 0.007331        | 26.0 | -15.0| 21.0 Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen |
| 5              | 240        | 30.5 | -38.4| 16.5 | 0.007340        | 32.0 | -36.0| 16.0 Right Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13 |
| 6              | 192        | 57.5 | -36.3| 23.3 | 0.007112        | 60.0 | -38.0| 24.0 Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 13 |

Anatomic Likelihood Estimation

Fox PT, Lancaster JL. Mapping context and content: the BrainMap model. Nat Rev Neurosci. 2002 Apr;3(4):319-21.

> http://www.brainmap.org/ale/
> http://www.brainmap.org/scribe/

Table 15. ALE report of first 10 clusters: WC: weighted center.

Multi-Level Kernel Density Analysis (mKDA): Wager Methods

https://github.com/canlab/Canlab MKDA MetaAnalysis

Definitions for mKDA

1. Cluster Definitions (KDA documentation of Wager's scripts)
2. Clusters in yellow - these are the clusters that surpass the height-corrected threshold.
Table 18: mKDA report

| Contrast        | Folder              | Height threshold clusters | p<0.001 clusters | p<0.01 clusters | p<0.05 clusters | Description                                                                 |
|-----------------|---------------------|---------------------------|------------------|----------------|----------------|-----------------------------------------------------------------------------|
| Study column in file | currAnalysis_study_contrast | 2                          | 2                | 6              | 0              | Clusters found significant in both hemispheres, but very small               |
| Uniform (all contrasts) | currAnalysis_uniform_contrast | 95                         | 0                | 0              | NA             | NA                                                                          |
| Increase         | currAnalysis_study_increase | 2                          | 0                | 0              | 0              | One cluster in both hemispheres                                            |
| Increase, left   | currAnalysis_study_increase_left | 0                          | 2                | 0              | 0              | One small cluster in the left hemisphere                                    |
| Increase, left, GM | currAnalysis_study_increase_left_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Increase, right  | currAnalysis_study_increase_right | 1                          | 0                | 0              | 0              | Two clusters in the right hemisphere                                        |
| Increase, right, GM | currAnalysis_study_increase_right_GM | 1                          | 0                | 0              | 0              | Two small clusters in the right hemisphere                                  |
| Increase, right, WM | currAnalysis_study_increase_right_WM | 3                          | 0                | 2              | 0              | Multiple clusters in both hemispheres                                       |
| Decrease         | currAnalysis_study_decrease | 1                          | 0                | 0              | 0              | 1 (2?) tiny clusters in left hemisphere                                     |
| Decrease, left   | currAnalysis_study_decrease_left | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Decrease, left, GM | currAnalysis_study_decrease_left_GM | 1                          | 0                | 0              | 0              | Tiny cluster in left hemisphere                                             |
| Decrease, right  | currAnalysis_study_decrease_right | 2                          | 0                | 0              | 0              | Tiny cluster in right hemisphere                                            |
| Decrease, right, GM | currAnalysis_study_decrease_right_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Decrease, right, WM | currAnalysis_study_decrease_right_WM | 1                          | 3                | 1              | 0              | Small clusters in left hemisphere                                           |
| VBM              | currAnalysis_study_vbm | 1                          | 1                | 0              | 0              | Small clusters in left hemisphere                                           |
| GM               | currAnalysis_study_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Increase, GM     | currAnalysis_study_increase_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Decrease, GM     | currAnalysis_study_decrease_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| WM               | currAnalysis_study_WM | 2                          | 0                | 0              | 0              | Cluster in both                                                             |
| Increase, WM     | currAnalysis_study_increase_WM | 3                          | 0                | 2              | 0              | Clusters in both hemispheres                                                |
| Decrease, WM     | currAnalysis_study_decrease_WM | 1                          | 0                | 0              | 0              | Very tiny cluster in left hemisphere                                        |
| Left             | currAnalysis_study_left | 2                          | 0                | 0              | 0              | Clusters in left                                                            |
| Left, GM         | currAnalysis_study_left_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Left, WM         | currAnalysis_study_left_WM | 3                          | 4                | 0              | 0              | Clusters in left                                                            |
| Right            | currAnalysis_study_right | 1                          | 0                | 0              | 0              | Two clusters in the right hemisphere                                        |
| Right, GM        | currAnalysis_study_right_GM | 0                          | 0                | 0              | 0              | No significant clusters found                                               |
| Right, WM        | currAnalysis_study_right_WM | 2                          | 3                | 0              | 0              | Clusters in right                                                           |

3) Clusters in orange - these are incremental clusters that pass the most stringent extent-based threshold (p < .001) that are not within 10 mm of the clusters for the height-based threshold.

4) Clusters in red - these are incremental clusters that pass the medium extent-based threshold (p < .01) that are not within 10 mm of the clusters for the height-corrected and stringent extent-corrected thresholds.

5) Clusters in purple - these are incremental clusters that pass the lenient extent-based threshold (p < .05) that are not within 10 mm of the clusters for the height-corrected, as well as the stringent and medium extent-corrected thresholds.

Table mKDA report: Color of clusters in images: YELLOW, ORANGE, RED and PURPLE

The following cluster definitions used by Wager’s scripts are briefly summarized (see SI for extended analysis). Yellow indicates clusters surpass the height-corrected threshold and orange, red and purple clusters are not within 10 mm of the clusters for the height-corrected. Further, orange indicates clusters pass the most stringent extent-based threshold (p < .001), red indicates clusters that pass the medium extent-based threshold (p < .01) and purple indicates clusters pass the lenient extent-based threshold (p < .05). The primary mKDA analyses were done for acquired and congenital separately and combined. Additional analyses are found in the SI.

Cluster comparisons list

The following mKDA specific analyses were conducted. If no significant clusters were found, no image map was produced.

1. Cluster: Specific ROI cluster analysis
2. Cluster: All MNI Coordinate mapping
3. Cluster: Increase (all increase)
   (a) Cluster: Increase left (all left)
      i. Cluster: Increase left GM
      ii. Cluster: Increase left WM
(b) Cluster: Increase right (all right)
   i. Cluster: Increase right GM
   ii. Cluster: Increase right WM)
4. Cluster: Decrease (all decrease)
   (a) Cluster: Decrease left (all left)
      i. Cluster: Decrease left GM
      ii. Cluster: Decrease left WM)
   (b) Cluster: Decrease right (all right)
      i. Cluster: Decrease right GM
      ii. Cluster: Decrease right WM
5. Cluster: All VBM (only VBM)
6. Cluster: ALL DTI (Only DTI)
7. Cluster: ALL GM (irrespective of increase or decrease)
   (a) Cluster: GM increase
   (b) Cluster: GM decrease
8. Cluster: All WM (irrespective of increase or decrease)
   (a) Cluster: WM increase
   (b) Cluster: WM decrease
9. Cluster: All Left
   (a) Cluster: All left GM (to match regression figure panel)
   (b) Cluster: All left WM (to match regression figure panel)
10. Cluster: All right
    (a) Cluster: All right GM (to match regression figure panel)
    (b) Cluster: All right WM (to match regression figure panel)

The important information for results is contained in the cl variable in the Activation_clusters.mat file. This gives you a variable with 4 fields or cells, and within a cell is information about the regions (clusters/brain blobs) that pass the height threshold (referred to as cl{1}), the p < .001 threshold (referred to as cl{2}), the p < .01 threshold (referred to as cl{3}), and the p < .05 threshold (referred to as cl{4}), respectively.

Cluster mKDA: Specific ROI cluster analysis (currAnalysis study contrast)   Axial
Cluster mKDA: Increase left GM  No significant clusters found. No image map produced.

Cluster mKDA: Increase left WM  Axial

Coronal
Cluster mKDA: Decrease (all decrease)  Axial

Coronal

Cluster mKDA: Decrease left (all left)  No significant clusters found. No image map produced.

Cluster mKDA: Decrease left GM  Axial
Coronal

Cluster mKDA: Decrease left WM  Axial

Coronal
Cluster mKDA: Decrease right (all right) Axial

Cluster mKDA: Decrease right GM No significant clusters found. No image map produced.

Cluster mKDA: Decrease right WM Axial
Cluster mKDA: ALL DTI (Only DTI) Axial

No significant clusters found. No image map produced.

Cluster mKDA: ALL GM (irrespective of increase or decrease)  No significant clusters found. No image map produced.

Cluster mKDA: GM increase  No significant clusters found. No image map produced.

Cluster mKDA: GM decrease  No significant clusters found. No image map produced.
Cluster mKDA: All WM (irrespective of increase or decrease)  Axial

Cluster mKDA: WM increase  Axial

Coronal

Coronal
Cluster mKDA: WM decrease

Axial

Coronal
No significant clusters found. No image map produced.

Cluster mKDA: All left WM (match - regression figure panel)  Axial
Coronal

Cluster mKDA: All Right Axial

Coronal

Cluster mKDA: All right GM (match - regression figure panel) No significant clusters found. No image map produced.
Cluster mKDA: All right WM (match - regression figure panel)  

Axial

Coronal
Studies characteristics

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

Hearing loss vs Age – Fig.2.D
Studies characteristics (Figure 2.E, 2.F)

MRI Measures

- length
- Axial Kurtosis
- Radial Kurtosis
- AK
- MK
- RK
- Surface
- ADC
- GM+WM
- Vol proportion
- ratio GM/WM
- MD
- CT
- RD
- Mean Kurtosis
- asymmetry
- AD
- Thickness
- AD
- asymmetry
- Mean Kurtosis
- RD
- CT
- MD
- ratio GM/WM
- Vol proportion
- GM+WM
- ADC
- Surface
- RK
- MK
- AK
- Radial Kurtosis
- Axial Kurtosis

Frequency

Main Brain Areas

Region of interest: Frequency>5

- temporal
- frontal
- Thalamus
- parietal
- occipital
- insular cortex
- cingulate
- entorhinal
- brainstem
- cerebellum
- tract
- Total Cortex

Frequency

Frequency>5

- Angular gyrus
- dorsolateral prefrontal cortex
- IAC
- inferior parietal
- MGB
- occipital
- planum temporale
- splenium of corpus callosum
- ITG
- IFG
- fusiform gyrus
- anterior cingulate
- occipital
- Hippocampus
- Culmen
- transverse temporal gyrus
- Total Cortex
- supramarginal gyrus
- pars opercularis
- parietal lobe
- Parahippocampal Gyrus
- occipital lobe
- MGB
- LL
- inferior parietal
- IAC
- Angular gyrus
Brain structure (GM, WM) and MRI measures

Highlights
a. Most of the studies that measured Gray matter focus on cortical changes (volume, thickness and VBM).
b. White matter studies are more heterogeneous in their measurements.
c. Diffusion tensor (DT) derived measurements are the most frequent in white matter, followed by volume.
c.1 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

**Bilateral** - GM volume
- WM volume
- WM fractional anisotropy

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

|                  | AD | ADC | AK | asymmetry | Axial Kurtosis | CT | FA | GM+WM |
|------------------|----|-----|----|-----------|----------------|----|----|-------|
| GM               | 0  | 0   | 2  | 9         | 0              | 23 | 8  | 0     |
| WM               | 39 | 6   | 2  | 8         | 3              | 0  | 117| 0     |

|                  | 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     |

|                  | asymmetry | bilateral | left | right | total |
|------------------|-----------|-----------|------|-------|-------|
| GM               | 9         | 59        | 130  | 109   | 2     |
| WM               | 13        | 164       | 91   | 95    | 1     |
Brain structure (GM, WM) and side asymmetry

Matter vs Side

- asymmetry
- bilateral
- left
- right
- total

GM
WM
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

All GM MRI measures vs Age

All WM MRI measures vs 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 |

**WM FA right and Age**

| Age | Treatment effect (standardised mean difference) |
|-----|-----------------------------------------------|
| 20  | -2.0                                          |
| 30  | -1.5                                          |
| 40  | -1.0                                          |
| 50  | -0.5                                          |
| 60  | -0.0                                          |

**GM vol left and Age**

| Age | Treatment effect (standardised mean difference) |
|-----|-----------------------------------------------|
| 20  | 0.0                                           |
| 30  | 0.5                                           |
| 40  | 1.0                                           |
| 50  | 1.5                                           |
| 60  | 2.0                                           |
| 70  | 2.5                                           |

**Diagrams**

- **WM FA right and Age**
- **GM vol left and Age**
Meta-regression

Included variables by Etiology, Brain matter and MRI measure
Meta-regressions of Gray Matter in the Heschl Gyrus

Random effects model no intercept covariated by etiology and age

Table 24: Gray Matter in Heschl Gyrus

| Year & Author | Ptn | Age | Ctl | ROI | Etiology  | Hedge's G [95% CI] | Weights |
|---------------|-----|-----|-----|-----|-----------|--------------------|---------|
| total         |     |     |     |     |           |                    |         |
| 2011-Smith    | 1   | 1.16| HG  | congenital | 8.4% | 0.74 [0.10, 1.39] | 0.74 [0.10, 1.39] |
| right         |     |     |     |     |           |                    |         |
| 2003-Emmorey.2| 29.8 | 8.03 | HG  | congenital | 8.61% | 0.27 [-0.28, 0.83] | 0.27 [-0.28, 0.83] |
| 2003-Penhune.2| 29  | 32  | HG  | congenital | 8.03% | 0.12 [-0.72, 0.98] | 0.12 [-0.72, 0.98] |
| left          |     |     |     |     |           |                    |         |
| 2003-Shibata  | 21  | 25  | HG  | congenital | 8.63% | 2.84 [2.29, 3.38] | 2.84 [2.29, 3.38] |
| 2010-Li       | 14.56 | 8.21% | HG  | congenital | 0.27 [-0.28, 0.83] | 0.27 [-0.28, 0.83] |
| 2000-Emmorey.1| 23.8 | 8.61% | HG  | congenital | 0.36 [-0.20, 0.92] | 0.36 [-0.20, 0.92] |
| 2004-Penhune.1| 29  | 32  | HG  | congenital | 8.03% | 0.20 [-0.64, 1.04] | 0.20 [-0.64, 1.04] |

Acquired

| Year & Author | Ptn | Age | Ctl | ROI | Etiology  | Hedge's G [95% CI] | Weights |
|---------------|-----|-----|-----|-----|-----------|--------------------|---------|
| right         |     |     |     |     |           |                    |         |
| 2018-Uchida.1 | 70.1 | 23.3% | HG  | acquired | 21.38% | 0.03 [-0.07, 0.13] | 0.03 [-0.07, 0.13] |
| 2018-Uchida.3 | 70.1 | 23.58% | HG  | acquired | 6.07 [-0.16, 0.02] | 6.07 [-0.16, 0.02] |
| left          |     |     |     |     |           |                    |         |
| 2018-Uchida.2 | 70.1 | 23.3% | HG  | acquired | 21.38% | -0.00 [-0.10, 0.09] | -0.00 [-0.10, 0.09] |
| 2018-Uchida.4 | 70.1 | 23.56% | HG  | acquired | -0.15 [-0.23, -0.06] | -0.15 [-0.23, -0.06] |

Congenital

| Year & Author | Ptn | Age | Ctl | ROI | Etiology  | Hedge's G [95% CI] | Weights |
|---------------|-----|-----|-----|-----|-----------|--------------------|---------|
| right         |     |     |     |     |           |                    |         |
| 2018-Uchida.1 | 64.38 | 1.63% | HG  | acquired | 21.38% | -0.00 [-0.10, 0.09] | -0.00 [-0.10, 0.09] |
| 2018-Uchida.3 | 64.38 | 1.63% | HG  | acquired | -0.15 [-0.23, -0.06] | -0.15 [-0.23, -0.06] |
| bilateral     |     |     |     |     |           |                    |         |
| 2019-Ponticorvo| 69.14 | 1.64% | HG  | acquired | -0.01 [-0.56, 0.54] | -0.01 [-0.56, 0.54] |
| 2014-Profant.1 | 69.14 | 1.64% | HG  | acquired | -0.00 [-0.57, 0.53] | -0.00 [-0.57, 0.53] |

Hedge's G
Meta-regressions of Gray Matter in Congenital by severity and side (volume and VBM)

Random effects model no intercept covariated by severity and age

Table 25: Congenital Gray Matter by severity

|                           | HedgeG | se      | zval  | ci.lo  | ci.up  | pval      |
|---------------------------|--------|---------|--------|--------|--------|-----------|
| bilateral.profound        | 0.464  | 0.5432  | 0.8541 | -0.6007| 1.529  | 0.393     |
| left.moderate/severe      | -1.376 | 0.3607  | -3.815 | -2.083 | -0.669 | 0.0001363 |
| left.profound             | 0.3106 | 0.3396  | 0.9145 | -0.355 | 0.9761 | 0.3605    |
| left.severe               | 0.2423 | 0.4758  | 0.5092 | -0.6902| 1.175  | 0.6106    |
| left.severe/profound      | 1.371  | 0.61    | 2.248  | 0.1757 | 2.567  | 0.02457   |
| right.moderate/severe     | -1.39  | 0.3783  | -3.675 | -2.132 | -0.6488| 0.0002379 |
| right.profound            | -0.1366| 0.3964  | -0.3446| -0.9136| 0.6404 | 0.7304    |
| right.severe              | -0.1626| 0.462   | -0.352 | -1.068 | 0.7429 | 0.7248    |
| right.severe/profound     | 1.282  | 1.218   | 1.052  | -1.106 | 3.67   | 0.2927    |
| total.severe              | 0.436  | 1.227   | 0.3552 | -1.97  | 2.842  | 0.7225    |
| total.severe/profound     | 0.7545 | 1.213   | 0.622  | -1.623 | 3.132  | 0.5339    |
| Hl.age                    | -0.01079| 0.01055 | -1.023 | -0.03147| 0.009885| 0.3063    |
Congenital - Meta-regressions of Gray Matter Volume

Random effects model no intercept covarated by Big area

Table 26: REM by big area- Congenital - Gray Matter Volume

| Region         | HedgeG  | se      | zval    | ci.lo    | ci.up    | pval   | N   |
|----------------|---------|---------|---------|----------|----------|--------|-----|
| left cerebellum| 0.9013104| 0.3734628| 2.4133872| 0.1693367| 1.6332841| 0.0158050| 11  |
| left cingulate | 1.4999543| 0.9036636| 1.6598593| -0.2711937| 3.2711023| 0.0969428| 2   |
| left frontal   | -0.5879845| 0.4467854| -1.3160334| -1.4636677| 0.2876988| 0.1881628| 8   |
| left insular cortex| 0.0628005| 0.6065046| 0.1035449| -1.1259267| 1.2515276| 0.9175305| 4   |
| left occipital | -0.5251523| 0.4566856| -1.149207| -1.4202396| 0.3699351| 0.2501765| 7   |
| left parietal  | -0.8874850| 0.5149084| -1.7235784| -1.8966869| 0.1217169| 0.0847840| 6   |
| left temporal  | -0.1159681| 0.2235026| -0.5188668| -1.4636677| 0.2876988| 0.1881628| 8   |
| left Thalamus   | 1.2815547| 1.2134567| 1.0561191| -1.0967766| 3.6598861| 0.2909138| 1   |
| right cerebellum| 1.6815703| 0.7283854| 2.3086335| 0.2539651| 3.1091754| 0.1217169| 6   |
| right cingulate | -0.8017506| 1.1929769| -0.6720588| -3.1399424| 1.5364411| 0.5015462| 1   |
| right entorhinal| 0.0586466| 0.6339250| 0.0925119| -1.1838432| 1.3011364| 0.2629134| 4   |
| right frontal  | -2.5593121| 0.7143293| -3.5828186| -3.9591777| -1.1592525| 0.0003399| 3   |
| right insular cortex| -0.1339176| 0.5980210| -0.2239346| -1.3060172| 1.0381821| 0.8228082| 4   |
| right occipital | -1.7301425| 0.8957245| -1.9315566| -3.4857303| 0.0254452| 0.0534413| 2   |
| right parietal | -1.1125014| 0.4445211| -2.5026964| -1.9837468| -0.2412560| 0.0123251| 8   |
| right temporal | -0.5427415| 0.2729266| -1.9885987| -1.0776678| -0.007152| 0.0467455| 20  |

Table 27: Congenital - Gray Matter Volume

| Test                                | Estimates                                      |
|-------------------------------------|-----------------------------------------------|
| Mixed-effect model:                 | k = 114 : $\tau^2 = 1.35$ (SE= 0.22 ) $\Gamma^2= 91.08$ %, $H^2= 11.21$ |
| Residual heterogeneity:             | QE(df= 98 ) = 1048.28 , p.val= 7.0852856562191e-159 |
| Test of moderators (big areas):     | QM(df= 16 ) = 48.63 p.val= 3.78635028624703e-05 |
### Congenital – Gray Matter Volume

| Year & Author | N | ROI | Area | Weights | Hedge's G (95% CI) |
|--------------|---|-----|------|---------|-------------------|
| 2014–Kim.2   | 19 | PFC | frontal | 0.82% | 1.80 [-0.71, 3.90] |
| 2014–Kim.3   | 19 | Cuneus | cerebellum | 0.62% | 1.76 [-0.67, 3.84] |
| 2014–Kim.26  | 22 | Cerebellum | cerebellum | 0.83% | 1.91 [-0.74, 4.56] |
| 2014–Olulade.1 | 22 | Superior temporal gyrus | temporal | 0.92% | 1.12 [-0.58, 3.67] |
| 2005–Emmorey.4 | 50 | STG | temporal | 0.92% | 1.68 [-0.88, 4.48] |
| 2006–Allen.4  | 50 | anterior insula | insular cortex | 0.92% | 0.31 [-0.25, 0.87] |
| 2014–Kim.8   | 50 | insula | temporal | 0.92% | -0.27 [-0.48, 0.83] |
| 2010–Olulade.12 | 60 | postcentral gyrus | insular cortex | 0.92% | 0.26 [-0.30, 0.81] |
| 2010–Olulade.1 | 60 | postcentral gyrus | temporal | 0.92% | 0.34 [-0.26, 0.94] |
| 2014–Xia.4   | 40 | STG | temporal | 0.91% | 0.87 [-0.04, 1.72] |
| 2011–Smith.1 | 40 | prefrontal cortex | frontal | 0.91% | -0.04 [-0.88, 0.80] |
| 2010–Olulade.3 | 40 | temporal lobe | temporal | 0.91% | -0.13 [-0.75, 0.49] |
| 2014–Olulade.11 | 60 | postcentral gyrus | insular cortex | 0.91% | -0.35 [-1.98, 0.27] |
| 2014–Olulade.10 | 60 | insula | parietal | 0.91% | -0.39 [-1.02, 0.34] |
| 2014–Olulade.9 | 60 | insula | parietal | 0.91% | -0.80 [-0.87, -0.03] |
| 2014–Olulade.6 | 60 | insula | temporal | 0.91% | -0.15 [-0.76, 0.47] |
| 2014–Olulade.4 | 60 | insula | temporal | 0.92% | -0.04 [0.88, 0.80] |
| 2010–Li,.4    | 60 | insula | temporal | 0.92% | -0.87 [-0.04, 1.72] |
| 2008–Xia.5    | 50 | insula | temporal | 0.92% | -0.11 [-0.76, 0.47] |
| 2011–Smith.3 | 50 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2010–Li,.8    | 40 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.35   | 22 | insula | insular cortex | 0.92% | -0.07 [-0.16, -0.03] |
| 2010–Li,.2    | 22 | insula | parietal | 0.92% | -0.24 [-0.30, -0.03] |
| 2014–Kim.5    | 22 | insula | parietal | 0.92% | -0.24 [-0.30, -0.03] |
| 2014–Kim.32   | 22 | insula | parietal | 0.92% | -0.40 [-0.32, -0.47] |
| 2014–Kim.36   | 22 | insula | parietal | 0.92% | -0.40 [-0.32, -0.47] |
| 2014–Kim.39   | 22 | insula | parietal | 0.92% | -0.55 [-0.26, -0.59] |
| 2014–Kim.37   | 19 | insula | temporal | 0.92% | -0.72 [-1.27, -0.33] |
| 2014–Kim.10  | 19 | insula | temporal | 0.92% | 0.15 [-0.63, 0.94] |
| 2014–Kim.9    | 19 | insula | temporal | 0.92% | 0.15 [-0.63, 0.94] |
| 2014–Kim.7    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.6    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.5    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.4    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.3    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.2    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.1    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.32   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.36   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.39   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.37   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.10   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.9    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.7    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.6    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.5    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.4    | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2013–Pénicaud.2 | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.15   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |
| 2014–Kim.11   | 19 | insula | temporal | 0.92% | 0.79 [-0.23, 1.70] |

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**Note:** The table above represents the results of a meta-analysis comparing congenital gray matter volume across different studies. The results are presented with weights and Hedge's G values, indicating the magnitude and direction of the effect size. The study includes various ROI (regions of interest) and areas across different cerebellum, transverse temporal gyrus, precentral gyrus, and occipital regions. The data are summarized with statistical significance levels and effect sizes for each comparison. The effect sizes are reported with 95% confidence intervals, providing a measure of the uncertainty around the estimated effect. The table also indicates the number of studies (N) contributing to each comparison.
Acquired - Meta-regressions of Gray Matter by Volume

Random effects model no intercept covariated by Big area

### Table 28: REM by big area - Acquired - Gray Matter Volume

| Location            | HedgeG | se      | zval    | ci.lo  | ci.up  | pval    | N  |
|---------------------|--------|---------|---------|--------|--------|---------|----|
| left cingulate      | -2.8834593 | 1.7275069 | -1.6691449 | -6.269311 | 0.5023920 | 0.0950887 | 1  |
| left frontal        | -1.1400688 | 0.5267737 | -2.1642479 | -2.172526 | -0.1076114 | 0.0304453 | 10 |
| left hypothalamus   | -1.9371568 | 1.6261099 | -1.1912828 | -5.124274 | 1.2499600 | 0.2335426 | 1  |
| left insular cortex | -1.3534702 | 1.6409912 | -0.8247883 | -4.569754 | 1.8628133 | 0.4094918 | 1  |
| left occipital      | -1.3978319 | 1.6417994 | -0.8514023 | -4.615700 | 1.8200359 | 0.3954597 | 1  |
| left parietal       | 0.3896201  | 0.9454302 | 0.4121088 | -1.463389 | 2.2426292 | 0.6802597 | 3  |
| left temporal       | -0.8301541 | 0.6236257 | -1.3311735 | -2.052438 | 0.3921299 | 0.1831319 | 7  |
| right cingulate     | -1.4826100 | 0.9540207 | -1.5540648 | -3.352456 | 0.3873263 | 0.1201690 | 3  |
| right entorhinal    | 0.0070725  | 1.1610972 | 0.0060912 | -2.268636 | 2.2827812 | 0.9951399 | 2  |
| right frontal       | -1.4376558 | 0.7012092 | -2.0502524 | -2.812001 | -0.0633111 | 0.0403398 | 6  |
| right hypothalamus  | -2.0470474 | 1.1513226 | -1.7779663 | -4.303598 | 0.2095035 | 0.0754045 | 2  |
| right insular cortex| -1.5245544 | 1.1626676 | -1.3112555 | -3.803341 | 0.7542323 | 0.1897714 | 2  |
| right occipital     | -1.5236790 | 0.8157812 | -1.8677544 | -3.122581 | 0.0752228 | 0.0617963 | 4  |
| right parietal      | 0.3405078  | 0.9458955 | 0.3598846  | -1.513413 | 2.1944289 | 0.7188586 | 3  |
| right temporal      | 0.7270216  | 0.5141240 | 1.4140977 | -0.280643 | 1.7346863 | 0.1573332 | 10 |

### Table 29: Acquired - Gray Matter Volume

| Test                          | Estimates                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| 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 = 8.0149999705428e-63                       |
| Test of moderators (big areas)| QM(df = 15 ) = 29.35 p.val = 0.014479351188099                            |
Acquired – Gray Matter Volume

Year & Author   N   ROI   Area
right
2018−Pereira−Jorge.8  25  Fusiform gyrus  temporal
2013−Boyen.3  40  STG  temporal
2018−Pereira−Jorge.12  25  Entorhinal gyrus  entorhinal
2016−Pereira−Jorge.2  25  MFG  frontal
2016−Pereira−Jorge.10  25  MTG  temporal
2016−Pereira−Jorge.7  25  Precuneus  parietal
2018−Pereira−Jorge.5  25  Superior parietal gyrus  parietal
2019−Luan.2  25  dorsolateral prefrontal cortex  frontal
2018−Uchida.1  2082  HG  temporal
2018−Uchida.3  2082  HG  temporal
2018−Ren.3  25  cingulate gyrus  cingulate
2013−Boyen.12  40  prefrontal  frontal
2016−Pereira−Jorge.21  25  Lingual gyrus  occipital
2016−Pereira−Jorge.15  25  Superior marginal gyrus  parietal
2016−Pereira−Jorge.33  25  Posterior cingulate cortex  cingulate
2018−Pereira−Jorge.20  25  Lateral occipital gyrus  occipital
2018−Pereira−Jorge.19  25  Parahippocampal gyrus  entorhinal
2018−Pereira−Jorge.13  25  Insula  insular cortex
2018−Pereira−Jorge.24  25  Claustrum  insular cortex
2018−Boyen.5  40  hypothalamus  hypothalamus
2013−Boyen.6  40  occipital lobe  occipital
2013−Boyen.4  40  occipital lobe  occipital
2013−Boyen.10  40  precentral gyrus  frontal
2010−Husain.6  18  STG  temporal
2013−Boyen.8  40  hypothalamus  hypothalamus
2010−Husain.3  18  anterior cingulate  cingulate
2010−Husain.1  18  MFG  frontal
2010−Husain.7  18  MFG  frontal

left
2016−Pereira−Jorge.8  25  Fusiform gyrus  temporal
2018−Pereira−Jorge.1  25  Medial orbitofrontal gyrus  frontal
2016−Pereira−Jorge.6  25  Precuneus  parietal
2018−Pereira−Jorge.4  25  Superior parietal gyrus  parietal
2016−Pereira−Jorge.2  25  MFG  frontal
2018−Uchida.2  2082  HG  temporal
2018−Uchida.4  2082  HG  temporal
2018−Ren.1  25  Superior temporal sulcus  temporal
2013−Boyen.11  40  prefrontal  frontal
2013−Boyen.13  40  orbitofrontal  frontal
2018−Pereira−Jorge.16  25  Superior marginal gyrus  parietal
2018−Pereira−Jorge.17  25  STG  temporal
2013−Boyen.9  40  prefrontal gyrus  frontal
2018−Pereira−Jorge.14  25  Insula  insular cortex
2016−Pereira−Jorge.22  25  Middle occipital gyrus  occipital
2018−Pereira−Jorge.18  25  MTG  temporal
2013−Boyen.7  40  hypothalamus  hypothalamus
2010−Husain.2  18  MFG  frontal
2010−Husain.4  18  SFG  frontal
2010−Husain.10  18  SFG  frontal
2010−Husain.9  18  anterior cingulate  cingulate
2010−Husain.8  18  MFG  frontal

ROI Model for All Studies (Q = 257.10, df = 55, p = 0.000; I² = 98.6%)

RE Model for Subgroup (Q = 387.62, df = 31, p = 0.000; I² = 98.5%)
The diagram shows the relationship between residuals and squared Pearson residuals with theoretical and sample quantiles. The left plot illustrates the standard error with residual values, while the right plot displays the influence on fitted values with squared Pearson residuals. The plots include references to various studies, such as Pereira-Jorge et al. Neural Plast., Ren et al. Front Neurosci., Boyen et al. Hear Res., and Uchida et al. Front Aging Neurosci.
Congenital - White Matter by VOLUME

Random effects model no intercept covaried by Big area

Table 30: REM by big area - Congenital - White Matter Volume

|                      | HedgeG  | se       | zval     | ci_lo    | ci_up    | pval     | N  |
|----------------------|---------|----------|----------|----------|----------|----------|----|
| left cerebellum      | -1.1070810 | 0.6745058 | -1.6413217 | -2.4290881 | 0.2149260 | 0.1007306 | 2  |
| left cingulate       | -1.3786454 | 0.9926110 | -1.3889080 | -3.3241272 | 0.5668365 | 0.1648607 | 1  |
| left frontal         | -1.3402379 | 0.5684006 | -2.3579110 | -2.4542825 | -0.2261933 | 0.0183781 | 3  |
| left insular cortex  | 0.0079129  | 0.5504384 | 0.0143756 | -1.0709265 | 1.0867523 | 0.9885303 | 3  |
| left occipital       | 0.5024402  | 0.4846477 | 1.0367123 | -0.4474518 | 1.4523323 | 0.2998699 | 4  |
| left parietal        | -1.3081390 | 0.6914333 | -1.8919238 | -2.6633233 | 0.0470452 | 0.0585011 | 2  |
| left temporal        | -0.4780484 | 0.2210575 | -2.1625524 | -0.9113131 | -0.0447837 | 0.0305756 | 19 |
| left tract           | -1.3856308 | 0.7930734 | -1.7471658 | -2.9400261 | 0.1687645 | 0.0806086 | 2  |
| right cerebellum     | -1.5134943 | 0.9788737 | -1.5461589 | -3.4320516 | 0.4050629 | 0.1220662 | 1  |
| right forebrain      | -1.3856308 | 1.1215752 | -1.2354328 | -3.5838777 | 0.8126162 | 0.2166695 | 1  |
| right frontal        | -2.3098509 | 0.5696811 | -4.0546382 | -3.4264054 | -1.1932964 | 0.0000502 | 3  |
| right insular cortex | 0.7369857  | 0.5521197 | 1.3348296 | -0.3451490 | 1.8191204 | 0.1819321 | 3  |
| right temporal       | -0.5528945 | 0.2217554 | -2.4932631 | -0.9875270 | -0.1182620 | 0.0126575 | 19|

Table 31: Congenital White Matter Volume

| Test                              | Estimates                                                                 |
|-----------------------------------|---------------------------------------------------------------------------|
| 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= 3.3522027699225e-68                         |
| Test of moderators (big areas):   | QM(df= 13 )= 50.92 p.val= 2.07007590853841e-06                          |
Acquired - White Matter by VOLUME (ONLY BILATERAL)

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

Table 32: REM by big area - Acquired White Matter Volume

| Big Area         | HedgeG  | se      | zval     | ci.lo   | ci.up   | pval   | N |
|------------------|---------|---------|----------|---------|---------|--------|---|
| bilateral frontal| -0.5069 | 0.3500  | -1.448   | -1.1929 | 0.1791  | 0.1476 | 1 |
| bilateral occipital| -0.3876 | 0.3494  | -1.1093  | -1.0725 | 0.2972  | 0.2672 | 1 |
| bilateral parietal| -0.3876 | 0.3494  | -1.1093  | -1.0725 | 0.2972  | 0.2672 | 1 |
| bilateral temporal| -0.0298 | 0.3485  | -0.0855  | -0.7129 | 0.6533  | 0.9318 | 1 |
| bilateral Total Cortex| 0.2239 | 0.2691 | 0.8321 | -0.3035 | 0.7514 | 0.4053 | 2 |

Table 33: acquired White Matter Volume

Test Estimates

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

Acquired White Matter Volume

| Year & Author | N  | ROI     | Area        | Weights | Hedge's G [95% CI] |
|---------------|----|---------|--------------|---------|--------------------|
| bilateral     | 126| Total WM| Total Cortex |         |                    |
| 2014−Lin.1    | 126| Temporal| temporal     | 17.52%  | 0.45 [ 0.09, 0.81] |
| 2014−Lin.3    | 126| Total WM| Total Cortex |         |                    |
| 2018−Chen     | 45 | Total WM| Total Cortex |         |                    |
| 2014−Lin.5    | 126| occipital lobe | occipital | 12.26%  | -0.10 [-0.69, 0.48] |
| 2014−Lin.4    | 126| Parietal | parietal     | 17.55%  | -0.39 [-0.75, -0.03] |
| 2014−Lin.2    | 126| frontal  | frontal      | 17.49%  | -0.51 [-0.87, -0.15] |
| RE Model for Subgroup (Q = 18.10, df = 5, p = 0.00; I^2 = 71.5%) | | | | | -0.16 [-0.46, 0.13] |
| RE Model for All Studies (Q = 18.10, df = 5, p = 0.00; I^2 = 71.5%) | | | | | 100.00% -0.16 [-0.46, 0.13] |

Nothing is significant
Congenital - White Matter by FA fractional anisotropy

Random effects model no intercept covariated by Big area

Table 34: REM by big area - Congenital White Matter FA

| Test Estimates | HedgeG | se     | zval    | ci.lo     | ci.up     | pval    | N  |
|----------------|--------|--------|---------|-----------|-----------|---------|----|
| Mixed-effect model: | k= 44 : tau^2= 0.04 (SE= 0.04 ) I^2= 24.12 %, H^2= 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 |

Table 35: Congenital White Matter FA

| Test Estimates | HedgeG | se     | zval    | ci.lo     | ci.up     | pval    | N  |
|----------------|--------|--------|---------|-----------|-----------|---------|----|
| Mixed-effect model: | k= 44 : tau^2= 0.04 (SE= 0.04 ) I^2= 24.12 %, H^2= 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 |


### Congenital White Matter FA

| Year & Author | N | ROI & Area | Weight | Hedge's G [95% CI] |
|---------------|---|-----------|--------|-----------------|
| **right**     |    |           |        |                 |
| 2009-Wang.6   | 12 | pars opercularis temporal | 1.21%  | -0.16 [-1.29, 0.98] |
| 2004-Chang.2  | 20 | superior olivary nucleus brainstem | 1.78%  | -0.25 [-1.13, 0.63] |
| 2009-Wang.2   | 12 | HG temporal | 1.18%  | -0.48 [-1.63, 0.67] |
| 2012-Liu.1    | 98 | STG temporal | 4.06%  | -0.58 [-1.00, -0.17] |
| 2010-Liu.4    | 44 | optic radiation occipital | 2.73%  | -0.73 [-1.36, -0.09] |
| 2010-Liu.2    | 44 | HG temporal | 2.73%  | -0.73 [-1.36, -0.09] |
| 2018-Benetti.1 | 158 | inferior fronto-occipital fasciculus | I2 = 73.9% |                |
| 2017-Kim.5    | 37 | thalamus | 2.19%  | -0.77 [-1.53, -0.02] |
| 2017-Kim.4    | 37 | internal capsule | 2.02%  | -0.79 [-1.60, 0.01] |
| 2013-Miao.5   | 32 | thalamus | 2.33%  | -0.81 [-1.59, -0.09] |
| 2013-Miao.4   | 32 | external capsule | 2.33%  | -0.81 [-1.59, -0.09] |
| 2014-Hribar.9 | 28 | external capsule | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.8 | 28 | sagittal stratum | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.7 | 28 | posterior thalamic radiation | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.6 | 28 | retrolenticular part of internal capsule | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.5 | 28 | insular cortex | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.4 | 28 | STG | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.3 | 28 | planum temporale | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.2 | 28 | planum polare | 2.13%  | -0.82 [-1.59, -0.04] |
| 2014-Hribar.1 | 28 | HG | 2.13%  | -0.82 [-1.59, -0.04] |
| 2017-Kim.3    | 37 | temporal lobe WM | 2.01%  | -0.82 [-1.63, -0.01] |
| 2017-Kim.1    | 37 | STG | 2.01%  | -0.82 [-1.63, -0.01] |
| 2013-Miao.2   | 32 | STG/HG | 2.32%  | -0.82 [-1.56, -0.10] |
| 2018-Benetti.1 | 2/3 | posterior superior temporal sulcus | 2.14%  | -0.95 [-1.73, -0.18] |
| 2009-Wang.4   | 12 | STG | 1.08%  | -1.00 [-2.22, 0.21] |
| 2018-Zou.2    | 158 | STG | 4.67%  | -1.02 [-2.36, -0.69] |
| 2009-Kim.2    | 42 | superior temporal | 2.33%  | -1.40 [-2.12, -0.68] |
| 2009-Kim.3    | 42 | internal capsule | 2.31%  | -1.45 [-2.18, -0.73] |
| 2009-Kim.4    | 22 | superior longitudinal fasciculus | 2.27%  | -1.55 [-2.29, -0.81] |
| **left**      |    |           |        |                 |
| 2009-Kim.1    | 42 | Bilateral thalamus major | 2.32%  | 1.42 [0.70, 2.15] |
| 2009-Wang.1   | 12 | HG | 1.21%  | 0.11 [-1.02, 1.24] |
| 2004-Chang.1  | 20 | superior olivary nucleus | 1.79%  | -0.02 [-0.89, 0.86] |
| 2009-Wang.3   | 12 | STG | 1.20%  | -0.21 [-1.35, 0.92] |
| 2009-Wang.5   | 12 | pars opercularis | 1.19%  | -0.35 [-1.50, 0.79] |
| 2012-Liu.2    | 98 | HG | 4.08%  | -0.44 [-0.85, -0.02] |
| 2010-Liu.3    | 44 | optic radiation | 2.73%  | -0.73 [-1.36, -0.09] |
| 2010-Liu.1    | 44 | HG | 2.73%  | -0.73 [-1.36, -0.09] |
| 2014-Hribar.11 | 28 | planum temporale | 2.15%  | -0.74 [-1.51, 0.03] |
| 2014-Hribar.10 | 28 | HG | 2.15%  | -0.74 [-1.51, 0.03] |
| 2013-Miao.3   | 32 | STG/HG | 2.33%  | -0.81 [-1.53, -0.09] |
| 2017-Kim.2    | 37 | STG | 2.01%  | -0.82 [-1.63, -0.01] |
| 2013-Miao.1   | 32 | corpus callosum | 2.32%  | -0.83 [-1.55, -0.10] |
| 2018-Zou.1    | 158 | STG | 4.65%  | -1.09 [-1.42, -0.75] |
| 2009-Kim.5    | 42 | anterior thalamic radiation | 2.27%  | -1.55 [-2.29, -0.81] |

RE Model for All Studies (G = 69.00, df = 43, p = 0.01; I2 = 39.0%)
Acquired - White Matter by FA fractional anisotropy (ONLY RIGHT)

Random effects model no intercept covaried by Big area

Table 36: REM by big area - Acquired White Matter FA

| ROI                      | HedgeG | se     | zval    | ci.lo  | ci.up   | p.val   | N  |
|--------------------------|--------|--------|---------|--------|---------|---------|----|
| right frontal            | -1.4804586 | 0.3403176 | -4.350226 | -2.147469 | -0.8134483 | 0.0000136 | 2  |
| right occipital          | -0.9104754 | 0.3603273 | -2.526801 | -1.616704 | -0.2042469 | 0.0115107 | 2  |
| right parietal           | -1.7025869 | 0.4379232 | -3.887866 | -2.560901 | -0.8442731 | 0.0001011 | 1  |
| right temporal           | -1.7933682 | 0.4445829 | -4.038322 | -2.664735 | -0.922018  | 0.000549  | 1  |
| right tract              | -0.8811554 | 0.2271998 | -3.878328 | -1.326459 | -0.4358519 | 0.0001052 | 5  |

Table 37: acquired White Matter FA

| Test Estimates | Mixed-effect model: k = 11 : \( \tau^2 = 0 \) (SE = 0.15) \( \Gamma^2 = 0 \% \), \( H^2 = 1 \)
| 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

acquired White Matter FA

| Year & Author | N | ROI | Area | Weights Hedge's G [95% CI] |
|--------------|---|-----|------|---------------------------|
| right        |   |     |      |                           |
| 2010-Husain.8|  8| Inf. fronto-occipital fasciculus | tract | 8.56%  [-0.80 [-1.79, 0.18]] |
| 2010-Husain.7|  8| Sup. longitudinal fasciculus | tract | 8.48%  [-0.85 [-1.85, 0.14]] |
| 2010-Husain.2|  8| Inf. fronto-occipital fasciculus | tract | 8.47%  [-0.87 [-1.87, 0.12]] |
| 2010-Husain.5|  8| Sup. longitudinal fasciculus | tract | 8.47%  [-0.87 [-1.87, 0.12]] |
| 2010-Husain.4|  8| Sup. Occipital Fasciculus | occipital | 8.38%  [-0.91 [-1.91, 0.09]] |
| 2010-Husain.3|  8| Sup. Occipital Fasciculus, Corticospinal tract | tract | 8.37%  [-0.91 [-1.91, 0.09]] |
| 2010-Husain.1|  8| Inf. fronto-occipital fasciculus | tract | 8.34%  [-0.93 [-1.93, 0.07]] |
| 2016-Ma.1    | 29| Angular gyrus | parietal | 11.34% [-1.70 [-2.56, -0.84]] |
| 2016-Ma.3    | 29| temporal pole | temporal | 11.00% [-1.79 [-2.66, -0.92]] |
| 2016-Ma.2    | 29| Inferior frontal gyrus | frontal | 10.34% [-1.98 [-2.88, -1.08]] |

RE Model for Subgroup (Q = 9.03, df = 10, p = 0.53; \( I^2 = 0.0\% \))
RE Model for All Studies (Q = 9.03, df = 10, p = 0.53; \( I^2 = 0.0\% \))
acquired White Matter FA
Supplementary material: heterogeneity per model

**Heterogeneity: GM volume Right**

| Mean Difference | Standard Error | 1.83 | 0.915 | 0 |
|-----------------|----------------|------|--------|---|

**GM volume Right**

\[ z_i = \frac{y_i}{\sqrt{v_i + \tau^2}} \]

\[ x_i = \frac{1}{\sqrt{v_i + \tau^2}} \]

**Influence on Overall Result**

![Influence on Overall Result](image)

**Squared Pearson Residual**

![Squared Pearson Residual](image)

**Theoretical Quantiles**

![Theoretical Quantiles](image)
Heterogeneity: GM volume Left

\[ z_i = \frac{y_i}{\sqrt{v_i + \tau^2}} \]

\[ x_i = \frac{1}{\sqrt{v_i + \tau^2}} \]
Heterogeneity: WM FA Right

\[ z_i = \frac{y_i}{\sqrt{v_i + \tau^2}} \]

\[ x_i = \frac{1}{\sqrt{v_i + \tau^2}} \]

Squared Pearson Residual

Influence on Overall Result

Sample Quantiles

Theoretical Quantiles
Heterogeneity: WM FA Left

\[ x_i = \frac{1}{\sqrt{v_i + \tau^2}} \]

\[ z_i = \frac{y_i}{\sqrt{v_i + \tau^2}} \]

Influence on Overall Result

Squared Pearson Residual

Sample Quantiles

Theoretical Quantiles
Heterogeney: WM volume Right

\[ z_i = \frac{y_i}{\sqrt{v_i + \tau^2}} \]

\[ x_i = \frac{1}{\sqrt{v_i + \tau^2}} \]
Heterogeney: WM volume Left

$$x_i = 1/v_i + \tau^2$$

$$z_i = \frac{y_i}{\sqrt{v_i + \tau^2}}$$

Influence on Overall Result

Squared Pearson Residual

Theoretical Quantiles

Sample Quantiles
Meta-regressions of Gray Matter Volume & Brain Areas: Random effects model no intercept covarated by Side
### Gray matter Volume – parietal

| Year & Author       | N  | ROI                | Area                        | Weights | Hedge's G [95% CI] |
|--------------------|----|--------------------|-----------------------------|---------|-------------------|
| **right**          |    |                    |                             |         |                   |
| 2011–Smith         | 42 | parietal lobe, angular | parietal                  | 4.62%   | 1.27 [0.59, 1.95] |
| 2018–Pereira–Jorge.4 | 25 | Precuneus          | parietal                    | 4.59%   | 1.16 [0.30, 2.01] |
| 2018–Pereira–Jorge.2 | 22 | Superior parietal gyrus | parietal                  | 4.59%   | 1.14 [0.29, 2.00] |
| 2014–Olulade        | 60 | precuneus          | parietal                    | 4.99%   | −0.85 [−1.38, −0.32] |
| 2014–Kim.11        | 22 | postcentral gyrus  | parietal                    | 4.50%   | −1.22 [−2.14, −0.30] |
| 2018–Pereira–Jorge.5 | 25 | Supramarginal gyrus | parietal                  | 4.56%   | −1.28 [−2.16, −0.41] |
| 2014–Kim.9         | 19 | supramarginal gyrus | parietal                    | 4.34%   | −1.40 [−2.42, −0.37] |
| 2014–Kim.8         | 22 | inferior parietal  | parietal                    | 4.34%   | −1.40 [−2.42, −0.37] |
| 2014–Kim.10        | 19 | precuneus          | parietal                    | 4.43%   | −1.55 [−2.52, −0.59] |
| 2014–Kim.4         | 22 | inferior parietal  | parietal                    | 4.18%   | −1.99 [−3.12, −0.86] |
| 2014–Kim.3         | 19 | postcentral gyrus  | parietal                    | 4.15%   | −2.10 [−3.25, −0.95] |
| **left**           |    |                    |                             |         |                   |
| 2014–Kim.1         | 19 | postcentral gyrus  | parietal                    | 4.31%   | 1.55 [0.50, 2.60]   |
| 2018–Pereira–Jorge.3 | 25 | Precuneus          | parietal                    | 4.59%   | 1.15 [0.30, 2.01]   |
| 2018–Pereira–Jorge.1 | 22 | Superior parietal gyrus | parietal                  | 4.59%   | 1.15 [0.29, 2.00]   |
| 2007–Shibata       | 104 | SMG                | parietal                    | 5.11%   | −0.72 [−1.12, −0.33] |
| 2018–Pereira–Jorge.6 | 25 | Supramarginal gyrus | parietal                  | 4.59%   | −1.13 [−1.99, −0.28] |
| 2014–Kim.7         | 19 | inferior parietal  | parietal                    | 4.34%   | −1.40 [−2.42, −0.37] |
| 2014–Kim.6         | 19 | inferior parietal  | parietal                    | 4.33%   | −1.47 [−2.51, −0.44] |
| 2014–Kim.2         | 19 | precuneus          | parietal                    | 4.30%   | −1.57 [−2.62, −0.52] |
| 2014–Kim.5         | 19 | inferior parietal  | parietal                    | 4.26%   | −1.74 [−2.82, −0.66] |
| **bilateral**      |    |                    |                             |         |                   |
| 2014–Lin           | 126 | Parietal           | parietal                    | 5.14%   | 0.14 [−0.22, 0.50]  |
| 2018–Ren           | 52  | precuneus          | parietal                    | 4.98%   | −0.55 [−1.10, 0.01] |
| **NE Model for All Studies (Q = 157.94, df = 21, p = 0.00; I² = 89.9%)** | | | | 100.00% | −0.55 [−1.06, −0.04] |
Hedge's $G$ (95% CI)

| Year & Author | N  | ROI             | Area           | Weights |
|---------------|----|-----------------|----------------|---------|
| **right**     |    |                 |                |         |
| 2018–Pereira–Jorge.3 | 25  | MFG             | frontal        | −1.34 [−4.47, 1.80] |
| 2019–Luan.2    | 40  | precentral gyrus| frontal        | 3.53% [0.05, 0.57] |
| 2013–Boyen.2   | 40  | precentral gyrus| frontal        | 3.50% [−0.74, −1.35, −0.09] |
| 2010–Li        | 32  | precentral gyrus| frontal        | 3.49% [−0.89, −1.55, −0.22] |
| 2013–Boyen.7   | 22  | precentral gyrus| frontal        | 3.46% [−1.21, −1.97, −0.45] |
| 2010–Husain.2  | 18  | MFG             | frontal        | 3.40% [−1.28, −2.20, −0.35] |
| 2007–Shibata.2 | 104 | perisylvian     | frontal        | 3.13% [−3.43, −4.95, −1.91] |
| 2010–Husain.5  | 18  | MFG             | frontal        | 3.45% [−5.16, −5.97, −4.36] |
| **left**      |    |                 |                |         |
| 2014–Kim.1     | 19  | Orbital Gyrus   | frontal        | −0.91 [−1.72, −0.10] |
| 2011–Smith     | 42  | inferior frontal| frontal        | 2.91% [−6.67, −2.86] |
| 2018–Pereira–Jorge.1 | 40  | prefrontal      | frontal        | 3.56% [−0.50, 0.14, 0.68] |
| 2016–Pereira–Jorge.2 | 25  | MFG             | frontal        | 3.52% [−0.10, 0.06, 0.45] |
| 2007–Shibata.1 | 104 | SFG             | frontal        | −0.91 [−1.72, −0.10] |
| **bilateral** |    |                 |                |         |
| 2014–Lin       | 126 | frontal         | frontal        | 3.56% [0.50, 0.14, 0.68] |
| 2014–Profant   | 54  | SFG             | frontal        | 2.91% [−6.67, −2.86] |
| 2010–Husain.1  | 18  | MFG             | frontal        | −1.34 [−4.47, 1.80] |

RE Model for All Studies (Q = 467.30, df = 29, p = 0.00; $I^2 = 96.5%$)

Gray matter Volume – frontal

RE Model for Subgroup (Q = 180.80, df = 6, p = 0.00; $I^2 = 97.9%$)

RE Model for Subgroup (Q = 214.05, df = 17, p = 0.00; $I^2 = 94.2%$)

RE Model for Subgroup (Q = 29.89, df = 2, p = 0.00; $I^2 = 99.6%$)

RE Model for Subgroup (Q = 180.80, df = 17, p = 0.00; $I^2 = 94.2%$)

RE Model for Subgroup (Q = 214.05, df = 17, p = 0.00; $I^2 = 94.2%$)

RE Model for Subgroup (Q = 29.89, df = 2, p = 0.00; $I^2 = 99.6%$)

RE Model for Subgroup (Q = 180.80, df = 17, p = 0.00; $I^2 = 94.2%$)

RE Model for Subgroup (Q = 214.05, df = 17, p = 0.00; $I^2 = 94.2%$)

RE Model for Subgroup (Q = 29.89, df = 2, p = 0.00; $I^2 = 99.6%$)
### Gray matter Volume – cerebellum

| Year & Author | N | ROI | Area                  | Weights | Hedge’s G [95% CI] |
|--------------|---|-----|-----------------------|---------|-------------------|
| **right**    |    |     |                       |         |                   |
| 2014–Kim.1   | 19 | Culmen | cerebellum            | 6.34%   | 1.75 [0.67, 2.84] |
| 2014–Kim.3   | 22 | Culmen | cerebellum            | 6.68%   | 1.71 [0.72, 2.70] |
| 2010–Li,.1   | 32 | cerebellar hemisphere | cerebellum | 7.36%   | 1.59 [0.79, 2.39] |
| RE Model for Subgroup (Q = 0.06, df = 2, p = 0.97; $I^2 = 0.0\%$) | | | | | 1.07 [0.13, 2.21] |
| **left**     |    |     |                       |         |                   |
| 2014–Kim.4   | 22 | Culmen | cerebellum            | 6.74%   | 1.61 [0.64, 2.59] |
| 2014–Kim.6   | 22 | Declive | cerebellum         | 6.83%   | 1.44 [0.50, 2.39] |
| 2010–Li,.2   | 32 | cerebellar hemisphere | cerebellum | 7.45%   | 1.40 [0.62, 2.18] |
| 2014–Kim.9   | 22 | Culmen | cerebellum            | 6.90%   | 1.30 [0.37, 2.23] |
| 2014–Kim.2   | 22 | Culmen | cerebellum            | 6.90%   | 1.30 [0.37, 2.22] |
| 2014–Kim.5   | 22 | Culmen | cerebellum            | 6.92%   | 1.27 [0.34, 2.19] |
| 2014–Kim.6   | 22 | Culmen | cerebellum            | 6.92%   | 1.26 [0.34, 2.18] |
| 2014–Kim.7   | 22 | Culmen | cerebellum            | 6.95%   | 1.21 [0.30, 2.13] |
| 2010–Li,.3   | 32 | cerebellar hemisphere | cerebellum | 7.52%   | 1.17 [0.42, 1.93] |
| 2014–Olulade.2 | 60 | cerebellum | cerebellum    | 8.27%   | −0.72 [−1.25, −0.20] |
| 2014–Olulade.1 | 60 | cerebellum | cerebellum        | 8.23%   | −0.98 [−1.52, −0.45] |
| RE Model for Subgroup (Q = 80.79, df = 10, p = 0.00; $I^2 = 82.9\%$) | | | | | 0.88 [0.30, 1.46] |
| RE Model for All Studies (Q = 96.30, df = 13, p = 0.00; $I^2 = 80.5\%$) | | | | | 100.00% [1.04, 1.53] |

- RE Model for Subgroup (Q = 80.79, df = 10, p = 0.00; $I^2 = 82.9\%$)
- RE Model for All Studies (Q = 96.30, df = 13, p = 0.00; $I^2 = 80.5\%$)
| Year & Author               | N  | ROI                  | Area       | Weights | Hedge’s G [95% CI]   |
|----------------------------|----|----------------------|------------|---------|----------------------|
| **right**                  |    |                      |            |         |                      |
| 2018–Pereira–Jorge.2       | 25 | Lingual gyrus        | occipital  | 5.72%   | -1.13 [-1.98, -0.27] |
| 2010–Li,.3                 | 32 | occipital            | occipital  | 5.86%   | -1.23 [-1.99, -0.47] |
| 2018–Pereira–Jorge.1       | 25 | lateral occipital gyrus | occipital  | 5.67%   | -1.38 [-2.26, -0.49] |
| 2013–Boyen.2               | 40 | occipital lobe       | occipital  | 5.87%   | -1.79 [-2.53, -1.04] |
| 2013–Boyen.1               | 40 | occipital lobe       | occipital  | 5.87%   | -1.80 [-2.55, -1.05] |
| 2014–Kim                   | 19 | Cuneus               | occipital  | 5.15%   | -2.31 [-3.50, -1.11] |
| RE Model for Subgroup (Q = 256.56, df = 16, p = 0.00; $I^2 = 92.8\%$) |   |                      |            |         | -1.55 [-1.89, -1.21] |
| **left**                   |    |                      |            |         |                      |
| 2007–Shibata               | 104| occipital            | occipital  | 5.97%   | 2.52 [2.01, 3.04]    |
| 2011–Smith                 | 42 | mid–occipital        | occipital  | 5.85%   | -1.27 [-2.03, -0.51] |
| 2014–Olulade               | 60 | lingual gyrus        | occipital  | 6.15%   | -0.87 [-1.40, -0.34] |
| 2010–Li,.2                 | 32 | fusiform gyrus       | occipital  | 5.83%   | -1.39 [-2.17, -0.62] |
| 2010–Li,.1                 | 32 | occipital            | occipital  | 5.67%   | -1.40 [-2.28, -0.51] |
| 2018–Pereira–Jorge.3       | 25 | Middle occipital gyrus | occipital  | 6.07%   | -1.84 [-2.44, -1.24] |
| 2013–Pénicaud.2            | 66 | occipital –V3a/V7    | occipital  | 6.04%   | -2.14 [-2.77, -1.52] |
| 2013–Pénicaud.1            | 66 | occipital –V1/V2     | occipital  |         | -0.64 [-1.78, 0.51]  |
| RE Model for Subgroup (Q = 215.68, df = 7, p = 0.00; $I^2 = 96.0\%$) |   |                      |            |         |                      |
| **bilateral**              |    |                      |            |         |                      |
| 2000–Bavelier              | 20 | V1                   | occipital  | 5.68%   | 0.09 [-0.80, 0.97]   |
| 2014–Profant               | 54 | V1                   | occipital  | 6.31%   | -0.55 [-0.91, -0.18] |
| 2014–Lin                   | 126| occipital lobe       | occipital  |         | -0.38 [-0.70, -0.06] |
| RE Model for Subgroup (Q = 2.14, df = 2, p = 0.34; $I^2 = 12.3\%$) |   |                      |            |         |                      |
| RE Model for All Studies (Q = 256.56, df = 16, p = 0.00; $I^2 = 92.8\%$) |   |                      |            | 100.00% | -0.89 [-1.49, -0.29] |
Gray matter Volume − occipital

\[ x_i = \frac{1}{\sqrt{v_i + \tau^2}} \]

\[ z_i = \frac{y_i}{\sqrt{v_i + \tau^2}} \]

Mean Difference
Standard Error
0.623 0.467 0.311 0.156 0
−3 −2 −1 0 1 2 3
Gray matter Volume − occipital
Theoretical Quantiles
Sample Quantiles

Influence on Overall Result

Shibata DK. Am J
Li, et al. J Clin Rad.1
Li, et al. J Clin Rad.2
Li, et al. J Clin Rad.3
Smith et al. Cereb Cortex
Olulade et al. J Neurosci
Kim et al. Hear Res
Pénicaud et al. Neuroimage.1
Pénicaud et al. Neuroimage.2
Pereira−Jorge et al. Neural Plast.1
Pereira−Jorge et al. Neural Plast.2
Pereira−Jorge et al. Neural Plast.3
Boyen et al. Hear Res.1
Boyen et al. Hear Res.2
Bavelier et al. J Neurosci
Profant et al. Neuroscience
Lin et al. Neuroimage

Squared Pearson Residual

Mean Difference
Standard Error
0.623 0.467 0.311 0.156 0
−3 −2 −1 0 1 2 3
Gray matter Volume − occipital
Theoretical Quantiles
Sample Quantiles

Influence on Overall Result

Shibata DK. Am J
Li, et al. J Clin Rad.1
Li, et al. J Clin Rad.2
Li, et al. J Clin Rad.3
Smith et al. Cereb Cortex
Olulade et al. J Neurosci
Kim et al. Hear Res
Pénicaud et al. Neuroimage.1
Pénicaud et al. Neuroimage.2
Pereira−Jorge et al. Neural Plast.1
Pereira−Jorge et al. Neural Plast.2
Pereira−Jorge et al. Neural Plast.3
Boyen et al. Hear Res.1
Boyen et al. Hear Res.2
Bavelier et al. J Neurosci
Profant et al. Neuroscience
Lin et al. Neuroimage
Gray matter Volume – insular cortex

| Year & Author | N  | ROI          | Area          | Weights | Hedge's G [95% CI] |
|--------------|----|--------------|---------------|---------|-------------------|
| **right**    |    |              |               |         |                   |
| 2008–Allen.4 | 50 | anterior insula | insular cortex | 9.59%   | 0.31 [-0.25, 0.87]|
| 2008–Allen.2 | 50 | insula       | insular cortex | 9.59%   | 0.22 [-0.33, 0.78]|
| 2008–Allen.6 | 50 | posterior insula | insular cortex | 9.60%   | 0.01 [-0.55, 0.56]|
| 2014–Olulade | 60 | claustrum    | insular cortex | 9.64%   | -1.07 [-1.62, -0.53]|
| 2018–Pereira–Jorge.1 | 25 | Insula | insular cortex | 8.29%   | -1.48 [-2.38, -0.59]|
| 2018–Pereira–Jorge.3 | 25 | Claustrum | insular cortex | 8.24%   | -1.57 [-2.48, -0.66]|
|              |    |              |               |         |                   |
| **left**     |    |              |               |         |                   |
| 2008–Allen.5 | 50 | posterior insula | insular cortex | 9.54%   | 0.71 [0.14, 1.29] |
| 2008–Allen.1 | 50 | insula       | insular cortex | 9.56%   | 0.57 [0.01, 1.14] |
| 2008–Allen.3 | 50 | anterior insula | insular cortex | 9.58%   | 0.37 [-0.18, 0.93]|
| 2018–Pereira–Jorge.2 | 25 | Insula | insular cortex | 8.36%   | -1.35 [-2.23, -0.47]|
| 2014–Kim     | 22 | insula       | insular cortex | 8.01%   | -1.58 [-2.54, -0.61]|

RE Model for Subgroup (Q = 30.86, df = 5, p = 0.00; I² = 90.0%)
-0.54 [-1.23, 0.14]

RE Model for Subgroup (Q = 29.88, df = 4, p = 0.00; I² = 85.5%)

RE Model for All Studies (Q = 67.44, df = 10, p = 0.00; I² = 87.4%)
100.00% -0.38 [-0.93, 0.17]

Hedge's G
Mean Difference
Standard Error
0.499 0.374 0.249 0.125 0
−2 −1.5 −1 −0.5 0 0.5 1
Gray matter Volume − insular cortex
Theoretical Quantiles
Sample Quantiles

Gray matter Volume – insular cortex

Influence on Overall Result
Squared Pearson Residual

Allen et al. J Neurosci.1
Allen et al. J Neurosci.2
Allen et al. J Neurosci.3
Allen et al. J Neurosci.4
Allen et al. J Neurosci.5
Allen et al. J Neurosci.6
Kim et al. HR
Pereira–Jorge et al. Neural Plast.1
Pereira–Jorge et al. Neural Plast.2
Pereira–Jorge et al. Neural Plast.3

0.02 0.06 0.10 0.14
0.2 0.4 0.6 0.8 1.0 1.2 1.4
0.0 0.2 0.4 0.6 0.8 1.0 1.2

\[ z_i = \frac{y_i}{\sqrt{V_i + \tau}} \]
Meta-regressions of White Matter FA & Brain Areas: Random effects model no intercept covaried by Side

### White matter FA – tract

| Year & Author | N  | ROI                              | Area                          | Weights | Hedge's G [95% CI] |
|---------------|----|----------------------------------|-------------------------------|---------|-------------------|
| right         |    |                                  |                               |         |                   |
| 2010–Husain.5 | 32 | inferior fronto-occipital fasciculus tract | 4.75% –0.80 [−1.79, 0.18] |         |                   |
| 2013–Miao     | 28 | external capsule tract           | 8.87% –0.81 [−1.53, −0.09]   |         |                   |
| 2014–Hribar.2 | 26 | sagittal stratum tract          | 7.74% –0.82 [−1.59, −0.04]   |         |                   |
| 2014–Hribar.1 | 26 | superior longitudinal fasciculus tract | 7.74% –0.82 [−1.59, −0.04] |         |                   |
| 2010–Husain.4 | 18 | Corticospinal tract              | 4.70% –0.85 [−1.85, 0.14]    |         |                   |
| 2010–Husain.3 | 18 | uncinate fasciculus tract        | 4.65% –0.90 [−1.89, 0.10]    |         |                   |
| 2010–Husain.2 | 18 | superior longitudinal fasciculus tract | 4.62% –0.93 [−1.93, 0.07] |         |                   |
| 2010–Husain.1 | 18 | inferior fronto-occipital fasciculus tract | 4.62% –0.93 [−1.93, 0.07] |         |                   |
| 2009–Kim.1    |    | superior longitudinal fasciculus tract | 8.52% –1.55 [−2.29, −0.81] |         |                   |

RE Model for Subgroup (Q = 3.04, df = 8, p = 0.93; $I^2 = 0.0\%$)

| left          |    |                                  |                               |         |                   |
| 2009–Kim.2    |    | inferior fronto-occipital fasciculus tract | 8.52% –1.55 [−2.29, −0.81] |         |                   |

RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; $I^2 = 0.0\%$)

| bilateral     |    |                                  |                               |         |                   |
| 2018–Park.3   | 41 | uncinate fasciculus tract        | 11.75% –0.62 [−1.25, 0.01]   |         |                   |
| 2018–Park.2   | 41 | superior longitudinal fasciculus tract | 11.75% –0.62 [−1.25, 0.01] |         |                   |
| 2018–Park.1   | 41 | superior longitudinal fasciculus tract | 11.75% –0.62 [−1.25, 0.01] |         |                   |

RE Model for Subgroup (Q = 0.00, df = 2, p = 1.00; $I^2 = 0.0\%$)

RE Model for All Studies (Q = 8.45, df = 12, p = 0.75; $I^2 = 0.0\%$)

### Influence on Overall Result

**Squared Pearson Residual**

| Sample Quantiles | Theoretical Quantiles |
|-----------------|-----------------------|
| 0.00            | 0.00                  |
| 0.10            | 0.10                  |
| 0.20            | 0.20                  |
| 0.30            | 0.30                  |

**Influence on Overall Result**

| Sample Quantiles | Theoretical Quantiles |
|-----------------|-----------------------|
| 0.00            | 0.00                  |
| 0.10            | 0.10                  |
| 0.20            | 0.20                  |
| 0.30            | 0.30                  |

**Sample Quantiles**

- 0.00
- 0.10
- 0.20
- 0.30

**Theoretical Quantiles**

- 0.00
- 0.10
- 0.20
- 0.30
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

| Year & Author | N | ROI | Area | Weights | Hedge’s G [95% CI] |
|--------------|---|-----|------|---------|-------------------|
| **Right**    |   |     |      |         |                   |
| 2004–Chang.2 | Superior olivary nucleus | brainstem | 5.34% | -0.25 [-1.13, 0.63] |
| RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%) |   |     |      |         |                   |
| **Left**     |   |     |      |         |                   |
| 2004–Chang.1 | Superior olivary nucleus | brainstem | 5.34% | -0.02 [-0.89, 0.86] |
| RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%) |   |     |      |         |                   |
| **Bilateral**|   |     |      |         |                   |
| 2016–Wu.3    | 87 | acoustic radiation | brainstem | 5.87% | 2.52 [1.96, 3.09] |
| 2016–Wu.2    | 77 | acoustic radiation | brainstem | 5.87% | 2.12 [1.55, 2.69] |
| 2016–Wu.1    | 66 | acoustic radiation | brainstem | 5.89% | 1.02 [0.47, 1.58] |
| 2014–Profant | 39 | acoustic radiation | brainstem | 5.69% | 0.28 [-0.41, 0.96] |
| 2017–Zheng.8 | 110 | MGB | brainstem | 6.09% | 0.21 [-0.19, 0.60] |
| 2017–Zheng.6 | 110 | TB  | brainstem | 6.09% | 0.03 [-0.36, 0.43] |
| 2017–Zheng.4 | 110 | MGB | brainstem | 6.09% | -0.26 [-0.65, 0.14] |
| 2017–Zheng.3 | 110 | SON | brainstem | 6.09% | -0.30 [-0.69, 0.10] |
| 2017–Zheng.2 | 110 | TB  | brainstem | 6.09% | -0.42 [-0.82, -0.03] |
| 2017–Zheng.7 | 110 | SON | brainstem | 6.08% | -0.62 [-1.02, -0.22] |
| 2015–Huang.3 | 44 | IC  | brainstem | 5.81% | -0.62 [-1.23, -0.01] |
| 2015–Huang.1 | 44 | TB  | brainstem | 5.81% | -0.62 [-1.23, -0.01] |
| 2015–Huang.2 | 44 | SON | brainstem | 5.80% | -0.67 [-1.28, -0.06] |
| 2017–Zheng.5 | 110 | acoustic radiation | brainstem | 6.05% | -1.31 [-1.74, -0.88] |
| 2017–Zheng.1 | 110 | acoustic radiation | brainstem | 6.02% | -1.73 [-2.18, -1.27] |

RE Model for Subgroup (Q = 258.93, df = 16, p = 0.00; I² = 94.6%)
## 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|     | posterior thalamic radiation | Thalamus                  |         | 8.57% –0.82 [−1.59, −0.04] |
| 2014–Hribar.1|     | 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 = 39.55, df = 10, p = 0.00; I² = 68.4%) | | | | | -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; I² = 88.3%) | | | | | −1.22 [−2.05, −0.39] |
| RE Model for All Studies (Q = 29.55, df = 10, p = 0.00; I² = 68.4%) | | | | | 100.00% −1.05 [−1.42, −0.67] |

**Diagram**

- **Hedge’s G**
  - White matter FA – Thalamus
  - Theoretical Quantiles
  - Sample Quantiles
  - Mean Difference
  - Standard Error
  - Influence on Overall Result
  - Squared Pearson Residual
  - Theoretical Quantiles
  - Sample Quantiles
  - Mean Difference
  - Standard Error
  - Influence on Overall Result
  - Squared Pearson Residual

**Equations**

- $z_i = \frac{y_i}{\sqrt{v_i + \tau_2}}$
- $x_i = \frac{1}{\sqrt{v_i + \tau_2}}$

**Tables**

| ROI            | Area                      | Weights | Hedge’s G [95% CI] |
|----------------|---------------------------|---------|-------------------|
| thalamus       | Thalamus                  |         | 8.32% –0.79 [−1.60, 0.01] |
| internal capsule | Thalamus                |         | 8.32% –0.79 [−1.60, 0.01] |
| posterior thalamic radiation | Thalamus              |         | 8.57% –0.82 [−1.59, −0.04] |
| retrolenticular part of internal capsule | Thalamus  |         | 8.57% –0.82 [−1.59, −0.04] |
| internal capsule | Thalamus                |         | 8.94% –1.45 [−2.18, −0.73] |
| MGB            | Thalamus                  |         | 9.95% –0.62 [−1.23, −0.01] |
| AR             | Thalamus                  |         | 9.92% –0.67 [−1.28, −0.06] |
| LL             | Thalamus                  |         | 10.25% –0.71 [−1.28, −0.13] |
| IC             | Thalamus                  |         | 9.91% −1.30 [−1.92, −0.69] |
| IAC            | Thalamus                  |         | 8.27% −2.95 [−3.76, −2.14] |

**Notes**

- RE Model for Subgroup (Q = 26.57, df = 4, p = 0.00; I² = 88.3%)
- RE Model for All Studies (Q = 29.55, df = 10, p = 0.00; I² = 68.4%)
### White matter FA – frontal

| Year & Author | N  | ROI | Area          | Weights | Hedge’s G [95% CI]          |
|--------------|----|-----|---------------|---------|-----------------------------|
|              |    |     |               |         |                             |
| bilateral    |    |     |               |         |                             |
| 2014–Lyness.2 | 26 | precentral gyrus | frontal | 10.46% | 0.48 [−0.30, 1.26]          |
| 2014–Lyness.1 | 26 | frontal | frontal | 10.51% | −0.37 [−1.14, 0.41]        |
| 2017–Zheng.4  | 110| IFG  | frontal      | 15.52% | −0.43 [−0.83, −0.04]       |
| 2017–Zheng.1  | 110| MFG  | frontal      | 15.41% | −0.75 [−1.16, −0.35]       |
| 2017–Zheng.2  | 110| IFG  | frontal      | 15.39% | −0.80 [−1.21, −0.40]       |
| 2017–Zheng.3  | 110| MFG  | frontal      | 15.36% | −0.85 [−1.26, −0.44]       |
| RE Model for Subgroup (Q = 11.26, df = 5, p = 0.05; \(I^2\) = 55.6%) | | | | | −0.55 [−0.85, −0.26] |

RE Model for All Studies (Q = 19.84, df = 7, p = 0.01; \(I^2\) = 73.3%)

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**White matter FA – frontal**

- **Mean Difference**
- **Standard Error**
- **Influence on Overall Result**
- **Squared Pearson Residual**
- **Hedge’s G**
- **Theoretical Quantiles**
- **Sample Quantiles**

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White matter FA – cingulate

| Year & Author | N | ROI | Area | Weights | Hedge’s G [95% CI] |
|--------------|---|-----|------|---------|-------------------|
| **left**     |   |     |      |         |                   |
| 2009–Kim     | 42| Bilateral forceps major | cingulate | 16.06% | 1.42 [0.70, 2.15] |
| 2013–Miao    | 32| corpus callosum         | cingulate | 16.07% | -0.83 [-1.55, -0.10] |
| RE Model for Subgroup (Q = 18.57, df = 5, p = 0.00; I² = 94.6%) | | | | | 0.30 [-1.91, 2.51] |
| **bilateral**|   |     |      |         |                   |
| 2012–Li      | 41| splenium of corpus callosum | cingulate | 18.41% | -0.41 [-0.82, 0.00] |
| 2018–Park    | 41| forceps major           | cingulate | 16.85% | -0.62 [-1.25, 0.01] |
| 2017–Karns   | 41| splenium of corpus callosum | cingulate | 17.25% | -0.64 [-1.22, -0.07] |
| 2017–Kim     | 41| splenium of corpus callosum | cingulate | 15.37% | -0.84 [-1.64, -0.03] |
| RE Model for Subgroup (Q = 1.09, df = 3, p = 0.78; I² = 0.0%) | | | | | -0.56 [-0.83, -0.28] |
| RE Model for All Studies (Q = 27.88, df = 5, p = 0.00; I² = 85.8%) | | | | | 100.00% [-0.32, -0.99, 0.35] |

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Influence on Overall Result
### White matter FA − parietal

| Year & Author | N   | ROI                        | Area          | Weights | Hedge’s G [95% CI] |
|---------------|-----|----------------------------|---------------|---------|--------------------|
| **right**     |     |                            |               |         |                    |
| 2016−Ma       | 29  | Angular gyrus              | parietal      |         | 11.13% −1.70 [−2.56, −0.84] |
| RE Model for Subgroup (Q = 11.32, df = 5, p = 0.05; I² = 56.5%) | | | | | −1.70 [−2.56, −0.84] |
| **bilateral** |     |                            |               |         |                    |
| 2014−Lyness.1 | 26  | postcentral gyrus          | parietal      |         | 11.94% 0.50 [−0.28, 1.28] |
| 2014−Lyness.2 | 26  | parietal lobe              | parietal      |         | 12.05% 0.24 [−0.53, 1.01] |
| 2017−Zheng.1  | 110 | supramarginal gyrus        | parietal      |         | 16.25% 0.00 [−0.39, 0.39] |
| 2017−Zheng.2  | 110 | Angular gyrus              | parietal      |         | 16.24% −0.20 [−0.60, 0.19] |
| 2017−Zheng.3  | 110 | Angular gyrus              | parietal      |         | 16.15% −0.67 [−1.08, −0.27] |
| RE Model for Subgroup (Q = 11.32, df = 5, p = 0.05; I² = 56.5%) | | | | | −0.10 [−0.40, 0.20] |
| RE Model for All Studies (Q = 23.38, df = 6, p = 0.00; I² = 82.0%) | | | | | 100.00% −0.24 [−0.70, 0.21] |

**Theoretical Quantiles vs. Sample Quantiles**

**Squared Pearson Residual vs. Influence on Overall Result**

**Mean Difference vs. Standard Error**

**White matter FA − parietal**

**Hedge’s G**

**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 |    | Sup. Occipital Fasciculus | occipital | 11.55%  | −0.91 [−1.91, 0.09]  |
| 2010–Husain.1 |    | Superior Occipital Fasciculus | Corticospinal tract | 11.55%  | −0.91 [−1.91, 0.09]  |
| **left**      |    |                      |              |         | −0.81 [−1.28, −0.34] |
| 2010–Liu.1    | 44 | optic radiation      | occipital    | 28.71%  | −0.73 [−1.36, −0.09] |
| **bilateral** |    |                      |              |         | −0.73 [−1.36, −0.09] |
| 2014–Lyness   | 26 | occipital            | occipital    | 19.49%  | −0.05 [−0.82, 0.72]  |
| RE Model for All Studies (Q = 2.96, df = 4, p = 0.56; I² = 0.0%) |    |                      |              | 100.00% | −0.64 [−0.98, −0.30] |

**RE Model for Subgroup** (Q = 0.00, df = 0, p = 1.00; I² = 0.0%)

- **Hedge's G**: Calculated for each study with its 95% confidence interval (CI).
- **Weights**: Reflect the contribution of each study to the overall meta-analysis.
- **ROI**: Regions of Interest identified for each study.

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**Influence on Overall Result**

- **Squared Pearson Residual**
- **Influence**

**Theoretical Quantiles vs Sample Quantiles**

- **White matter FA – occipital**
- **Hedge's G**

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Meta-regressions of White Matter Volume & Brain Areas: Random effects model no intercept covariated by Side
### White matter Volume – insular cortex

| Year & Author | N  | ROI          | Area         | Weights | Hedge’s G [95% CI] |
|--------------|----|--------------|--------------|---------|-------------------|
| **right**    |    |              |              |         |                   |
| 2008–Allen.6 | 50 | posterior insula | insular cortex |         | 16.24% 0.88 [0.30, 1.47] |
| 2008–Allen.2 | 50 | insula       | insular cortex |         | 16.35% 0.81 [0.23, 1.38] |
| 2008–Allen.4 | 50 | anterior insula | insular cortex |         | 16.69% 0.52 [-0.04, 1.09] |
| RE Model for Subgroup (Q = 0.86, df = 2, p = 0.65; I² = 0.0%) | | | | | 0.73 [0.40, 1.06] |
| **left**     |    |              |              |         |                   |
| 2008–Allen.5 | 50 | posterior insula | insular cortex |         | 16.88% 0.25 [-0.31, 0.80] |
| 2008–Allen.1 | 50 | insula       | insular cortex |         | 16.94% -0.03 [-0.58, 0.52] |
| 2008–Allen.3 | 50 | anterior insula | insular cortex |         | 16.90% -0.19 [-0.75, 0.36] |
| RE Model for Subgroup (Q = 1.24, df = 2, p = 0.54; I² = 0.0%) | | | | | 0.01 [-0.31, 0.33] |

RE Model for All Studies (Q = 11.60, df = 5, p = 0.04; I² = 57.0%)
## White matter Volume – frontal

| Year & Author | N  | ROI           | Area        | Weights       | Hedge's G [95% CI]    |
|--------------|----|---------------|-------------|---------------|----------------------|
| **right**    |    |               |             |               |                      |
| 2010–Li,3    | 32 | prefrontal cortex | frontal    |               | 14.00% -1.24 [-2.00, -0.48] |
| 2010–Li,1    | 32 | prefrontal cortex | frontal    |               | 13.78% -1.66 [-2.47, -0.85] |
| 2007–Shibata | 104| perisylvian    | frontal    |               | 14.42% -3.95 [-4.62, -3.29] |
| RE Model for Subgroup (Q = 32.91, df = 2, p < 0.00; I² = 93.3%) |    |               |             | -2.30 [-3.96, -0.65] |
| **left**     |    |               |             |               |                      |
| 2010–Li,2    | 32 | prefrontal cortex | frontal    |               | 13.98% -1.29 [-2.06, -0.53] |
| 2009–Kim,2   | 42 | medial frontal | frontal    |               | 14.19% -1.35 [-2.07, -0.63] |
| 2009–Kim,1   | 42 | superior frontal | frontal    |               | 14.18% -1.38 [-2.10, -0.66] |
| RE Model for Subgroup (Q = 0.00, df = 2, p = 0.99; I² = 0.0%) |    |               |             | -1.34 [-1.77, -0.90] |
| **bilateral**|    |               |             |               |                      |
| 2014–Lin     | 126| frontal       | frontal    |               | 15.45% -0.51 [-0.87, -0.15] |
| RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%) |    |               |             | -0.51 [-0.87, -0.15] |
| RE Model for All Studies (Q = 80.40, df = 6, p = 0.00; I² = 91.1%) |    |               |             | 100.00% -1.62 [-2.44, -0.80] |

---

*Figure: Mean difference and sample quantiles for White matter Volume – frontal.*

*Shibata DK. Am J.*

*Lin et al. Neuroimage.*

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*Equation:*

\[
x_i = \frac{1}{N} \sum_{j=1}^{N} x_{ij} - \bar{y}
\]

*Equation:*

\[
z_i = \frac{y_i - \bar{y}}{\sqrt{\tau^2 + 1}}
\]

*Equation:*

\[
\text{Squared Pearson Residual} = (x_i - \bar{x})^2
\]
**White matter Volume – occipital**

| Year & Author | N  | ROI          | Area          | Weights | Hedge’s G [95% CI] |
|---------------|----|--------------|---------------|---------|-------------------|
| left          |    |              |               |         |                   |
| 2007–Shibata  | 104 | occipital    | occipital     |         | 20.00% 3.27 [2.68, 3.86] |
| 2013–Pénicaud | 66  | occipital    | 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; I² = 97.9%) | | | | | 0.46 [-1.73, 2.69] |
| 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; I² = 0.0%) | | | | | -0.39 [-0.75, -0.03] |
| RE Model for All Studies (Q = 161.69, df = 4, p = 0.00; I² = 97.9%) | | | | | 100.00% 0.29 [-1.43, 2.02] |
White matter Volume – occipital

Year & Author | N  | ROI            | Area       | Weights | Hedge's G [95% CI]
---           | ---|-----------------|------------|---------|-------------------
left
2007–Shibata | 104| occipital       | occipital  | 20.50%  | 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; I² = 97.9%)

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; I² = 0.0%)

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

Hedge’s G

White matter Volume – occipital

Squared Pearson Residual

Mean Difference

Influence on Overall Result

White matter Volume – occipital

Theoretical Quantiles

Sample Quantiles
White matter Volume – corpus callosum

| Year & Author | N   | ROI                  | Area                      | Weights | Hedge's G [95% CI] |
|---------------|-----|----------------------|---------------------------|---------|-------------------|
| bilateral     |     |                      |                           |         |                   |
| 2006–Kara.2   |     | corpus callosum (middle area) |                         |         | 25.20% 0.15 [−0.51, 0.60] |
| 2006–Kara.4   |     | corpus callosum (total area) |                         |         | 25.14% −0.20 [−0.85, 0.46] |
| 2006–Kara.1   |     | corpus callosum (anterior area) |                       |         | 24.89% −0.34 [−1.00, 0.32] |
| 2006–Kara.3   |     | corpus callosum (posterior area) |                      |         | 24.78% −0.39 [−1.05, 0.27] |

RE Model for Subgroup (Q = 1.55, df = 3, p = 0.67; I² = 0.0%)

RE Model for All Studies (Q = 1.55, df = 3, p = 0.67; I² = 0.0%)

Theoretical Quantiles
Sample Quantiles

White matter Volume – corpus callosum

Kara et al. J Neurorad.1
Kara et al. J Neurorad.2
Kara et al. J Neurorad.3
Kara et al. J Neurorad.4
Supplementary material: Forest-plots of other Measures

Hesch gyrus FA white matter

**White matter FA and HG**

| Year & Author   | N | ROI | Area     | Weights     | Hedge's G [95% CI]         |
|----------------|---|-----|----------|-------------|---------------------------|
| **right**      |   |     |          |             |                           |
| 2009–Wang.2    | 12| HG  | temporal | 6.48%       | -0.48 [-1.63, 0.67]       |
| 2010–Liu.2     | 44| HG  | temporal | 7.34%       | -0.73 [-1.36, -0.09]      |
| 2014–Hribar.1  | 28| HG  | temporal | 7.14%       | -0.82 [-1.59, -0.04]      |
| RE Model for Subgroup (Q = 2.06, df = 3, p = 0.56; $I^2 = 0.0\%$) |   |     |          | -0.51 [-0.81, -0.21]      |
| **left**       |   |     |          |             |                           |
| 2009–Wang.1    | 12| HG  | temporal | 6.52%       | 0.11 [-1.02, 1.24]        |
| 2010–Liu.1     | 98| HG  | temporal | 7.59%       | -0.44 [-0.85, -0.02]      |
| 2014–Hribar.2  | 44| HG  | temporal | 7.34%       | -0.73 [-1.36, -0.09]      |
| RE Model for Subgroup (Q = 2.06, df = 3, p = 0.56; $I^2 = 0.0\%$) |   |     |          | -0.51 [-0.81, -0.21]      |
| **bilateral**  |   |     |          |             |                           |
| 2014–Profant   | 39| HG  | temporal | 7.27%       | -0.31 [-1.00, 0.37]       |
| 2018–Park      | 41| HG  | temporal | 7.34%       | -0.62 [-1.25, 0.01]       |
| 2015–Huang     | 44| HG  | temporal | 7.37%       | -0.62 [-1.23, -0.01]      |
| 2017–Zheng.2   | 110| HG | temporal  | 7.58%       | -1.12 [-1.54, -0.70]      |
| 2017–Karns     | 49| HG  | temporal | 7.36%       | -1.29 [-1.91, -0.67]      |
| RE Model for Subgroup (Q = 117.94, df = 5, p = 0.00; $I^2 = 97.5\%$) |   |     |          | -1.58 [-3.16, -0.01]      |
| **asymmetry**  |   |     |          |             |                           |
| 2009–Wang.3    | 12| HG  | temporal | 6.52%       | 0.07 [-1.06, 1.20]        |
| RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; $I^2 = 0.0\%$) |   |     |          | 0.07 [-1.06, 1.20]        |

RE Model for All Studies (Q = 138.52, df = 13, p = 0.00; $I^2 = 93.9\%$)
STG Volume White matter

**White matter FA and STG**

| Year & Author | N  | ROI | Area       | Weights | Hedge’s G [95% CI] |
|---------------|----|-----|------------|---------|--------------------|
| **right**     |    |     |            |         |                    |
| 2012–Li       | 98 | STG | temporal   | 8.31%   | −0.58 [−1.00, −0.17]|
| 2014–Hribar   | 28 | STG | temporal   | 6.55%   | −0.82 [−1.59, −0.04]|
| 2017–Kim.1    | 37 | STG | temporal   | 6.38%   | −0.82 [−1.63, −0.01]|
| 2009–Wang.2   | 12 | STG | temporal   | 4.55%   | −1.00 [−2.22, 0.21] |
| 2018–Zou.2    | 158| STG | temporal   | 8.65%   | −1.02 [−1.35, −0.69]|
| **left**      |    |     |            |         |                    |
| 2009–Wang.1   | 12 | STG | temporal   | 4.87%   | −0.21 [−1.35, 0.92] |
| 2017–Kim.2    | 37 | STG | temporal   | 6.38%   | −0.82 [−1.63, −0.01]|
| 2018–Zou.1    | 158| STG | temporal   | 8.64%   | −1.09 [−1.42, −0.75]|
| **bilateral** |    |     |            |         |                    |
| 2016–Wu.2     | 77 | STG | temporal   | 8.06%   | 0.72 [0.25, 1.19]   |
| 2016–Wu.3     | 87 | STG | temporal   | 8.24%   | 0.60 [0.17, 1.03]   |
| 2016–Wu.1     | 66 | STG | temporal   | 7.80%   | 0.10 [−0.42, 0.63]  |
| 2017–Zheng.2  | 110| STG | temporal   | 8.41%   | −0.03 [−0.42, 0.37] |
| 2017–Zheng.1  | 110| STG | temporal   | 8.27%   | −1.21 [−1.63, −0.78]|
| **asymmetry** |    |     |            |         |                    |
| 2009–Wang.3   | 12 | STG | temporal   | 4.88%   | −0.13 [−1.26, 1.00] |
| **RE Model for All Studies** (Q = 96.47, df = 13, p = 0.00; I² = 84.5%) | | | | 100.00% | −0.44 [−0.80, −0.08]|

Hedge’s G
**Measures of White matter Integrity**

**White matter: RD**

| Year & Author | N  | ROI                   | Area                          | Weights | Hedge's G [95% CI] |
|--------------|----|-----------------------|-------------------------------|---------|--------------------|
| **right**    |    |                       |                               |         |                    |
| 2016-Ma.1    | 29 | HG temporal           | temporal                     |         | 3.79% [2.15, 3.08] |
| 2016-Christofferson et al. | | fusiform gyrus right posterior superior temporal sulcus–STG |         |         |                    |
| 2012-U.1     | 98 | STG temporal          | temporal                     |         | 3.99% [1.10, 1.54] |
| 2013-Miao.1  | 32 | corpus callosum       | cingulate                    |         | 3.89% [0.81, 1.53] |
| 2017-Shiell  | 29 | planum temporale      | temporal                     |         | 3.85% [-0.98, -1.75, -0.18] |
| **left**     |    |                       |                               |         |                    |
| 2016-Ma.2    | 29 | inferior frontal gyrus| frontal                      |         | 3.82% [0.97, 2.73] |
| 2012-U.2     | 98 | HG temporal           | temporal                     |         | 3.99% [0.67, 1.54] |
| 2013-Miao.3  | 32 | STG/HG temporal       | temporal                     |         | 3.89% [0.75, 1.47] |
| **bilateral**|    |                       |                               |         |                    |
| 2016-Chinnadurai.2 | 50 | IC Thalamus            | Thalamus                      | 3.07% | [9.65, 11.66] |
| 2016-Chinnadurai.3 | 50 | LL Thalamus            | Thalamus                      | 3.57% | [4.57, 7.17] |
| 2016-Chinnadurai.1 | 50 | JAC Thalamus           | Thalamus                      | 3.68% | [1.67, 3.14] |
| 2014-Lyness.1 | 26 | frontal               | frontal                      | 3.78% | [0.99, 2.88] |
| 2017-Karns.1 | 49 | HG temporal            | temporal                     | 3.93% | [0.49, 1.69] |
| 2014-Lyness.6 | 26 | occipital             | occipital                    | 3.85% | [0.15, 1.78] |
| 2012-U.3     | 98 | HG temporal            | temporal                     | 3.99% | [0.47, 1.32] |
| 2017-Karns.4 | 49 | pSTG temporal          | temporal                     | 3.95% | [0.02, 1.17] |
| 2017-Karns.2 | 49 | STG temporal           | temporal                     | 3.95% | [0.09, 1.05] |
| 2014-Lyness.5 | 26 | parietal lobe         | parietal                     | 3.87% | [0.00, 0.77] |
| 2014-Lyness.4 | 26 | temporal               | temporal                     | 3.87% | [0.00, 0.77] |
| 2014-Lyness.3 | 26 | postcentral gyrus      | parietal                     | 3.87% | [0.00, 0.77] |
| 2014-Lyness.2 | 26 | precentral gyrus       | frontal                      | 3.87% | [0.00, 0.77] |
| 2014-Profant.1 | 39 | acoustic radiation     | brainstem                    | 3.90% | [-0.19, -0.67, -0.49] |
| 2014-Profant.2 | 39 | HG temporal            | temporal                     | 3.90% | [-0.73, -1.43, -0.03] |
| **RE Model for All Studies (Q = 247.85, df = 25, p = 0.00; I² = 96.5%)** | | | | | 100.00% [1.19, 1.91] |

**RE Model for Subgroup (Q = 31.31, df = 6, p = 0.00; I² = 84.5%)**

**RE Model for Subgroup (Q = 31.31, df = 6, p = 0.00; I² = 84.5%)**

**RE Model for Subgroup (Q = 31.31, df = 6, p = 0.00; I² = 84.5%)**
White matter: MD

| Year & Author | N | ROI | Area | Weights | Hedge's G [95% CI] |
|---------------|---|-----|------|---------|-------------------|
| right         |    |     |      |         |                   |
| 2016–Ma.1     | 29 | HG  | temporal | 5.78% | 2.14 [1.22, 3.07] |
| 2017–Shiell   | 28 | planum temporale | temporal | 5.72% | -0.85 [-1.65, -0.06] |
| RE Model for Subgroup (Q = 23.21, df = 1, p = 0.00; I² = 95.7%) | | | | | 0.63 [-2.30, 3.57] |
| left          |    |     |      |         |                   |
| 2016–Ma.2     | 29 | inferior frontal gyrus | frontal | 5.49% | 1.81 [0.93, 2.68] |
| RE Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%) | | | | | 1.81 [0.93, 2.68] |
| bilateral     |    |     |      |         |                   |
| 2014–Lyness.1 | 26 | frontal | frontal | 5.84% | 1.94 [0.99, 2.88] |
| 2014–Lyness.6 | 26 | occipital | occipital | 5.65% | 0.97 [0.15, 1.78] |
| 2014–Lyness.5 | 26 | parietal lobe | parietal | 5.74% | 0.61 [-0.18, 1.40] |
| 2015–Huang.3  | 44 | IC | brainstem | 6.27% | 0.28 [-0.32, 0.88] |
| 2015–Huang.1  | 44 | TB | brainstem | 6.27% | 0.20 [-0.40, 0.79] |
| 2015–Huang.2  | 44 | SON | brainstem | 6.27% | 0.09 [-0.51, 0.68] |
| 2015–Huang.6  | 44 | HG | temporal | 6.28% | 0.00 [-0.59, 0.59] |
| 2015–Huang.5  | 44 | AR | Thalamus | 6.28% | 0.00 [-0.59, 0.59] |
| 2015–Huang.4  | 44 | MGB | Thalamus | 6.28% | 0.00 [-0.59, 0.59] |
| 2014–Lyness.4 | 26 | temporal | temporal | 5.79% | 0.00 [-0.77, 0.77] |
| 2014–Lyness.2 | 26 | precentral gyrus | frontal | 5.79% | 0.00 [-0.77, 0.77] |
| 2014–Profant.1 | 39 | acoustic radiation | brainstem | 6.04% | -0.04 [-0.72, 0.64] |
| 2014–Profant.2 | 39 | HG | temporal | 6.00% | -0.64 [-1.34, 0.06] |
| 2014–Lyness.3 | 26 | postcentral gyrus | parietal | 5.52% | -1.37 [-2.23, -0.51] |
| RE Model for Subgroup (Q = 37.15, df = 1, p = 0.00; I² = 69.6%) | | | | | 0.12 [-0.21, 0.46] |
| RE Model for All Studies (Q = 75.05, df = 16, p = 0.00; I² = 83.4%) | | | | | 100.00% | 0.28 [-0.15, 0.70] |

Hedge's G
White matter: Mean Kurtosis

### WM & Mean Kurtosis

| Year & Author  | N  | ROI       | Area     | Weights | Hedge's G [95% CI] |
|---------------|----|-----------|----------|---------|-------------------|
| bilateral     |     |           |          |         |                   |
| 2017−Zheng.9  | 110| STG       | temporal |         | 3.77%  0.60 [0.20, 1.00] |
| 2017−Zheng.19 | 110| IFG       | frontal  |         | 3.79%  0.38 [-0.01, 0.78] |
| 2017−Zheng.17 | 110| HG        | temporal |         | 3.79%  0.38 [-0.02, 0.78] |
| 2017−Zheng.18 | 110| MFG       | frontal  |         | 3.80%  0.22 [-0.17, 0.62] |
| 2017−Zheng.13 | 110| acoustic radiation | brainstem |         | 3.81%  0.13 [-0.26, 0.52] |
| 2017−Zheng.15 | 110| SON       | brainstem|         | 3.81%  0.05 [-0.35, 0.44] |
| 2017−Zheng.24 | 110| Hippocampus | entorhinal |       | 3.81%  0.00 [-0.39, 0.39] |
| 2017−Zheng.23 | 110| supramarginal gyrus | parietal |         | 3.81%  0.00 [-0.39, 0.39] |
| 2017−Zheng.22 | 110| Angular gyrus | parietal |         | 3.81%  0.00 [-0.39, 0.39] |
| 2017−Zheng.21 | 110| STG       | temporal |         | 3.81%  0.00 [-0.39, 0.39] |
| 2017−Zheng.16 | 110| MGB       | brainstem|         | 3.81% -0.11 [-0.50, 0.29] |
| 2017−Zheng.20 | 110| MTG       | temporal |         | 3.80% -0.20 [-0.59, 0.20] |
| 2017−Zheng.12 | 110| Hippocampus | entorhinal |       | 3.80% -0.32 [-0.71, 0.08] |
| 2017−Zheng.14 | 110| TB        | brainstem|         | 3.79% -0.46 [-0.86, -0.07] |
| 2017−Zheng.4  | 110| MGB       | brainstem|         | 3.79% -0.47 [-0.86, -0.07] |
| 2016−Chinnadurai.1 | 50 | IAC       | Thalamus |         | 3.10% -0.48 [-1.04, 0.08] |
| 2017−Zheng.7  | 110| IFG       | frontal  |         | 3.78% -0.50 [-0.90, -0.10] |
| 2016−Chinnadurai.2 | 50 | IC        | Thalamus |         | 3.09% -0.53 [-1.09, 0.03] |
| 2017−Zheng.8  | 110| MTG       | temporal |         | 3.78% -0.56 [-0.96, -0.16] |
| 2017−Zheng.5  | 110| HG        | temporal |         | 3.78% -0.58 [-0.98, -0.18] |
| 2017−Zheng.1  | 110| acoustic radiation | brainstem |       | 3.78% -0.70 [-1.10, -0.29] |
| 2017−Zheng.3  | 110| SON       | brainstem|         | 3.76% -0.71 [-1.11, -0.30] |
| 2017−Zheng.11 | 110| supramarginal gyrus | parietal |         | 3.76% -0.73 [-1.13, -0.32] |
| 2017−Zheng.6  | 110| MFG       | frontal  |         | 3.76% -0.84 [-1.25, -0.44] |
| 2017−Zheng.2  | 110| TB        | brainstem|         | 3.74% -0.92 [-1.51, -0.34] |
| 2016−Chinnadurai.3 | 50 | LL        | Thalamus |         | 3.01% -1.07 [-1.49, -0.65] |
| 2017−Zheng.10 | 110| Angular gyrus | parietal |         | 3.70% -1.07 [-1.49, -0.65] |

RE Model for Subgroup (Q = 110.59, df = 26, p = 0.00; I² = 76.6%)  
RE Model for All Studies (Q = 110.59, df = 26, p = 0.00; I² = 76.6%)
## White matter: AD

### WM & AD

| Year & Author | N | ROI | Area                                      | Weights | Hedge’s G [95% CI] |
|--------------|---|-----|-------------------------------------------|---------|--------------------|
| **right**    |    |     |                                           |         |                    |
| 2016−Ma.2    | 29 | HG  | temporal                                 | 2.03%   | 2.04 [1.13, 2.95]  |
| 2016−Bennett.1 | 98 | STG | temporal                                 | 2.43%   | 0.65 [0.10, 1.40]  |
| 2016−Bennett.1 | 98 | STG | temporal                                 | 2.47%   | 0.33 [-0.41, 1.00] |
| 2012−Li.1    | 28 | STG | temporal                                 | 3.43%   | -0.15 [-0.55, 0.26]|
| 2017−Shell.1 | 28 | planum temporale | temporal | 2.38%   | -0.45 [-1.22, 0.32]|
| 2014−Hribar.2 | 28 | subcallosal cortex | cingulate | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.1 | 28 | cingulate gyrus anterior division | cingulate | 2.36%   | -0.82 [-1.59, -0.04]|
| RE Model for Subgroup (Q = 33.41, df = 6, p = 0.00; I² = 86.4%) |          |     |                                           |         |                    |
| **left**     |    |     |                                           |         |                    |
| 2012−Li.2    | 98 | HG  | temporal                                 | 3.42%   | 0.39 [-0.02, 0.80]  |
| 2014−Hribar.14 | 28 | SFG | frontal                                  | 2.37%   | -0.77 [-1.54, -0.00]|
| 2014−Hribar.12 | 28 | SFG | frontal                                  | 2.37%   | -0.77 [-1.54, -0.00]|
| 2014−Hribar.8 | 28 | insular cortex | insular cortex | 2.37%   | -0.77 [-1.54, -0.00]|
| 2014−Hribar.23 | 28 | insular cortex | insular cortex | 2.37%   | -0.77 [-1.54, -0.00]|
| 2014−Hribar.22 | 28 | pSGS | cingulate | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.21 | 28 | external capsule | tract | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.20 | 28 | posterior corona radiata | Thalamus | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.19 | 28 | superior corona radiata | Thalamus | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.18 | 28 | superior corona radiata | Thalamus | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.17 | 28 | retrocallosal part of internal capsule | Thalamus | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.16 | 28 | posterior limb of the internal capsule | Thalamus | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.15 | 28 | anterior limb of the internal capsule | Thalamus | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.13 | 28 | Frontal orbital cortex | frontal | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.11 | 28 | Frontal Pole | frontal | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.10 | 28 | Frontal medial cortex | frontal | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.9 | 28 | subcallosal cortex | cingulate | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.7 | 28 | subcallosal cortex | cingulate | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.6 | 28 | STG | temporal                                 | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.5 | 28 | planum polare | temporal | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.4 | 28 | planum temporale | temporal | 2.36%   | -0.82 [-1.59, -0.04]|
| 2014−Hribar.3 | 28 | HG  | temporal                                 | 2.36%   | -0.82 [-1.59, -0.04]|
| **bilateral**|    |     |                                           |         |                    |
| 2017−Karns.1 | 49 | HG  | temporal                                 | 2.95%   | 0.46 [-0.11, 1.03]  |
| 2017−Karns.4 | 49 | HG  | temporal                                 | 2.96%   | 0.32 [-0.25, 0.88]  |
| 2014−Profant.1 | 39 | acoustic radiation | brainstem | 2.62%   | 0.17 [-0.51, 0.85]  |
| 2017−Karns.2 | 49 | pSTG | temporal | 2.97%   | 0.09 [-0.47, 0.65]  |
| 2017−Karns.3 | 49 | pSTG | temporal | 2.97%   | 0.02 [-0.54, 0.56]  |
| 2016−Chinnadurai.2 | 50 | IC | Thalamus | 2.99%   | -0.06 [-0.61, 0.50] |
| 2016−Chinnadurai.3 | 50 | LL | Thalamus | 2.99%   | -0.08 [-0.63, 0.46] |
| 2016−Chinnadurai.1 | 50 | LM | Thalamus | 2.99%   | -0.13 [-0.68, 0.43] |
| 2014−Profant.2 | 39 | HG  | temporal | 2.61%   | -0.34 [-1.02, 0.35] |
| 2016−Li.1 | 98 | STG | temporal | 3.42%   | -0.34 [-0.64, -0.02]|
| RE Model for Subgroup (Q = 9.40, df = 9, p = 0.40; I² = 16.1%) |          |     |                                           |         |                    |

RE Model for All Studies (Q = 103.36, df = 38, p = 0.00; I² = 64.4%)

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

| Year & Author | N  | ROI                  | Area               | Weights | Hedge's G [95% CI] |
|--------------|----|----------------------|--------------------|---------|--------------------|
| **right**    |    |                      |                    |         |                    |
| 2018–Kumar.2 | 100| STG temporal         |                    | 11.01%  | 0.39 [-0.00, 0.79] |
| 2012–Li.2    | 32 | anterior occipital gyrus occipital | 9.15%  | -2.08 [-2.95, -1.21] |
| **left**     |    |                      |                    |         |                    |
| 2018–Kumar.1 | 100| STG temporal         |                    | 11.01%  | 0.39 [-0.00, 0.79] |
| 2014–Hribar  | 28 | HG temporal          |                    | 9.56%   | -0.87 [-1.65, -0.10] |
| 2012–Li.1    | 32 | middle frontal gyrus frontal | 8.94%  | -2.37 [-3.29, -1.45] |
| **bilateral**|    |                      |                    |         |                    |
| 2006–Kara.4  | 39 | corpus callosum genu corpus callosum | 10.09%  | 0.05 [-0.60, 0.70] |
| 2006–Kara.1  |    | corpus callosum (anterior thalamus) corpus callosum | 10.09%  | -0.10 [-0.76, 0.55] |
| 2006–Kara.2  |    | corpus callosum (middle thalamus) corpus callosum | 10.08%  | -0.19 [-0.85, 0.56] |
| 2006–Kara.3  |    | corpus callosum (posterior thalamus) corpus callosum | 10.06%  | -0.37 [-1.03, 0.28] |
| 2006–Kara.5  |    | splenium of corpus callosum corpus callosum | 10.01%  | -0.69 [-1.36, -0.01] |

RE Model for Subgroup (Q = 25.77, df = 1, p = 0.00; $\hat{I}^2 = 96.1\%$)

RE Model for Subgroup (Q = 25.77, df = 1, p = 0.00; $\hat{I}^2 = 96.1\%$)

RE Model for Subgroup (Q = 33.07, df = 2, p = 0.00; $\hat{I}^2 = 93.7\%$)

RE Model for Subgroup (Q = 25.77, df = 1, p = 0.00; $\hat{I}^2 = 96.1\%$)

RE Model for All Studies (Q = 62.54, df = 9, p = 0.00; $\hat{I}^2 = 88.3\%$)

Hedge’s G
### White matter: VBM

#### WM & VBM

| Year & Author     | N  | ROI          | Area                | Weights | Hedge's G [95% CI] |
|------------------|----|--------------|---------------------|---------|-------------------|
| **right**        |    |              |                     |         |                   |
| 2010–Leporé.7    | 30 | MTG          | temporal            | 6.12%   | 0.73 [-0.01, 1.47]|
| 2010–Leporé.4    | 30 | STG          | temporal            | 6.12%   | 0.73 [-0.01, 1.47]|
| 2010–Leporé.1    | 30 | STG          | temporal            | 6.12%   | 0.73 [-0.01, 1.47]|
| 2018–Kumar.2     | 100| STG         | temporal            | 7.03%   | -1.47 [-1.92, -1.03]|
| **left**         |    |              |                     |         |                   |
| 2010–Leporé.6    | 30 | MTG          | temporal            | 6.12%   | 0.73 [-0.01, 1.47]|
| 2010–Leporé.5    | 30 | Intraparietal sulcus | parietal | 6.12% | 0.73 [-0.01, 1.47]|
| 2010–Leporé.3    | 30 | STG          | temporal            | 6.12%   | 0.73 [-0.01, 1.47]|
| 2010–Leporé.2    | 30 | STG          | temporal            | 6.12%   | 0.73 [-0.01, 1.47]|
| 2018–Kumar.1     | 100| STG         | temporal            | 7.00%   | -1.64 [-2.10, -1.19]|
| **bilateral**    |    |              |                     |         |                   |
| 2010–Leporé.13   |    | Splenium of corpus callosum | cingulate | 6.12% | 0.72 [-0.02, 1.46]|
| 2010–Leporé.12   | 30 | temporal lobe | temporal           | 6.13%   | 0.68 [-0.06, 1.42]|
| 2010–Leporé.8    | 30 | frontal lobe | frontal             | 6.14%   | 0.66 [-0.07, 1.40]|
| 2010–Leporé.11   | 30 | parietal lobe | parietal           | 6.16%   | 0.56 [-0.18, 1.29]|
| 2010–Leporé.14   |    | Corpus callosum | cingulate         | 6.18%   | 0.40 [-0.32, 1.13]|
| 2010–Leporé.10   | 30 | occipital lobe | occipital         | 6.19%   | 0.26 [-0.46, 0.98]|
| 2010–Leporé.9    | 30 | Limbic lobe | cingulate           | 6.20%   | 0.01 [-0.71, 0.73]|

**RE Model for Subgroup (Q = 49.03, df = 3, p = 0.00; I² = 91.5%)**

0.15 [-0.97, 1.27]

**RE Model for Subgroup (Q = 62.80, df = 4, p = 0.00; I² = 90.6%)**

0.23 [-0.75, 1.20]

**RE Model for Subgroup (Q = 49.03, df = 3, p = 0.00; I² = 91.5%)**

0.15 [-0.97, 1.27]

**RE Model for Subgroup (Q = 62.80, df = 4, p = 0.00; I² = 90.6%)**

0.23 [-0.75, 1.20]

**RE Model for Subgroup (Q = 3.03, df = 6, p = 0.81; I² = 0%)**

0.46 [0.19, 0.74]

**RE Model for All Studies (Q = 132.56, df = 15, p = 0.00; I² = 82.9%)**

100.00% 0.30 [-0.11, 0.71]

![Hedge's G](image)