

SUPPLEMENTARY MATERIAL

Blunted brain responses to neutral faces in healthy first-degree relatives of patients with schizophrenia: an image-based fMRI meta-analysis

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Supplementary Methods

Literature search

PubMed search employed a combination of the following keywords: (“schizophren*” OR “psychosis”) AND (“relatives” OR “first-degree” OR “siblings” OR “twins” OR “brothers” OR “sisters” OR “offspring” OR “parents” OR “genetic risk”) AND (“neuroimaging” OR “fMRI” OR “functional Magnetic Resonance Imaging”) AND (“emotion*” OR “affect” OR “mood” OR “face” OR “facial”).

Web of Science review was based on the following keywords: TS=(schizophren* OR psychosis) AND TS=(relatives OR first-degree OR siblings OR twins OR brothers OR sisters OR offspring OR parents OR genetic risk) AND TS=(neuroimaging OR fMRI OR functional magnetic resonance) AND TS=(emotion* OR affect* OR mood OR face OR facial).

Study exclusion

50 studies were excluded due to the following reasons:

- 12 studies did not include neutral faces^{1–12}
- 11 studies used non-relevant task design (1 structural magnetic resonance imaging¹³, 2 non-visual stimuli^{14,15}, 2 resting state^{16,17}, 6 studies employed scenes or stories instead of faces^{18–23})
- 7 were conference abstracts^{24–30}
- 7 studies employed the same dataset as in another included study^{31–37}
- 6 studies were systematic reviews or meta-analyses^{38–43}
- 6 study did not include a group of first-degree relatives^{44–49}
- 1 study was a method paper⁵⁰

Sensitivity analysis combining image- and coordinate-based meta-analysis

In order to assess the robustness of our image-based meta-analytic results, we performed a sensitivity analysis wherein we added 2 studies reporting brain coordinates. The SDM methodology allows to conduct such meta-analyses that combines 3D statistical images and peak coordinates by leveraging its ability to reconstruct 3D statistical maps from image coordinates. This involves converting t-values of peak coordinates into effect sizes and gradually imputing effect sizes for surrounding voxels, considering proximity to peaks and accounting for estimation inaccuracies through multiple imputations^{51,52}.

Table S1. Quality assessment checklist adapted from Zheng et al., 2018⁵³. For each study and each item, a score of 0/0.5/1 is assigned (0 if criteria not met, 0.5 if partially met, 1 if clearly met). Total score is 12 out of 12.

Category 1: Sample characteristics
Patients were evaluated with specific standardized diagnostic criteria
Important demographic data (age, gender, and education) were reported with mean (or median) and standard deviations (or range))
Healthy comparison subjects were evaluated to exclude psychiatric and medical illnesses
Important clinical variables were reported with mean (or median) and standard deviations (or range))
Sample size per group > 10
Category 2: Methodology and reporting
Whole brain analysis was automated with no a-priori regional selection
Magnet strength at least 1.5T
Whole brain coverage of fMRI scans
The acquisition and preprocessing techniques were clearly described so that they could be reproduced
Coordinates reported in a standard space
Significant results are reported after correction for multiple testing using a standard statistical procedure (FDR, FWE or permutation-based methods)
Conclusions were consistent with the results obtained and the limitations were discussed

Table S2. Main objective and main results of the included studies

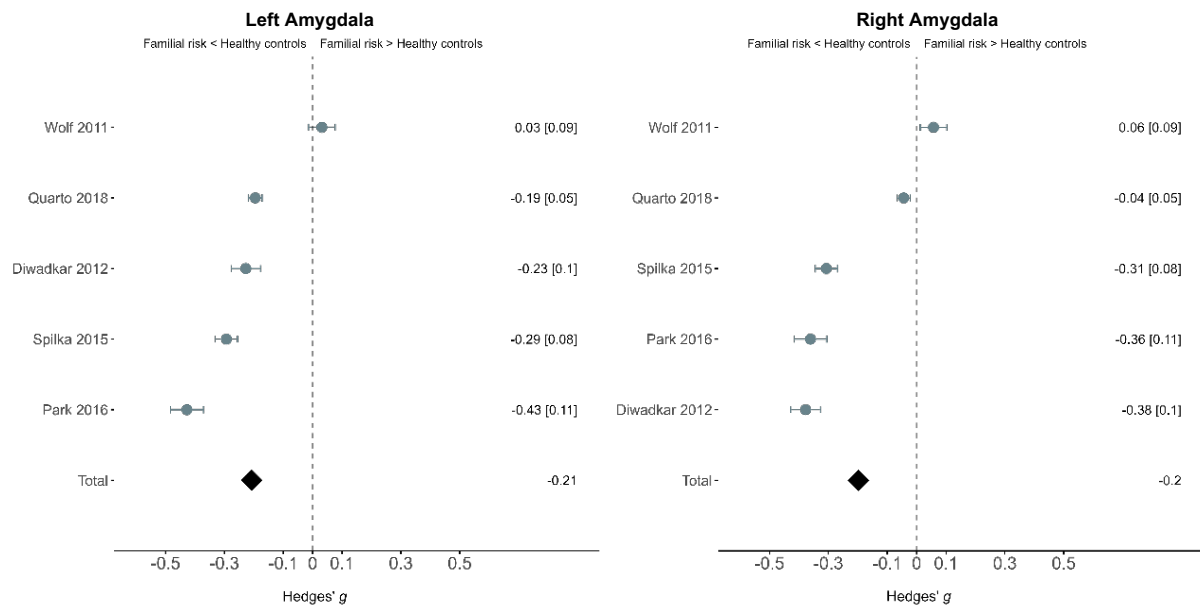
Reference	Main objective	Main results	Quality score
Diwadkar et al., 2012 ⁵⁴	To investigate effective brain connectivity associated with emotional processing in schizophrenia	Abnormal connectivity during emotion processing in offspring of patients with schizophrenia	11
Oertel et al., 2019 ⁵⁵	To investigate associative memory in schizophrenia	Abnormal brain activity during retrieval in patients with schizophrenia and to a lesser degree in first-degree relatives	12
Park et al., 2016 ⁵⁶	To investigate implicit emotion processing in schizophrenia	Abnormal brain activity to fearful and neutral faces in first-degree relatives	11
Pirnia et al., 2015 ⁵⁷	To investigate associative memory in schizophrenia	Abnormal brain activity to successful encoding in patients with schizophrenia	11.5
Quarto et al., 2018 ⁵⁸	To investigate effective brain connectivity associated with emotional processing in schizophrenia	Abnormal connectivity during emotion processing in both schizophrenia patients and first-degree relatives	11.5
Spilka et al., 2015 ⁵⁹	To investigate implicit emotion processing in schizophrenia	Abnormal brain activity to emotions in first-degree relatives and patients with schizophrenia.	11.5
Wolf et al., 2011 ⁶⁰	To identify and modulate emotion processing in schizophrenia	Abnormal brain activity to emotion identification induced by GABAergic modulation in first-degree relatives	11

Table S3. MNI coordinates of within-group meta-analysis. We employed the Hammersmith brain atlas (n30r83, © Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved⁶¹) in order to determine the name of brain structures.

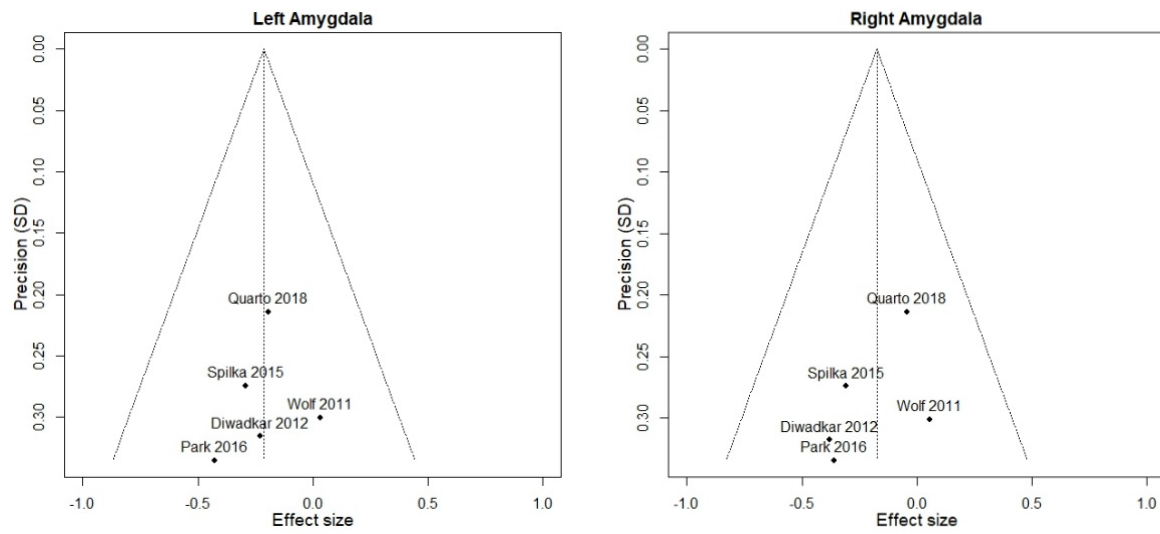
Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
<i>Healthy controls - Activations</i>			
Amygdala	Left	-22, -3, -16	4.5863
Amygdala	Right	22, -3, -14	4.4872
Insula	Left	-32, 4, -10	5.2278
Insula	Right	32, 4, -4	4.8726
Putamen	Left	-22, 8, 6	5.4896
Putamen	Right	26, 7, -2	5.7281
Occipital lobe (Fusiform Face Area)	Left	-44, -81, -5	4.0052
Occipital lobe (Fusiform Face Area)	Right	42, -86, -8	3.93463
<i>Healthy controls - Deactivations</i>			
Posterior cingulate gyrus	Left	-4, -31, 26	3.9956
Posterior cingulate gyrus	Right	6, -33, 28	3.9061
Superior parietal gyrus	Left	-12, -61, 44	3.3147
Superior parietal gyrus	Right	12, -70, 40	3.6446
Occipital lobe	Left	-30, -82, 24	3.7414
Occipital lobe	Right	40, -84, 24	3.3893
Pre-subgenual frontal cortex	Left	-10, 26, -12	4.4617
Pre-subgenual frontal cortex	Right	8, 28, -10	4.6346
<i>First-degree relatives - Deactivations</i>			
Superior temporal gyrus	Left	-64, -23, 4	3.7838
Superior temporal gyrus	Right	59, -28, 8	5.0942
Middle inferior temporal gyrus	Left	-54, -12, -16	2.5841
Middle inferior temporal gyrus	Right	54, -20, -16	4.0745
Precentral gyrus	Left	-11, -32, 66	3.3799
Precentral gyrus	Right	2, -28, 66	3.6165
Postcentral gyrus	Left	-14, -32, 68	3.5393
Postcentral gyrus	Right	34, -32, 52	3.6572
Subgenual frontal cortex	Left	1, 22, -12	3.5019
Subgenual frontal cortex	Right	-12, 22, -14	3.4752
Parahippocampal gyrus	Left	-22, -30, -22	4.4278
Parahippocampal gyrus	Right	34, -21, -22	3.3432

Table S4. MNI coordinates of between-group meta-analysis. We employed the Hammersmith brain atlas (n30r83, © Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved⁶¹) in order to determine the name of brain structures.

Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
<i>First-degree relatives < Healthy controls</i>			
Hippocampus	Left	-26, -22, -12	-2.8437
Parahippocampal gyrus	Left	-20, -18, -20	-2.8497
Hippocampus	Right	28, -12, -16	-3.141
Insula	Left	-40, -10, 8	-3.96045
Insula	Right	64, 20, -4	-2.423
Putamen	Left	-17, 4, -9	-2.60312
Amygdala	Right	28, 0, -26	-2.8438
Amygdala	Left	-22, -4, -24	-2.18346
Inferior lateral parietal lobe	Left	-46, -52, 28	-2.6742
Inferior lateral parietal lobe	Right	52, -27, 39	-2.10457
Superior parietal gyrus	Right	8, -52, 68	-3.47912
Superior parietal gyrus	Left	-22, -52, 62	-2.34547
Cerebellum	Left	-18, -48, -32	-2.85079
Cerebellum	Right	16, -36, -34	-2.2929
Inferior frontal gyrus	Right	52, 22, 12	-2.36139
Precentral gyrus	Right	2, -24, 68	-3.25278
Precentral gyrus	Left	-16, -24, 74	-2.70431
Postcentral gyrus	Left	-10, -30, 76	-2.79808
Postcentral gyrus	Right	8, -31, 76	-2.76954
Posterior cingulate gyrus	Left	-10, -22, 40	-2.41395
Posterior cingulate gyrus	Right	10, -7, 42	-2.37083

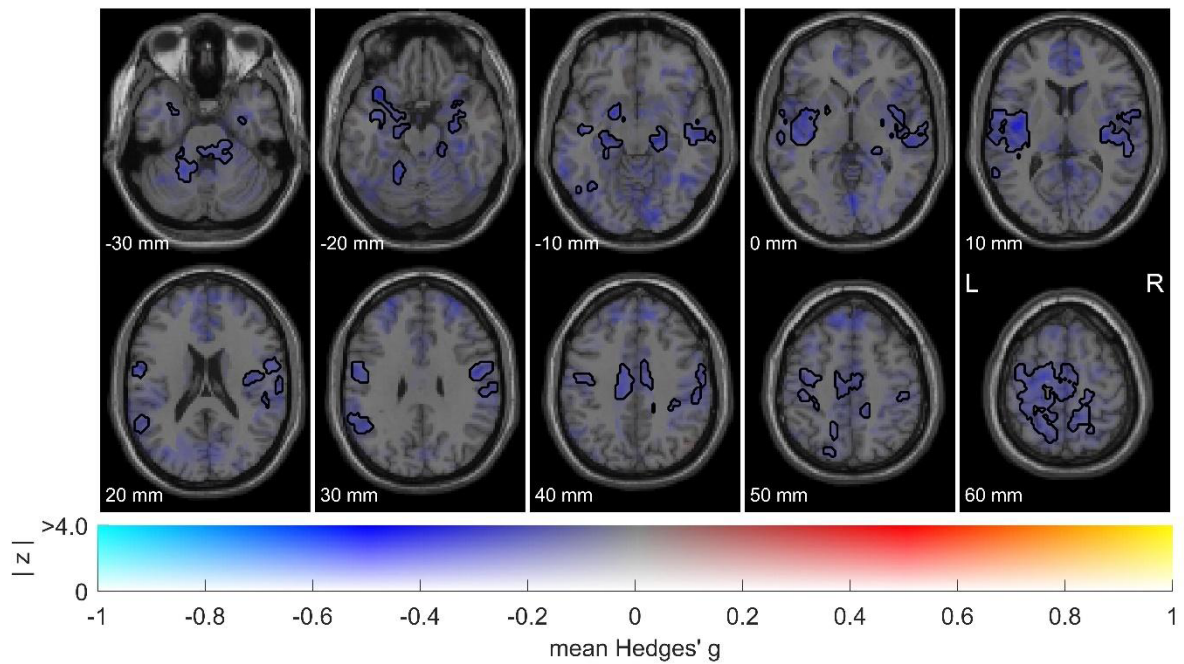


Supplementary Figure S1. Forest plots depicting the mean $\pm$ variance of effect sizes for group comparison in the left and right amygdala (defined using the Melbourne Subcortex Atlas⁶²). The black diamonds represent the overall effect size.



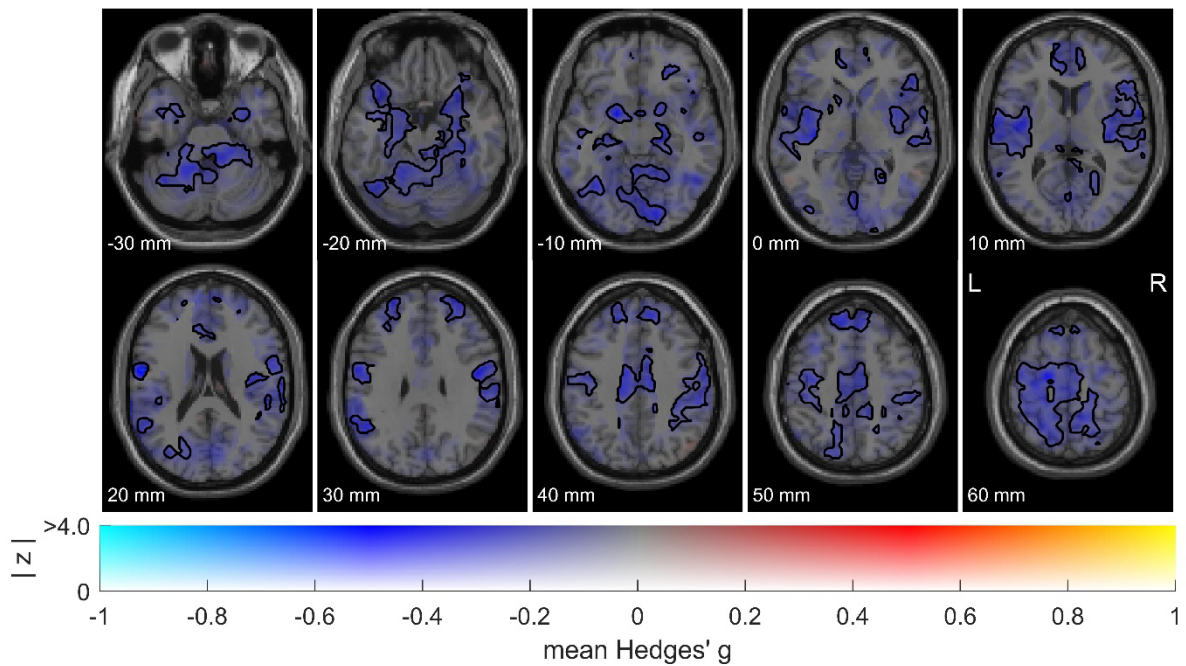
Supplementary Figure S2. Funnel plots in left and right amygdala. The symmetrical distribution of studies suggests no evidence for publication bias.

First-degree relatives > Healthy controls



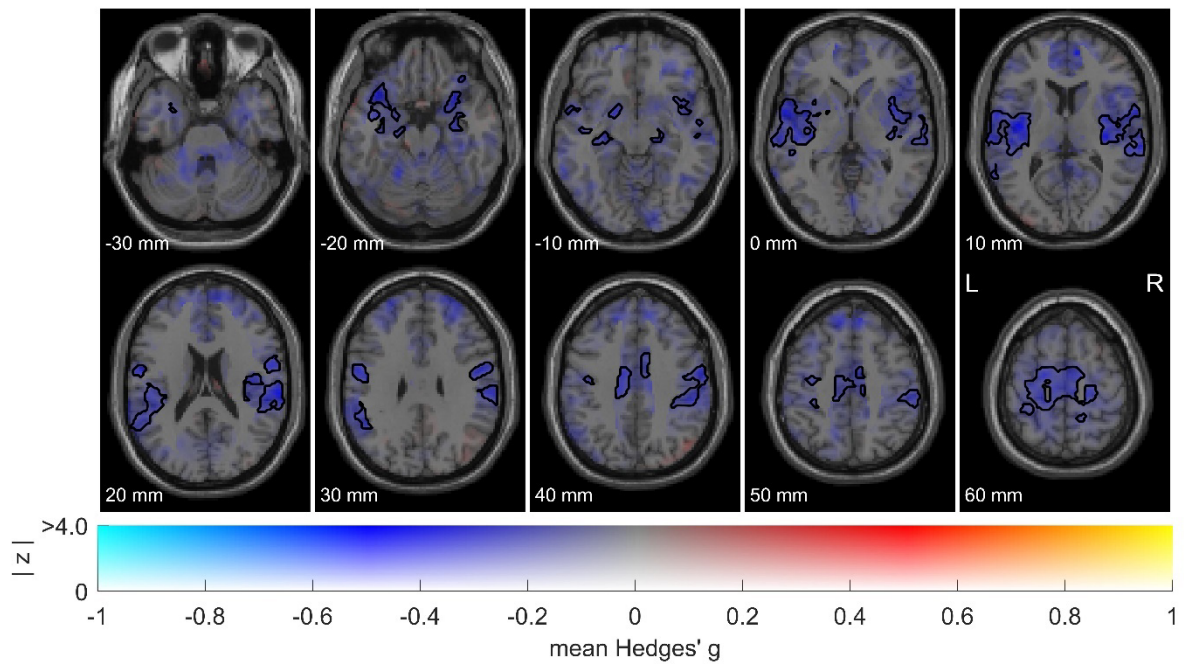
Supplementary Figure S3. Combined image- and coordinate-based between-group meta-analysis of functional neuroimaging studies investigating brain responses to neutral faces in healthy first-degree relatives of patients with schizophrenia versus healthy controls ($n = 7$ studies; 157 first-degree relatives and 207 healthy controls). *These are dual-coded images^{63,64} in which color represents mean Hedges' g (brain regions showing activations are depicted in red while deactivations are depicted in blue), and transparency represents z -values. Black line contours denote significant (de-)activations at $p_{TFCE} < 0.05$.*

First-degree relatives > Healthy controls



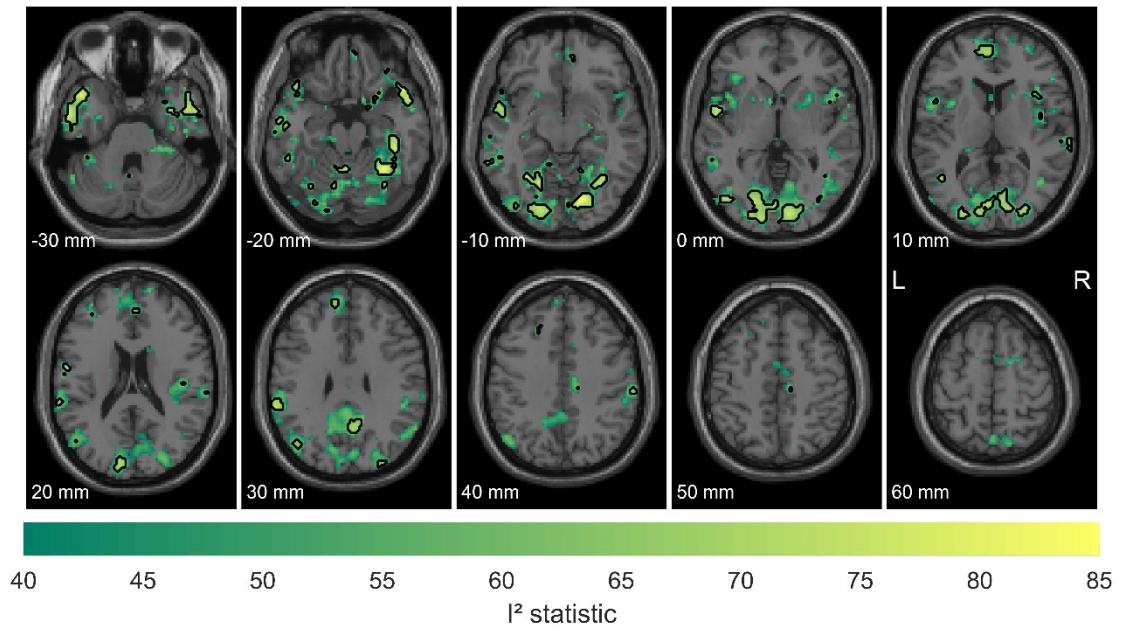
Supplementary Figure S4. Meta-analysis without studies with partial brain coverage (1 study excluded⁶⁰, n = 4 studies; 100 first-degree relatives and 125 healthy controls). These are dual-coded images^{63,64} in which color represents mean Hedges' g (brain regions showing activations are depicted in red while deactivations are depicted in blue), and transparency represents z-values. Black line contours denote significant (de-)activations at $p_{TFCE} < 0.05$.

First-degree relatives > Healthy controls



Supplementary Figure S5. Meta-analysis (with mean age and quality of the study as covariates) of functional neuroimaging studies investigating brain responses to neutral faces in healthy first-degree relatives of patients with schizophrenia versus healthy controls ($n = 5$ studies; 120 first-degree relatives and 150 healthy controls). These are dual-coded images^{63,64} in which color represents mean Hedges' g (brain regions showing activations are depicted in red while deactivations are depicted in blue), and transparency represents z -values. Black line contours denote significant (de-)activations at $p_{TFCE} < 0.05$.

First-degree relatives > Healthy controls



Supplementary Figure S6. Whole-brain heterogeneity map. Heterogeneity map displaying for each voxel the I^2 statistic. Since an I^2 statistic lower than 40% is commonly interpreted as low heterogeneity⁶⁵, the map was thresholded at $I^2 > 40\%$. Black line contours denote clusters showing at least substantial heterogeneity ($I^2 > 60\%$).

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