

Appendix 1 to Gao X, Zhang W, Yao L, et al. Association between structural and functional brain alterations in drug-free patients with schizophrenia: a multimodal meta-analysis. *J Psychiatry Neurosci* 2017.

DOI: 10.1503/jpn.160219

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Table S1

Imaging Methodology Quality Assessment Checklist

Category 1: Subjects

1. Patients were evaluated prospectively, specific diagnostic criteria were applied, and demographic data was reported
2. Healthy comparison subjects were evaluated prospectively, psychiatric and medical illnesses were excluded, and demographic data was reported
3. Important variables (e.g. illness duration, severity of illness, drug status, non-drug therapy status) were checked either by stratification or statistically
4. Sample size per group > 10, and no significant difference in age and sex existed

Category 2: Methods for image acquisition and analysis

5. Magnet strength at least 1.5T
 6. Whole brain analysis was automated with no a-priori regional selection
-

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7. Coordinates reported in a standard space

8. The imaging technique used was clearly described so as it could be reproduced

9. Measurements were clearly described so that they could be reproduced

10. Results have been corrected for multiple comparison

Category 3: Results and conclusions

11. Statistical parameters for significant and important non-significant differences were provided

12. Conclusions were consistent with the results obtained and the limitations were discussed

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Table S2

Meta-analysis results of structural MRI

| | MNI | SDM-Z | P | Voxels | Cluster breakdown (number of voxels) |
|-----------------------------------------------------------------------|-------------|--------|-------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Cluster of decreased gray matter volume (patients<controls) | | | | | |
| Left fusiform gyrus | -26,-54,-16 | -2.584 | 0.000154853 | 771 | Left fusiform gyrus (382) Left cerebellum, hemispheric lobule VI (182) Left parahippocampal gyrus (21) Left hippocampus (15) |
| Left inferior frontal gyrus | -46,16,0 | -2.497 | 0.00023222 | 649 | Left inferior frontal gyrus (314) Left insula (166) |

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| | | | | | |
|-------------------------------|------------|--------|-------------|-----|---------------------------------------------------|
| | | | | | Left temporal pole, superior temporal gyrus (106) |
| Right superior temporal gyrus | 52,-6,-6 | -2.098 | 0.002043664 | 330 | Right superior temporal gyrus (124) |
| | | | | | Right insula (97) |
| | | | | | Right rolandic operculum (12) |
| | | | | | Right middle temporal gyrus (11) |
| | | | | | Right temporal pole, superior temporal gyrus (10) |
| Left supramarginal gyrus | -56,-40,36 | -2.387 | 0.000490248 | 293 | Left supramarginal gyrus (117) |
| | | | | | Left inferior parietal gyrus (104) |
| | | | | | Left superior temporal gyrus (64) |

Cluster of increased gray matter volume (patients>controls)

| | | | | | |
|---------------------|----------|-------|-------------|-----|------------------------------------|
| Right lingual gyrus | 6,-34,-6 | 1.895 | 0.000005186 | 466 | Right lingual gyrus (62) |
| | | | | | Cerebellum, vermic lobule III (36) |

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| | | | | | |
|--------------------------------------------|----------|-------|-------------|-----|-----------------------------------------------|
| | | | | | Left cerebellum, hemispheric lobule IV/V (31) |
| | | | | | Left lingual gyrus (18) |
| Right superior frontal gyrus, orbital part | 6,60,-22 | 1.617 | 0.000805080 | 155 | Right gyrus rectus (79) |
| | | | | | Right superior frontal gyrus (38) |

(a) Voxel probability threshold: $P=0.005$

(b) Peak height threshold: $z=1$

(c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

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Table S3

Analyses of subgroups and sensitivity analyses of structural studies

| Subgroup analysis | Increased gray matter volume | | Decreased gray matter volume | | | |
|------------------------------------------------------------------|------------------------------|------------------------|------------------------------|---------------|----------------|--------------------|
| | Right lingual | Right superior frontal | Left fusiform | Left inferior | Right superior | Left supramarginal |
| | gyrus | gyrus | gyrus | frontal gyrus | temporal gyrus | gyrus |
| Studies with slice thickness \leq 1.5 mm at acquisition (n=13) | YES | YES | NO | NO | YES | YES |
| Studies using \leq 8 mm smoothing kernel (n=10) | YES | YES | YES | NO | NO | YES |
| Studies using 1.5T MRI (n=10) | NO | NO | YES | YES | YES | NO |
| Studies with an additional correction step (n=9) | YES | YES | YES | YES | YES | YES |
| Studies of drug-naive patients (n=14) | YES | YES | YES | YES | YES | YES |

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Jackknife sensitivity analysis, discarded study

| | | | | | | |
|------------------------|-----|-----|-----|-----|-----|-----|
| 2003Salgado-Pineda | YES | YES | YES | YES | YES | YES |
| 2005Jayakumar | YES | YES | YES | YES | YES | YES |
| 2007Prasad | YES | YES | YES | YES | YES | YES |
| 2007Chua | YES | YES | YES | YES | YES | YES |
| 2008Meda | YES | YES | YES | YES | YES | YES |
| 2008Witthaus | YES | YES | YES | YES | YES | YES |
| 2010Venkatasubramanian | YES | YES | YES | YES | YES | YES |
| 2011Berge | YES | YES | YES | YES | YES | YES |
| 2013Suazo | YES | YES | YES | YES | YES | YES |
| 2013WentingRen | YES | YES | YES | YES | YES | YES |

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| | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|
| 2013XiaofengGuo(S) | YES | YES | YES | YES | YES | YES |
| 2013XiaofengGuo(L) | YES | YES | YES | YES | YES | YES |
| 2014WenbinGuo | YES | YES | YES | YES | YES | YES |
| 2014JunLi | YES | YES | YES | YES | YES | YES |
| 2014Nenadic | YES | YES | YES | YES | YES | YES |
| 2016Yue | YES | YES | YES | YES | YES | YES |

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Table S4

Meta-analysis results of functional MRI

| | MNI | SDM-Z | P | Voxels | Cluster breakdown (number of voxels) |
|---------------------------------------------------------|-----------|--------|-------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cluster of hypoactivation (patients<controls) | | | | | |
| Right inferior frontal gyrus, opercular part | 46,10,30 | -3.221 | 0.000006437 | 893 | Right inferior frontal gyrus, opercular part (432) Right inferior frontal gyrus, triangular part (152) Right precentral gyrus (98) Right middle frontal gyrus (17) |
| Right angular gyrus | 40,-60,52 | -2.719 | 0.000062704 | 331 | Right angular gyrus (166) Right inferior parietal (excluding supramarginal and angular) gyrus (140) |

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Right superior parietal gyrus (25)

| | | | | | |
|--------------|-----------|--------|-------------|-----|--------------------|
| Right insula | 38,14,-14 | -2.439 | 0.000266016 | 339 | Right insula (197) |
|--------------|-----------|--------|-------------|-----|--------------------|

Right inferior frontal gyrus, orbital part (44)

Right temporal pole, superior temporal gyrus (30)

Cluster of hyperactivation (patients>controls)

| | | | | | |
|---------------|----------|-------|----|------|------------------------------------|
| Left striatum | -28,-2,4 | 3.273 | ~0 | 2761 | Left superior temporal gyrus (685) |
|---------------|----------|-------|----|------|------------------------------------|

Left insula (564)

Left rolandic operculum (335)

Left lenticular nucleus, putamen (296)

Left striatum (189)

Left heschl gyrus (164)

Left postcentral gyrus (69)

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| | | | | | |
|-------------------------------|-------------|-------|-------------|-----|----------------------------------------|
| | | | | | Left supramarginal gyrus (44) |
| | | | | | Left pons (17) |
| Right striatum | 26,-2,8 | 1.919 | 0.000929713 | 212 | Right insula (71) |
| | | | | | Right striatum (48) |
| | | | | | Right lenticular nucleus, putamen (34) |
| Left inferior occipital gyrus | -34,-76,-12 | 2.178 | 0.000299335 | 168 | Left fusiform gyrus (83) |
| | | | | | Left inferior occipital gyrus (42) |

(a) Voxel probability threshold: $P=0.005$

(b) Peak height threshold: $z=1$

(c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

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Table S5

Analyses of subgroups and sensitivity analyses of functional studies

| Subgroup analysis | Hyperactivation | | | Hypoactivation | | |
|----------------------------------------------------------|-----------------|----------------|-------------------------------|----------------------------------------------|---------------------|--------------|
| | Left striatum | Right striatum | Left inferior occipital gyrus | Right inferior frontal gyrus, opercular part | Right angular gyrus | Right insula |
| Studies with slice thickness <5 mm at acquisition (n=13) | YES | NO | NO | YES | NO | YES |
| Studies using ≥ 8 mm smoothing kernel (n=15) | YES | YES | YES | YES | YES | YES |
| Studies using 1.5T MRI (n=8) | YES | NO | NO | YES | NO | NO |
| Studies with an additional correction step (n=16) | YES | YES | YES | YES | YES | YES |
| Studies performing task (n=11) | YES | NO | NO | YES | NO | YES |

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| Studies of drug-naive patients (n=8) | YES | YES | YES | YES | YES | NO |
|--------------------------------------------------------|-----|-----|-----|-----|-----|-----|
| Jackknife sensitivity analysis, discarded study | | | | | | |
| 1997Andreason | YES | YES | YES | YES | YES | YES |
| 2010Scheef | YES | YES | YES | YES | YES | YES |
| 2013Ren | YES | NO | NO | YES | NO | YES |
| 2015Guo | YES | YES | YES | YES | YES | YES |
| 2014 Hadley | YES | YES | YES | YES | YES | YES |
| 2003Hofer | YES | YES | YES | YES | YES | YES |
| 2004Jones | YES | YES | YES | YES | YES | YES |
| 2005Weiss | YES | YES | YES | YES | YES | YES |
| 2005Boksman | YES | YES | YES | YES | YES | YES |

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| | | | | | | |
|--------------------------|-----|-----|-----|-----|-----|-----|
| 2008Scheuerecker | YES | YES | YES | YES | YES | YES |
| 2010Comilo | YES | YES | YES | YES | YES | YES |
| 2011Nejad | YES | YES | YES | YES | YES | YES |
| 2013Bin | YES | YES | YES | YES | YES | YES |
| 2014Schlagenhauf | YES | YES | YES | YES | YES | YES |
| 2015Lesh | YES | YES | YES | YES | YES | YES |
| 2016Zheng | YES | YES | YES | YES | YES | YES |
| 2016Cui (1) [†] | YES | YES | YES | YES | YES | YES |
| 2016Cui (2) | YES | YES | YES | YES | YES | YES |

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Table S6

Regions with altered gray matter volume showing significant statistical heterogeneity between studies (voxelwise $p < 0.005$)

| Description | MNI coordinate | SDM-Z | P | Voxels |
|---------------------|-----------------------|--------------|----------|---------------|
| Right insula | 38,-16,-2 | 4.039 | ~0 | 1372 |
| Left fusiform gyrus | -36,-60,-16 | 2.414 | 0.00026 | 264 |

Table S7

Regions with altered regional metabolism showing significant statistical heterogeneity between studies (voxelwise $p < 0.005$)

| Description | MNI coordinate | SDM-Z | P | Voxels |
|--------------------|-----------------------|--------------|----------|---------------|
| Left insula | -36,-6,10 | 2.209 | 0.00155 | 184 |

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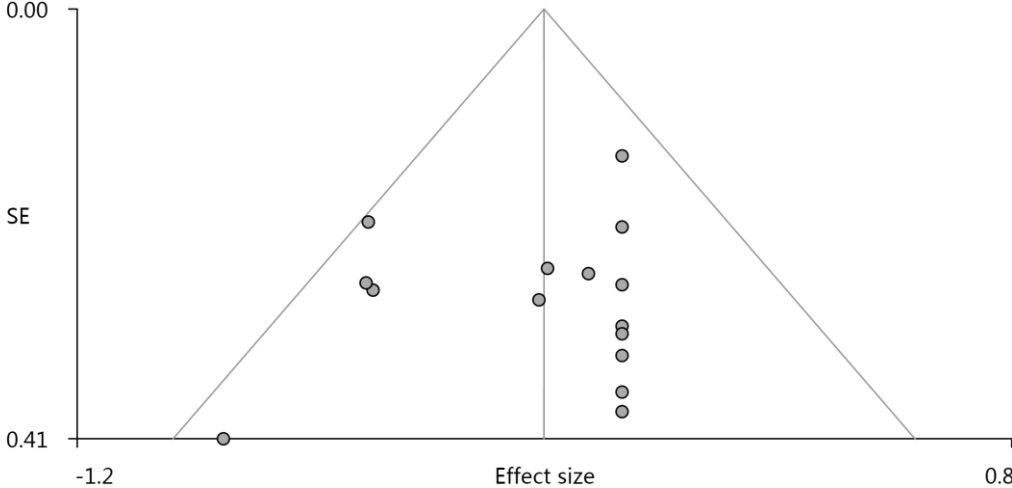
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Table S8

Results of the funnel plots and Eager test

| Brain areas | Funnel plots | Eager test |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Left fusiform gyrus |  <p>The funnel plot displays individual study effect sizes as grey circles. The plot is bounded by a triangle with vertices at (-1.2, 0.41), (0.8, 0.41), and (0.00, 0.00). A vertical line is drawn at an effect size of 0.00. The x-axis is labeled 'Effect size' and has tick marks at -1.2 and 0.8. The y-axis is labeled 'SE' and has tick marks at 0.00 and 0.41. There are 15 data points in total, with a cluster of 10 points near the 0.00 effect size line and 5 points scattered to the left.</p> | T= -0.74, P= 0.473 |

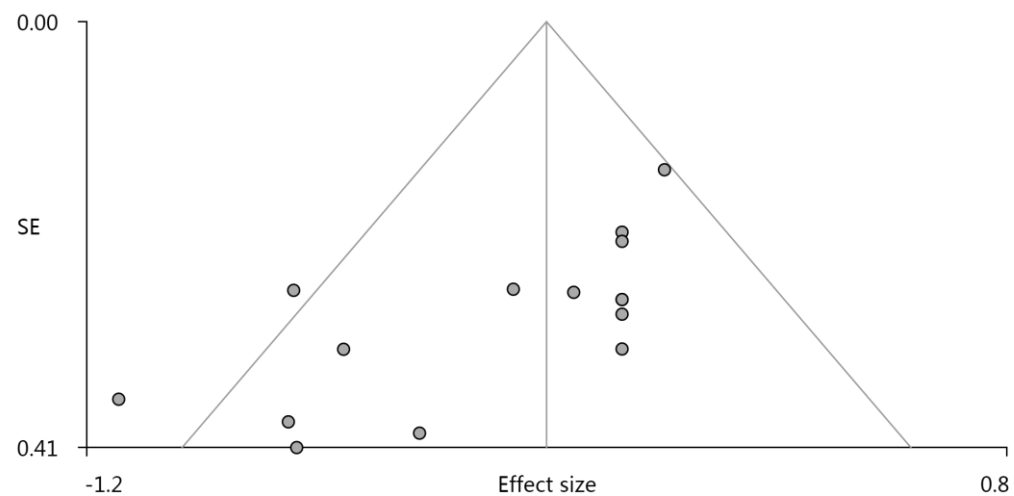
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Left inferior frontal gyrus



T= -3.65, P 0.003

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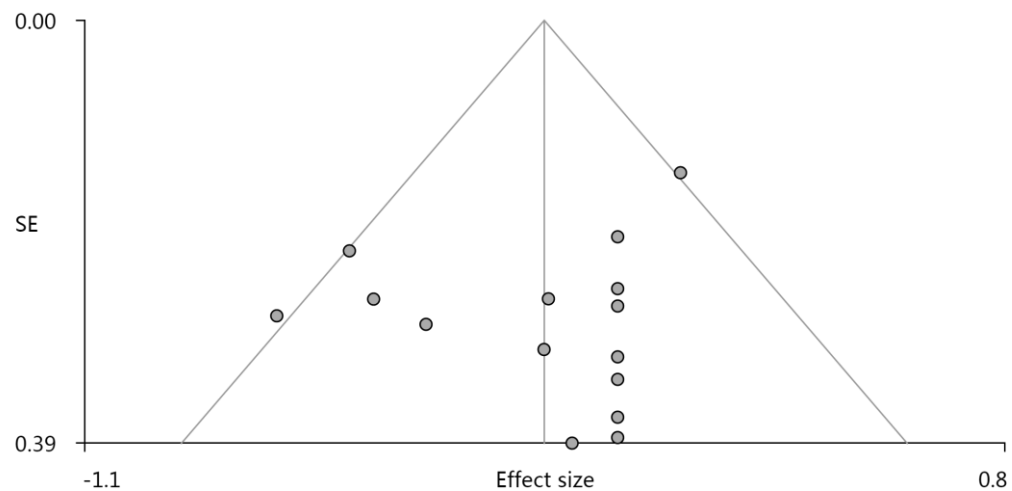
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Right superior temporal

gyrus



T=-0.96, P= 0.355

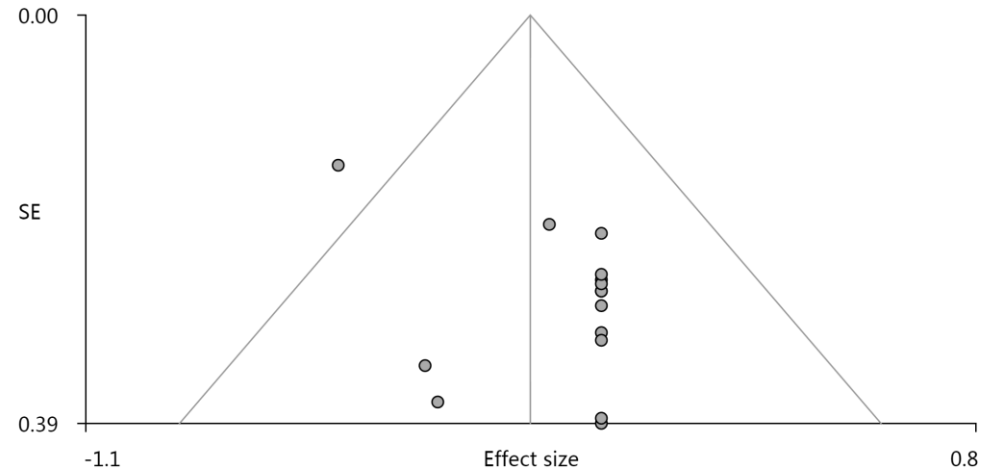
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Left supramarginal gyrus



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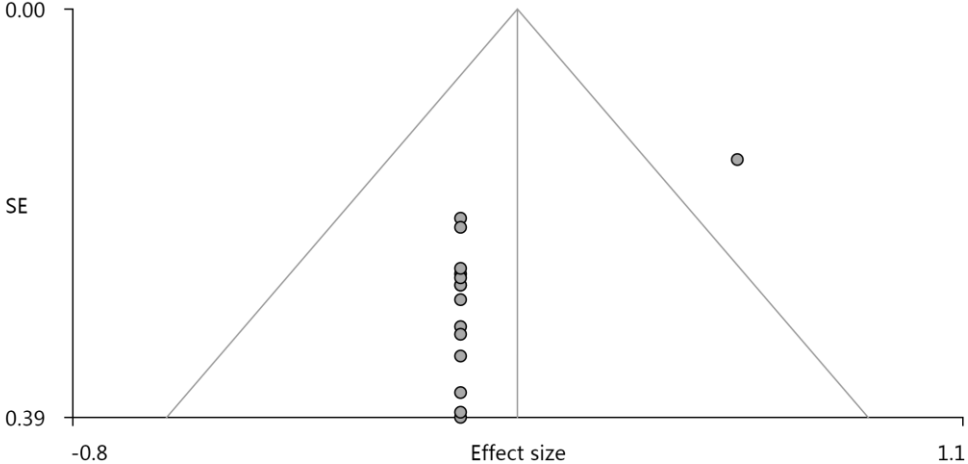
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Right lingual gyrus

T= -3.75, P= 0.002



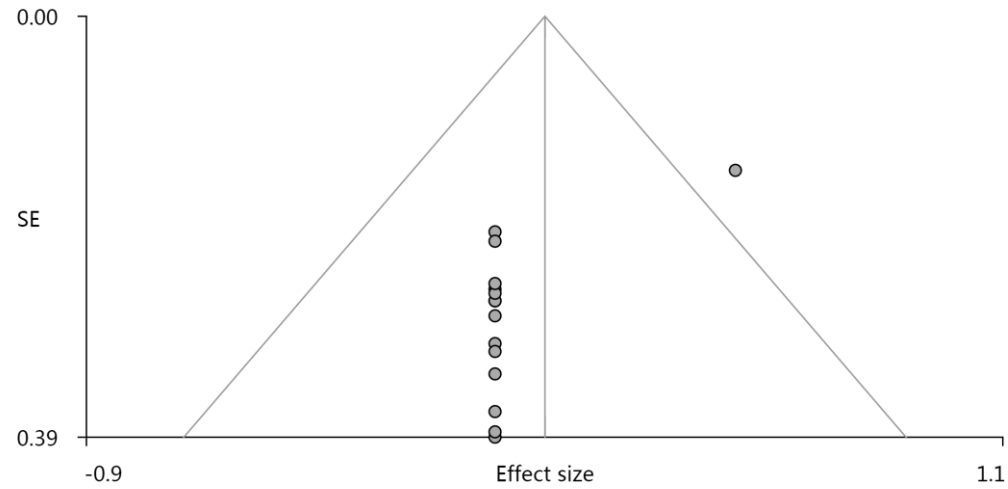
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Right superior frontal
gyrus, orbital part



T= -3.80, P= 0.002

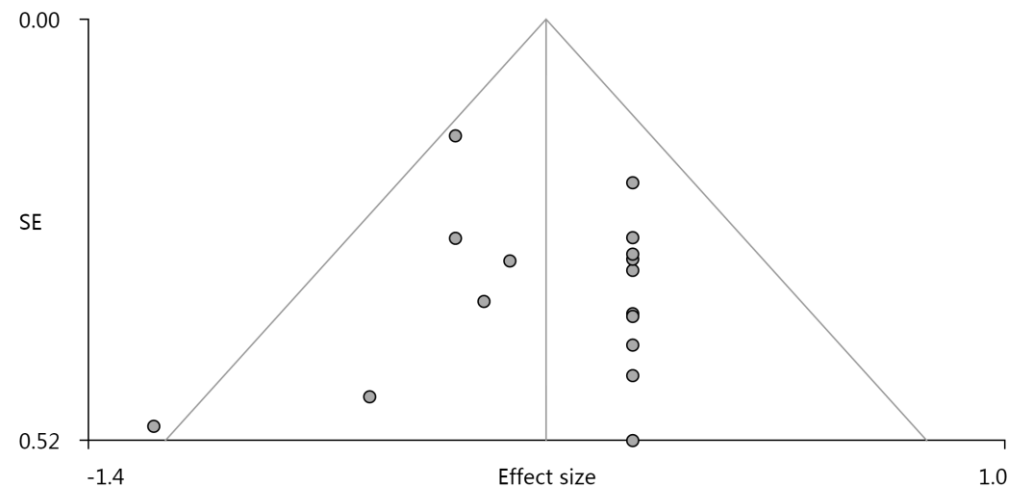
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Right inferior frontal gyrus



T=0.49, P= 0.629

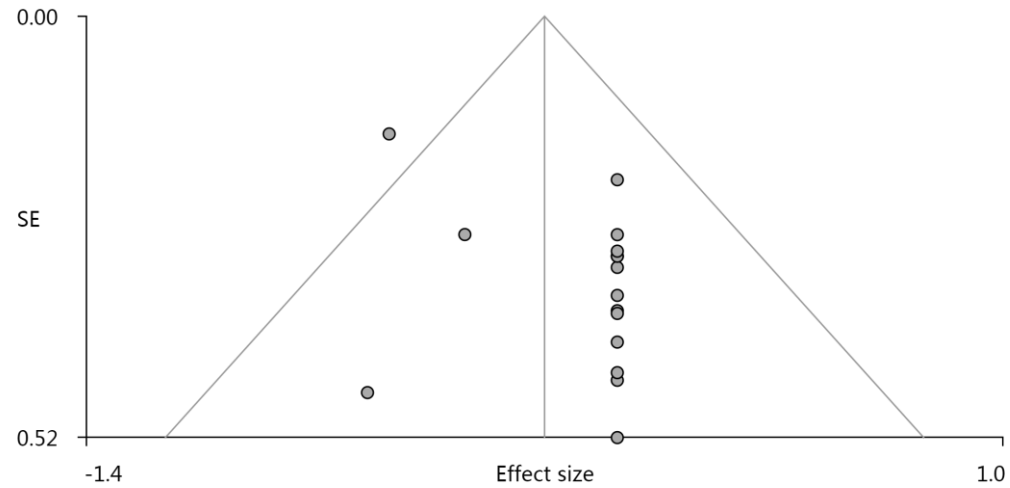
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Right angular gyrus



T= 2.63, P= 0.020

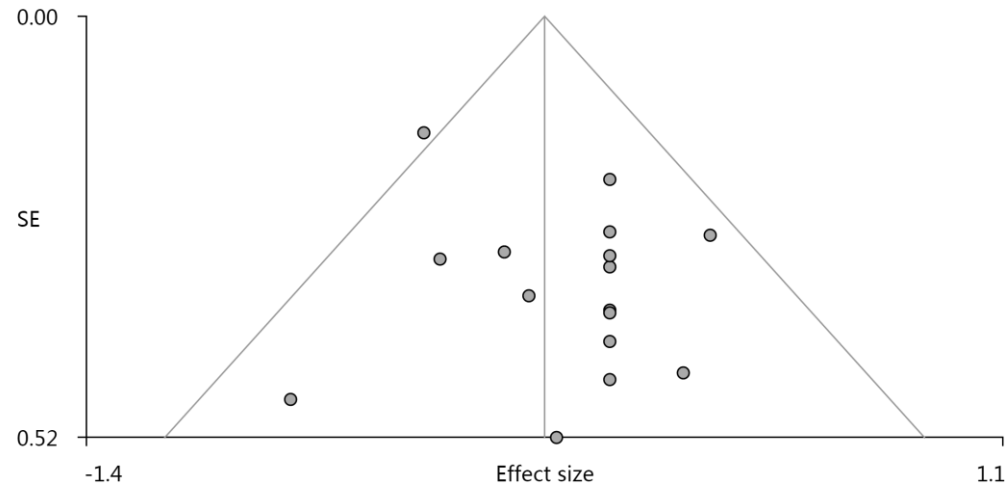
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Right insula



T=1.48, P= 0.161

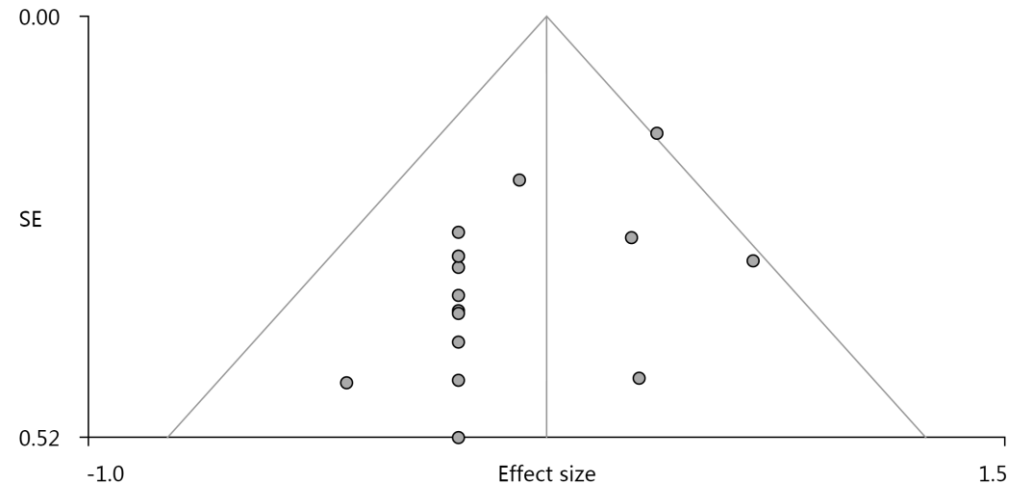
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Left striatum



T=-2.61, P= 0.021

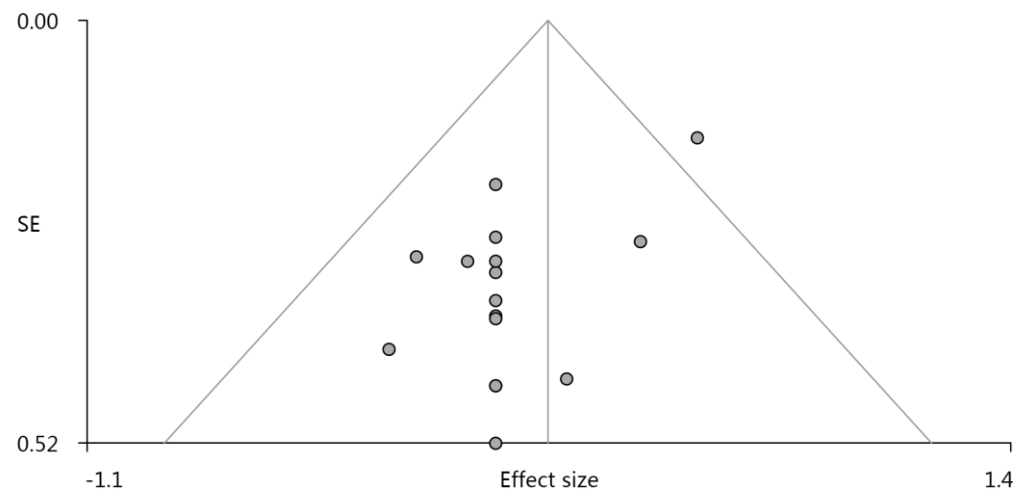
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Right striatum



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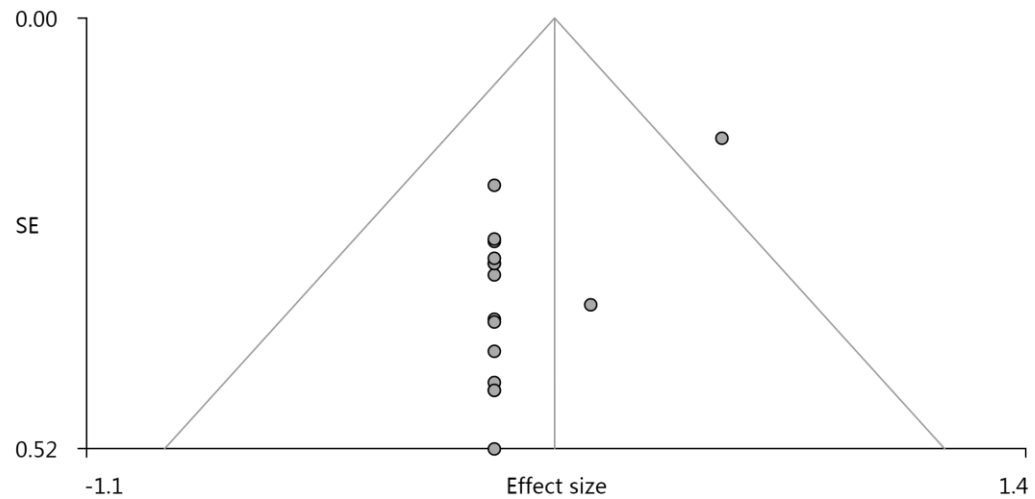
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Left inferior occipital

gyrus



T=-3.61, P= 0.003

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