Supplementary Materials

**SM 1 Method**

*SM 1.1 Symptom score conversion algorithms*

Global SANS (Summary) Score = -2.0671 + (0.665\*PANSS Negative score)

Global SANS (Summary) Score = 1.0863 + (0.2943\*Total SANS (composite) score)

*SM 1.2 Imaging descriptives and quality control*

Parcellations were visually inspected and statistically evaluated for outliers following standardized ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols). Each image parcellation was individually examined by a neuroimaging expert at each site by overlaying the parcellation label of each structure on the T1-weighted brain scan. Further, we collected study-wide statistics (means, minimums, maximums, and standard deviations; see SM Figure 1s) as well as histogram and diagnostic plots in order to identify non-normally distributed data and major outliers. A subject was considered a statistical outlier if its thickness was >2.698 standard deviations away from the global mean. For each subject that was marked as a statistical outlier, individual sites were asked to re-inspect the subject’s parcellations in order to verify that it was properly segmented. If a subject was a statistical outlier, but was properly segmented it was kept in the analysis. Otherwise the subject was removed (see SM Table 2s for details).



SM Figure 1s. Left (A-B) and right (C-D) medial orbitofrontal cortical thickness descriptives (min/mean/sd/max) by study site.

**SM 2 Results**

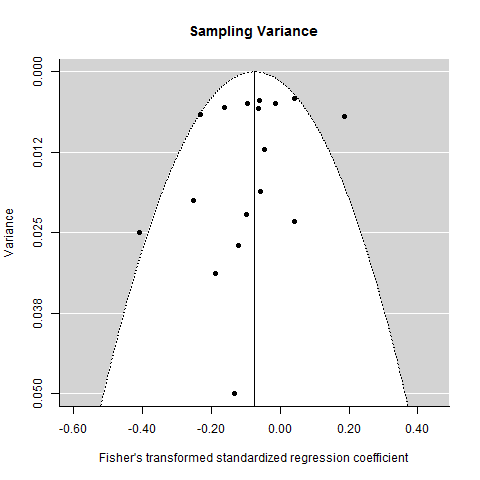
*SM 2.1 Detailed results of meta-analyses*

1. Main model: left MOFC <- global SANS + gender + age + site (if applicable)

In the main model we investigated the effect of global SANS scores on left MOFC thickness, covarying for gender , age and the number of sites as dummy variables (where applicable). Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of the global SANS score on left MOFC thickness. Results were based on estimates from 17 studies using a restricted maximum likelihood (REML) approach. Also provided are estimates and significance levels for effect size heterogeneity between studies.

|  |
| --- |
| Random-Effects Model (k = 17; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0067 (SE = 0.0057) |
| tau (square root of estimated tau^2 value): 0.0816 |
| I^2 (total heterogeneity / total variability): 42.38% |
| H^2 (total variability / sampling variability): 1.74 |
|  |
| Test for Heterogeneity: |
| Q(df = 16) = 26.3994, p-val = 0.0487 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.0752 0.0321 -2.3446 0.0190 -0.1381 -0.0123 \* |

*Funnel plot main model*



SM Figure 2s. Funnel plot. Individual study regression coefficients are plotted against sample variance (a measure of the precision of the data).

1. Exploratory model: right MOFC <- global SANS + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of the global SANS score on right MOFC thickness. Results were based on estimates from 17 studies.

|  |
| --- |
| Random-Effects Model (k = 17; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0080 (SE = 0.0063) |
| tau (square root of estimated tau^2 value): 0.0892 |
| I^2 (total heterogeneity / total variability): 46.78% |
| H^2 (total variability / sampling variability): 1.88 |
|  |
| Test for Heterogeneity: |
| Q(df = 16) = 28.4025, p-val = 0.0283 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.0643 0.0335 -1.9207 0.0548 -0.1299 0.0013 . |

1. Effects of covariates: left MOFC <- global SANS + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of age on left MOFC thickness. Results were based on estimates from 17 studies.

|  |
| --- |
| Random-Effects Model (k = 17; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0117 (SE = 0.0078) |
| tau (square root of estimated tau^2 value): 0.1083 |
| I^2 (total heterogeneity / total variability): 56.43% |
| H^2 (total variability / sampling variability): 2.30 |
|  |
| Test for Heterogeneity: |
| Q(df = 16) = 36.1039, p-val = 0.0028 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.2372 0.0371 -6.3925 <.0001 -0.3100 -0.1645 \*\*\* |

1. Effects of covariates: left MOFC <- global SANS + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of gender on left MOFC thickness. Results were based on estimates from 17 studies.

|  |
| --- |
| Random-Effects Model (k = 17; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0026) |
| tau (square root of estimated tau^2 value): 0 |
| I^2 (total heterogeneity / total variability): 0.00% |
| H^2 (total variability / sampling variability): 1.00 |
|  |
| Test for Heterogeneity: |
| Q(df = 16) = 13.5923, p-val = 0.6291 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.0900 0.0227 -3.9592 <.0001 -0.1346 -0.0455 \*\*\* |

1. Effects of covariates: left MOFC <- global SANS + illness severity + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of illness severity on left MOFC thickness. Results were based on estimates from 9 studies.

|  |
| --- |
| Random-Effects Model (k = 9; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0387 (SE = 0.0254) |
| tau (square root of estimated tau^2 value): 0.1967 |
| I^2 (total heterogeneity / total variability): 81.26% |
| H^2 (total variability / sampling variability): 5.34 |
|  |
| Test for Heterogeneity: |
| Q(df = 8) = 44.9511, p-val < .0001 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| 0.0446 0.0755 0.5908 0.5546 -0.1034 0.1927 |

1. Effects of covariates: left MOFC <- global SANS + illness severity + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS score on left MOFC thickness. Results were based on estimates from 9 studies.

|  |
| --- |
| Random-Effects Model (k = 9; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0145 (SE = 0.0126) |
| tau (square root of estimated tau^2 value): 0.1205 |
| I^2 (total heterogeneity / total variability): 61.91% |
| H^2 (total variability / sampling variability): 2.63 |
|  |
| Test for Heterogeneity: |
| Q(df = 8) = 21.8200, p-val = 0.0053 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.1126 0.0536 -2.0998 0.0357 -0.2177 -0.0075 \* |

1. Effects of covariates: left MOFC <- global SANS + length of illness + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of length of illness estimates on left MOFC thickness. Results were based on estimates from 13 studies.

|  |
| --- |
| Random-Effects Model (k = 13; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0539 (SE = 0.0271) |
| tau (square root of estimated tau^2 value): 0.2321 |
| I^2 (total heterogeneity / total variability): 86.66% |
| H^2 (total variability / sampling variability): 7.50 |
|  |
| Test for Heterogeneity: |
| Q(df = 12) = 51.8783, p-val < .0001 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.0922 0.0719 -1.2836 0.1993 -0.2331 0.0486 |

1. Effects of covariates: left MOFC <- global SANS + length of illness + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Results were based on estimates from 13 studies.

|  |
| --- |
| Random-Effects Model (k = 13; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of total heterogeneity): 0.0079 (SE = 0.0069) |
| tau (square root of estimated tau^2 value): 0.0892 |
| I^2 (total heterogeneity / total variability): 48.94% |
| H^2 (total variability / sampling variability): 1.96 |
|  |
| Test for Heterogeneity: |
| Q(df = 12) = 22.8334, p-val = 0.0292 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| -0.0681 0.0373 -1.8240 0.0682 -0.1413 0.0051 . |

1. Moderation analysis of age of onset on the association between global SANS scores and left MOFC thickness

Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of age of onset on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Results were based on estimates from 13 studies.

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity): 0.0077 (SE = 0.0072)

tau (square root of estimated tau^2 value): 0.0875

I^2 (residual heterogeneity / unaccounted variability): 46.82%

H^2 (unaccounted variability / sampling variability): 1.88

R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:

QE(df = 11) = 20.0562, p-val = 0.0446

Test of Moderators (coefficient(s) 2):

QM(df = 1) = 0.1133, p-val = 0.7365

Model Results:

se zval pval ci.lb ci.ub

intrcpt -0.0651 0.0370 -1.7578 0.0788 -0.1377 0.0075 .

I(AO\_mean - 23.83) 0.0050 0.0149 0.3365 0.7365 -0.0242 0.0342

1. Moderation analysis of antipsychotic medication on the association between global SANS scores and left MOFC thickness

To investigate potentially moderating effects of antipsychotic medication, we derived the percentages of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients in each sample. Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of antipsychotic medication on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Percentages of participants on typical, atypical and combined antipsychotic medication were mean centered and compared to the percentage of unmedicated patients (baseline). The intercept refers to the effect of global SANS score on left MOFC thickness after accounting for antipsychotic medication. Results were based on estimates from 13 studies.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | | --- | | Mixed-Effects Model (k = 13; tau^2 estimator: REML) | |  | | tau^2 (estimated amount of residual heterogeneity): 0.0039 (SE = 0.0056) | | tau (square root of estimated tau^2 value): 0.0621 | | I^2 (residual heterogeneity / unaccounted variability): 32.04% | | H^2 (unaccounted variability / sampling variability): 1.47 | | R^2 (amount of heterogeneity accounted for): 0.00% | |  | | Test for Residual Heterogeneity: | | QE(df = 9) = 11.9256, p-val = 0.2175 | |  | | Test of Moderators (coefficient(s) 2,3,4): | | QM(df = 3) = 2.6632, p-val = 0.4465 | |  | | Model Results: | |  | | estimate se zval pval ci.lb ci.ub | | intrcpt -0.0489 0.0318 -1.5375 0.1242 -0.1112 0.0134 | | I(MED\_a\_perc - 68.72) 0.0042 0.0031 1.3557 0.1752 -0.0019 0.0103 | | I(MED\_b\_perc - 8.536) 0.0009 0.0048 0.1812 0.8562 -0.0086 0.0103 | | I(MED\_t\_perc - 11.1) 0.0022 0.0038 0.5879 0.5566 -0.0052 0.0097 | |

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED\_a\_perc) or typical (MED\_t\_perc) antipsychotics, both antipsychotic medication types (MED\_b\_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline).

1. Moderation analysis of handedness on the association between global SANS scores and left MOFC thickness

To investigate potentially moderating effects of handedness, we derived the percentage of ambidextrous, left- and right-handed participants. Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of handedness on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Percentages of ambidextriuos and left-handed partipicants were mean centered and compared to the right-handed group (baseline). The intercept refers to the effect of global SANS score on left MOFC thickness after accounting for handedness. Results were based on estimates from 14 studies.

|  |
| --- |
| Mixed-Effects Model (k = 14; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of residual heterogeneity): 0.0061 (SE = 0.0059) |
| tau (square root of estimated tau^2 value): 0.0780 |
| I^2 (residual heterogeneity / unaccounted variability): 44.65% |
| H^2 (unaccounted variability / sampling variability): 1.81 |
| R^2 (amount of heterogeneity accounted for): 0.00% |
|  |
| Test for Residual Heterogeneity: |
| QE(df = 11) = 19.0779, p-val = 0.0597 |
|  |
| Test of Moderators (coefficient(s) 2,3): |
| QM(df = 2) = 1.0884, p-val = 0.5803 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| intrcpt -0.0603 0.0342 -1.7634 0.0778 -0.1273 0.0067 . |
| I(HAND\_a\_perc - 3.591) 0.0010 0.0074 0.1399 0.8888 -0.0134 0.0154 |
| I(HAND\_l\_perc - 8.688) -0.0113 0.0116 -0.9744 0.3299 -0.0341 0.0115 |

N.B.: predictor abbreviations refer to the percentage of ambidextrous (HAND\_a\_perc), left-handed (HAND\_l\_perc) and right-handed patients (intrcpt, i.e. baseline).

1. Left MOFC thickness differences by antipsychotic medication type percentages

We also investigated whether left MOFC thickness differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients. Shown below are the estimate, the standard error, p value and the confidence intervals of mean left MOFC thickness for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 13 studies.

|  |
| --- |
| Mixed-Effects Model (k = 13; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of residual heterogeneity): 0.0060 (SE = 0.0030) |
| tau (square root of estimated tau^2 value): 0.0777 |
| I^2 (residual heterogeneity / unaccounted variability): 95.96% |
| H^2 (unaccounted variability / sampling variability): 24.73 |
| R^2 (amount of heterogeneity accounted for): 44.87% |
|  |
| Test for Residual Heterogeneity: |
| QE(df = 9) = 249.4885, p-val < .0001 |
|  |
| Test of Moderators (coefficient(s) 2,3,4): |
| QM(df = 3) = 12.2740, p-val = 0.0065 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| intrcpt 2.4841 0.0222 111.8192 <.0001 2.4405 2.5276 \*\*\* |
| I(MED\_a\_perc - 68.72) -0.0058 0.0019 -3.1327 0.0017 -0.0094 -0.0022 \*\* |
| I(MED\_b\_perc - 8.536) -0.0026 0.0033 -0.7653 0.4441 -0.0091 0.0040 |
| I(MED\_t\_perc - 11.1) -0.0065 0.0022 -2.9253 0.0034 -0.0109 -0.0021 \*\* |

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED\_a\_perc) or typical (MED\_t\_perc) antipsychotics, both antipsychotic medication types (MED\_b\_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline).

1. Global SANS score differences by antipsychotic medication type percentages

Furthermore, We also investigated whether global SANS scores differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients. Shown below are the estimate, the standard error, p value and the confidence intervals of mean global SANS scores for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 13 studies.

|  |
| --- |
| Mixed-Effects Model (k = 13; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of residual heterogeneity): 7.3158 (SE = 3.5444) |
| tau (square root of estimated tau^2 value): 2.7048 |
| I^2 (residual heterogeneity / unaccounted variability): 98.34% |
| H^2 (unaccounted variability / sampling variability): 60.25 |
| R^2 (amount of heterogeneity accounted for): 0.00% |
|  |
| Test for Residual Heterogeneity: |
| QE(df = 9) = 483.0582, p-val < .0001 |
|  |
| Test of Moderators (coefficient(s) 2,3,4): |
| QM(df = 3) = 2.6231, p-val = 0.4535 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| intrcpt 8.7936 0.7616 11.5460 <.0001 7.3009 10.2863 \*\*\* |
| I(MED\_a\_perc - 68.72) -0.0229 0.0627 -0.3648 0.7153 -0.1457 0.1000 |
| I(MED\_b\_perc - 8.536) 0.1342 0.1142 1.1748 0.2401 -0.0897 0.3581 |
| I(MED\_t\_perc - 11.1) -0.0591 0.0758 -0.7793 0.4358 -0.2078 0.0895 |

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED\_a\_perc) or typical (MED\_t\_perc) antipsychotics, both antipsychotic medication types (MED\_b\_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline).

1. Left MOFC thickness differences by antipsychotic medication type percentages, covarying for gender and age

We also investigated whether left MOFC thickness differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients, when additionally controlling for gender and age. Shown below are the estimate, the standard error, p value and the confidence intervals of mean left MOFC thickness for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 13 studies.

|  |
| --- |
| Mixed-Effects Model (k = 13; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of residual heterogeneity): 0.0076 (SE = 0.0043) |
| tau (square root of estimated tau^2 value): 0.0873 |
| I^2 (residual heterogeneity / unaccounted variability): 96.44% |
| H^2 (unaccounted variability / sampling variability): 28.06 |
| R^2 (amount of heterogeneity accounted for): 30.46% |
|  |
| Test for Residual Heterogeneity: |
| QE(df = 7) = 235.2282, p-val < .0001 |
|  |
| Test of Moderators (coefficient(s) 2,3,4,5,6): |
| QM(df = 5) = 10.1896, p-val = 0.0700 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| intrcpt 2.4799 0.0267 92.8312 <.0001 2.4276 2.5323 \*\*\* |
| I(Age\_mean - 34.72) -0.0041 0.0100 -0.4115 0.6807 -0.0237 0.0155 |
| I(MED\_a\_perc - 68.72) -0.0056 0.0022 -2.5524 0.0107 -0.0098 -0.0013 \* |
| I(MED\_b\_perc - 8.536) -0.0016 0.0046 -0.3361 0.7368 -0.0106 0.0075 |
| I(MED\_t\_perc - 11.1) -0.0053 0.0035 -1.5391 0.1238 -0.0121 0.0015 |
| I(MF\_ratio - 2.255) -0.0091 0.0386 -0.2365 0.8130 -0.0848 0.0666 |

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED\_a\_perc) or typical (MED\_t\_perc) antipsychotics, both antipsychotic medication types (MED\_b\_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline) as well as the ratio of males versus females (MF\_ratio).

1. Left MOFC thickness differences by antipsychotic medication type percentages, covarying for gender and length of illness

We also investigated whether left MOFC thickness differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients, when additionally controlling for gender and length of ilness. Shown below are the estimate, the standard error, p value and the confidence intervals of mean left MOFC thickness for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 11 studies.

|  |
| --- |
| Mixed-Effects Model (k = 11; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of residual heterogeneity): 0.0087 (SE = 0.0057) |
| tau (square root of estimated tau^2 value): 0.0932 |
| I^2 (residual heterogeneity / unaccounted variability): 97.07% |
| H^2 (unaccounted variability / sampling variability): 34.16 |
| R^2 (amount of heterogeneity accounted for): 31.69% |
|  |
| Test for Residual Heterogeneity: |
| QE(df = 5) = 187.9049, p-val < .0001 |
|  |
| Test of Moderators (coefficient(s) 2,3,4,5,6): |
| QM(df = 5) = 9.6171, p-val = 0.0868 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| intrcpt 2.4693 0.0348 70.9461 <.0001 2.4011 2.5376 \*\*\* |
| I(LOI\_mean - 10.74) -0.0077 0.0119 -0.6514 0.5148 -0.0310 0.0155 |
| I(MED\_a\_perc - 68.72) -0.0051 0.0025 -2.0599 0.0394 -0.0100 -0.0002 \* |
| I(MED\_b\_perc - 8.536) 0.0013 0.0074 0.1793 0.8577 -0.0132 0.0159 |
| I(MED\_t\_perc - 11.1) -0.0042 0.0036 -1.1451 0.2522 -0.0113 0.0030 |
| I(MF\_ratio - 2.255) 0.0089 0.0644 0.1384 0.8899 -0.1172 0.1350 |

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED\_a\_perc) or typical (MED\_t\_perc) antipsychotics, both antipsychotic medication types (MED\_b\_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline) as well as the ratio of males versus females (MF\_ratio) and mean length of illness (LOI\_mean).

1. Moderation analysis of single vs multisite status on the association between global SANS scores and left MOFC thickness

Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of single vs multisite status on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. The intercept refers to the effect of global SANS score on left MOFC thickness after accounting for single vs multisite status. Results were based on estimates from 17 studies.

|  |
| --- |
| Mixed-Effects Model (k = 17; tau^2 estimator: REML) |
|  |
| tau^2 (estimated amount of residual heterogeneity): 0.0078 (SE = 0.0066) |
| tau (square root of estimated tau^2 value): 0.0886 |
| I^2 (residual heterogeneity / unaccounted variability): 45.43% |
| H^2 (unaccounted variability / sampling variability): 1.83 |
| R^2 (amount of heterogeneity accounted for): 0.00% |
|  |
| Test for Residual Heterogeneity: |
| QE(df = 15) = 25.9669, p-val = 0.0384 |
|  |
| Test of Moderators (coefficient(s) 2): |
| QM(df = 1) = 0.6443, p-val = 0.4222 |
|  |
| Model Results: |
|  |
| estimate se zval pval ci.lb ci.ub |
| intrcpt -0.0954 0.0409 -2.3295 0.0198 -0.1756 -0.0151 \* |
| as.factor(multisite)1 0.0567 0.0706 0.8027 0.4222 -0.0817 0.1950 |

1. Effects of covariates: left MOFC <- global SANS + CPZ + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of current chlorpromazine equivalents (CPZ, based on Woods *et al*. (2003)) on left MOFC thickness. Results were based on estimates from 12 studies.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | | --- | | Random-Effects Model (k = 12; tau^2 estimator: REML) | |  | | tau^2 (estimated amount of total heterogeneity): 0.0003 (SE = 0.0040) | | tau (square root of estimated tau^2 value): 0.0160 | | I^2 (total heterogeneity / total variability): 2.26% | | H^2 (total variability / sampling variability): 1.02 | |  | | Test for Heterogeneity: | | Q(df = 11) = 9.7194, p-val = 0.5558 | |  | | Model Results: | |  | | estimate se zval pval ci.lb ci.ub | | -0.0413 0.0301 -1.3717 0.1701 -0.1003 0.0177 | |

1. Effects of covariates: left MOFC <- global SANS + CPZ + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness, controlling for current chlorpromazine equivalents (based on Woods *et al*. (2003)). Results were based on estimates from 12 studies.

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| |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | |  | | --- | | Random-Effects Model (k = 12; tau^2 estimator: REML) | |  | | tau^2 (estimated amount of total heterogeneity): 0.0120 (SE = 0.0104) | | tau (square root of estimated tau^2 value): 0.1093 | | I^2 (total heterogeneity / total variability): 52.08% | | H^2 (total variability / sampling variability): 2.09 | |  | | Test for Heterogeneity: | | Q(df = 11) = 22.4039, p-val = 0.0214 | |  | | Model Results: | |  | | estimate se zval pval ci.lb ci.ub | | -0.0950 0.0462 -2.0564 0.0397 -0.1856 -0.0045 \* | | |

1. Effects in DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorder only: left MOFC <- global SANS + CPZ + gender + age + site (if applicable)

Schizophrenia inclusion criteria were site-specific. In detail, five sites included only patients with DSM-IV subtypes of schizophrenia. Eight sites also included schizoaffective and schizophreniform patients in their samples, while only a minority of sites (Nsites=4; 7% of our total sample) also included a few patients with other psychotic disorders, such as psychotic disorder NOS.

Of those sites where individual diagnostic codes for patients were available to us (Nsites=11, including the four sites with patients with other psychotic disorders), 77% of patients were diagnosed with Schizophrenia subtypes and 12% with schizoaffective / -phreniform disorders.

To ensure that our results were not influenced by including patients with other psychotic disorders, we repeated the analyses including only patients with DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorders.

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness, including only patients with DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorders. Results were based on estimates from 16 studies.

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***SM 2.2 Exploratory analyses on ten more frontal regions***

Univariate models were used to analyse the effect of negative symptoms on ten other frontal regions (separately for the left and right hemisphere; see SM Table 3s), controlling for sex, age and site (if applicable). After Bonferroni correction for multiple testing (ten regions per hemisphere = 20 tests), two regions remained significant on the left hemisphere, while no effect was observed in any of the regions on the right side (SM Table 3s).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | *left hemisphere* | | *right hemisphere* | |  |
| region-of-interest | βstd | *p* | βstd | *p* | Nsites |
| caudalmiddlefrontal | -0.0196 | 0.5052 | -0.0474 | 0.1406 | 17 |
| lateralorbitofrontal | -0.0756 | 0.0017 | -0.0732 | 0.0114 | 17 |
| caudalanteriorcingulate | -0.0164 | 0.5169 | -0.0547 | 0.0921 | 13 |
| parsopercularis | -0.0821 | 0.001 | -0.0357 | 0.2544 | 15 |
| parsorbitalis | -0.0512 | 0.0512 | -0.0479 | 0.0897 | 13 |
| parstriangularis | -0.0659 | 0.0101 | -0.0422 | 0.086 | 15 |
| rostralanteriorcingulate | 0.0137 | 0.6022 | -0.0434 | 0.1884 | 13 |
| rostralmiddlefrontal | -0.0509 | 0.0446 | -0.0484 | 0.0613 | 17 |
| superiorfrontal | -0.0662 | 0.0223 | -0.0640 | 0.0264 | 17 |
| frontalpole | -0.0398 | 0.1149 | 0.0006 | 0.9821 | 13 |

SM Table 3s. Exploratory analyses on ten more frontal regions.

**References**

**Woods, SW** (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *The Journal of Clinical Psychiatry* ***64*(6)**, 663–667.

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