Supplementary material

Brain structural abnormalities in adult major depressive disorder using voxel- and source-based morphometry: findings from the REST-meta-MDD Consortium

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# Interaction between MDD group with age and gender

For the VBM analysis, we examined the effects of the interaction between age and gender in the general linear model with Matlab 2019b. In this model, the grey matter volume of the 6 significant regions (MDD vs HCs) were extracted and included as the dependent variable, separately. Group, age, gender, the interaction between group and age, education, and sites were included as the independent variables. Results were corrected with Bonferroni method at p < 0.05 (i.e. threshold was puncorrected < 0.05/n = 0.0083, 6 means number of regions). A significant interaction between group and age was found for precuneus (t = -3.442, p < 0.0001). Within the MDD patient group, patients tended to have less age-related decreases in precuneus. Detailed results were shown in the following Table S2.

Then, we performed the general linear model for examining the interaction between group and gender, with the same analyses as interaction between group and age. No significant findings were found for the 6 regions in the interaction between group and gender (Table S2).

Also. we performed the source-based morphometry analysis again. This time, we applied the general linear model with Matlab 2019b. In this model, the loading coefficients of 13 structural networks were included as dependent variable, separately. Group, age, gender, the interaction between group and age, education, and sites were included as the independent variables. Results were corrected with Bonferroni method at p < 0.05 (i.e. threshold was puncorrected < 0.05/n = 0.0038, n =13 means number of ICs). No significant findings were found for 13 networks in the interaction between group and age. Same analyses were then performed for the interaction between group and gender in the general linear model. Detailed results for these significances were shown in the following Table S3.

Figure S1. Thirteen structural sources identified by source-based morphometry method. Sagittal, coronal, and axial slices are shown with the ICBM52 MNI brain template.

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Figure S2. Decreased grey matter volume in FEDN MDD patients (A) and recurrent MDD patients (B), compared to healthy controls. These results were shown at an uncorrected p < 0.05.

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Figure S3. Validation analyses of thirty structural covariance networks in MDD patients vs. healthy controls, and FEDN patients vs. recurrent patients. (A) The loading coefficients in the prefrontal network and superior temporal networks were significantly lower in MDD patients compared to healthy subjects. Compared to recurrent MDD patients, FEDN patients showed higher loading coefficients in ten networks (B), and a lower loading coefficient in the prefrontal network (C).



Table S1. Sample characteristics of 1082 depressive patients and 990 healthy controls for each site

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Site | Sample size  N | | Gender  male, N(%) | | | | Age  years, mean(SD) | | | | Education  years, mean(SD) | | | | Illness duration  months, mean(SD) | HAMD | HAMA |
| MDD | HC | MDD | HC | X2 | p | MDD | HC | t | p | MDD | HC | t | p | MDD | MDD | MDD |
| S1 | 74 | 74 | 31(41.89) | 32(43.24) | 0.03 | 0.868 | 31.72(8.19) | 31.80(8.99) | -0.06 | 0.954 | 13.80(2.94) | 15.23(2.26) | -3.32 | 0.001 | 5.37 (5.23) | 24.86 (4.81) | NA |
| S2 | 30 | 30 | 6(20.00) | 9(30.00) | 0.80 | 0.371 | 43.87(12.94) | 44.60(12.39) | -0.22 | 0.823 | 10.30(4.30) | 10.40(4.75) | -0.09 | 0.932 | 41.16(90.57) | 23.60 (3.30) | NA |
| S6 | 15 | 15 | 6(40.00) | 6(40.00) | 0.00 | 1.000 | 30.80(10.94) | 28.47(10.89) | 0.59 | 0.563 | 12.73(4.06) | 14.67(3.54) | -1.39 | 0.175 | 36.40 (39.75) | 23.13 (6.25) | NA |
| S7 | 38 | 49 | 15(39.47) | 19(38.78) | 0.00 | 0.947 | 42.58(11.85) | 41.43(13.41) | 0.42 | 0.677 | 10.37(4.63) | 13.16(6.07) | -2.36 | 0.021 | 43.89 (44.04) | 22.24(4.42) | 22.24(4.41) |
| S8 | 59 | 63 | 21(35.59) | 26(41.27) | 0.41 | 0.520 | 32.20(9.34) | 31.06(10.52) | 0.63 | 0.529 | 10.85(4.01) | 13.16(2.46) | -3.87 | <0.001 | 16.62 (24.78) | 23.98 (8.57) | 18.92 (10.59) |
| S9 | 45 | 50 | 22(48.89) | 31(62.00) | 1.65 | 0.199 | 29.00(8.77) | 28.92(8.59) | 0.04 | 0.964 | 13.64(2.74) | 15.72(3.04) | -3.48 | 0.001 | 29.59 (42.65) | NA | 12.36(6.71) |
| S10 | 50 | 29 | 22(44.00) | 19(65.52) | 3.40 | 0.065 | 33.00(10.63) | 33.14(8.21) | -0.06 | 0.952 | 11.28(3.39) | 12.21(3.12) | -1.20 | 0.232 | 10.95 (21.76) | 20.70 (3.77) | 16.72 (5.12) |
| S11 | 28 | 29 | 11(39.29) | 10(34.48) | 0.14 | 0.707 | 31.50(10.40) | 32.83(9.98) | -0.49 | 0.625 | 11.43(2.75) | 15.17(3.49) | -4.49 | <0.001 | 30.13(22.64)\* | 23.38(4.37)\* | NA |
| S13 | 25 | 17 | 11(44.00) | 6(35.29) | 0.32 | 0.573 | 32.28(9.30) | 34.00(10.50) | -0.56 | 0.580 | 13.64(2.08) | 13.12(2.32) | 0.76 | 0.450 | NA | 25.24 (3.90) | NA |
| S14 | 64 | 32 | 21(32.81) | 15(46.88) | 1.80 | 0.180 | 30.53(7.09) | 29.59(5.00) | 0.67 | 0.505 | 13.72(3.35) | 14.59(2.82) | -1.27 | 0.207 | 6.08 (4.17) | 21.33(3.44) | NA |
| S15 | 43 | 50 | 14(32.56) | 26(52.00) | 3.57 | 0.059 | 51.02(11.89) | 46.48(17.65) | 1.43 | 0.156 | 9.12(5.16) | 11.80(4.45) | -2.69 | 0.008 | 30.54 (51.52) | 27.63(5.87) | NA |
| S17 | 41 | 41 | 14(34.15) | 13(31.71) | 0.06 | 0.814 | 21.68(3.00) | 20.63(1.77) | 1.93 | 0.058 | 13.15(1.48) | 13.78(1.57) | -1.88 | 0.063 | NA | 20.66(5.69) | 15.22(4.91) |
| S18 | 21 | 20 | 6(28.57) | 8(40.00) | 0.60 | 0.440 | 31.43(6.98) | 30.10(7.52) | 0.59 | 0.561 | 12.29(3.99) | 12.40(3.14) | -0.10 | 0.920 | 12.05(10.84) | 24.76 (5.55) | 26.19 (8.20) |
| S19 | 51 | 36 | 14(27.45) | 18(50.00) | 4.61 | 0.032 | 38.25(11.51) | 35.86(10.27) | 1.00 | 0.321 | 8.78(3.90) | 9.94(3.84) | -1.38 | 0.172 | 73.50 (86.11) | 22.18(8.07) | NA |
| S20 | 257 | 242 | 95(36.96) | 78(32.23) | 1.23 | 0.267 | 39.37(13.00) | 39.99(15.86) | -0.48 | 0.629 | 10.88(3.48) | 12.88(3.97) | -6.00 | <0.001 | 50.49(66.34) | 20.97 (5.80) | 22.72 (8.85) |
| S21 | 86 | 70 | 38(44.19) | 31(44.29) | 0.00 | 0.990 | 34.71(12.63) | 36.13(12.64) | -0.70 | 0.486 | 11.65(2.89) | 12.83(2.59) | -2.65 | 0.009 | 85.82(92.05) | 14.37 (8.17) | 13.94 (8.73) |
| S22 | 29 | 20 | 14(48.28) | 12(60.00) | 0.65 | 0.419 | 34.14(9.95) | 24.35(7.07) | 3.79 | 0.000 | 11.59(2.81) | 13.30(2.13) | -2.31 | 0.026 | 38.90 (43.63) | 23.00 (5.12) | 9.63(7.67) |
| S23 | 27 | 29 | 14(51.85) | 11(37.93) | 1.10 | 0.295 | 26.67(8.43) | 33.28(11.81) | -2.39 | 0.020 | 13.37(3.34) | 14.45(4.16) | -1.06 | 0.292 | 23.04(28.12) | 19.19(8.55) | NA |
| S24 | 31 | 31 | 8(25.81) | 11(35.48) | 0.68 | 0.409 | 32.06(8.19) | 31.61(7.49) | 0.23 | 0.821 | 12.77(4.04) | 14.42(1.88) | -2.06 | 0.044 | 11.97(8.04) | 24.10(4.00) | 20.19 (6.42) |
| S25 | 68 | 63 | 21(30.88) | 29(46.03) | 3.18 | 0.075 | 66.75(6.29) | 69.63(5.86) | -2.71 | 0.008 | 11.44(2.94) | 12.83(3.01) | -2.66 | 0.009 | NA | 6.66(4.83) | NA |
| Total/Mean | 1082 | 990 | 404(0.37) | 410(0.41) | 3.60 | 0.058 | 37.23(14.20) | 37.45(15.67) | -0.34 | 0.732 | 11.63(3.71) | 13.25(3.73) | -9.95 | <0.001 | 38.34(61.51) | 20.75(7.48) | 19.09 (9.04) |

Abbreviation: SD, standard deviation; MDD, major depressive disorder; HAMD, Hamilton depression rating scale; HAMA, Hamilton anxiety scale

Table S2. Statistics for the interactions with age and gender for VBM significant regions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Region ID | Name | Interaction with age | | Interaction with gender | |
| t | puncorrected | t | puncorrected |
| region1 | Dorsal anterior cingulate cortex | -1.466 | 0.143 | 0.005 | 0.996 |
| region2 | Left super temporal gyrus | -0.906 | 0.365 | 0.137 | 0.891 |
| region3 | Right super temporal gyrus | -0.442 | 0.658 | -0.461 | 0.645 |
| region4 | Right inferior frontal gyrus | -0.127 | 0.899 | 0.147 | 0.883 |
| region5 | Precuneus | -3.442 | <0.001\* | -0.714 | 0.475 |
| region6 | Middle cingulate cortex | 0.129 | 0.897 | 0.864 | 0.388 |

Note. p threshold after Bonferroni multiple comparison method is puncorrected = 0.0083.

Table S3. Statistics for the interactions with age and gender for structural networks

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Network ID | Name | Interaction with age | | Interaction with gender | |
| t | puncorrected | t | puncorrected |
| network1 | Medial default mode network | 0.450 | 0.653 | -0.582 | 0.560 |
| network2 | Cerebellar network A | 0.375 | 0.708 | 0.767 | 0.443 |
| network3 | Cerebellar network B | -0.468 | 0.640 | 1.124 | 0.261 |
| network4 | Basal ganglia network | -0.079 | 0.937 | 0.999 | 0.318 |
| network5 | Superior temporal network | 0.681 | 0.496 | -1.119 | 0.263 |
| network6 | Posterior default mode network | -0.629 | 0.530 | 2.263 | 0.024 |
| network7 | Temporal pole network | -1.115 | 0.265 | -0.268 | 0.789 |
| network8 | Prefrontal network | -1.774 | 0.076 | 0.184 | 0.854 |
| network9 | Medial prefrontal network | 0.536 | 0.592 | -0.758 | 0.449 |
| network10 | Angular network | -1.800 | 0.072 | 1.459 | 0.145 |
| network11 | Superior temporal network | -0.334 | 0.738 | 0.855 | 0.393 |
| network12 | Parietal network | -0.527 | 0.598 | 0.619 | 0.536 |
| network13 | Visual network | -0.654 | 0.513 | 1.109 | 0.268 |

Note. p threshold after Bonferroni multiple comparison method is puncorrected = 0.0038.