**Supplementary**

A comparative meta-analysis of structural magnetic resonance imaging studies and gene expression profiles revealing the similarities and differences between late life depression and mild cognitive impairment

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**Preprocessing of gene expression from the Allen Human Brain Atlas** **(AHBA) database and Z-map of LLD and MCI**

The microarray-based gene expression data were acquired from the Allen Human Brain Atlas (AHBA) website (<https://human.brain-map.org/>). The gene expression datasets were extracted from the post-mortem brain tissues of six donors, who were a 24-year-old (H0351.2001) and a 39-year-old (H0351.2002) African American male; a 57-year-old (H0351.1009), a 31-year-old (H0351.1012) and a 55-year-old (H0351.1016) European-ancestry male; as well as a 49-year-old Hispanic female (H0351.1015) (Hawrylycz et al., 2015). The profiles included 20,737 gene expressions represented by 58,692 probes. As right hemisphere samples were only available in two out of the six donors in the AHBA dataset, only tissue samples from the left hemisphere (n = all 6 donors) were included.

The expression data were preprocessed according to the 5 major steps: (i) probe-to-gene annotations; (ii) data filtering to discriminate expression signal from noise; (iii) probe selection to measure the expression level of a single gene at different exon; (iv) assigning and mapping samples to the HCP atlas (https://humanconnectome.org/); (v) normalizing expression values to account for outlying values and inter-participant variances. The open-source code concerning the preprocessing procedure was used (<https://github.com/BMHLab/AHBAprocessing>). After preprocessing, each tissue sample had 10,027 probes. All brain tissue samples were then spatially coregistered to a cortical parcellation atlas with 360 regions from the human connectome project (HCP) (Glasser et al., 2016). The mean gene expression value of all brain tissue samples in each region was calculated, and the expression level of all genes in the left hemisphere regions was used for regression analysis.

***Table S1.* Demographic, clinical characteristics, and quality assessment of LLD studies.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| study | Diagnostic  Tool | Sample Size  (Female%) | | Age  mean (SD) | | Education  mean (SD) | | MMSE  mean (SD) | | Medication | NOS |
| LLD | HCs | LLD | HCs | LLD | HCs | LLD | HCs |
| Colloby et al. ([2011](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_1" \o "Colloby, 2011 #3)) | DSM-IV | 38  (71%) | 30  (67%) | 74.10  (6.10) | 74.40  (6.40) | - | - | 28.80  (1.10) | 29.50  (0.80) | - | 6 |
| Egger et al. ([2008](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_2" \o "Egger, 2008 #4)) | DSM-IV | 14  (71%) | 20  (65%) | 71.40  (7.49) | 72.30  (7.70) | 9.40  (2.24) | 10.80  (2.69) | 27.21  (0.97) | 28.57  (0.81) | - | 8 |
| Harada et al. ([2016](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_4" \o "Harada, 2016 #49)) | DSM-IV | 45  (58%) | 61  (72%) | 60.20  (8.20) | 62.90  (7.60) | 13.30  (2.30) | 13.60  (2.30) | 28.00  (2.20) | 28.80  (1.70) | 91% | 7 |
| Hwang et al. ([2010](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_6" \o "Hwang, 2010 #6)) | DSM-IV | 70  (0%) | 26  (0%) | 79.40  (5.30) | 79.50  (4.30) | 7.80  (4.60) | 8.10  (5.40) | 26.50  (3.40) | 27.80  (2.10) | - | 7 |
| Koolschijn et al. ([2010](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_7" \o "Koolschijn, 2010 #7)) | DSM-IV | 28  (100%) | 38  (100%) | 64.04  (10.90) | 61.89  (11.03) | 10.89  (4.05) | 11.08  (2.93) | 27.39  (2.46) | 28.54  (1.56) | 79% | 6 |
| Marano et al. (2015) | DSM-IV | 17  (59%) | 17  (47%) | 66.90  (6.40) | 66.00  (7.90) | 15.10  (2.40) | 15.40  (2.80) | 28.80  (0.70) | 28.20  (1.90) | 100% | 7 |
| Oudega et al. ([2014](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_9" \o "Oudega, 2014 #9)) | DSM-IV | 55  (66%) | 23  (52%) | 72.30  (7.80) | 70.30  (6.30) | - | - | - | - | 13% | 6 |
| Ribeiz et al. ([2013](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_10" \o "Ribeiz, 2013 #10)) | DSM-IV | 30  (77%) | 22  (77%) | 70.73  (6.59) | 70.41  (7.58) | 6.50  (5.49) | 9.91  (5.12) | 24.90  (4.19) | 27.95  (1.84) | 13% | 6 |
| Ries et al. ([2009](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_11" \o "Ries, 2009 #11)) | DSM-IV | 15  (67%) | 32  (56%) | 66.30  (5.30) | 68.40  (7.40) | 14.60  (2.40) | 17.30  (2.30) | 29.00  (1.00) | 29.20  (1.90) | - | 7 |
| Sin et al. ([2018](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_12" \o "Sin, 2018 #12)) | DSM-V | 29  (66%) | 23  (64%) | 68.58  (5.09) | 67.10  (4.80) | - | - | - | - | 100% | 5 |
| Tsa et al. ([2022](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_13" \o "Tsai, 2022 #13)) | DSM-IV | 36  (78%) | 17  (53%) | 65.60  (7.30) | 64.10  (7.90) | 9.70  (4.80) | 10.90  (5.20) | - | - | 89% | 6 |
| Xie et al. ([2012](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_14" \o "Xie, 2012 #48)) | DSM-IV | 18  (48%) | 25  (48%) | 68.61  (6.81) | 74.28  (8.25) | 14.61  (2.57) | 15.32  (2.87) | 28.06  (1.21) | 28.92  (1.22) | 89% | 5 |
| Yuan et al. ([2008](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_15" \o "Yuan, 2008 #15)) | DSM-IV | 19  (53%) | 16  (50%) | 67.10  (7.20) | 67.70  (3.80) | 12.60  (4.30) | 13.10  (4.90) | 27.90  (2.60) | 28.10  (1.40) | 100% | 8 |
| Mean/Summary |  | 414  (57%) | 350  (61%) | 69.97 | 68.52 | 10.63 | 12.73 | 27.43 | 28.65 |  |  |

LLD, late-life depression; DSM: Diagnostic and Statistical Manual of Mental Disorders; MMSE, Mini Mental State Examination; NOS, Newcastle-Ottawa scale. All the diagnoses of depression relied on DSM. Articles were classified as having good, moderate, or poor quality using NOS scores of 9–8, 7–5, and 4–0, respectively; only those with good or moderate quality are eligible for meta-analysis.

***Table S2.* Demographic, clinical characteristics, and quality assessment of MCI studies.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| study | Diagnostic  Tool | Sample Size  (Female%) | | Age  mean (SD) | | Education  mean (SD) | | MMSE  mean (SD) | | Medication | NOS |
| MCI | HCs | MCI | HCs | MCI | HCs | MCI | HCs |
| Agosta et al. ([2011](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_1" \o "Agosta, 2011 #1)) | Petersen (2001) | 15  (47%) | 15  (60%) | 70.40  (7.20) | 69.80  (6.00) | 9.00  (4.60) | 12.30  (3.60) | 25.80  (0.90) | 28.80  (1.50) | - | 9 |
| Barbeau et al. (2008) | Petersen (2001) | 28  (57%) | 28  (46%) | 69.30  (8.60) | 63.30  (7.20) | - | - | 27.40  (1.40) | 28.90  (1.00) | - | 5 |
| Benavides-Varela et al. (2020) | Petersen (2001) | 43  (42%) | 37  (46%) | 75.44  (47.44) | 68.89  (113.99) | 11.00  (21.67) | 12.35  (19.57) | 26.39  (2.84) | 28.73  (1.17) | - | 7 |
| Bonekamp et al. (2010) | DSM-IV | 10  (50%) | 20  (50%) | 72.70  (5.30) | 75.30  (4.80) | - | - | 26.30  (2.90) | 28.90  (1.20) | - | 5 |
| Bozzali et al. (2006) | Petersen (2001) | 14  (55%) | 20  (65%) | 70.50  (10.50) | 65.80  (6.80) | - | - | 25.80  (1.70) | 27.30  (1.20) | - | 5 |
| Bozzali et al. (2006) | Petersen (2001) | 8  (55%) | 20  (65%) | 70.50  (10.50) | 65.80  (6.80) | - | - | 24.80  (1.50) | 27.30  (1.20) | - | 5 |
| Bozzali et al. (2012) | Petersen (2001) | 23  (52%) | 14  (29%) | 71.20  (6.70) | 68.00  (8.50) | 10.30  (4.50) | 12.80  (2.90) | 24.90  (1.20) | 28.90  (1.20) | - | 6 |
| Brambati et al. (2009) | Petersen (2001) | 25  (68%) | 13  (62%) | 73.40  (6.87) | 75.00  (5.00) | 13.21  (4.49) | 14.90  (5.00) | 27.38  (1.79) | 29.10  (1.20) | - | 8 |
| Brys et al. (2009) | Petersen (2001) | 8  (88%) | 21  (71%) | 70.30  (8.30) | 65.00  (10.00) | 12.30  (3.20) | 15.00  (3.80) | 27.30  (1.90) | 29.70  (0.50) | - | 6 |
| Brys et al. (2009) | Petersen (2001) | 16  (63%) | 21  (71%) | 71.10  (6.90) | 65.00  (10.00) | 14.40  (3.60) | 15.00  (3.80) | 28.40  (1.70) | 29.70  (0.50) | - | 6 |
| Caroli et al. ([2007](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_9" \o "Caroli, 2007 #9)) | Petersen (2004) | 9  (44%) | 17  (53%) | 69.00  (3.00) | 69.00  (3.00) | 11.40  (5.70) | 9.80  (4.10) | 26.80  (1.80) | 27.80  (1.60) | - | 6 |
| Caroli et al. ([2007](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_9" \o "Caroli, 2007 #9)) | Petersen (2004) | 14  (43%) | 17  (53%) | 71.00  (8.00) | 69.00  (3.00) | 8.60  (3.60) | 9.80  (4.10) | 27.00  (2.00) | 27.80  (1.60) | - | 6 |
| Chen et al. ([2020](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_10" \o "Chen, 2020 #10)) | Petersen (2004) | 20  (35%) | 29  (59%) | 71.35  (5.90) | 70.69  (5.40) | 10.88  (2.90) | 12.17  (3.20) | 27.45  (2.10) | 28.55  (1.40) | 0% | 8 |
| Chetelat et al. ([2002](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_11" \o "Chetelat, 2002 #11)) | Petersen (2001) | 22  (55%) | 22  (55%) | 71.00  (8.00) | 66.60  (7.20) | - | - | 27.30  (1.50) | - | - | 5 |
| Clerx et al. ([2013](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_12" \o "Clerx, 2013 #12)) | Petersen (2001) | 18  (0%) | 18  (0%) | 65.11  (4.50) | 64.56  (3.40) | - | - | 27.61  (2.30) | 28.89  (0.90) | - | 7 |
| Defrancesco et al. ([2014](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_14" \o "Defrancesco, 2014 #13)) | Petersen (2004) | 13  (69%) | 28  (57%) | 73.30  (6.70) | 72.20  (7.10) | 10.30  (4.50) | 9.50  (3.70) | 25.20  (1.70) | 28.60  (1.20) | 0% | 7 |
| Defrancesco et al. ([2014](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_14" \o "Defrancesco, 2014 #13)) | Petersen (2004) | 14  (57%) | 28  (57%) | 72.80  (7.80) | 72.20  (7.10) | 9.60  (2.80) | 9.50  (3.70) | 27.50  (1.80) | 28.60  (1.20) | 0% | 7 |
| Derflinger et al. ([2011](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_15" \o "Derflinger, 2011 #14)) | Petersen (2001) | 24  (54%) | 30  (67%) | 69.00  (9.00) | 67.00  (8.70) | 10.40  (2.00) | 10.60  (1.70) | 26.80  (1.70) | - | - | 7 |
| Dos Santos et al. ([2011](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_16" \o "Dos Santos, 2011 #15)) | NIA-AA | 60  (57%) | 32  (53%) | 70.33  (6.32) | 68.69  (7.36) | 9.40  (1.59) | 10.15  (2.04) | 26.38  (1.78) | 29.22  (0.79) | - | 6 |
| Eustache et al. ([2016](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_18" \o "Eustache, 2016 #16)) | NIA-AA | 14  (50%) | 14  (57%) | 71.10  (4.70) | 70.90  (4.60) | 11.00  (2.90) | 11.90  (2.80) | 25.80  (1.50) | 28.40  (0.80) | - | 7 |
| Ford et al. ([2014](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_19" \o "Ford, 2014 #17)) | Petersen (2001) | 65  (54%) | 55  (47%) | 70.00  (-) | 75.00  (-) | 11.20  (3.20) | 11.70  (2.90) | 28.00  (-) | 29.00  (-) | - | 6 |
| Gold et al. ([2010](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_21" \o "Gold, 2010 #18)) | Petersen (2001) | 12  (42%) | 14  (50%) | 77.90  (6.30) | 77.00  (4.40) | 15.30  (1.90) | 16.40  (2.70) | - | - | - | 8 |
| Gupta et al. ([2019](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_22" \o "Gupta, 2019 #19)) | NIA-AA | 39  (36%) | 171  (51%) | 73.24  (7.44) | 71.66  (5.43) | 8.20  (5.19) | 9.16  (5.54) | - | - | 0% | 5 |
| Haller et al. ([2014](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_23" \o "Haller, 2014 #20)) | Petersen (2004) | 17  (41%) | 17  (65%) | 70.70  (4.60) | 68.30  (2.80) | 10.20  (-) | 10.20  (-) | 28.30  (1.20) | 29.20  (1.10) | - | 9 |
| Hamalainen et al. ([2007](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_24" \o "Hamalainen, 2007 #21)) | Petersen (2001) | 14  (71%) | 21  (81%) | 72.40  (7.30) | 71.20  (4.90) | 8.10  (2.60) | 7.90  (2.90) | 25.60  (3.10) | 27.70  (2.00) | 0% | 8 |
| Hamalainen et al. ([2007](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_25" \o "Hamalainen, 2007 #22)) | Petersen (2001) | 56  (73%) | 22  (50%) | 72.56  (4.09) | 72.90  (4.50) | 6.60  (1.58) | 6.80  (1.70) | 23.68  (2.25) | 26.90  (1.80) | 0% | 6 |
| Han et al. ([2021](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_26" \o "Han, 2021 #23)) | Petersen (2004) | 165  (64%) | 71  (-) | 73.50  (7.36) | 70.40  (3.90) | 8.74  (5.37) | - | 22.40  (6.10) | - | - | 7 |
| Han et al. ([2012](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_27" \o "Han, 2012 #24)) | Petersen (2001) | 17  (59%) | 18  (61%) | 69.70  (7.60) | 66.50  (6.20) | 8.80  (4.00) | 8.40  (5.60) | 25.20  (3.50) | 29.20  (0.70) | 0% | 7 |
| Hirata et al. ([2005](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_30" \o "Hirata, 2005 #25)) | Petersen (2001) | 30  (48%) | 41  (52%) | 70.60  (8.40) | 70.10  (7.70) | - | - | 26.00  (1.50) | 28.70  (1.50) | - | 6 |
| Hong et al. ([2015](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_31" \o "Hong, 2015 #26)) | Petersen (2001) | 29  (68%) | 28  (68%) | 70.50  (5.17) | 70.60  (6.48) | 8.60  (4.36) | 8.80  (6.16) | 25.50  (2.81) | 28.70  (1.36) | - | 9 |
| Hoppstadter et al. ([2013](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_32" \o "Hoppstadter, 2013 #27)) | Petersen (2004) | 14  (29%) | 10  (60%) | 68.00  (4.00) | 67.80  (4.69) | 11.30  (2.50) | 12.90  (3.80) | 27.85  (1.29) | 28.88  (1.05) | - | 7 |
| Jauhiainen et al. ([2008](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_34" \o "Jauhiainen, 2008 #28)) | Petersen (2004) | 7  (43%) | 13  (85%) | 74.70  (1.90) | 74.40  (1.20) | 7.90  (1.00) | 8.80  (0.70) | 25.40  (1.00) | 27.90  (0.70) | - | 7 |
| Kang et al. ([2019](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_35" \o "Kang, 2019 #29)) | Petersen (2001) | 30  (47%) | 37  (60%) | 76.90  (4.30) | 73.90  (2.00) | 9.00  (4.80) | 10.80  (4.00) | 21.70  (4.30) | 27.10  (1.70) | 0% | 6 |
| Kang et al. ([2019](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_35" \o "Kang, 2019 #29)) | Petersen (2001) | 35  (54%) | 37  (60%) | 77.30  (4.10) | 73.90  (2.00) | 9.60  (4.30) | 10.80  (4.00) | 21.70  (4.50) | 27.10  (1.70) | 0% | 6 |
| Kim et al. ([2020](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_36" \o "Kim, 2020 #30)) | DSM-IV | 10  (70%) | 9  (67%) | 73.10  (7.90) | 70.70  (3.50) | - | - | 16.50  (4.90) | 28.60  (1.10) | 0% | 5 |
| Kunst et al. ([2019](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_38" \o "Kunst, 2019 #31)) | Petersen (2001) | 27  (63%) | 58  (69%) | 69.80  (6.90) | 67.50  (7.30) | 14.30  (3.00) | 15.40  (2.50) | 27.10  (1.30) | 28.50  (1.20) | - | 6 |
| Lee et al. ([2010](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_39" \o "Lee, 2010 #32)) | Petersen (2001) | 78  (59%) | 21  (-) | 70.50  (8.00) | 70.70  (2.70) | 9.40  (4.90) | - | 25.10  (2.40) | - | - | 7 |
| Liu et al. ([2022](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_40" \o "Liu, 2022 #33)) | Petersen (2001) | 114  (60%) | 101  (64%) | 72.35  (5.23) | 71.69  (4.95) | 10.78  (3.71) | 10.24  (2.73) | 24.11  (1.01) | 28.31  (0.97) | - | 7 |
| Mitolo et al. ([2013](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_42" \o "Mitolo, 2013 #34)) | Petersen (2001) | 20  (50%) | 14  (71%) | 74.75  (6.93) | 68.64  (4.53) | 7.85  (4.39) | 8.57  (4.88) | 25.80  (3.35) | 29.57  (0.75) | - | 7 |
| Pa et al. ([2009](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_44" \o "Pa, 2009 #35)) | Petersen (2004) | 26  (50%) | 36  (64%) | 68.00  (6.60) | 64.80  (8.20) | 17.50  (1.70) | 17.00  (2.00) | 28.70  (1.20) | 29.80  (0.60) | - | 6 |
| Pennanen et al. ([2005](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_45" \o "Pennanen, 2005 #36)) | Petersen (2001) | 51  (67%) | 32  (59%) | 72.00  (5.00) | 74.00  (4.00) | 7.00  (2.00) | 7.00  (2.00) | 24.00  (2.00) | 27.00  (2.00) | - | 7 |
| Rami et al. ([2009](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_46" \o "Rami, 2009 #37)) | Petersen (2001) | 14  (69%) | 27  (63%) | 72.90  (4.80) | 74.30  (5.30) | 7.40  (4.20) | 9.40  (5.20) | 26.00  (2.00) | 27.40  (1.00) | - | 6 |
| Rami et al. ([2012](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_47" \o "Rami, 2012 #38)) | Petersen (2001) | 14  (-) | 24  (-) | 71.60  (5.30) | 71.40  (6.60) | 8.50  (5.00) | 9.00  (4.70) | 24.80  (1.60) | 28.10  (1.40) | - | 6 |
| Remillard-Pelchat et al. ([2022](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_48" \o "Remillard-Pelchat, 2022 #39)) | Petersen (2004) | 17  (29%) | 41  (39%) | 67.90  (4.40) | 63.20  (8.20) | 12.10  (3.80) | 14.60  (4.10) | - | - | - | 6 |
| Saykin et al. ([2006](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_51" \o "Saykin, 2006 #40)) | Petersen (2004) | 40  (43%) | 40  (70%) | 72.90  (7.10) | 71.00  (5.10) | 16.30  (3.30) | 16.60  (2.70) | 27.20  (2.20) | 29.10  (1.00) | 3% | 8 |
| Schmidt-Wilcke et al. ([2009](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_52" \o "Schmidt-Wilcke, 2009 #41)) | Petersen (2001) | 18  (44%) | 18  (44%) | 65.70  (7.20) | 63.00  (10.70) | 13.00  (3.60) | 12.60  (3.30) | - | - | - | 8 |
| Serra et al. ([2013](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_53" \o "Serra, 2013 #42)) | Petersen (2004) | 15  (27%) | 28  (37%) | 70.90  (9.00) | 63.40  (8.90) | 11.30  (4.40) | 13.10  (3.50) | 25.40  (1.70) | 28.40  (1.70) | - | 6 |
| Shiino et al. ([2006](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_54" \o "Shiino, 2006 #43)) | Petersen (2004) | 20  (50%) | 88  (55%) | 67.70  (9.00) | 68.70  (8.70) | - | - | 26.80  (1.88) | 29.09  (1.47) | - | 6 |
| Trivedi et al. ([2006](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_56" \o "Trivedi, 2006 #44)) | Petersen (2004) | 15  (40%) | 15  (40%) | 73.30  (6.72) | 73.60  (7.10) | 16.30  (2.81) | 16.70  (2.50) | 27.80  (1.80) | 29.70  (0.50) | - | 8 |
| van de Mortel et al. ([2021](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_58" \o "van de Mortel, 2021 #47)) | NIA-AA | 295  (43%) | 351  (54%) | 71.00  (7.47) | 75.00  (5.79) | 15.90  (2.64) | 16.30  (2.70) | 28.30  (1.55) | 29.10  (1.13) | 0% | 6 |
| Venneri et al. ([2011](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_59" \o "Venneri, 2011 #46)) | Petersen (2001) | 25  (48%) | 25  (60%) | 70.52  (6.44) | 70.29  (6.49) | 8.96  (4.41) | 9.32  (4.46) | 28.24  (1.23) | 28.68  (1.52) | - | 7 |
| Wang et al. ([2012](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_60" \o "Wang, 2012 #47)) | Petersen (2001) | 40  (40%) | 30  (37%) | 77.30  (6.60) | 76.10  (7.20) | 11.40  (4.30) | 13.50  (2.60) | - | - | - | 6 |
| Xie et al. ([2012](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_61" \o "Xie, 2012 #48)) | Petersen (2004) | 17  (65%) | 25  (48%) | 75.12  (6.62) | 74.28  (8.25) | 13.47  (2.07) | 15.32  (2.87) | 27.29  (1.83) | 28.92  (1.22) | 48% | 6 |
| You et al. ([2021](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_62" \o "You, 2021 #49)) | NIA-AA | 60  (55%) | 30  (57%) | 67.32  (9.44) | 64.67  (8.01) | 9.00  (-) | 10.00  (-) | 24.00  (-) | 28.00  (-) | 0% | 7 |
| Zhao et al. ([2015](file://C:\\Users\\Administrator\\Desktop\\Supp_20240207.docx" \l "_ENREF_64" \o "Zhao, 2015 #50)) | Petersen (2001) | 34  (59%) | 34  (47%) | 68.00  (7.60) | 66.90  (6.70) | 10.80  (3.30) | 11.50  (3.90) | 25.50  (1.60) | 29.20  (0.90) | - | 7 |
| Mean/Summary |  | 1878  (52%) | 2046  (52%) | 71.57 | 70.82 | 11.30 | 12.40 | 25.83 | 28.65 |  |  |

MCI: mild cognitive impairment; NIA-AA: National Institute on Aging and Alzheimer’s Association; DSM: Diagnostic and Statistical Manual of Mental Disorders; MMSE, Mini Mental State Examination; NOS, Newcastle-Ottawa scale. All the diagnoses of MCI relied on reliable clinical criteria. The criteria proposed by Petersen (2001) include (i) memory complaint, preferably corroborated by an informant; (ii) impaired memory function for age and education; (iii) preserved general cognitive function; (iv) intact activities of daily living; and (v) not demented. The criteria proposed by Petersen (2004) include (i) memory complaint usually corroborated by an informant; (ii) objective memory impairment for age; (iii) essentially preserved general cognitive function; (iv) largely intact functional activities; and (v) not demented. Articles were classified as having good, moderate, or poor quality using NOS scores of 9–8, 7–5, and 4–0, respectively; only those with good or moderate quality are eligible for meta-analysis.

***Table S3.* Results of meta-analysis, heterogeneity assessment and publication bias of GM atrophy in LLD and MCI.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Cluster | | Peak | | | *I2* | Egger's *p* |
| Description | Voxels | MNI (x,y,z) | SDM-*Z* | *p* |
| *LLD < HC* |  |  |  |  |  |  |
| R. gyrus rectus | 1215 | 2,22,-18 | -3.237 | 0.0006 | 4.70 | 0.669 |
| L.middle temporal gyrus | 154 | -50,-66,12 | -2.503 | 0.0061 | 13.55 | 0.903 |
| L. inferior frontal gyrus, orbital part | 96 | -38,32,-12 | -2.466 | 0.0068 | 6.88 | 0.801 |
| R. anterior thalamic projections | 78 | 46,32,6 | -2.29 | 0.0110 | 3.31 | 0.558 |
| L. anterior cingulate/ paracingulate gyri | 63 | 0,42,8 | -2.172 | 0.0149 | 6.12 | 0.799 |
| R. insula | 36 | 42,10,-4 | -2.055 | 0.0199 | 1.60 | 0.513 |
| R. median cingulate/ paracingulate gyri | 32 | 12,-40,44 | -2.143 | 0.0161 | 14.11 | 0.339 |
| L. insula | 24 | -30,16,2 | -1.898 | 0.0288 | 35.04 | 0.493 |
| L. middle temporal gyrus | 24 | -60,-46,2 | -1.908 | 0.0282 | 16.20 | 0.928 |
| *MCI < HC* |  |  |  |  |  |  |
| R. parahippocampal gyrus | 12069 | 24,-2,-28 | -5.342 | <0.001 | 49.69 | 0.181 |
| L. hippocampus | 6143 | -26,-8,-14 | -5.831 | <0.001 | 5.96 | 0.251 |
| L. precuneus | 2325 | 0,-44,38 | -3.693 | 0.001 | 0.21 | 0.967 |
| L. angular gyrus | 656 | -50,-62,28 | -2.831 | 0.0023 | 51.24 | 0.312 |

R., right; L., left; MNI, Montreal Neurological Institute; SDM, signed differential mapping; uncorrected *p*<0.05, and voxel extent ≥10.

***Table S4.* Shared abnormal regions in GM between LLD and MCI.**

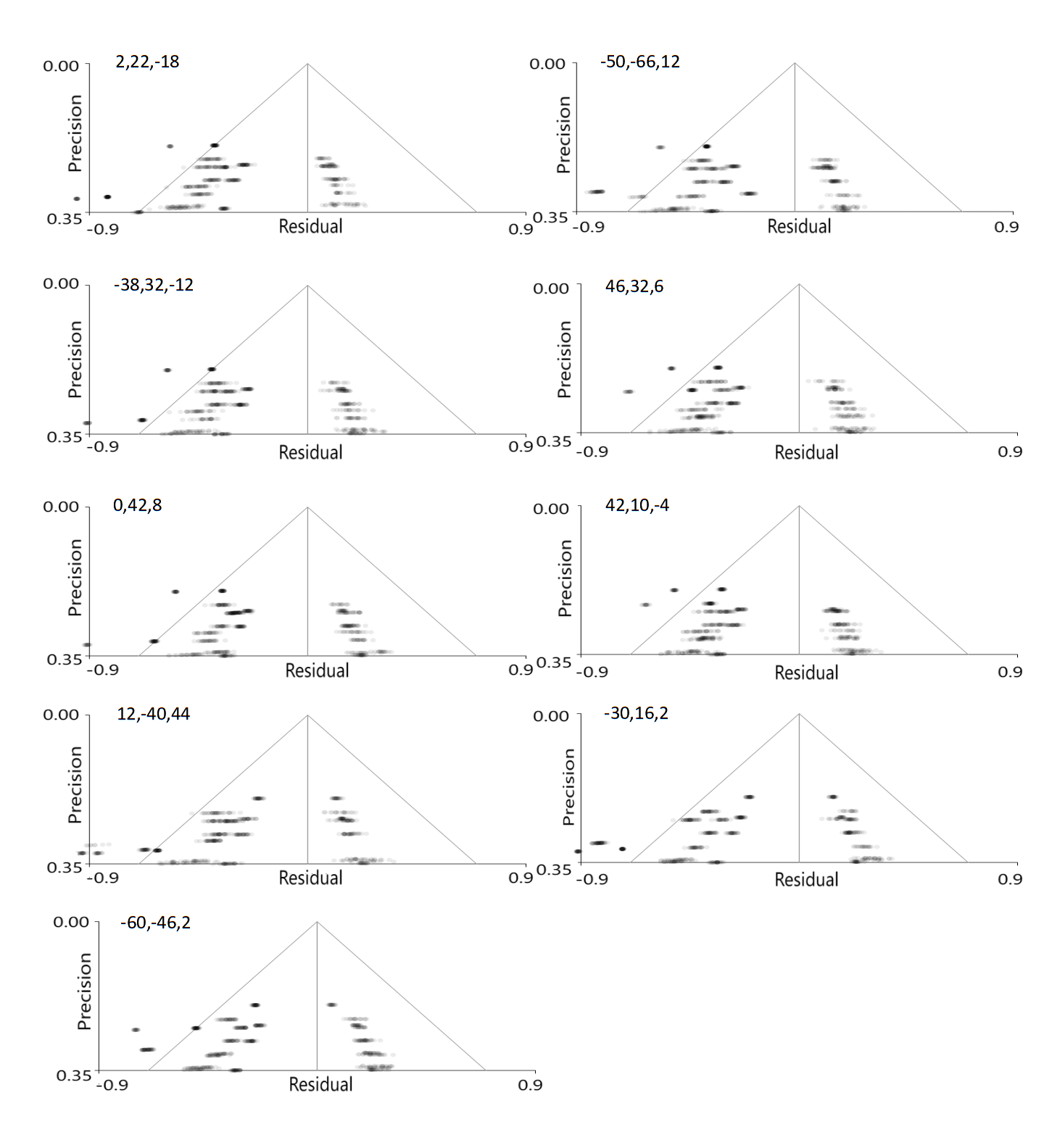
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cluster | | Peak | *I2* | |
| Region | Voxels | MNI (x,y,z) | MCI < HC | LLD < HC |
| R.median cingulate/  paracingulate gyri | 16 | 4,-30,50 | 3.83 | 27.75 |
| R. insula | 10 | 34,16,2 | 3.09 | 6.59 |

R., right; L., left; MNI, Montreal Neurological Institute; threshold with p=0.0025, peak height threshold with *p*=0.00025, voxel extent ≥10.

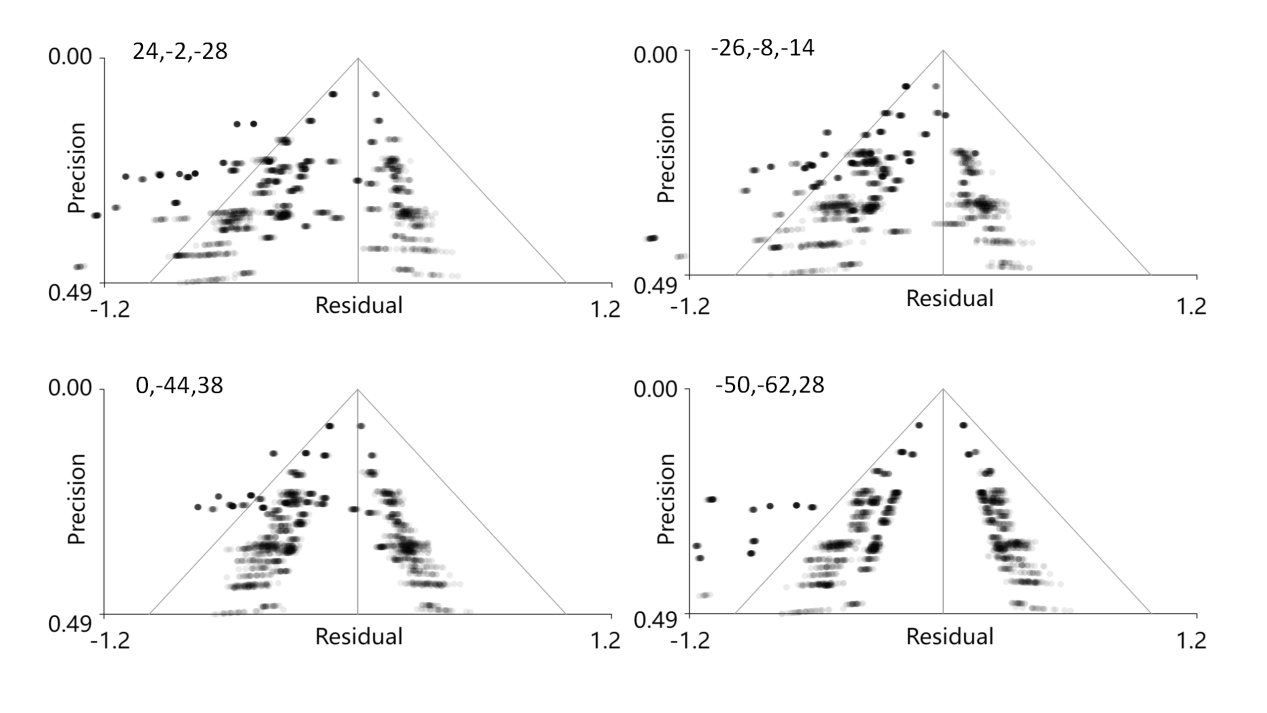
***Table S5.* Discrepant abnormal regions in GM between LLD and MCI.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Cluster | | Peak | | | *I2* | Egger's *p* |
| Region | Voxels | MNI (x,y,z) | SDM-*Z* | *p* |
| L. hippocampus | 179 | -26,-14,-18 | -2.251 | 0.0122 | 9.78 | 0.492 |
| R. parahippocampal gyrus | 86 | 26,0,-32 | -2.017 | 0.0219 | 24.22 | 0.574 |

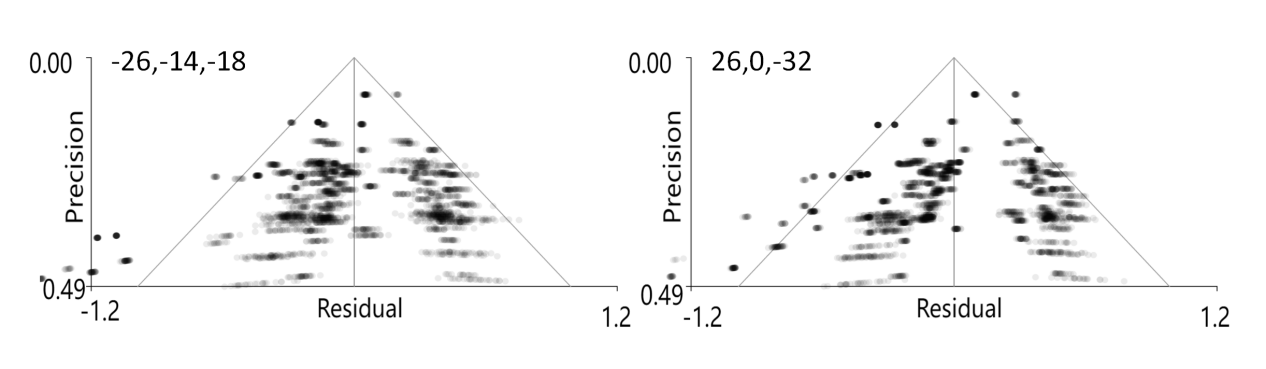
R., right; L., left; MNI, Montreal Neurological Institute; SDM, signed differential mapping; uncorrected *p*<0.05, and voxel extent ≥1.



***Figure S1.* Funnel plot analysis for significant coordinates in comparison between LLDs and HCs.**



***Figure S2.* Funnel plot analysis for significant coordinates in comparison between MCIs and HCs.**



***Figure S3.*** **Funnel plot analysis for significant coordinates in conjunction analysis (shared abnormality between LLD and MCI).**

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