# Supplementary S2 – Main analyses

## Inter-hemispheric mean diffusivity



**Figure S2.1**. Average mean diffusivity across three main inter-hemispheric white matter tracts.  
LA – left tau asymmetric; S – tau symmetric – RA – right tau asymmetric.

## Network Based Statistics

Whole-brain connectome analysis using Network Based Statistics (NBS) showed some minor differences between the tau asymmetry groups (Table S2.1; Fig. S2.2). Higher functional connectivity in the left asymmetric group compared to the symmetric group was found in a cluster of nodes primarily located in the right hemisphere which also included a few inter-hemispheric connections (threshold=3.0; C=9, p=0.018). The right asymmetric group showed reduced structural connectivity compared to the symmetric group in a cluster of nodes within the right hemisphere (threshold=3.0; C=4, p=0.016). However, as the statistical significance levels were relatively uncertain as with higher thresholds, we did not encounter any significant components as we did with lower thresholds, we did not conclude anything robust from this analysis. Moreover, these current differences are likely due to tau burden in the affected hemisphere for subjects with asymmetric tau distribution which we were not able to adjust for (i.e., we adjusted for global average tau uptake).

***Table S2.1****. NBS analysis comparisons of functional and structural connectivity between tau asymmetry groups.   
Each column represents a contrast between groups and each row shows the t-statistic threshold (t) used. Each cell represents the maximum detected component size C and the significance level i.e., C (p-value). A – tau asymmetric; LA – left tau asymmetric; S – tau symmetric – RA – right tau asymmetric; FC – functional connectivity; SC – structural connectivity.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **FC** | **A > S** | **A < S** | **LA > S** | **LA < S** | **RA > S** | **RA < S** |
| **t = 2.5** | 19 (p=0.045) | - | 23 (p=0.041) | - | 11 (p=0.072) | 2 (p=0.239) |
| **t = 3.0** | 2 (p=0.077) | - | 9 (p=0.018) | - | 3 (p=0.056) | 1 (p=0.161) |
| **t = 3.5** | - | - | 1 (p=0.053) | - | 1 (p=0.054) | - |
| **SC** | **A > S** | **A < S** | **LA > S** | **LA < S** | **RA > S** | **RA < S** |
| **t = 2.5** | 1 (p=0.684) | 5 (p=0.104) | 3 (p=0.231) | 6 (p=0.074) | 2 (p=0.423) | 13 (p=0.031) |
| **t = 3.0** | - | 2 (p=0.081) | 1 (p=0.384) | 1 (p=0.241) | 2 (p=0.156) | 4 (p=0.016) |
| **t = 3.5** | - | 1 (p=0.073) | 1 (p=0.127) | - | - | - |



**Figure S2.2**. Components detected using NBS analysis between the tau asymmetry groups.  
FC – functional connectivity; SC – structural connectivity; LA – left tau asymmetric; S – tau symmetric – RA – right tau asymmetric; C – component size; NBS – Network Based Statistic; t – threshold used in NBS

## Difference in Aβ onset between hemispheres across ROIs



**Figure S2.4**. Difference between the SILA-estimated Aβ onset between hemispheres across ROIs.

## Longitudinal association between baseline Aβ laterality and tau laterality over time

***Table S2.2****. Demographics of the longitudinal dataset.   
Categorical variables have been presented as 'count (%)', normally distributed continuous variables as 'mean (SD)' and non-normally distributed variables as ‘median [IQR]’. T- – tau negative; T+ – tau positive; M – male; F – female; CU – cognitively unimpaired; MCI – mild cognitive impairment; AD – Alzheimer’s disease; SUVR – standardised uptake value ratio; LI – laterality index; Aβ – amyloid-beta; MMSE – Mini‐Mental State Examination; mPACC – modified Preclinical Alzheimer Cognitive Composite.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Longitudinal A+ (n=289)** | | |
|  |  | **T- (n=180)** | **T+ (n=109)** | **P-value** |
| **Age, years** | | 73.09 (7.89) | 72.08 (7.06) | 0.264 |
| **Sex** | **M** | 92 (51%) | 57 (52%) | 0.941 |
| **F** | 88 (49%) | 52 (48%) |  |
| **Education, years** | | 12.78 (4.08) | 12.98 (3.68) | 0.670 |
| **Diagnosis** | **CU** | 116 (64%) | 36 (33%) | <0.001 |
| **MCI** | 64 (36%) | 69 (63%) |  |
| **AD** | 0 (0%) | 4 (4%) |  |
| **Temporal tau, SUVR** | | 1.19 [1.14,1.24] | 1.61 [1.42,2.00] | <0.001 |
| **Absolute Temporal tau LI** | | 1.31 (1.17) | 8.32 (6.10) | <0.001 |
| **Global Aβ, SUVR** | | 1.27 (0.19) | 1.50 (0.20) | <0.001 |
| **ApoE4** | **0** | 62 (34%) | 17 (16%) | 0.001 |
| **1** | 99 (55%) | 71 (65%) |  |
| **2** | 19 (11%) | 21 (19%) |  |
| **MMSE** | | 29.00 [27.00,29.25] | 27.00 [26.00,29.00] | <0.001 |
| **mPACC** | | -0.56 [-1.53,-0.00] | -1.50 [-2.40,-0.63] | <0.001 |

**Table S2.3**. Summary of the linear mixed effects model within A+ subsample predicting tau laterality over time with baseline Aβ laterality at Global ROI.  
The statistical significance of the baseline Aβ laterality and its interaction with time are annotated with **green** if it reached p<0.05 and **red** if it did not.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| A+ (n=289 with a total of 707 datapoints) LME: Tau LI ~ time \* (AgeBAS + Sex + Aβ LIBAS) + [time | participant] | | | | |
| **ROI** | **Global** | | | |
|  | **β** | **SE** | **95% CI** | **p** |
| **Intercept** | -0.052 | 0.056 | [-0.162, 0.058] | 0.350 |
| **Time** | -0.001 | 0.016 | [-0.032, 0.031] | 0.964 |
| **AgeBAS** | -0.007 | 0.040 | [-0.086, 0.072] | 0.864 |
| **Sex** | 0.023 | 0.081 | [-0.135, 0.181] | 0.776 |
| **Aβ LIBAS** | 0.379 | 0.040 | [0.301, 0.458] | **<0.001** |
| **Time × AgeBAS** | -0.000 | 0.012 | [-0.023, 0.022] | 0.994 |
| **Time × Sex** | -0.000 | 0.023 | [-0.046, 0.045] | 0.995 |
| **Time × Aβ LIBAS** | 0.025 | 0.012 | [0.003, 0.048] | **0.028** |

**Table S2.4**. Summary of the linear mixed effects model within A+T- subsample predicting tau laterality over time with baseline Aβ laterality at Braak ROIs.  
The statistical significance of the baseline Aβ laterality and its interaction with time are annotated with **green** if it reached p<0.05 and **red** if it did not. Furthermore, **\*** indicates whether the p-value survived the statistical threshold after Bonferroni correction.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| A+T- (n=180 with a total of 452 datapoints)  LME: **Tau LI** ~ **time** \* (AgeBAS + Sex + **Aβ LIBAS**) + [time | participant] | | | | | | | | | | | | |
| **ROI** | **Braak I-II** | | | | **Braak III-IV** | | | | **Braak V-VI** | | | |
|  | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** |
| **Intercept** | -0.014 | 0.106 | [-0.221, 0.193] | 0.894 | -0.041 | 0.067 | [-0.173, 0.092] | 0.546 | -0.046 | 0.076 | [-0.195, 0.102] | 0.539 |
| **Time** | 0.030 | 0.026 | [-0.021, 0.082] | 0.250 | 0.021 | 0.029 | [-0.036, 0.078] | 0.479 | 0.013 | 0.035 | [-0.056, 0.081] | 0.713 |
| **AgeBAS** | -0.013 | 0.075 | [-0.161, 0.134] | 0.861 | -0.044 | 0.048 | [-0.138, 0.050] | 0.360 | -0.096 | 0.054 | [-0.201, 0.010] | 0.075 |
| **Sex** | -0.023 | 0.151 | [-0.318, 0.273] | 0.881 | -0.086 | 0.096 | [-0.274, 0.103] | 0.372 | 0.017 | 0.107 | [-0.193, 0.228] | 0.871 |
| **Aβ LIBAS** | 0.067 | 0.074 | [-0.077, 0.212] | **0.363** | 0.246 | 0.048 | [0.152, 0.339] | **<0.001\*** | 0.202 | 0.053 | [0.098, 0.306] | **<0.001\*** |
| **Time × AgeBAS** | -0.026 | 0.019 | [-0.063, 0.010] | 0.158 | -0.019 | 0.021 | [-0.059, 0.022] | 0.366 | -0.018 | 0.025 | [-0.066, 0.030] | 0.464 |
| **Time × Sex** | -0.041 | 0.037 | [-0.113, 0.032] | 0.269 | 0.059 | 0.041 | [-0.022, 0.139] | 0.153 | 0.036 | 0.049 | [-0.060, 0.131] | 0.464 |
| **Time × Aβ LIBAS** | 0.054 | 0.019 | [0.017, 0.091] | **0.004\*** | 0.080 | 0.020 | [0.039, 0.120] | **<0.001\*** | 0.048 | 0.025 | [-0.000, 0.096] | **0.050** |

**Table S2.5**. Summary of the linear mixed effects model within A+T+ subsample predicting tau laterality over time with baseline Aβ laterality at Braak ROIs.  
The statistical significance of the baseline Aβ laterality and its interaction with time are annotated with **green** if it reached p<0.05 and **red** if it did not. Furthermore, **\*** indicates whether the p-value survived the statistical threshold after Bonferroni correction.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| A+T+ (n=109 with a total of 255 datapoints)  LME: **Tau LI** ~ **time** \* (AgeBAS + Sex + **Aβ LIBAS**) + [time | participant] | | | | | | | | | | | | |
| **ROI** | **Braak I-II** | | | | **Braak III-IV** | | | | **Braak V-VI** | | | |
|  | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** |
| **Intercept** | -0.047 | 0.121 | [-0.284, 0.190] | 0.700 | -0.088 | 0.075 | [-0.235, 0.059] | 0.242 | -0.054 | 0.074 | [-0.199, 0.091] | 0.466 |
| **Time** | -0.010 | 0.036 | [-0.080, 0.060] | 0.778 | 0.002 | 0.020 | [-0.037, 0.041] | 0.917 | -0.017 | 0.027 | [-0.069, 0.035] | 0.526 |
| **AgeBAS** | -0.058 | 0.089 | [-0.232, 0.116] | 0.511 | -0.032 | 0.055 | [-0.140, 0.075] | 0.555 | 0.015 | 0.054 | [-0.091, 0.122] | 0.781 |
| **Sex** | 0.041 | 0.175 | [-0.303, 0.384] | 0.817 | 0.108 | 0.109 | [-0.106, 0.323] | 0.321 | 0.068 | 0.107 | [-0.143, 0.278] | 0.528 |
| **Aβ LIBAS** | 0.280 | 0.088 | [0.107, 0.453] | **0.002\*** | 0.679 | 0.054 | [0.573, 0.784] | **<0.001\*** | 0.584 | 0.053 | [0.481, 0.688] | **<0.001\*** |
| **Time × AgeBAS** | 0.009 | 0.026 | [-0.042, 0.061] | 0.719 | 0.002 | 0.015 | [-0.027, 0.030] | 0.898 | 0.003 | 0.020 | [-0.035, 0.042] | 0.871 |
| **Time × Sex** | 0.063 | 0.054 | [-0.043, 0.169] | 0.243 | -0.008 | 0.030 | [-0.068, 0.051] | 0.781 | -0.009 | 0.039 | [-0.087, 0.068] | 0.810 |
| **Time × Aβ LIBAS** | 0.024 | 0.026 | [-0.028, 0.076] | **0.369** | 0.004 | 0.015 | [-0.026, 0.034] | **0.783** | 0.033 | 0.019 | [-0.005, 0.071] | **0.090** |

## Longitudinal association between baseline Aβ/tau laterality and mPACC scores

***Table S2.6****. Summary of the linear mixed effects models predicting mPACC scores over time with pathological asymmetry across the ROIs: (1) baseline tau laterality as predictor; (2) baseline tau laterality as predictor after adjusting for tau load; (3) baseline Aβ laterality as predictor after adjusting for tau load, tau laterality, and Aβ load.  
The statistical significance of the interaction between time and baseline Aβ/tau laterality is annotated with* ***green*** *if it reached p<0.05 and* ***red*** *if it did not. Furthermore,* ***\**** *indicates whether the p-value survived the statistical threshold after Bonferroni correction.*

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| A+ (n=259 with a total of 606 datapoints) | | | | | | | | | | | | |
| LME #1: **mPACC** ~ **time** \* (AgeBAS + Sex + **Tau LIBAS**) + [time | participant] | | | | | | | | | | | | |
| **ROI** | **Braak I-II** | | | | **Braak III-IV** | | | | **Braak V-VI** | | | |
|  | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** |
| **Intercept** | 0.139 | 0.060 | [0.020, 0.257] | 0.022 | 0.140 | 0.057 | [0.028, 0.253] | 0.015 | 0.157 | 0.057 | [0.045, 0.270] | 0.006 |
| **Time** | -0.160 | 0.029 | [-0.216, -0.104] | <0.001 | -0.163 | 0.026 | [-0.214, -0.112] | <0.001 | -0.157 | 0.025 | [-0.205, -0.108] | <0.001 |
| **AgeBAS** | -0.122 | 0.043 | [-0.206, -0.038] | 0.004 | -0.129 | 0.041 | [-0.209, -0.050] | 0.001 | -0.147 | 0.041 | [-0.227, -0.067] | <0.001 |
| **Sex** | 0.170 | 0.086 | [0.002, 0.338] | 0.048 | 0.189 | 0.082 | [0.028, 0.349] | 0.021 | 0.153 | 0.082 | [-0.007, 0.313] | 0.060 |
| **Tau LIBAS** | 0.034 | 0.043 | [-0.051, 0.119] | 0.432 | -0.203 | 0.040 | [-0.281, -0.126] | <0.001 | -0.206 | 0.040 | [-0.284, -0.128] | <0.001 |
| **Time × AgeBAS** | -0.015 | 0.021 | [-0.056, 0.025] | 0.462 | -0.021 | 0.019 | [-0.058, 0.016] | 0.256 | -0.035 | 0.018 | [-0.070, 0.000] | 0.053 |
| **Time × Sex** | -0.021 | 0.041 | [-0.101, 0.060] | 0.616 | -0.017 | 0.037 | [-0.089, 0.056] | 0.655 | -0.031 | 0.035 | [-0.100, 0.038] | 0.372 |
| **Time ×  Tau LIBAS** | -0.036 | 0.020 | [-0.076, 0.004] | **0.076** | -0.134 | 0.019 | [-0.172, -0.095] | **<0.001\*** | -0.157 | 0.019 | [-0.194, -0.121] | **<0.001\*** |
| LME #2: **mPACC** ~ **time** \* (AgeBAS + Sex + Tau loadBAS + **Tau LIBAS**) + [time | participant] | | | | | | | | | | | | |
| **ROI** | **Braak I-II** | | | | **Braak III-IV** | | | | **Braak V-VI** | | | |
|  | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** |
| **Intercept** | 0.154 | 0.057 | [0.043, 0.266] | 0.007 | 0.157 | 0.056 | [0.047, 0.267] | 0.005 | 0.163 | 0.057 | [0.051, 0.275] | 0.004 |
| **Time** | -0.153 | 0.026 | [-0.204, -0.101] | <0.001 | -0.156 | 0.024 | [-0.203, -0.110] | <0.001 | -0.156 | 0.024 | [-0.203, -0.108] | <0.001 |
| **AgeBAS** | -0.133 | 0.040 | [-0.212, -0.054] | 0.001 | -0.134 | 0.039 | [-0.212, -0.057] | 0.001 | -0.150 | 0.041 | [-0.230, -0.071] | <0.001 |
| **Sex** | 0.148 | 0.081 | [-0.010, 0.307] | 0.067 | 0.166 | 0.080 | [0.010, 0.321] | 0.037 | 0.148 | 0.081 | [-0.011, 0.307] | 0.068 |
| **Tau loadBAS** | -0.241 | 0.041 | [-0.321, -0.161] | <0.001 | -0.217 | 0.057 | [-0.330, -0.104] | <0.001 | -0.093 | 0.055 | [-0.200, 0.014] | 0.088 |
| **Tau LIBAS** | 0.083 | 0.042 | [0.001, 0.164] | 0.046 | -0.044 | 0.057 | [-0.156, 0.068] | 0.444 | -0.143 | 0.054 | [-0.250, -0.037] | 0.008 |
| **Time × AgeBAS** | -0.020 | 0.019 | [-0.057, 0.017] | 0.282 | -0.028 | 0.017 | [-0.062, 0.005] | 0.097 | -0.036 | 0.018 | [-0.071, -0.002] | 0.039 |
| **Time × Sex** | -0.033 | 0.037 | [-0.106, 0.040] | 0.373 | -0.035 | 0.034 | [-0.101, 0.031] | 0.304 | -0.035 | 0.034 | [-0.102, 0.032] | 0.306 |
| **Time ×  Tau loadBAS** | -0.117 | 0.019 | [-0.155, -0.080] | <0.001 | -0.163 | 0.025 | [-0.213, -0.114] | <0.001 | -0.077 | 0.025 | [-0.125, -0.029] | 0.002 |
| **Time ×  Tau LIBAS** | -0.010 | 0.019 | [-0.047, 0.028] | **0.611** | -0.015 | 0.025 | [-0.065, 0.034] | **0.549** | -0.104 | 0.025 | [-0.153, -0.055] | **<0.001\*** |
| LME #3: **mPACC** ~ **time** \* (AgeBAS + Sex + Tau loadBAS + Tau LIBAS + Aβ loadBAS + **Aβ LIBAS**) + [time | participant] | | | | | | | | | | | | |
| **ROI** | **Braak I-II** | | | | **Braak III-IV** | | | | **Braak V-VI** | | | |
|  | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** | **β** | **SE** | **95% CI** | **p** |
| **Intercept** | 0.158 | 0.057 | [0.047, 0.270] | 0.005 | 0.154 | 0.054 | [0.048, 0.261] | 0.004 | 0.157 | 0.055 | [0.050, 0.265] | 0.004 |
| **Time** | -0.154 | 0.026 | [-0.206, -0.102] | <0.001 | -0.159 | 0.024 | [-0.206, -0.112] | <0.001 | -0.158 | 0.024 | [-0.206, -0.110] | <0.001 |
| **AgeBAS** | -0.131 | 0.040 | [-0.210, -0.052] | 0.001 | -0.124 | 0.038 | [-0.199, -0.049] | 0.001 | -0.125 | 0.039 | [-0.203, -0.048] | 0.001 |
| **Sex** | 0.140 | 0.081 | [-0.019, 0.299] | 0.083 | 0.169 | 0.077 | [0.018, 0.320] | 0.028 | 0.158 | 0.078 | [0.005, 0.311] | 0.043 |
| **Tau loadBAS** | -0.232 | 0.043 | [-0.317, -0.148] | <0.001 | -0.145 | 0.058 | [-0.258, -0.031] | 0.013 | -0.051 | 0.054 | [-0.156, 0.054] | 0.338 |
| **Tau LIBAS** | 0.083 | 0.042 | [0.001, 0.165] | 0.048 | -0.043 | 0.056 | [-0.152, 0.067] | 0.446 | -0.101 | 0.054 | [-0.207, 0.004] | 0.060 |
| **Aβ loadBAS** | -0.031 | 0.043 | [-0.115, 0.053] | 0.466 | -0.156 | 0.042 | [-0.238, -0.073] | <0.001 | -0.191 | 0.042 | [-0.274, -0.108] | <0.001 |
| **Aβ LIBAS** | -0.053 | 0.040 | [-0.132, 0.026] | 0.190 | 0.080 | 0.039 | [0.004, 0.157] | 0.040 | 0.048 | 0.040 | [-0.031, 0.126] | 0.233 |
| **Time × AgeBAS** | -0.019 | 0.019 | [-0.056, 0.018] | 0.315 | -0.029 | 0.017 | [-0.063, 0.005] | 0.091 | -0.036 | 0.018 | [-0.071, -0.001] | 0.045 |
| **Time × Sex** | -0.029 | 0.038 | [-0.103, 0.045] | 0.442 | -0.029 | 0.034 | [-0.096, 0.038] | 0.397 | -0.030 | 0.035 | [-0.098, 0.038] | 0.386 |
| **Time ×  Tau loadBAS** | -0.122 | 0.020 | [-0.161, -0.083] | <0.001 | -0.169 | 0.027 | [-0.221, -0.117] | <0.001 | -0.076 | 0.025 | [-0.125, -0.026] | 0.003 |
| **Time ×  Tau LIBAS** | -0.007 | 0.019 | [-0.045, 0.030] | 0.699 | -0.016 | 0.026 | [-0.066, 0.035] | 0.540 | -0.104 | 0.026 | [-0.155, -0.052] | <0.001 |
| **Time ×  Aβ loadBAS** | 0.017 | 0.020 | [-0.021, 0.056] | 0.382 | 0.012 | 0.019 | [-0.025, 0.049] | 0.515 | -0.005 | 0.019 | [-0.042, 0.032] | 0.795 |
| **Time ×  Aβ LIBAS** | -0.007 | 0.019 | [-0.044, 0.030] | **0.702** | -0.005 | 0.017 | [-0.039, 0.028] | **0.751** | -0.004 | 0.018 | [-0.039, 0.031] | **0.821** |