*Supplementary materials*

**Symptom persistence relates to volume and asymmetry of the limbic system after mild traumatic brain injury**

**Cheryl Vanier1,2¶\*, Priya Santhanam1¶, Nicholas Rochester1,3, Lauren Carter1, Mike Lim4, Amir Kilani4, Shivani Venkatesh2, Sherwin Azad4, Thomas Knoblauch1,5, Tapasya Surti6, Colin Brown2, Justin Sanchez2, Leon Ma7, Shaunaq Parikh8, Leo Germin9, Enrico Fazzini2 and Travis Snyder1,2,4,10,11**

¶Authors contributed equally to this manuscript

1: Imgen Research Group, Las Vegas NV, USA

2: Touro University Nevada College of Osteopathic Medicine, Henderson NV, USA

3: Central Michigan University College of Medicine, Saginaw MI, USA

4: Sunrise Health Graduate Medical Education Consortium, Department of Radiology, Las Vegas NV, USA

5: Department of Interdisciplinary Health Sciences, University of Nevada, Las Vegas, Las Vegas NV, USA

6: University of Texas Health Science Center, Houston TX, USA

7: Loyola University Medical Center, Department of Anesthesiology, Maywood IL, USA

8: University of Pittsburgh, Department of Family Medicine, Pittsburgh PA, USA

9: Clinical Neurology Specialists, Las Vegas NV, USA

10: HCA Healthcare (Nashville, TN), Mountain View Hospital, Las Vegas NV. USA

11: SimonMed Imaging, Las Vegas NV, USA

**\*** Correspondence: cheryl.vanier@imgen-research.com

**Supplemental Tables**

**Table S1.** Most common combinations of symptoms (Balance problems=Bal, Cognitive deficits=Cog, Fatigue=Fat, Anxiety=Anx, Depression=Dep, Emotional lability=EL). Headache was not included in combination with other groups because 96% of participants reported having headaches. The expected values are the calculated number of participants in a symptom group based on the probability of symptoms co-occurring or not. The 95% confidence interval (CI) is based on the observed values for each symptom group. Expected values that lie outside the 95% CI were evidence for incongruence between observed and expected values. The larger value between E and O is in bold.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **#** | **Symptoms** | **Expected** | **Observed** | **95% CI** | |
| 1 | Headache | 10 | **53** | 46 | 58 |
| 1 | Cog | 34 | **55** | 45 | 64 |
| 1 | Bal | 25 | **44** | 35 | 52 |
| 2 | Bal+Cog | 86 | **125** | 110 | 139 |
| 2 | Cog+Dep | **14** | 2 | 0 | 6 |
| 2 | Cog+Anx | **18** | 4 | 1 | 9 |
| 2 | Cog+Fat | **10** | 4 | 1 | 8 |
| 2 | Bal+Anx | **13** | 4 | 1 | 8 |
| 3 | Bal+Cog+EL | **18** | 11 | 6 | 17 |
| 3 | Bal+Cog+Dep | **36** | 3 | 1 | 8 |
| 3 | Bal+Cog+Anx | **45** | 10 | 5 | 17 |
| 3 | Bal+Cog+Fat | **25** | 11 | 6 | 17 |
| 4 | Bal+Cog+Anx+Dep | 19 | **49** | 41 | 56 |
| 4 | Bal+Cog+Fat+EL | 5 | **12** | 7 | 15 |
| 4 | Bal+Cog+Fat+Dep | **10** | 2 | 0 | 6 |
| 4 | Bal+Cog+Fat+Anx | **13** | 6 | 2 | 11 |
| 5 | Bal+Cog+Anx+Dep+EL | 4 | **19** | 14 | 22 |
| 5 | Bal+Cog+Fat+Anx+Dep | 1 | **17** | 13 | 18 |
| 6 | Bal+Cog+Fat+Anx+Dep+EL | 5 | **36** | 30 | 39 |

**Table S2.** Right and left side limbic structure volumes (cm3), adjusted for TIV using regression, shown as mean and standard deviation (SD). Derived values used in the analysis (total volume, laterality indices) are in Table S3.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Total** | | **No LOC** | | **LOC** | |
|  | **Left** | **Right** | **Left** | **Right** | **Left** | **Right** |
| Amygdala | 1.86 (0.29) | 1.73 (0.26) | 1.86 (0.30) | 1.73 (0.27) | 1.86 (0.28) | 1.74 (0.26) |
| Parahippocampus | 2.33 (0.27) | 2.38 (0.30) | 2.33 (0.26) | 2.39 (0.30) | 2.33 (0.29) | 2.36 (0.31) |
| Hippocampus | 4.07 (0.40) | 4.19 (0.41) | 4.07 (0.40) | 4.19 (0.42) | 4.08 (0.38) | 4.19 (0.37) |
| Entorhinal cortex | 2.70 (0.53) | 2.52 (0.54) | 2.71 (0.53) | 2.55 (0.53) | 2.65 (0.53) | 2.45 (0.55) |
| Rostral ACC | 1.26 (0.21) | 2.05 (0.37) | 1.26 (0.20) | 2.05 (0.36) | 1.27 (0.23) | 2.08 (0.40) |
| Caudal ACC | 0.80 (0.22) | 1.59 (0.34) | 0.81 (0.23) | 1.60 (0.34) | 0.78 (0.21) | 1.56 (0.36) |
| PCC | 1.52 (0.34) | 1.43 (0.31) | 1.53 (0.35) | 1.44 (0.31) | 1.49 (0.34) | 1.40 (0.31) |
| Isthmus Cingulate | 2.52 (0.37) | 2.13 (0.29) | 2.53 (0.38) | 2.15 (0.30) | 2.50 (0.36) | 2.11 (0.28) |
| Lateral OFC | 10.20 (1.12) | 9.20 (0.98) | 10.15 (1.12) | 9.17 (0.94) | 10.30 (1.13) | 9.30 (1.07) |
| Medial OFC | 4.60 (0.52) | 7.76 (0.96) | 4.59 (0.49) | 7.74 (0.92) | 4.64 (0.58) | 7.81 (1.08) |
| Ventral Diencephalon | 3.57 (0.43) | 3.55 (0.44) | 3.58 (0.44) | 3.55 (0.46) | 3.54 (0.40) | 3.54 (0.41) |
| Nucleus Accumbens | 0.64 (0.11) | 0.60 (0.11) | 0.65 (0.11) | 0.60 (0.11) | 0.64 (0.12) | 0.60 (0.11) |
| Thalamus | 7.90 (0.75) | 7.92 (0.79) | 7.86 (0.76) | 7.87 (0.78) | 8.01 (0.71) | 8.03 (0.80) |

**Table S3**. Mean and standard deviation (SD) for total regional volume (cm3), and median (interquartile range) for laterality index and side-independent laterality index for limbic structures. Adjusted right and left values that were used to compute total volume and indices are in Table S2. P-values are from t-tests or Mann-Whitney tests comparing LOC groups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Total** | **no LOC** | **LOC** | **P-value** |
|  | TIV | 1493 (151) | 1475 (146) | 1537 (155) | **<0.001** |
| Total Volume | Amygdala | 3.59 (0.53) | 3.59 (0.53) | 3.6 (0.51) | 0.759 |
| Parahippocampal gyrus | 4.71 (0.51) | 4.72 (0.50) | 4.70 (0.53) | 0.721 |
|  | Hippocampus | 8.26 (0.75) | 8.26 (0.78) | 8.27 (0.69) | 0.866 |
|  | Entorhinal cortex | 5.22 (0.93) | 5.26 (0.93) | 5.10 (0.94) | 0.067 |
|  | Rostral ACC | 3.31 (0.53) | 3.3 (0.51) | 3.35 (0.59) | 0.364 |
|  | Caudal ACC | 2.39 (0.50) | 2.41 (0.49) | 2.35 (0.51) | 0.187 |
|  | PCC | 2.94 (0.63) | 2.96 (0.63) | 2.88 (0.62) | 0.181 |
|  | Isthmus Cingulate | 4.65 (0.62) | 4.67 (0.64) | 4.60 (0.59) | 0.252 |
|  | Lateral OFC | 19.40 (1.96) | 19.32 (1.92) | 19.60 (2.07) | 0.141 |
|  | Medial OFC | 12.37 (1.41) | 12.34 (1.33) | 12.45 (1.61) | 0.420 |
|  | Ventral Diencephalon | 7.12 (0.81) | 7.13 (0.83) | 7.09 (0.76) | 0.596 |
|  | Nucleus Accumbens | 1.24 (0.20) | 1.24 (0.20) | 1.23 (0.21) | 0.656 |
|  | Thalamus | 15.82 (1.44) | 15.73 (1.44) | 16.04 (1.42) | **0.028** |
| LI | Amygdala | -0.03  (-0.06, -0.00) | -0.03  (-0.07, -0.00) | -0.03  (-0.06, -0.00) | 0.440 |
|  | Parahippocampal gyrus | 0.01  (-0.02, 0.04) | 0.01  (-0.02, 0.05) | 0.01  (-0.03, 0.04) | 0.173 |
|  | Hippocampus | 0.02  (-0.00, 0.04) | 0.02  (-0.00, 0.03) | 0.02  (-0.00, 0.04) | 0.848 |
|  | Entorhinal cortex | -0.03  (-0.09, 0.02) | -0.03  (-0.09, 0.02) | -0.04  (-0.09, 0.01) | 0.328 |
|  | Rostral ACC | 0.24  (0.20, 0.28) | 0.24  (0.20, 0.28) | 0.23  (0.19, 0.28) | 0.971 |
|  | Caudal ACC | 0.33  (0.27, 0.40) | 0.33  (0.26, 0.40) | 0.33  (0.28, 0.40) | 0.939 |
|  | PCC | -0.03  (-0.07, 0.01) | -0.03  (-0.07, 0.01) | -0.03  (-0.07, 0.01) | 0.968 |
|  | Isthmus Cingulate | -0.08  (-0.12, -0.05) | -0.08  (-0.11, -0.05) | -0.09  (-0.12, -0.05) | 0.488 |
|  | Lateral OFC | -0.05  (-0.08, -0.02) | -0.05  (-0.08, -0.02) | -0.05  (-0.07, -0.03) | 0.869 |
|  | Medial OFC | 0.26  (0.23, 0.28) | 0.26  (0.23, 0.28) | 0.25  (0.23, 0.28) | 0.858 |
|  | Ventral Diencephalon | 0.00  (-0.03, 0.02) | 0.00  (-0.03, 0.02) | 0.00  (-0.03, 0.02) | 0.496 |
|  | Nucleus Accumbens | -0.04  (-0.08, 0.01) | -0.04  (-0.08, 0.00) | -0.03  (-0.08, 0.02) | 0.240 |
|  | Thalamus | 0.00  (-0.02, 0.02) | 0.00  (-0.02, 0.02) | 0.00  (-0.02, 0.02) | 0.862 |
| siLI | Amygdala | 0.03  (0.02, 0.06) | 0.03  (0.02, 0.06) | 0.03  (0.01, 0.06) | 0.661 |
|  | Parahippocampal gyrus | 0.03  (0.02, 0.06) | 0.03  (0.01, 0.06) | 0.04  (0.02, 0.06) | 0.172 |
|  | Hippocampus | 0.02  (0.01, 0.03) | 0.02  (0.01, 0.03) | 0.02  (0.01, 0.04) | 0.221 |
|  | Entorhinal cortex | 0.06  (0.02, 0.11) | 0.06  (0.03, 0.11) | 0.06  (0.02, 0.11) | 0.610 |
|  | Rostral ACC | 0.04  (0.02, 0.08) | 0.04  (0.02, 0.08) | 0.04  (0.02, 0.08) | 0.857 |
|  | Caudal ACC | 0.07  (0.03, 0.12) | 0.07  (0.03, 0.12) | 0.06  (0.03, 0.10) | 0.314 |
|  | PCC | 0.04  (0.02, 0.06) | 0.04  (0.02, 0.07) | 0.04  (0.02, 0.06) | 0.927 |
|  | Isthmus Cingulate | 0.03  (0.02, 0.06) | 0.03  (0.01, 0.06) | 0.04  (0.02, 0.06) | 0.216 |
|  | Lateral OFC | 0.03  (0.01, 0.04) | 0.03  (0.01, 0.05) | 0.02  (0.01, 0.04) | 0.389 |
|  | Medial OFC | 0.02  (0.01, 0.04) | 0.02  (0.01, 0.04) | 0.02  (0.01, 0.04) | 0.796 |
|  | Ventral Diencephalon | 0.03  (0.01, 0.05) | 0.03  (0.01, 0.05) | 0.03  (0.01, 0.05) | 0.185 |
|  | Nucleus Accumbens | 0.04  (0.02, 0.08) | 0.04  (0.02, 0.07) | 0.05  (0.02, 0.09) | 0.053 |
|  | Thalamus | 0.02  (0.01, 0.03) | 0.02  (0.01, 0.03) | 0.02  (0.01, 0.03) | 0.620 |

**Table S4.** Correlations among volumetric structures based on total volume (upper matrix), laterality index (center matrix), or side-independent laterality (lower matrix). For volume, the Pearson correlations of the z-scores computed from the TIV-adjusted values are reported. For LI and Si-LI, the Kendall’s tai correlations of the indices based on TIV-adjusted volumes are reported. Coefficients >|0.3| are bolded to draw attention to the relationships that were moderate or large.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Amygdala | Parahippo | Hippoc | Entorh  Cortex | Rostral ACC | Caudal ACC | PCC | Isthmus Cing | Lateral OFC | Medial OFC | Ventral Dienceph | Nucleus Accumb | Thalamus |
| **Volume** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parahipp. Gyrus | 0.08 |  |  |  |  |  |  |  |  |  |  |  |  |
| Hippocampus | **0.47** | **0.41** |  |  |  |  |  |  |  |  |  |  |  |
| Entorhinal Cortex | 0.05 | 0.23 | 0.07 |  |  |  |  |  |  |  |  |  |  |
| Rostral ACC | 0.20 | -0.07 | 0.04 | -0.03 |  |  |  |  |  |  |  |  |  |
| Caudal ACC | -0.15 | 0.02 | -0.08 | -0.02 | 0.15 |  |  |  |  |  |  |  |  |
| PCC | **-0.37** | -0.04 | -0.25 | 0.05 | 0.05 | 0.38 |  |  |  |  |  |  |  |
| Isthmus Cingulate | -0.03 | 0.15 | -0.09 | 0.14 | -0.04 | 0.17 | **0.34** |  |  |  |  |  |  |
| Lateral OFC | **0.37** | 0.11 | 0.23 | 0.06 | 0.31 | -0.05 | -0.17 | 0.05 |  |  |  |  |  |
| Medial OFC | 0.26 | 0.10 | 0.27 | 0.16 | 0.25 | -0.02 | -0.15 | 0.02 | **0.60** |  |  |  |  |
| Ventral Diencephalon | **0.43** | 0.15 | **0.47** | 0.02 | 0.03 | -0.16 | -0.43 | -0.11 | 0.14 | 0.14 |  |  |  |
| Nucleus Accumbens | **0.54** | 0.08 | 0.23 | -0.01 | 0.28 | -0.12 | -0.32 | -0.03 | **0.46** | **0.41** | 0.27 |  |  |
| Thalamus | 0.17 | 0.16 | 0.31 | 0.08 | -0.02 | -0.05 | -0.09 | 0.06 | 0.26 | **0.31** | 0.17 | 0.15 |  |
| TIV | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **LI** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parahipp. Gyrus | -0.01 |  |  |  |  |  |  |  |  |  |  |  |  |
| Hippocampus | 0.09 | 0.22 |  |  |  |  |  |  |  |  |  |  |  |
| Entorhinal Cortex | 0.12 | 0.02 | 0.08 |  |  |  |  |  |  |  |  |  |  |
| Rostral ACC | -0.01 | 0.00 | 0.04 | 0.04 |  |  |  |  |  |  |  |  |  |
| Caudal ACC | -0.04 | 0.04 | 0.03 | 0.01 | 0.19 |  |  |  |  |  |  |  |  |
| PCC | 0.00 | 0.02 | 0.00 | -0.02 | -0.03 | 0.08 |  |  |  |  |  |  |  |
| Isthmus Cingulate | 0.05 | 0.03 | 0.09 | -0.01 | -0.01 | 0.03 | 0.14 |  |  |  |  |  |  |
| Lateral OFC | -0.05 | -0.02 | -0.01 | -0.01 | -0.05 | -0.06 | 0.00 | -0.02 |  |  |  |  |  |
| Medial OFC | -0.01 | 0.01 | -0.01 | 0.05 | 0.13 | 0.17 | -0.04 | -0.06 | 0.02 |  |  |  |  |
| Ventral Diencephalon | 0.00 | 0.09 | 0.14 | 0.02 | 0.06 | 0.04 | -0.05 | -0.01 | -0.03 | 0.10 |  |  |  |
| Nucleus Accumbens | -0.02 | 0.00 | 0.02 | 0.00 | 0.02 | 0.07 | 0.05 | -0.01 | 0.02 | 0.06 | -0.01 |  |  |
| Thalamus | 0.01 | 0.00 | 0.01 | -0.01 | 0.05 | 0.08 | -0.02 | -0.04 | 0.00 | 0.06 | 0.09 | 0.05 |  |
| TIV | 0.00 | 0.00 | 0.04 | 0.02 | -0.01 | 0.00 | -0.01 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 |
| **siLI** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parahipp. Gyrus | -0.02 |  |  |  |  |  |  |  |  |  |  |  |  |
| Hippocampus | 0.01 | 0.06 |  |  |  |  |  |  |  |  |  |  |  |
| Entorhinal Cortex | 0.05 | 0.02 | 0.01 |  |  |  |  |  |  |  |  |  |  |
| Rostral ACC | 0.02 | -0.01 | 0.01 | 0.01 |  |  |  |  |  |  |  |  |  |
| Caudal ACC | 0.03 | 0.00 | 0.03 | -0.01 | 0.05 |  |  |  |  |  |  |  |  |
| PCC | -0.01 | 0.00 | 0.03 | 0.06 | 0.01 | 0.01 |  |  |  |  |  |  |  |
| Isthmus Cingulate | -0.02 | -0.07 | 0.06 | 0.03 | 0.05 | 0.04 | 0.04 |  |  |  |  |  |  |
| Lateral OFC | 0.02 | -0.04 | 0.00 | 0.04 | 0.06 | 0.03 | 0.05 | -0.01 |  |  |  |  |  |
| Medial OFC | 0.04 | 0.06 | 0.04 | 0.01 | 0.04 | 0.08 | 0.03 | 0.00 | 0.01 |  |  |  |  |
| Ventral Diencephalon | 0.01 | 0.01 | 0.04 | -0.02 | -0.01 | -0.02 | 0.06 | 0.08 | 0.00 | 0.04 |  |  |  |
| Nucleus Accumbens | 0.02 | -0.01 | 0.04 | -0.04 | 0.03 | 0.02 | -0.03 | 0.04 | 0.02 | 0.05 | 0.06 |  |  |
| Thalamus | 0.03 | -0.02 | 0.07 | -0.02 | -0.02 | -0.01 | 0.00 | 0.06 | -0.03 | -0.01 | 0.08 | 0.06 |  |
| TIV | 0.07 | 0.08 | 0.09 | 0.14 | 0.09 | 0.06 | 0.00 | 0.10 | 0.08 | 0.11 | 0.02 | 0.02 | 0.04 |

**Table S5**. Mean (SE) z-scores for volume, and median (interquartile range) for laterality index (LI) and side-independent laterality (siLI), reported separately for the groups that did not (-) / did (+) have each symptom. For age, sex, and LOC covariates, the percent of participants who had a characteristic (e.g.,<40, F) for those who did not (-) and those who had (+) a symptom are reported. For DOI to DOS, the median and interquartile range endpoints are reported. Values corresponding to odds ratios having p<0.05 from Table 4 are in bold. Reference condition for age was <40, for sex was female, and for LOC none.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Headache** | **Balance** | **Cognitive** | **Fatigue** | **Anxiety** | **Depression** | **Emotional Lability** |
| **Covariates** |  |  |  |  |  |  |  |  |
| Age | >40  <40 | 97%  95% | 67%  75% | 74%  80% | 22%  23% | 33%  35% | 28%  30% | 15%  19% |
| Sex | M  F | 97%  94% | 74%  68% | 77%  77% | 21%  25% | 36%  32% | 29%  30% | 15%  20% |
| LOC | No LOC  LOC | 96%  97% | **69%**  **79%** | **74%**  **85%** | **20%**  **29%** | 32%  40% | **24%**  **42%** | **14%**  **26%** |
| DOI to DOS | -Symptom | 141 (93,286) | 103 (64,190) | 100 (58,159) | 98 (58,173) | 97 (57,176) | 96 (57,168) | 99 (57,173) |
|  | +Symptom | 98 (56,173) | 94 (56,168) | 98 (56,181) | 101 (50,189) | 101 (56,172) | 105 (55,210) | 90 (56,184) |
| **Volume z-scores (mean, SE)** | |  |  |  |  |  |  |  |
| Amygdala | -Symptom | -0.05 (0.19) | 0.16 (0.08) | 0.20 (0.10) | 0.04 (0.05) | 0.03 (0.05) | 0.03 (0.05) | 0.03 (0.05) |
|  | +Symptom | 0.00 (0.04) | -0.06 (0.05) | -0.06 (0.05) | -0.13 (0.09) | -0.06 (0.08) | -0.07 (0.08) | -0.12 (0.10) |
| Parahipp Gyrus | -Symptom | 0.17 (0.20) | 0.05 (0.08) | 0.13 (0.09) | 0.02 (0.05) | 0.01 (0.05) | 0.00 (0.05) | 0.04 (0.05) |
|  | +Symptom | -0.01 (0.04) | -0.02 (0.05) | -0.04 (0.05) | -0.06 (0.09) | -0.03 (0.07) | 0.00 (0.08) | -0.19 (0.11) |
| Hippocampus | -Symptom | 0.11 (0.21) | 0.12 (0.08) | 0.09 (0.09) | 0.05 (0.05) | 0.00 (0.05) | 0.01 (0.05) | 0.04 (0.05) |
|  | +Symptom | 0.00 (0.04) | -0.05 (0.05) | -0.03 (0.05) | -0.18 (0.10) | 0.00 (0.08) | -0.04 (0.08) | -0.20 (0.10) |
| Entorhinal Cortex | -Symptom | 0.09 (0.23) | 0.11 (0.09) | 0.18 (0.09) | 0.00 (0.05) | 0.04 (0.05) | 0.03 (0.05) | 0.00 (0.05) |
|  | +Symptom | 0.00 (0.04) | -0.04 (0.05) | -0.05 (0.05) | 0.01 (0.10) | -0.08 (0.07) | -0.08 (0.08) | -0.02 (0.11) |
| Rostral ACC | -Symptom | -0.29 (0.20) | 0.06 (0.08) | 0.02 (0.09) | 0.03 (0.05) | -0.04 (0.06) | -0.02 (0.05) | -0.02 (0.05) |
|  | +Symptom | 0.01 (0.04) | -0.02 (0.05) | 0.00 (0.05) | -0.09 (0.09) | 0.07 (0.07) | 0.05 (0.07) | 0.12 (0.12) |
| Caudal ACC | -Symptom | 0.39 (0.25) | 0.01 (0.08) | 0 (0.10) | 0.04 (0.05) | 0 (0.05) | 0.02 (0.05) | 0.01 (0.05) |
|  | +Symptom | -0.02 (0.04) | 0.00 (0.05) | 0 (0.05) | -0.15 (0.09) | 0 (0.08) | -0.05 (0.08) | -0.05 (0.10) |
| PCC | -Symptom | 0.08 (0.23) | -0.17 (0.08) | -0.19 (0.09) | -0.01 (0.05) | -0.08 (0.05) | -0.04 (0.05) | -0.01 (0.05) |
|  | +Symptom | 0.00 (0.04) | 0.07 (0.05) | 0.05 (0.05) | 0.03 (0.09) | 0.15 (0.08) | 0.10 (0.08) | 0.06 (0.10) |
| Isthmus Cingulate | -Symptom | 0.20 (0.25) | 0 (0.08) | 0.11 (0.08) | -0.01 (0.05) | -0.03 (0.05) | 0.03 (0.05) | 0.05 (0.05) |
|  | +Symptom | -0.01 (0.04) | 0 (0.05) | -0.03 (0.05) | 0.03 (0.10) | 0.06 (0.08) | -0.07 (0.08) | -0.22 (0.10) |
| Lateral OFC | -Symptom | -0.15 (0.23) | 0.20 (0.08) | 0.20 (0.09) | 0.02 (0.05) | 0 (0.05) | -0.01 (0.05) | 0.02 (0.05) |
|  | +Symptom | 0.01 (0.04) | -0.08 (0.05) | -0.06 (0.05) | -0.07 (0.01) | -0.01 (0.08) | 0.02 (0.08) | -0.09 (0.11) |
| Medial OFC | -Symptom | -0.31 (0.20) | 0.06 (0.07) | 0.15 (0.08) | 0.02 (0.05) | -0.01 (0.05) | -0.03 (0.05) | 0.01 (0.05) |
|  | +Symptom | 0.01 (0.04) | -0.03 (0.05) | -0.04 (0.05) | -0.08 (0.11) | 0.02 (0.08) | 0.06 (0.08) | -0.06 (0.11) |
| Ventral Diencephalon | -Symptom | -0.22 (0.21) | 0.12 (0.08) | 0.03 (0.09) | 0.04 (0.05) | 0.07 (0.05) | 0.06 (0.05) | 0.03 (0.05) |
|  | +Symptom | 0.01 (0.04) | -0.05 (0.05) | -0.01 (0.05) | -0.14 (0.09) | -0.13 (0.07) | -0.13 (0.08) | -0.16 (0.10) |
| Nucleus Accumbens | -Symptom | -0.08 (0.23) | 0.18 (0.08) | 0.33 (0.10) | 0.06 (0.05) | 0.08 (0.05) | 0.07 (0.05) | 0.04 (0.05) |
|  | +Symptom | 0.00 (0.04) | -0.07 (0.05) | -0.10 (0.05) | -0.21 (0.09) | -0.15 (0.07) | -0.18 (0.08) | -0.18 (0.09) |
| Thalamus | -Symptom | **0.59 (0.25)** | 0.02 (0.08) | 0.07 (0.10) | -0.03 (0.05) | -0.06 (0.06) | -0.05 (0.05) | 0.01 (0.05) |
|  | +Symptom | **-0.02 (0.04)** | -0.01 (0.05) | -0.02 (0.05) | 0.12 (0.09) | 0.11 (0.07) | 0.13 (0.07) | -0.05 (0.09) |
| **Laterality index (Median, IQR)** | | |  |  |  |  |  |  |
| Amygdala | -Symptom | -0.05 (-0.09, -0.03) | -0.04 (-0.07, -0.01) | -0.04 (-0.08, -0.00) | -0.03 (-0.06, -0.00) | -0.03 (-0.07, -0.00) | -0.03 (-0.07, -0.00) | -0.03 (-0.06, -0.00) |
|  | +Symptom | -0.03 (-0.06, -0.00) | -0.03 (-0.06, 0.00) | -0.03 (-0.06, -0.00) | -0.04 (-0.07, -0.00) | -0.03 (-0.06, 0.00) | -0.03 (-0.06, 0.00) | -0.03 (-0.07, -0.00) |
| Parahipp Gyrus | -Symptom | 0.01 (-0.04, 0.06) | 0.02 (-0.02, 0.05) | 0.02 (-0.01, 0.05) | 0.01 (-0.02, 0.05) | 0.01 (-0.02, 0.05) | 0.01 (-0.02, 0.05) | 0.01 (-0.02, 0.05) |
|  | +Symptom | 0.01 (-0.02, 0.04) | 0.01 (-0.02, 0.04) | 0.01 (-0.03, 0.04) | 0.01 (-0.02, 0.03) | 0.01 (-0.03, 0.04) | 0 (-0.03, 0.04) | 0.01 (-0.03, 0.04) |
| Hippocampus | -Symptom | 0.01 (0.00, 0.05) | 0.02 (0.00, 0.03) | 0.02 (0.00, 0.04) | 0.02 (0.00, 0.04) | 0.02 (0.00, 0.04) | 0.02 (-0.00, 0.03) | 0.02 (-0.00, 0.03) |
|  | +Symptom | 0.02 (-0.00, 0.04) | 0.02 (-0.00, 0.04) | 0.01 (-0.00, 0.03) | 0.01 (-0.01, 0.04) | 0.01 (-0.01, 0.03) | 0.02 (-0.00, 0.04) | 0.01 (-0.00, 0.04) |
| Entorhinal Cortex | -Symptom | -0.02 (-0.09, 0.04) | -0.02 (-0.10, 0.05) | -0.04 (-0.09, 0.01) | -0.03 (-0.09, 0.02) | -0.04 (-0.10, 0.02) | -0.04 (-0.09, 0.01) | -0.04 (-0.10, 0.01) |
|  | +Symptom | -0.04 (-0.09, 0.02) | -0.04 (-0.09, 0.01) | -0.03 (-0.09, 0.03) | -0.04 (-0.09, 0.03) | -0.03 (-0.08, 0.03) | -0.03 (-0.09, 0.03) | -0.02 (-0.08, 0.04) |
| Rostral ACC | -Symptom | 0.23 (0.18, 0.27) | 0.25 (0.21, 0.29) | 0.24 (0.20, 0.29) | 0.24 (0.20, 0.28) | 0.24 (0.20, 0.28) | 0.24 (0.20, 0.28) | 0.24 (0.20, 0.28) |
|  | +Symptom | 0.24 (0.20, 0.28) | 0.24 (0.19, 0.28) | 0.24 (0.20, 0.28) | 0.24 (0.18, 0.28) | 0.24 (0.19, 0.28) | 0.24 (0.20, 0.28) | 0.24 (0.19, 0.27) |
| Caudal ACC | -Symptom | 0.39 (0.29, 0.41) | 0.36 (0.29, 0.42) | 0.34 (0.28, 0.41) | 0.33 (0.27, 0.40) | 0.33 (0.27, 0.41) | 0.33 (0.27, 0.40) | 0.34 (0.27, 0.40) |
|  | +Symptom | 0.33 (0.27, 0.40) | 0.32 (0.26, 0.39) | 0.33 (0.26, 0.40) | 0.33 (0.25, 0.39) | 0.33 (0.27, 0.39) | 0.34 (0.27, 0.39) | 0.32 (0.24, 0.40) |
| PCC | -Symptom | -0.03 (-0.05, 0.01) | -0.03 (-0.07, 0.02) | -0.03 (-0.07, 0.02) | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) |
|  | +Symptom | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) | -0.03 (-0.07, 0.01) | -0.04 (-0.07, 0.00) | -0.03 (-0.08, 0.01) |
| Isthmus Cingulate | -Symptom | -0.07 (-0.10, -0.05) | -0.08 (-0.11, -0.04) | -0.08 (-0.10, -0.04) | -0.08 (-0.12, -0.05) | -0.08 (-0.11, -0.05) | -0.08 (-0.11, -0.05) | -0.08 (-0.11, -0.05) |
|  | +Symptom | -0.08 (-0.12, -0.05) | -0.08 (-0.12, -0.05) | -0.08 (-0.12, -0.05) | -0.08 (-0.11, -0.05) | -0.08 (-0.12, -0.05) | -0.08 (-0.12, -0.05) | -0.09 (-0.12, -0.05) |
| Lateral OFC | -Symptom | -0.06 (-0.09, -0.03) | -0.06 (-0.08, -0.03) | -0.06 (-0.08, -0.03) | -0.05 (-0.08, -0.03) | -0.05 (-0.08, -0.03) | -0.05 (-0.08, -0.03) | -0.05 (-0.08, -0.02) |
|  | +Symptom | -0.05 (-0.08, -0.02) | -0.05 (-0.07, -0.02) | -0.05 (-0.08, -0.02) | -0.04 (-0.07, -0.02) | -0.05 (-0.08, -0.02) | -0.05 (-0.08, -0.02) | -0.06 (-0.08, -0.02) |
| Medial OFC | -Symptom | 0.26 (0.22, 0.28) | 0.26 (0.23, 0.28) | 0.25 (0.23, 0.27) | 0.26 (0.23, 0.28) | 0.26 (0.23, 0.28) | 0.26 (0.23, 0.28) | 0.26 (0.23, 0.28) |
|  | +Symptom | 0.26 (0.23, 0.28) | 0.25 (0.23, 0.28) | 0.26 (0.23, 0.28) | 0.25 (0.23, 0.28) | 0.25 (0.23, 0.27) | 0.25 (0.23, 0.27) | 0.25 (0.24, 0.28) |
| Ventral Diencephalon | -Symptom | 0.01 (-0.01, 0.03) | 0 (-0.03, 0.02) | -0.01 (-0.02, 0.02) | -0.01 (-0.03, 0.02) | -0.01 (-0.03, 0.02) | 0 (-0.03, 0.02) | 0 (-0.03, 0.02) |
|  | +Symptom | 0 (-0.03, 0.02) | 0 (-0.03, 0.02) | 0 (-0.03, 0.02) | 0.01 (-0.02, 0.03) | 0 (-0.03, 0.03) | 0 (-0.03, 0.03) | -0.01 (-0.03, 0.03) |
| Nucleus Accumbens | -Symptom | -0.04 (-0.08, 0.05) | -0.04 (-0.08, 0.00) | -0.04 (-0.09, 0.00) | -0.04 (-0.09, 0.01) | -0.04 (-0.08, 0.01) | -0.04 (-0.08, 0.01) | -0.04 (-0.08, 0.01) |
|  | +Symptom | -0.04 (-0.08, 0.01) | -0.04 (-0.08, 0.01) | -0.04 (-0.08, 0.01) | -0.03 (-0.07, 0.01) | -0.03 (-0.08, 0.01) | -0.03 (-0.08, 0.00) | -0.02 (-0.07, 0.01) |
| Thalamus | -Symptom | -0.01 (-0.02, 0.03) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) |
|  | +Symptom | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) | 0 (-0.02, 0.02) |
| **siLI (Median, IQR)** | |  |  |  |  |  |  |  |
| Amygdala | -Symptom | 0.04 (0.02, 0.08) | 0.03 (0.01, 0.06) | 0.04 (0.02, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) |
|  | +Symptom | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.05) | 0.03 (0.01, 0.06) |
| Parahipp Gyrus | -Symptom | 0.05 (0.01, 0.10) | 0.04 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.04 (0.02, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.02, 0.06) |
|  | +Symptom | 0.03 (0.02, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) |
| Hippocampus | -Symptom | 0.02 (0.01, 0.05) | 0.01 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) |
|  | +Symptom | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.04) |
| Entorhinal Cort | -Symptom | 0.06 (0.05, 0.10) | 0.06 (0.03, 0.11) | 0.05 (0.02, 0.10) | 0.05 (0.02, 0.11) | 0.06 (0.03, 0.11) | 0.05 (0.02, 0.11) | 0.06 (0.03, 0.11) |
|  | +Symptom | 0.06 (0.02, 0.11) | 0.05 (0.02, 0.11) | 0.06 (0.03, 0.11) | 0.06 (0.02, 0.10) | 0.06 (0.02, 0.11) | 0.06 (0.02, 0.11) | 0.06 (0.02, 0.11) |
| Rostral ACC | -Symptom | 0.04 (0.03, 0.09) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) |
|  | +Symptom | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.05 (0.02, 0.08) | 0.04 (0.02, 0.07) | 0.04 (0.02, 0.07) | 0.05 (0.02, 0.07) |
| Caudal ACC | -Symptom | 0.06 (0.05, 0.10) | 0.07 (0.04, 0.12) | 0.06 (0.03, 0.13) | 0.07 (0.03, 0.12) | 0.07 (0.03, 0.12) | 0.07 (0.03, 0.12) | 0.06 (0.03, 0.11) |
|  | +Symptom | 0.07 (0.03, 0.12) | 0.07 (0.03, 0.11) | 0.07 (0.03, 0.11) | 0.07 (0.03, 0.12) | 0.06 (0.03, 0.12) | 0.06 (0.03, 0.12) | 0.07 (0.03, 0.13) |
| PCC | -Symptom | 0.03 (0.01, 0.05) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.07) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.06) |
|  | +Symptom | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.07) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.07) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.07) | 0.05 (0.02, 0.07) |
| Isthmus Cing | -Symptom | 0.03 (0.02, 0.04) | 0.04 (0.02, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) |
|  | +Symptom | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.01, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.02, 0.06) | 0.03 (0.01, 0.05) |
| Lateral OFC | -Symptom | 0.03 (0.02, 0.05) | 0.02 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) |
|  | +Symptom | 0.03 (0.01, 0.04) | 0.03 (0.01, 0.04) | 0.03 (0.01, 0.04) | 0.03 (0.01, 0.04) | 0.03 (0.01, 0.04) | 0.03 (0.01, 0.04) | 0.03 (0.01, 0.04) |
| Medial OFC | -Symptom | 0.03 (0.02, 0.04) | 0.02 (0.01, 0.05) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) |
|  | +Symptom | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.04) |
| Ventral Dienceph | -Symptom | 0.02 (0.02, 0.03) | 0.03 (0.01, 0.05) | 0.02 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) |
|  | +Symptom | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.02 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.05) | 0.03 (0.01, 0.06) |
| Nucleus Accumbens | -Symptom | 0.05 (0.01, 0.09) | 0.04 (0.02, 0.07) | 0.05 (0.03, 0.08) | 0.05 (0.02, 0.08) | 0.05 (0.02, 0.08) | 0.05 (0.02, 0.08) | 0.05 (0.02, 0.08) |
|  | +Symptom | 0.04 (0.02, 0.08) | 0.05 (0.02, 0.08) | 0.04 (0.02, 0.08) | 0.04 (0.02, 0.07) | 0.04 (0.02, 0.07) | 0.04 (0.02, 0.06) | 0.04 (0.02, 0.07) |
| Thalamus | -Symptom | 0.03 (0.01, 0.05) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) |
|  | +Symptom | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.03) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.03) |

**Table S6.** Adjusted odds of symptom presentation for laterality index (LI) and side-independent laterality (siLI) for limbic brain regions. Details follow Table 4. No p-values were<0.05 after the Benjamini-Hochberg adjustment.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Headache** | **Balance** | **Cognitive** | **Fatigue** | **Anxiety** | **Depression** | **Emotional Lability** |
|  |  |  |  |  |  |  |  |  |
| **LI** |  |  |  |  |  |  |  |  |
|  | Amygdala | 1.23  0.50,1.88  ASLD | 1.16  0.87,1.41  ASLD | 1.12  0.75,1.50  ASLD | 0.94  0.77,1.89  ASL | 1.17  0.91,1.44  ASLD | 1.06  0.56,1.29  ASLD | 1.08  0.54,1.35  ASLD |
|  | Parahipp gyrus | 1.19  0.40,1.81  ASLD | 0.82  0.68,1.05  ASLD | 0.74  0.28,0.92  ASLD | 0.83  0.71,4.73  ASLD | 0.84  0.70,1.07  ASLD | 0.87  0.65,1.17  ASLD | 0.94  0.76,2.49  ASLD |
|  | Hippocampus | 0.83  0.53,2.48  ASLD | 0.97  0.83,3.75  ASLD | 0.80  0.64,1.04  ASLD | 0.87  0.71,1.20  ASL | 0.85  0.71,1.09  ASLD | 1.04  0.37,1.23  ASLD | 0.97  0.83,9.18  ASLD |
|  | Entorhinal cortex | 0.91  0.62,6.88  ASLD | 0.99  0.94,>100  ASLD | 1.11  0.72,1.37  ASLD | 1.05  0.42,1.27  ASL | 1.17  0.90,1.41  ASLD | 1.20  0.93,1.46  ASLD | 1.31  1.00,1.66  ASLD |
|  | Rostral ACC | 0.98  0.85,15.70  ASLD | 0.86  0.71,1.16  ASLD | 0.98  0.85,15.70  ASLD | 0.91  0.62,1.47  ASL | 0.98  0.85,8.21  ASLD | 1.11  0.75,1.35  ASLD | 0.93  0.74,1.91  ASLD |
|  | Caudal ACC | 0.66  0.40,1.34  ASLD | 0.76  0.57,0.97  ASLD | 0.98  0.83,12.47  ASLD | 0.82  0.66,1.75  ASLD | 0.91  0.76,1.32  SLD | 0.99  0.73,>100  ASLD | 0.86  0.50,1.35  ASLD |
|  | PCC | 0.83  0.54,2.53  ASLD | 0.94  0.78,1.70  ASLD | 0.90  0.74,1.40  ASLD | 1.04  0.03,2.15  ASLS\*L\* | 0.95  0.80,1.82  ASLD | 0.86  0.71,1.15  ASLD | 1.02  0.01,1.14  ASLD |
|  | Isthmus Cingulate | 0.82  0.53,2.09  ASLD | 0.85  0.70,1.12  ASLD | 0.83  0.68,1.11  ASLD | 0.94  0.77,1.93  ASL | 0.96  0.81,2.27  ASLD | 0.95  0.80,2.16  ASLD | 0.91  0.73,1.68  ASL |
|  | Lateral OFC | 1.24  0.51,1.90  ASLD | 1.26  1.01,1.53  ASLD | 1.11  0.71,1.36  ASLD | 1.16  0.23,1.37  ASLD | 1.07  0.62,1.27  ASLD | 1.08  0.65,1.30  ASLD | 0.95  0.47,3.15  ASLD |
|  | Medial OFC | 1.16  0.32,2.91  ASLD | 0.96  0.81,2.94  ASLD | 1.08  0.55,1.32  ASLD | 1.03  0.13,1.20  ASL | 1.01  0.01,1.10  ASLD | 1.03  0.14,1.19  ASLD | 1.13 0.73,11.13 ASLD |
|  | Ventral Diencephalon | 0.72  0.46,1.43  ASLD | 1.06  0.54,1.28  ASLD | 1.09  0.63,1.34  ASLD | 1.32  1.04,1.64  ASL | 1.06  0.56,1.27  ASLD | 1.07  0.57,1.29  ASLD | 1.15  0.72,1.45  ASLD |
|  | Nucleus Accumbens | 0.77  0.49,1.76  ASLD | 0.95  0.80,2.18  ASLD | 1.13  0.76,1.39  ASLD | 1.27  1.00,1.58  ASL | 0.98  0.88,14.87  ASLD | 0.97  0.83,3.60  ASLD | 1.17  0.79,1.80  ASLD |
|  | Thalamus | 1.09  0.14,1.58  ASLD | 1.02  0.09,1.15  ASLD | 0.96  0.81,3.29  ASLD | 0.96  0.80,2.61  ASL | 0.96  0.82,2.39  ASLD | 1.01  0.03,1.13  ASLD | 1.1  0.61,1.39  ASLD |
| **siLI** |  |  |  |  |  |  |  |  |
|  | Amygdala | 0.82  0.54,2.08  ASLD | 1.09  0.68,1.32  ASLD | 0.95  0.77,2.30  ASLD | 1.18  0.88,1.45  ASL | 1.06  0.59,1.26  ASLD | 1.03  0.23,1.20  ASLD | 0.99  0.96,>100  ASLD |
|  | Parahippocampus | 0.80  0.52,1.87  ASLD | 0.91  0.76,1.41  ASLD | 0.96  0.81,3.61  ASLD | 0.85  0.70,1.63  ASLD | 1.01  0.03,1.11  ASLD | 1.03  0.31,1.21  ASLD | 1.03  0.16,1.23  ASLD |
|  | Hippocampus | 0.87  0.59,3.25  ASLD | 1.16  0.86,1.41  ASLD | 1.25  0.96,1.56  ASLD | 1.11  0.74,1.36  ASL | 1.13  0.83,1.35  ASLD | 1.05  0.47,1.25  ASLD | 1.21  0.89,1.52  ASLD |
|  | Entorhinal cortex | 0.87  0.57,3.81  ASLD | 0.89  0.73,1.28  ASLD | 1.24  0.95,1.54  ASLD | 0.97  0.81,4.64  ASL | 0.96  0.82,2.54  ASLD | 1.06  0.54,1.28  ASLD | 0.99  0.00,1.34  ASLD |
|  | Rostral ACC | 0.86  0.56,2.92  ASLD | 0.98  0.87,12.67  ASLD | 0.91  0.75,1.51  ASLD | 1.01  0.02,1.13  ASL | 0.99  0.89,23.9  ASLD | 0.93  0.77,1.70  ASLD | 0.99  0.85,>100  ASLD |
|  | Caudal ACC | 0.94  0.66,21.37  ASLD | 0.98  0.84,5.90  ASLD | 0.97  0.81,4.39  ASLD | 1.03  0.19,1.21  ASL | 0.97  0.83,2.71  ASLD | 0.96  0.80,2.87  ASLD | 1.13  0.71,1.42  ASLD |
|  | PCC | 1.03  0.00,1.37  ASLD | 1.02  0.06,1.15  ASLD | 0.92  0.76,1.60  ASLD | 1.12  0.74,1.37  ASL | 1.00  0.54,>100  ASLD | 1.08  0.65,1.30  ASLD | 1.02  0.03,1.44  ASLD |
|  | Isthmus Cingulate | 1.18  0.37,1.82  ASLD | 0.95  0.79,1.93  ASLD | 1.07  0.55,1.31  ASLD | 0.91  0.74,1.52  ASL | 1.02  0.15,1.17  ASLD | 1.10  0.71,1.33  ASLD | 0.96  0.80,5.18  ASLD |
|  | Lateral OFC | 0.64  0.29,2.96  ASLDS\*D\* | 1.05  0.46,1.26  ASLD | 0.96  0.80,2.98  ASLD | 1.07  0.08,1.23  ASLD | 1.04  0.43,1.23  ASLD | 0.96  0.81,2.63  ASLD | 0.96  0.00,1.83  ASLD |
|  | Medial OFC | 0.49  0.24,1.20  ASLDS\*D\* | 0.92  0.76,1.46  ASLD | 1.16  0.83,1.43  ASLD | 1.05  0.43,1.27  ASL | 0.94  0.79,1.71  ASLD | 0.83  0.22,1.03  ASLD | 0.98  0.86,45.96  ASLD |
|  | Ventral Diencephalon | 1.29  0.54,2.05  ASLD | 1.05  0.44,1.25  ASLD | 1.09  0.64,1.33  ASLD | 1.02  0.03,1.14  ASL | 1.07  0.63,1.27  ASLD | 1.03  0.22,1.20  ASLD | 1.28  0.97,1.61  ASL |
|  | Nucleus Accumbens | 0.94  0.67,24.1  ASLD | 1.14  0.82,1.38  ASLD | 0.89  0.72,1.34  ASLD | 0.87  0.71,1.26  ASL | 0.91  0.76,1.32  ASLD | 0.83  0.68,1.06  ASLD | 0.87  0.69,1.34  ASLD |
|  | Thalamus | 0.71  0.47,1.23  ASLD | 1.08  0.62,1.30  ASLD | 1.22  0.93,1.52  ASLD | 0.89  0.71,1.38  ASL | 1.15  0.87,1.38  ASLD | 1.17  0.89,1.42  ASLD | 1.09  0.57,1.36  ASLD |

**Table S7**. Cutpoints for intervals in the TIV-adjusted scale for quartiles, used in Kaplan-Meier plots.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Minimum** | **Q1 to Q2** | **Q2 to Q3** | **Q3 to Q4** | **Maximum** |
| LI |  |  |  |  |  |  |
|  | Amygdala | -0.21891 | -0.06435 | -0.03138 | -0.00203 | 0.13433 |
|  | Parahippocampus | -0.1564 | -0.0232 | 0.0112 | 0.045 | 0.1877 |
|  | Hippocampus | -0.162321 | -0.000272 | 0.016062 | 0.035643 | 0.134935 |
|  | Entorhinal cortex | -0.4064 | -0.0935 | -0.0348 | 0.0181 | 0.2692 |
|  | Rostral ACC | -0.0358 | 0.197 | 0.2387 | 0.281 | 0.427 |
|  | Caudal ACC | -0.0684 | 0.268 | 0.3325 | 0.403 | 0.631 |
|  | PCC | -0.1963 | -0.0696 | -0.0317 | 0.0115 | 0.1875 |
|  | Isthmus Cingulate | -0.2404 | -0.1153 | -0.0814 | -0.0494 | 0.0795 |
|  | Lateral OFC | -0.1881 | -0.076 | -0.052 | -0.0243 | 0.0655 |
|  | Medial OFC | 0.125 | 0.232 | 0.255 | 0.277 | 0.373 |
|  | Ventral Diencephalon | -0.14028 | -0.03047 | -0.00403 | 0.02251 | 0.15969 |
|  | Nucleus Accumbens | -0.3049 | -0.0812 | -0.03769 | 0.00793 | 0.15021 |
|  | Thalamus | -0.181956 | -0.016955 | -0.000288 | 0.019433 | 0.113342 |
| siLI |  |  |  |  |  |  |
|  | Amygdala | 5.74E-05 | 0.0158 | 3.13E-02 | 0.0576 | 0.1875 |
|  | Parahippocampus | 0.000218 | 0.0157 | 0.034184 | 0.0574 | 0.1767 |
|  | Hippocampus | 0.000038 | 0.00888 | 0.018371 | 0.03386 | 0.17835 |
|  | Entorhinal cortex | 0.00015 | 0.0246 | 0.05738 | 0.1084 | 0.3714 |
|  | Rostral ACC | 0.000133 | 0.019 | 0.042153 | 0.077 | 0.2744 |
|  | Caudal ACC | 0.00116 | 0.0336 | 0.06662 | 0.1162 | 0.3997 |
|  | PCC | 0.000193 | 0.0178 | 0.040384 | 0.0643 | 0.2194 |
|  | Isthmus Cingulate | 0.000146 | 0.0154 | 0.032841 | 0.0575 | 0.1611 |
|  | Lateral OFC | 1.09E-05 | 0.0121 | 2.56E-02 | 0.0447 | 0.1361 |
|  | Medial OFC | 2.36E-05 | 0.0096 | 2.24E-02 | 0.0389 | 0.1305 |
|  | Ventral Diencephalon | 2.86E-05 | 0.0118 | 2.66E-02 | 0.0486 | 0.1637 |
|  | Nucleus Accumbens | 0.000272 | 0.0209 | 0.04439 | 0.0778 | 0.2669 |
|  | Thalamus | 6.73E-05 | 0.00911 | 1.75E-02 | 0.03456 | 0.1816 |