**Supplementary information**

Table S1: aiWBO main cell types simulated

|  |  |
| --- | --- |
| Cell types | Markers |
| Neurons (N=6) | DCX/Doublecortin, GAP43, MAP2, NeuN/RBFOX3, SLC17A7/VGLUT1, TUBB3 |
| Astrocytes (N=7) | CNTF, GFAP, GLAST-1/EAAT1, GLT-1/EAAT2, Neurotropin3, NGF, S100B |
| Oligodendrocytes (N=12) | miR-212 (-), Oligodendrocyte Apoptosis (-), BDNF (-), CNTF, Fibrinogen, LNRGF, Neurotropin3, NGF, Olig2, OPC-Differentiation, PDGF-R-alpha, Sox9 |
| Microglia (N=4) | AIF, CCL-4/MIP-1beta, CD11B/ITGAM, Neurotropin3 |
| Endothelial cells (N=3) | Mesoderm, VEGF, PIAS1/2 |
| Pericytes (N=5) | Amyloid-Beta-Oligomers/aggregation (-),  ETaR (-), PDGFR, TGFbR1/ALK5, TLR2/4 |

Table S2: aiWBO main Rostral Caudal Brain Regions simulated

|  |  |
| --- | --- |
| Rostral Caudal Brain Regions | Markers |
| Forebrain (N=11) | Emx1, FOXG1, GBX2, HOXA2, MAP2, NGF, Otx2, PAX6, Six3, Tbr-2/Tbr2, TUBB3 |
| Midbrain (N=16) | GBX2, HOXA2, DOPA decarboxylase, Engrailed-1&2, FOXA2, HOXA3, HOXB3, Irx1/2, Lmx1a, Lmx1b, Otx2, PAX3, PAX5, PAX7, PITX3, Tyrosine hydroxylase/TH |
| Hindbrain (N=10) | Irx3, EGR2/Krox20, GBX2, HOXA4, HOXB1, ISL1/Isl-1, LHX2/LH2, Lmx1b, PAX2, PAX5 |

Table S3: aiWBO main Ventral Dorsal Brain Regions simulated

|  |  |
| --- | --- |
| Ventral Dorsal Brain Regions | Markers |
| Ventral Forebrain | Dlx1/2, FOXG1, GSX2/GSH2, LHX2/LH2, LHX6, NKX-2.1/TITF1, Olig2, Otx2, Six3 |
| Pontine Nuclei (Ventral) | PCSK9 |
| Inferior Olive Complex (Ventral) | Deep Cerebellar Nuclei (-), Calbindin/CALB1, VGLUT2 |
| Cerebellum (Dorsal Hindbrain) | Olig2, GAD65, ATOH1, Tbr-1, VGLUT1 |
| Choroid Plexus (Dorsal Forebrain) | AQP1, En-1&2/Engrailed-1&2, Epithelial Cells, GBX2, PAX2, RSPO2, TTR/transthyretin |
| Deep Cerebellar Nuclei (Dorsal) | Cerebellum-PurL (-), Climbing Fibers, InfOlivaryCplx, Mossy Fibers, Pontine Nucleus |
| Thalamus (Dorsal Forebrain) | Calbindin/CALB1, Calretinin/CALB2, Parvalbumin (PV) |
| Hippocampus (Ventral and Dorsal) | FZD9, PROX1, GABARb, SLC17A7/VGLUT1 |

Table S4: aiWBO main Cerebral Cortical Layers simulated

|  |  |
| --- | --- |
| Cerebral Cortical Layers (outer to innermost) | Markers |
| Layer 1 (N=5) | Calbindin/CALB1, Reelin, Integrin-B1, nNOS/NOS1, Tbr-1/Tbr1 |
| Layer 2/3 (N=13) | Alzheimer's Disease (AD) (-), Neurofibrillary Tangles/(NFTs) (-), Calbindin/CALB1, Calretinin/Calb2, NEFH/N200, Reelin, BRN-2/POU3F2, CUX1, LMO4, MAP1b, PCP-2, SATB2, Tbr-1/Tbr1 |
| Layer 4 (N=7) | SATB2, Reelin, CUX1, MAP1b, NECAB1/STIP1, RORbeta, Tbr-1/Tbr1 |
| Layer 5 (N=16) | Neurofibrillary Tangles/(NFTs) (-), BRN-2/POU3F2, Calbindin/CALB1, Calretinin/CALB2, FOXP2, LMO4, TLE4, Reelin, FezF2, SATB2, Ctip2/BCL11B, ETV1/ER81, FOXO1/3, NEFH/N200, Sox5, Tbr-1/Tbr1 |
| Layer 6 (N=13) | ETV1/ER81, FezF2, SATB2, Reelin, Ctip2/BCL11B, DARPP-32, FOXP2, MAP1b, NEFH/N200, PCP-2, Sox5, Tbr-1/Tbr1, TLE4 |

Table S5: aiWBO main Cerebellar Cortical Layers simulated

|  |  |
| --- | --- |
| Cerebellar Cortical Layers (outer to innermost) | Markers |
| Layer 1 (Molecular Layer) (N=2) | GAD67, MX1 |
| Layer 2 (Purkinje Layer) (N=11) | Cerebellum-MolL-StC (-), Cerebellum-PurL-BasC (-), Calbindin/CALB1, GAD67, Astrocytes, Cerebellum-MolL-PFC, Climbing Fibers, MX1, Myosin IIb/MYH10, Parvalbumin (PV), PCP-2 |
| Layer 3 (Granular Layer) (N=5) | Cerebellum-GranL-GolC (-), Mossy Fibers, Neurons, NeuN/RBFOX3, NeuroD1 |
| Layer 4 (White Layer) (N=4) | Oligodendrocytes, MAP2K6/MEK6, Parvalbumin (PV), Plp1 |

Table S6: Effect on synaptic markers of synaptogenesis and function

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| --- | --- | --- | --- | --- | --- |
| Synaptic Marker | WT-Average | WT-±95%CI | APOE4-Average | APOE4-±95%CI | p value |
| Homer | 0.042 | 0.002 | 0.018 | 0.005 | <0.001 |
| PSD95 | 0.969 | 0.005 | 0.694 | 0.204 | <0.05 |
| SLC17A7/VGLUT1 | -0.026 | 0.037 | -0.110 | 0.013 | <0.01 |
| SYN-1/Synapsin1 | 0.968 | 0.002 | 0.976 | 0.000 | <0.001 |
| Synaptic dysfunction | -0.998 | 0.001 | 0.696 | 0.051 | <0.001 |
| Synaptic plasticity | 1.000 | 0.000 | 0.999 | 0.000 | <0.001 |
| Synaptogenesis | 0.828 | 0.026 | 0.117 | 0.045 | <0.001 |