Supplemental information

Astrocytic cell adhesion genes linked to schizophrenia correlate with synaptic programs in neurons

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**Table S2.** Canonical marker genes for cell type identities. Related to Figure 3.

| Gene name   | Marker identity   | Species  |
|-------------|-------------------|----------|
| POU5F1/Oct4 | stem cell         | human    |
| MKI67       | stem cell         | human    |
| DCX         | neural identity   | human    |
| MAP2        | neural identity   | human    |
| MAPT        | neural identity   | human    |
| NCAM1       | neural identity   | human    |
| RBFOX3      | neural identity   | human    |
| SYN1        | neural identity   | human    |
| TUBB3       | neural identity   | human    |
| EMX2        | neuronal progenitor| human    |
| HES1        | neuronal progenitor| human    |
| MSI1        | neuronal progenitor| human    |
| NEUROD1     | neuronal progenitor| human    |
| OTX2        | neuronal progenitor| human    |
| Aldh111     | astrocyte         | mouse    |
| Slc1a3      | astrocyte         | mouse    |
| Slc1a2      | astrocyte         | mouse    |
| Gfap        | astrocyte         | mouse    |
| Notch1      | astrocyte         | mouse    |
| S100b       | astrocyte         | mouse    |
| Cnp         | oligodendrocytes  | mouse    |
| Mag         | oligodendrocytes  | mouse    |
| Mog         | oligodendrocytes  | mouse    |
| Mbp         | oligodendrocytes  | mouse    |
| Cspg4       | oligodendrocytes  | mouse    |
| Olig2       | oligodendrocytes  | mouse    |
| Sox10       | oligodendrocytes  | mouse    |
| Pycard      | microglia         | mouse    |
| Itgam       | microglia         | mouse    |
| Cd40        | microglia         | mouse    |
| Ptprc       | microglia         | mouse    |
| Cd68        | microglia         | mouse    |
| Adgre1      | microglia         | mouse    |
| Alf1        | microglia         | mouse    |
| Spi1        | microglia         | mouse    |
| Tmem119     | microglia         | mouse    |
| C1qa        | microglia homeostatic| mouse |
| C1qb        | microglia homeostatic| mouse |
| Cx3cr1      | microglia homeostatic| mouse |
| Cst3        | microglia homeostatic| mouse |
$P2ry12$ microglia homeostatic mouse
Table S18. Gene set association results for CNS traits for genes induced in neurons by astrocytes. Related to Figure 7.

| NGENES | BETA  | BETA_STD | SE    | P       | Trait       | Cell type | Neuron gene set                                      |
|--------|-------|----------|-------|---------|-------------|-----------|------------------------------------------------------|
| 1603   | 0.07168 | 0.01974  | 0.03025 | 0.0089136 | Intelligence | neurons   | All induced genes (FDR < 5%)                         |
| 1529   | 0.05221 | 0.01427  | 0.02324 | 0.012329  | AD          | neurons   | All induced genes (FDR < 5%)                         |
| 1547   | -0.00961 | -0.00268 | 0.00444 | 0.98473   | ASD         | neurons   | All induced genes (FDR < 5%)                         |
| 1565   | 0.22387 | 0.06228  | 0.03209 | 1.57E-12  | schizophrenia| neurons   | All induced genes (FDR < 5%)                         |
| 219    | 0.15833 | 0.01673  | 0.07892 | 0.022417  | Intelligence| neurons   | Induced synaptic genes (FDR < 5%)                    |
| 208    | 0.02687 | 0.00281  | 0.06090 | 0.3295    | AD          | neurons   | Induced synaptic genes (FDR < 5%)                    |
| 212    | 0.00732 | 0.00078  | 0.01130 | 0.25858   | ASD         | neurons   | Induced synaptic genes (FDR < 5%)                    |
| 217    | 0.40510 | 0.04360  | 0.08055 | 2.49E-07  | schizophrenia| neurons   | Induced synaptic genes (FDR < 5%)                    |
| 1383   | 0.05463 | 0.01406  | 0.03242 | 0.045981  | Intelligence| neurons   | Induced non-synaptic genes (FDR < 5%)                |
| 1320   | 0.05580 | 0.01425  | 0.02487 | 0.01244   | AD          | neurons   | Induced non-synaptic genes (FDR < 5%)                |
| 1334   | -0.01211 | -0.00315 | 0.00473 | 0.99476   | ASD         | neurons   | Induced non-synaptic genes (FDR < 5%)                |
| 1347   | 0.18399 | 0.04779  | 0.03432 | 4.21E-08  | schizophrenia| neurons   | Induced non-synaptic genes (FDR < 5%)                |
| NGENES | BETA     | BETA_STD | SE     | P       | Trait     | cell type       | Glial gene set                                                                 |
|--------|----------|----------|--------|---------|-----------|-----------------|--------------------------------------------------------------------------------|
| 117    | 0.24610  | 0.01906  | 0.10666| 0.01053 | Intelligence| glial cells     | Genes positively associated to neuron eigengene                                |
| 113    | -0.05260 | -0.00406 | 0.08267| 0.73769 | AD        | glial cells     | Genes positively associated to neuron eigengene                                |
| 115    | 0.02617  | 0.00207  | 0.01581| 0.04898 | ASD       | glial cells     | Genes positively associated to neuron eigengene                                |
| 116    | 0.27640  | 0.02181  | 0.11079| 0.00631 | schizophrenia| glial cells     | Genes positively associated to neuron eigengene                                |
| 15     | 0.86757  | 0.02412  | 0.31360| 0.00284 | Intelligence| glial cells     | Synaptic genes positively associated to neuron eigengene                       |
| 13     | 0.64955  | 0.01707  | 0.23029| 0.00240 | AD        | glial cells     | Synaptic genes positively associated to neuron eigengene                       |
| 13     | -0.06292 | -0.00168 | 0.05209| 0.88646 | ASD       | glial cells     | Synaptic genes positively associated to neuron eigengene                       |
| 14     | 0.91359  | 0.02512  | 0.35489| 0.00503 | schizophrenia| glial cells     | Synaptic genes positively associated to neuron eigengene                       |
| 101    | 0.16398  | 0.01180  | 0.11385| 0.07490 | Intelligence| glial cells     | Non-synaptic genes positively associated to neuron eigengene                   |
| 99     | -0.15064 | -0.01090 | 0.08868| 0.95531 | AD        | glial cells     | Non-synaptic genes positively associated to neuron eigengene                   |
| 101    | 0.03426  | 0.00254  | 0.01675| 0.02043 | ASD       | glial cells     | Non-synaptic genes positively associated to neuron eigengene                   |
| 101    | 0.18440  | 0.01358  | 0.11766| 0.05855 | schizophrenia| glial cells     | Non-synaptic genes positively associated to neuron eigengene                   |
**Figure S1.** Alignment effect on transcriptome. A) Representative images of neuron monocultures and neuron-glia cocultures from 4 independent cell lines, staining for left: DAPI (blue) GFAP (green) and MAP2 (magenta), and right: DAPI (blue) CX43 (red) Syn1 (green) and MAP2 (magenta), Scale bar= 100um. B) Variance partitioning by human and mixed reference genome reveals 329 genes for which cross-species mapping explains >10% of variation in read counts. On average cross-species mapping explains only 0.78% of the variation in the read counts. C) PCA components 7 and 8 the cluster data set according to alignment. D) PCA of RNAseq data from day 28 neurons aligned to mixed reference genome. E) Canonical marker gene expression for pluripotency, neuronal progenitor cells and neuronal identity at different stages of differentiation and culture conditions. Related to Figure 2.
Figure S2. Variance explained by model covariates and GO terms for genes induced by astrocytes in neurons. A) Variance explained in gene expression for model covariates. B) Transcriptome-wide significantly induced genes are enriched for functions in neuronal development and synapse. Related to Figure 3.
Figure S3. Glial genes that associate with neuronal maturation are predominantly expressed by mouse astrocytes and enriched for synaptic genes. A) tSNE projection of scRNA-seq data showing average expression of 846 genes that were associated with astrocyte eigengene and induced in coculture. B) The 123 positively associated genes had the highest expression in astrocytes in the single cell atlas of adult mouse brain. The 36 negatively associated genes were uniformly expressed across glial cell types in the mouse brain atlas. C) The 159 glial genes have synaptic functions in SynGO. D) Glial genes with negative association to neuron maturation are reduced in astrocytes after contact with neurons. Related to Figure 4 and Figure 5.
**Figure S4.** Transcripts encoding members of the cholesterol synthesis pathway are induced in astrocytes after contact with neurons. Related to Figure 5.
Figure S5. Neurons in sandwich culture and coculture with glial cells have global transcriptional changes. A) Hierarchical clustering of neurons in sandwich and coculture. B) Volcano plot of differential gene expression between neurons in coculture and sandwich culture. C) Neurons in coculture have on average higher expression of genes that associate with the astrocyte eigengene (p=1.9x10^{-26} paired t-test). D) The average levels of the transcripts that associate with the astrocyte eigengene are consistently higher in all neuronal lines. E) Gene-wise associations for 123 glial genes whose high expression induce synaptic gene programs in neurons. The heat-map coloring indicates the standardized z-score of gene-wise p-values from MAGMA. The genes are ordered by the strength of association (z-score value) to schizophrenia. Synaptic genes are colored in red. Genes with direct evidence through coding variants and fine mapping in schizophrenia are indicated by arrows. Genes located in genome-wide significant loci in PGC3 for schizophrenia are highlighted by blue boxes. Related to Figure 7.
