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Oligodendrocyte secreted factors shape hippocampal GABAergic neuron transcriptome and physiology

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► To cite this version:

Elisa Mazuir, Louis Richevaux, Merie Nassar, Noémie Robil, Pierre de La Grange, et al.. Oligodendrocyte secreted factors shape hippocampal GABAergic neuron transcriptome and physiology. *Cerebral Cortex*, 2021, 31 (11), pp.5024-5041. 10.1093/cercor/bhab139 . hal-03051982v2

HAL Id: hal-03051982

<https://hal.science/hal-03051982v2>

Submitted on 20 Oct 2021

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**Oligodendrocyte secreted factors shape hippocampal
GABAergic neuron transcriptome and physiology**

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|-------------------------------|--|
| Journal: | <i>Cerebral Cortex</i> |
| Manuscript ID | CerCor-2020-00934.R1 |
| Manuscript Type: | Original Article |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | <p>Mazuir, Elisa; Sorbonne Universite, Neuroscience Richevaux, Louis; Université de Paris, Integrative Neuroscience and Cognition Center Nassar, Merie; Université de Paris, Integrative Neuroscience and Cognition Center Robil, Noemie; Genosplice, GenoSplice technology de la Grange, Pierre; Genosplice, GenoSplice technology Lubetzki, Catherine; Hopital Universitaire Pitie Salpetriere, Department of Neurology Fricker, Desdemona; Université de Paris, CNRS UMR8002 Sol-Foulon, Nathalie; Sorbonne Universite, Neuroscience</p> |
| Keywords: | GABAergic neurons, neuro-glia interactions, oligodendrocytes, secreted factors, single-cell RNAseq |
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3 **Oligodendrocyte secreted factors shape hippocampal GABAergic neuron transcriptome**
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5 **and physiology**
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10 Running title: Oligodendroglial factors shape GABAergic neurons
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ABSTRACT

Oligodendrocytes form myelin for central nervous system axons and release factors which signal to neurons during myelination. Here, we ask how oligodendroglial factors influence hippocampal GABAergic neuron physiology. In mixed hippocampal cultures GABAergic neurons fired action potentials of short duration and received high frequencies of excitatory synaptic events. In purified neuronal cultures without glial cells, GABAergic neuron excitability increased and the frequency of synaptic events decreased. These effects were largely reversed by adding oligodendrocyte conditioned medium. We compared the transcriptomic signature with the electrophysiological phenotype of single neurons in these three culture conditions. Genes expressed by single pyramidal or GABAergic neurons largely conformed to expected cell-type specific patterns. Multiple genes of GABAergic neurons were significantly downregulated by the transition from mixed cultures containing glial cells to purified neuronal cultures. Levels of these genes were restored by the addition of oligodendrocyte conditioned medium to purified cultures. Clustering genes with similar changes in expression between different culture conditions revealed processes affected by oligodendroglial factors. Enriched genes are linked to roles in synapse assembly, action potential generation and transmembrane ion transport, including of zinc. These results provide new insight into the molecular targets by which oligodendrocytes influence neuron excitability and synaptic function.

Keywords: GABAergic neurons, neuro-glia interactions, oligodendrocytes, secreted factors, single-cell RNAseq

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3 Communication between oligodendrocytes and neurons is crucial for circuit maturation
4
5 but still not completely understood. The fast transmission of action potentials relies on insulat-
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7 ing properties of myelin sheath which is interrupted at nodes of Ranvier, small axonal domains
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9 highly enriched in voltage-gated Na⁺ channels (Sherman and Brophy 2005). The profile of my-
10
11 elination and nodes of Ranvier controls the timing of impulse transmission, critical for coinci-
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13 dent arrival of synaptic inputs transmitted by multiple axons in sensory systems (Seidl 2014;
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15 Freeman et al. 2016; Arancibia-Cárcamo et al. 2017; Monje 2018). Both oligodendrocytes and
16
17 oligodendrocyte precursor cells (OPCs or NG2 cells) sense neuronal activity, which triggers
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19 their differentiation and maturation into myelinating oligodendrocytes (Barres & Raff, 1993;
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21 Demerens et al. 1996). Adaptive myelination acts to reinforce selected circuits during learning
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23 (McKenzie et al. 2014; Bechler et al. 2018; Monje 2018; Stedehouder et al. 2018). Oligoden-
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25 drocytes also release lactate to provide metabolic support to axons (Fünfschilling et al. 2012;
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27 Lee et al. 2012; Saab et al. 2016).

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33 Factors secreted by oligodendrocytes induce early formation of node-like clusters,
34
35 termed prenodes, enriched in Nav channels, Nfasc186 and Ankyrin-G, along the axons of reti-
36
37 nal ganglion cells and some hippocampal GABAergic neurons (parvalbumin or somatostatin
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39 immunopositive) before myelination (Kaplan et al. 1997; Freeman et al. 2015; Bonetto et al.
40
41 2019; Dubessy et al. 2019). These early clusters are associated with an increased axonal con-
42
43 duction velocity along GABAergic axons (Freeman et al. 2015). In addition, [oligodendrocyte](#)
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45 [lineage cells](#) close to the soma of pyramidal neurons modulate glutamatergic neurotransmission
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47 [via secreted factors](#) and restrain high-frequency firing [through the rapid uptake of K⁺](#) (Sakry et
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49 al. 2014; Birey et al. 2015; Battfeld et al. 2016; Jang et al. 2019; Xin et al. 2019). Moreover,
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51 oligodendroglial exosomes and OPC secreted protein NG2 mediate glia signaling to neurons
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3 (Frühbeis et al. 2013; Sakry et al. 2015). The identity of molecular targets by which oligoden-
4 drocyte secreted factors affect GABAergic neuron excitability and synaptic interactions remain
5 unknown.
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10 The present study aimed to identify targets of oligodendrocyte mediated regulation of
11 GABAergic hippocampal neurons. Electrophysiological phenotypes of rat hippocampal neu-
12 rons were compared in mixed cultures, (with glial cells, CTRL) and purified neuron cultures
13 (without glial cells, PUR). We then tested the effects of adding oligodendrocyte conditioned
14 medium (OCM) to purified cultures. OCM tended to reverse changes in GABAergic neuron
15 physiology and anatomy induced by eliminating glial cells from cultures. Single-cell RNA-
16 sequencing of GABAergic neuron cytoplasm collected in patch electrodes let us explore mo-
17 lecular targets of OCM-induced regulation. RNA-seq analysis was validated by the presence of
18 cell-type specific genes, including those for subclasses of GABAergic neurons. Major targets
19 of oligodendrocyte factor signaling to GABAergic neurons included ion channels and trans-
20 porters contributing to the regulation of membrane potential and action potential generation as
21 well as transmembrane transport of zinc.
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41 MATERIALS AND METHODS

42 **Animals**

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44 Care and use of rats in all experiments conformed to institutional policies and guidelines
45 (UPMC, INSERM, and European Community Council Directive 86/609/EEC). The following
46 rat strains were studied: Sprague-Dawley or Wistar rats (Janvier Breeding Center) and VGAT-
47 Venus Wistar rats in which a green fluorescent protein variant is selectively expressed in GA-
48 BAergic cells (Uemastu et al. 2008). We assume that fluorescent cells in cultures correspond
49 to GABAergic neurons.
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Culture Media

We used the following culture media. NM, neurobasal medium (21103ium (2Gibco) supplemented with 0.5 mM L-glutamine, B27 (1×; Invitrogen), and penicillin-streptomycin (100 IU/mL). BS, Bottenstein-Sato medium: DMEM Glutamax supplemented with transferrin (50 µg/mL), albumin (50 µg/mL), insulin (5 µg/mL), progesterone (20 nM), putrescine (16 µg/mL), sodium selenite (5 ng/mL), T3 (40 ng/mL), T4 (40 ng/mL) and PDGF (10 ng/ml).

Preparation of oligodendrocyte conditioned medium

Glial cell cultures were prepared from cerebral cortices of P2 Wistar rats as described previously (Mazuir et al. 2020). After meninges were removed, cortices were incubated for 35 min in papain (30 U/mL; Worthington), supplemented with L-cysteine (0.24 mg/mL) and DNase (50 µg/mL) in DMEM at 37°. They were then mechanically homogenized and passed through a 0.70 µm filter. Cells were re-suspended in DMEM with 10% FCS and 1% penicillin-streptomycin. After 7 to 14 days *in vitro* (DIV), oligodendroglial lineage cells were purified from glial cell cultures which initially contain astrocytes and microglial cells. After cultures were shaken overnight at 230 rpm and 37°C, overlying oligodendroglial and microglial cells could be selectively detached. Microglia were then eliminated by differential adhesion (McCarthy and de Vellis 1980). Collected cells were incubated in dishes for 15 min. Non-adherent cells were retrieved and centrifuged in DMEM for 5 min at 1500 rpm. They were re-suspended and seeded at a density of $1.5 \times 10^5 / \text{cm}^2$ on Polyethylene-imine (PEI)-coated dishes with BS medium and 0.5% PDGF. Immunostaining showed that $90 \pm 4\%$ of cells were positive for the oligodendroglial marker O4⁺, $7.2 \pm 2.5\%$ were GFAP⁺ astrocytes and $4.6 \pm 0.7\%$ were CD11b⁺ immunopositive microglial cells (Mazuir et al. 2020). Medium from these cultures was collected after 48 hours, filtered (0.22 µm) and stored for use as oligodendrocyte conditioned medium.

Neuronal cultures

Experiments were performed in three different culture conditions (Fig. 1A). Control (CTRL) was mixed hippocampal cultures containing neurons, astrocytes, and oligodendrocyte lineage cells (Sup. Fig1A). They were prepared from E18 rat embryos and were seeded on polyethyleneimine precoated glass coverslips at a density of 50,000 cells/35 mm² (Freeman et al. 2015). Purified neuron cultures (PUR) were prepared by adding anti-mitotic agents (FdU and U 5μM) for 12 hours, starting at 24 hours after dissection. Immunostaining showed these cultures contained less than 5% astrocytes and virtually no oligodendrocytes. In OCM cultures oligodendrocyte conditioned medium was added to purified neuron cultures. Conditioned medium (500 μl/well) was added at 3 days *in vitro* (DIV). One-third of the medium was replaced with neurobasal medium (NM) at 7 DIV, and then twice a week. Axon initial segments were visualized by 20 min exposure to an anti-Nfasc antibody (clone A12/18, Antibodies Incorporated) coupled to Alexa 594 (using Apex antibody labeling kit, ref A10474, Thermofisher) before recordings (Sup. Fig1B).

Patch-clamp electrophysiological recording and analysis

Electrophysiological recordings were made from cultures at 17 DIV. Dishes were transferred to a recording chamber mounted on a BX51WI microscope (Olympus, France) and superfused with ACSF containing (in mM): 124 NaCl, 2.5 KCl, 26 NaHCO₃, 1 NaH₂PO₄, 2 CaCl₂, 2 MgCl₂, and 11 glucose, bubbled with 5% CO₂ in O₂ (pH 7.3, 305-315 mOsm/L). Temperature was kept at 34° C. Recordings were made with glass pipettes pulled using a Brown-Flaming electrode puller (Sutter Instruments) from borosilicate glass of external diameter 1.5 mm (Clark Capillary Glass, Harvard Apparatus). Pipette resistance was 6 MΩ when filled with a solution containing (in mM): 135 K-gluconate, 1.2 KCl, 10 HEPES, 0.2 ethylene glycol tetraacetic acid (EGTA), 2 MgCl₂, 4 MgATP, 0.4 Tris-GTP, 10 Na₂-phosphocreatine and 2.7 biocytin. RNase

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3 inhibitor was added (40U/ μ l, Thermo Fischer Scientific; 5 μ l in 1ml) when harvesting cell con-
4 tents. Pipette solution pH was adjusted to 7.3 with KOH and the osmolarity was 290 mOsm.
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6 Whole-cell current-clamp recordings were made using a MultiClamp 700B amplifier and
7
8 pCLAMP software (Molecular Devices). Potential signals were filtered at 6 kHz and digitized
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10 at 20–50 kHz.
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15 Recordings in the whole-cell current clamp configuration were made from fluorescent GA-
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17 BAergic neurons and non-fluorescent pyramidal shaped neurons in cultures prepared from
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19 VGAT-Venus Wistar rats. Excitatory postsynaptic potential (EPSP) and action potential (AP)
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21 frequencies, membrane potential and input resistance were measured at resting potential. Re-
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23 sponses to families of hyperpolarizing and depolarizing current steps of duration 800 ms were
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25 recorded from holding potentials near -60 mV. Current intensities were manually adjusted to
26
27 induce a maximal hyperpolarization close to -100 mV. Incremental positive steps of +1/10 of
28
29 that value were then applied until the cell was depolarized above rheobase several times. After
30
31 recording electrical data for ~10 min, neuronal contents were aspirating into the glass electrode
32
33 tip. They were extracted into a tube containing 3.5 μ l of lysis buffer with RNase inhibitor as a
34
35 first step to prepare a library of neuronal total RNA (Qiu et al., 2012). Electrophysiological
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37 signals were analyzed with AxographX and routines written in MATLAB (The Mathwork;
38
39 Huang et al. 2017). EPSP and AP frequencies were measured from baseline records of duration
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41 at least 3000 ms. [Sup. Fig2](#) shows procedures used to measure active and passive membrane
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43 parameters.
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53 **Reconstruction of neuronal morphology**

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55 Pipettes used for patch-clamp recordings included 2.7 mM biocytin. Cultures containing filled
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57 cells were fixed at 17 DIV with PFA4% (diluted in PBS 1X; pH 7.2) for 10 min at room tem-
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59 perature (RT). Coverslips were washed three times with PBS 1X and blocked with 5% normal
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3 goat serum containing 0.1% Triton for 15 min at RT. Biotin-filled cells and their axon initial
4 segments were visualized. Cultures were incubated with anti-Neurofascin (1:100, ab31457,
5 Abcam) for 2 hours at RT. After three PBS rinses, they were incubated with Streptavidine-
6 Alexa 488 (ThermoFisher Scientific) to visualize biotin-filled neurons and anti-rabbit-Alexa
7 594 (1:1000, ThermoFisher Scientific) for Neurofascin for 1 hour at RT. Stained cultures were
8 mounted with Fluoromount-G.
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11 Images of stained cells were acquired on a upright spinning disk microscope (Intelligent Imag-
12 ing Innovations, Inc) using a 20x glycerol immersion objective (NA 1.0), a CSU-W1 spinning
13 disk head (Yokogawa) and a sCMOS ORCA-Flash4.0 camera (Hamamatsu). Multiple tile re-
14 gions each with Z step series of separation 1.1 μm were acquired for each cell. Tile scans were
15 stitched using Fiji software with BigStitcher plugin. Neuronal arborizations were drawn with
16 the semi-automatic filament tracer tool of IMARIS software (Bitplane). The axon was identi-
17 fied from Neurofascin immunostaining of its initial segment. Axonal and dendritic lengths and
18 data for Sholl analyses were derived by the IMARIS software.
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39 **Statistical analysis of electrophysiological properties and morphology**

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41 Statistical analyses were performed using GraphPad Prism version 7.0. Experiments for each
42 condition were carried out in at least 3 independent cultures from at least 3 different litters.
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44 Electrophysiological parameters in Figs. 1 and 2 were compared using the Mann-Whitney test
45 (for PYR CTRL vs. GABA CTRL) and using Kruskal Wallis and Dunn's multiple comparison
46 *post hoc* test (for GABA CTRL vs. GABA PUR, GABA PUR vs. GABA OCM and GABA
47 CTRL vs. GABA OCM). P-values are given in Table 1.
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56 Axonal and dendritic lengths were compared (Fig. 3) using Kruskal Wallis and Dunn's multiple
57 comparison *post hoc* test (for GABA CTRL vs. GABA PUR and GABA PUR vs. GABA OCM
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3 and GABA CTRL vs. GABA OCM). Dendritic arborizations were assessed with Sholl analysis
4 which measures the number of dendrites which intersect circles of increasing distance from the
5 neuronal soma (20 μm increments were used). They were analyzed using a linear mixed-effects
6 model (LMM) with culture condition and radial distance as fixed effects, and the cell identifier
7 number as a random effect to account for the successive measurements over the concentric rings
8 (Wilson et al. 2017). Significance for the main effects of condition, distance and their interaction
9 was then evaluated using ANOVA Type II Wald chi-square tests. Analyses were made with R
10 (R Development Core Team, ver 3.5.1, 2019) and plots were generated with the ggplot2 pack-
11 age (Wickham et al., 2016). LMM was fitted with the function lmer in the lme4 package (Bates
12 et al., 2015). When a factor had a significant effect or when a significant interaction was found
13 between condition and distance, *post-hoc* pairwise comparisons were completed with Tukey's
14 method. Data were square root transformed before modeling to improve model assumptions of
15 linearity, normality and constant variance of residuals,
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34 Data are given as mean \pm SD (*i.e.* standard deviation) in Table 1 and in the text. The level of
35 statistical significance was set at $p < 0.05$ for all tests. Significance is represented as numbers
36 of asterisks: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$
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44 **cDNA synthesis, library preparation and sequencing**

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47 mRNA capture, reverse transcription and amplification was achieved using the SMART-Seq
48 v4 ultra low input RNA Kit (Takara, 634891). This kit improves synthesis of the full-length
49 cDNA via a template switching mechanism for synthesis of the second strand cDNA. 5 μl of
50 sample was used for hybridization with the 3'smart-seq primer, then poly{T}-primed mRNA
51 was converted to cDNA by reverse transcriptase and PCR amplification was done, according
52 to the kit instructions. Full-length cDNA was then processed with a Nextera XT DNA Library
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3 Preparation Kit (Illumina, FC-131-1096). This kit aims to fragment and add adapter sequences
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5 onto template DNA with a single tube Nextera XT tagmentation reaction and so generate mul-
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7 ti-plex sequencing libraries. The resulting indexed paired-end libraries were sequenced by next-
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9 generation sequencing (NGS), using NextSeq500 2x75pb, 33 million of reads per sample (Illu-
10
11 mina NextSeq 500 platform) (Sup. Fig3A).
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18 RNA-seq data analysis

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20 RNA-Seq data analysis was performed by GenoSplice technology (www.genosplice.com). Se-
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22 quencing, data quality, read distribution (to check for ribosomal contamination for instance),
23
24 and insert size estimation were done with FastQC, Picard-Tools, Samtools and rseqc. Reads
25
26 were mapped using STARv2.4.0 (Dobin et al. 2013) on the rn6 Rat genome assembly. The
27
28 regulation of gene expression was studied as in (Noli et al. 2015). For each gene of the Rat
29
30 FAST DB v2016_1 annotations, reads aligning on constitutive regions (not prone to alternative
31
32 splicing) were counted. Normalization and differential gene expression was assessed from these
33
34 reads using DESeq2 running on R (v.3.2.5, Love et al. 2014). FastQC was used for quality
35
36 control, sequencing quality per base and sequence, per base sequence and GC content, N con-
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38 tent, overrepresented sequences, sequence lengths. Sequence coverage of introns and exons was
39
40 used to ensure that the sequences derived from mRNA rather than genomic DNA.
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46 From 64 samples, 21 passed these control quality steps. Others were discarded due to sample
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48 quality (n=32) or contamination detected from marker expression (n=11) based on the follow-
49
50 ing *GFAP*, *Aquaporin 4*, *Slc1a2*, *PDGFRA*, *MOG*, *Itgam* (Sup. Fig3 B, D, E).
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52

53 Genes were considered as expressed if their FPKM (*i.e.* Fragments Per Kilobase Million) value
54
55 was greater than 98% of the background FPKM value from intergenic regions (Sup. Fig4). Data
56
57

58 accessibility: GEO access for reviewers (ref: GSE146291) -
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60 <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE146291>, (code: cbcfewamlbmztep).

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3 Clustering and heatmap analyses were performed using “dist” and “hclust” functions in R, with
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5 Euclidean distance and Ward agglomeration method.
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8 Genes were considered to be differentially expressed when the uncorrected p-value ≤ 0.05 and
9
10 fold-change ≥ 1.5 .
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12

13 Enriched **gene ontology** (GO) terms were assessed, from the identity of differentially expressed
14
15 genes, with the DAVID Functional Annotation Tool (v6.8), (Huang et al. 2007). GO terms were
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17 considered enriched when fold enrichment ≥ 2.0 and uncorrected p-value ≤ 0.05 (1.3 value in
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19 GO term graph matches with a p value of 0.05), and at least 2 regulated genes in the path-
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21 way/term.
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25 A Pearson correlation-based approach was used to compare single-cell RNA values with elec-
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27 trophysiological parameters for neurons (Fig. 6). The procedure was restricted to genes ex-
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29 pressed in at least five samples, with coefficients greater than 0.6 and significant p-values
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31 ($p < 0.05$).
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37 **RESULTS**

38 39 **Oligodendrocyte secreted factors control the electrophysiological properties of hippocam- 40 41 pal GABAergic neurons** 42 43 44

45 We first asked how the presence of glial cells or oligodendrocyte secreted factors af-
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47 fected GABAergic neuron phenotype. Hippocampal neuron cultures were prepared from
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49 VGAT-Venus rat embryos so that GABAergic interneurons could be identified. Spontaneous
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51 activity and active and passive membrane properties were recorded in the current clamp mode
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53 from fluorescent GABAergic neurons (n=36). These properties were compared with those of
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55 unlabeled pyramidal cells (n=11). We further compared the physiology of GABAergic neurons
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57 in control cultures (CTRL) with those in purified cultures lacking glial cells (PUR) and with
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3 those in purified cultures supplemented with oligodendrocyte conditioned medium (OCM)
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5 (Fig. 1A, B).
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8 Spontaneous synaptic events and spiking activity of recorded cells was quantified at
9
10 resting potential with no injected current (Fig. 1C-E). In pyramidal cells (PYR), frequencies of
11
12 excitatory postsynaptic potentials (EPSP) and action potentials (AP) were low in CTRL cultures
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14 (PYR CTRL, EPSPs, 7 ± 2 Hz; APs, 0.03 ± 0.01 Hz; $n=11$). Mean resting potential was -63 ± 9
15
16 mV and mean input resistance was 330 ± 218 M Ω (Fig. 1F, G; Table 1). EPSP frequency and
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18 AP discharge rate were both higher in GABAergic neurons from the same cultures. Mean EPSP
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20 frequency was 70 ± 13 Hz and AP discharge frequency was 0.6 ± 0.5 Hz (GABA CTRL, $n=11$).
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25 In PUR neuronal cultures, both EPSP frequency and AP discharge by GABAergic neu-
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27 rons were reduced (GABA PUR, EPSPs, 6 ± 2 Hz, $n=10$; APs, 0.03 ± 0.03 Hz, $n=11$). This despite
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29 a more depolarized mean resting membrane potential (GABA PUR, -49 ± 11 mV vs GABA
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31 CTRL, -55 ± 5 mV) and a significantly higher input resistance than in control cultures (GABA
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33 PUR, 144 ± 46 M Ω vs GABA CTRL, 74 ± 53 M Ω). Supplementing PUR cultures with oligoden-
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35 drocyte conditioned medium tended to increase EPSP and AP frequencies towards CTRL levels
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37 (GABA OCM, EPSPs, 19 ± 4 Hz, $n=13$; APs, 0.4 ± 0.03 Hz, $n=12$). Mean membrane potential
38
39 and input resistance also reverted towards values in CTRL mixed cultures (GABA OCM, -54 ± 7
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41 mV and 110 ± 104 M Ω). These data suggest that oligodendrocyte secreted factors influence ac-
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43 tive and passive aspects of the physiological phenotype of GABAergic neurons.
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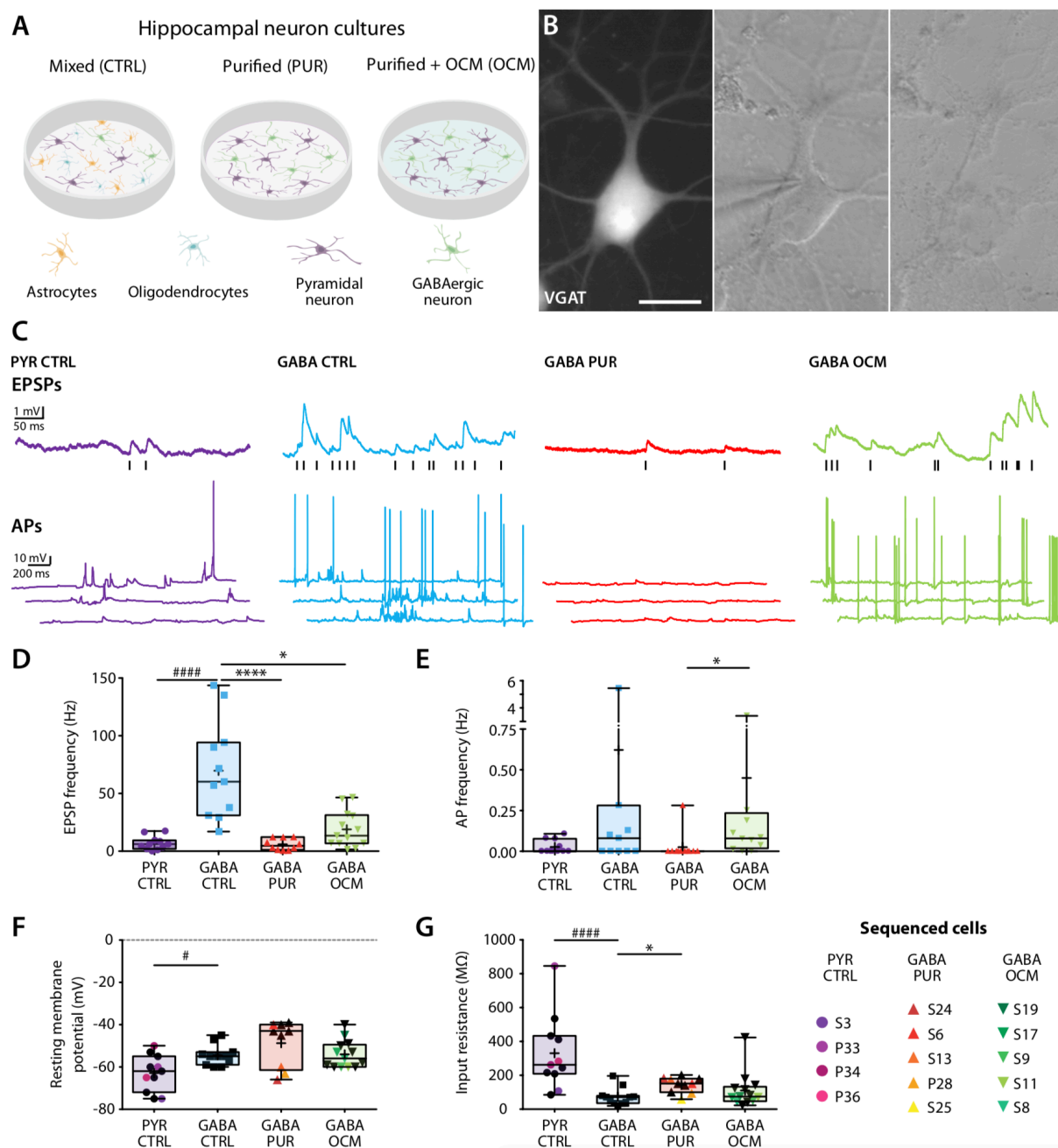


Figure 1: Patch clamp recording and cytosol harvesting of hippocampal neurons. (A) Schematic representation of the culture conditions: neurons from mixed cultures (CTRL), containing hippocampal neurons and glial cells, were compared with those of purified cultures (PUR), which in some cases were treated with oligodendroglia conditioned medium (OCM). (B) Soma and proximal dendrites of a green fluorescent GABAergic neuron (VGAT⁺ cell; left). Patch pipette sealed to the neuronal membrane for electrical recording (middle). After aspiration of

the cytosolic content (right). Scale bar: 20 μm (C) Representative voltage recordings of pyramidal and GABAergic neurons at 17 DIV in different culture conditions. Top, excitatory postsynaptic potentials (EPSPs), indicated by black lines. Bottom, spontaneous action potential (AP) firing. (D, E) EPSP (D) and AP (E) frequencies measured from neurons in different conditions. EPSP, PYR CTRL vs. GABA CTRL, $p < 0.0001$ (Mann-Whitney test #); GABA CTRL vs. GABA PUR, $p < 0.0001$; GABA CTRL vs. GABA OCM, $p = 0.0123$. AP, GABA PUR vs. GABA OCM, $p = 0.0126$ (Kruskal-Wallis and Dunn's *post hoc* *). (F, G) Resting membrane potential (F) and input resistance (G) of recorded neurons in different conditions. Color symbols show cells from which sequence data was derived. Mann-Whitney test for PYR CTRL vs. GABA CTRL significance levels indicated with #, Kruskal-Wallis and Dunn's *post hoc* for GABA CTRL vs. PUR vs. OCM indicated by *. P-values are given in Table 1. Boxplots represent the median (middle line), the mean (+ sign), 25th and 75th percentiles (box) and the top and bottom values (whiskers).

| | PYR CTRL | | | GABA CTRL | | | GABA PUR | | | GABA OCM | | |
|--------------------------------------|----------|------|----|-----------|------|----|----------|------|----|----------|------|----|
| | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Resting membrane potential (mV) | -63 | 9 | 11 | -55 | 5 | 11 | -49 | 11 | 9 | -54 | 7 | 13 |
| Neuronal Input Resistance (Mohm) | 330 | 218 | 11 | 74 | 53 | 11 | 144 | 46 | 10 | 110 | 104 | 13 |
| Tau 1 (ms) | 31 | 16 | 11 | 12 | 10 | 11 | 15 | 7 | 10 | 14 | 6 | 12 |
| Sag ratio at -100 mV | 1.10 | 0.10 | 11 | 1.27 | 0.10 | 11 | 1.17 | 0.10 | 10 | 1.33 | 0.20 | 13 |
| Rheobase current | 121 | 83 | 11 | 427 | 284 | 11 | 169 | 121 | 10 | 347 | 276 | 13 |
| Firing rate at 200 pA (Hz) | 26 | 19 | 11 | 3 | 7 | 11 | 21 | 23 | 10 | 7 | 12 | 13 |
| Input-output slope (Hz/nA) | 225 | 150 | 11 | 99 | 48 | 11 | 188 | 139 | 10 | 113 | 115 | 12 |
| AP threshold (at 10V/s) | -30.5 | 3.3 | 11 | -32.2 | 3.5 | 11 | -31.8 | 5.7 | 10 | -35.3 | 2.9 | 13 |
| AP width (ms) | 1.51 | 0.80 | 11 | 0.50 | 0.20 | 11 | 0.96 | 0.60 | 10 | 0.74 | 0.50 | 13 |
| AP AHP (mV) | -19.5 | 4.4 | 11 | -27.6 | 3.3 | 11 | -23.8 | 3.2 | 10 | -29.4 | 7.3 | 13 |
| AP rise amplitude | 78 | 7 | 11 | 61 | 9 | 11 | 56 | 13 | 10 | 68 | 8 | 13 |
| AP maximum depolarization rate (V/s) | 325 | 212 | 11 | 294 | 68 | 11 | 192 | 105 | 10 | 327 | 103 | 13 |
| AP maximum repolarization rate (V/s) | -61 | 28 | 11 | -164 | 82 | 11 | -91 | 57 | 10 | -119 | 51 | 13 |
| Onset latency at rheobase | 349 | 251 | 11 | 167 | 172 | 11 | 28 | 24 | 10 | 64 | 86 | 13 |

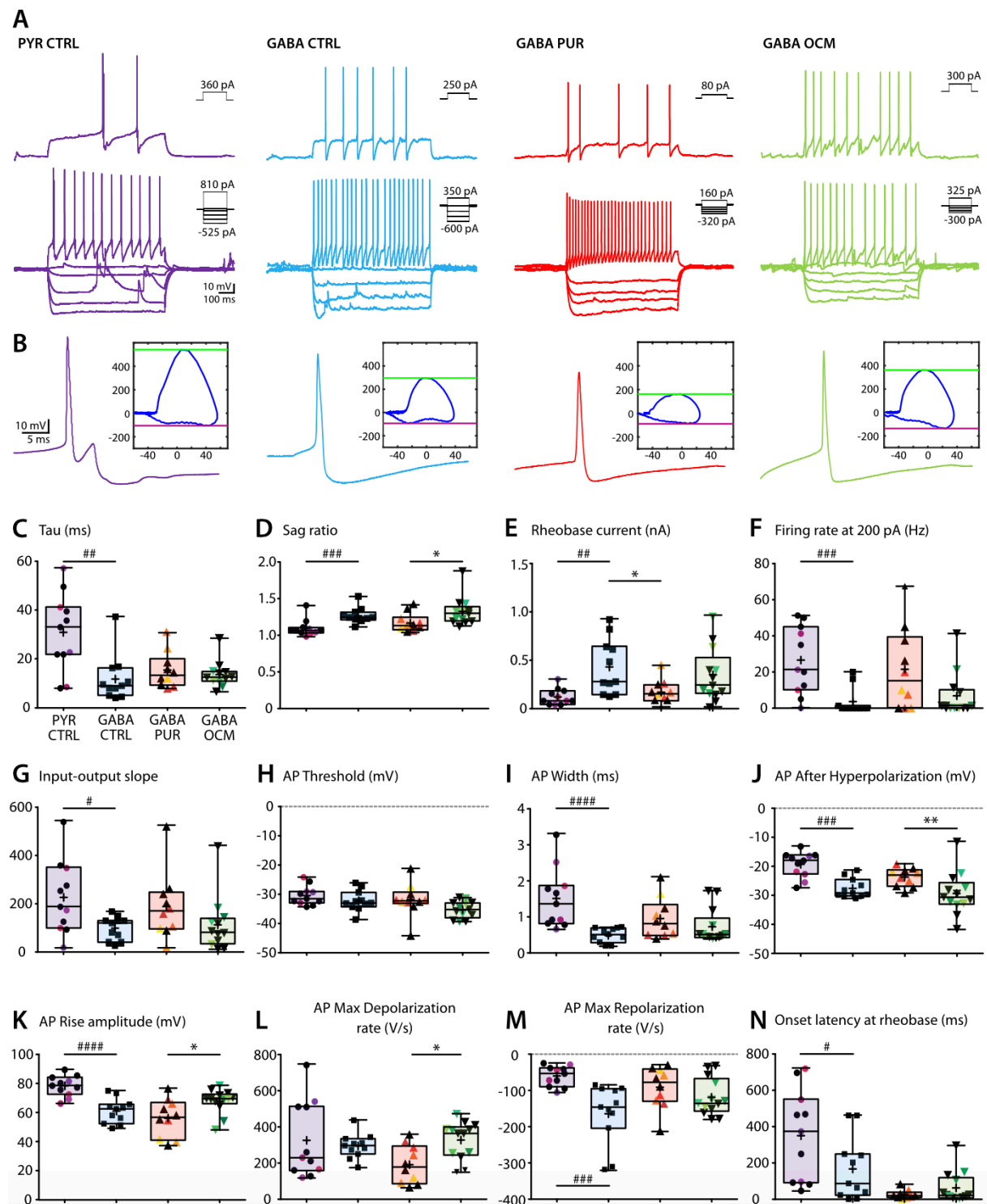
| | PYR CTRL vs GABA CTRL | | GABA CTRL vs GABA PUR | | GABA PUR vs GABA OCM | | GABA CTRL vs GABA OCM | |
|--------------------------------------|-----------------------|--------------|-----------------------|--------------|----------------------|--------------|-----------------------|--------------|
| | p value (MW) | Significance | p value (KW) | Significance | p value (KW) | Significance | p value (KW) | Significance |
| Resting membrane potential (mV) | 0.0175 | * | 0.6894 | ns | 0.6360 | ns | >0.9999 | ns |
| Neuronal Input Resistance (Mohm) | <0.0001 | *** | 0.0156 | * | 0.1240 | ns | >0.9999 | ns |
| Tau 1 (ms) | 0.0041 | ** | 0.2966 | ns | >0.9999 | ns | 0.4235 | ns |
| Sag ratio at -100 mV | 0.0005 | *** | 0.1387 | ns | 0.0317 | * | >0.9999 | ns |
| Rheobase current | 0.0019 | ** | 0.0464 | * | 0.1854 | ns | >0.9999 | ns |
| Firing rate at 200 pA (Hz) | 0.0008 | *** | 0.0523 | ns | 0.4131 | ns | 0.9355 | ns |
| Input-output slope (Hz/nA) | 0.0336 | * | 0.3019 | ns | 0.1416 | ns | >0.9999 | ns |
| AP threshold (at 10V/s) | 0.1932 | ns | 0.5216 | ns | 0.0571 | ns | 0.9382 | ns |
| AP width (ms) | <0.0001 | **** | 0.1396 | ns | 0.5170 | ns | >0.9999 | ns |
| AP AHP (mV) | 0.0003 | *** | 0.1268 | ns | 0.0075 | ** | >0.9999 | ns |
| AP rise amplitude | <0.0001 | **** | >0.9999 | ns | 0.0480 | * | 0.2263 | ns |
| AP maximum depolarization rate (V/s) | 0.529 | ns | 0.1148 | ns | 0.0151 | * | >0.9999 | ns |
| AP maximum repolarization rate (V/s) | 0.0001 | *** | 0.0815 | ns | 0.5344 | ns | >0.9999 | ns |
| Onset latency at rheobase | 0.0281 | * | 0.1681 | ns | >0.9999 | ns | 0.3630 | ns |

Table 1: Electrophysiological properties of pyramidal and GABAergic neurons. Top, mean values, SD and number of cells for each parameter and culture condition. Bottom, p-values and significance levels from Mann-Whitney (MW) tests (PYR CTRL vs. GABA CTRL) and from

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3 Kruskal-Wallis (KW) and Dunn's multiple comparison *post-hoc* test (GABA CTRL vs. PUR
4 vs. OCM).
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8 We next asked whether the properties of fluorescent and non-fluorescent cells were con-
9 sistent with those of GABAergic neurons and pyramidal cells respectively (Pelkey et al. 2017).
10 In control cultures, the mean resting potential of fluorescent neurons was significantly more
11 depolarized (GABA CTRL, -55 ± 5 mV vs. PYR CTRL, -63 ± 9 mV; Fig. 1F), and their input
12 resistance was significantly lower than that of non-fluorescent cells (74 ± 53 M Ω vs. 330 ± 218
13 M Ω ; Fig. 1G). Comparing neuronal responses to depolarizing and hyperpolarizing step current
14 injections (Sup. Fig. 2, Fig. 2) revealed significant differences in the membrane time constant
15 tau (Fig. 2C, GABA CTRL, 12 ± 10 ms vs. PYR CTRL, 31 ± 16 ms), sag ratio, which is linked
16 to the presence of an h-current, (Fig. 2D, 1.27 ± 0.10 vs 1.10 ± 0.10), rheobase current (Fig. 2E,
17 427 ± 284 pA vs 121 ± 83 pA) and firing rate induced by a 200 pA step current injection (Fig. 2F,
18 3 ± 7 Hz vs 26 ± 19 Hz). Input-output plots of the number of APs against the injected current had
19 a mean initial slope of 99 ± 48 Hz/pA in fluorescent cells, significantly lower than 224 ± 150
20 Hz/pA for non-fluorescent cells (Fig. 2G). Action potential width in fluorescent neurons was
21 short, 0.50 ± 0.20 ms (Fig. 2I), as is characteristic of some interneurons, compared to an AP
22 width of 1.51 ± 0.8 ms in non-fluorescent neurons. AP thresholds were similar: -32.2 ± 3.5 mV in
23 fluorescent cells (Fig. 2H) and -30.5 ± 3.3 mV in non-fluorescent cells. AP rising amplitude (Fig.
24 2K) was 61 ± 9 mV in fluorescent cells, significantly lower than a value of 78 ± 7 mV in non-
25 fluorescent cells. Maximum depolarization and repolarization rates were 294 ± 68 V/s and -
26 164 ± 82 V/s respectively in fluorescent cells, compared to 325 ± 212 V/s (Fig. 2L) and -61 ± 28
27 V/s (Fig. 2M) in non-fluorescent neurons. Action potential after hyper-polarizations (AHP)
28 were larger in fluorescent cells at -27.6 ± 3.3 mV compared to -19.5 ± 4.4 mV (Fig. 2J). The la-
29 tency to the first AP at rheobase was significantly shorter, 167 ± 172 ms compared to 349 ± 251
30 ms (Fig. 2N). Overall these data confirm that fluorescent neurons from VGAT-Venus animals
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correspond to GABAergic neurons, and non-fluorescent cells to pyramidal cells. Table 1 summarizes these physiological data and provides statistical support for comparisons.



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3 **Figure 2:** Glial factors affect the electrophysiological properties of GABAergic neurons. (A)
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5 Voltage responses to depolarizing and hyperpolarizing current steps recorded from representa-
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7 tive neurons at 17 DIV in the different conditions. Top, action potentials initiated at rheobase;
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9 bottom, current intensities as shown in insets. (B) Action potential waveforms and phase plots
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11 (Y axis, dV/dt (V/s); X axis, membrane potential (mV)). Green line, maximum depolarization
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13 rate; blue line, maximum repolarization rate. (C) to (N), Effects of culture conditions (PYR
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15 CTRL, GABA CTRL, GABA PUR and GABA OCM) on 12 parameters characterizing neu-
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17 ronral intrinsic properties. Each symbol is one neuron. Color symbols correspond to sequenced
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19 cells as in Fig. 1 F, G. Significance levels indicated as in Fig. 1, *i.e.* # for Mann-Whitney test
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21 and * for Kruskal-Wallis and Dunn's *post hoc* test. Parameters measured as shown in Sup. Fig.
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23 2. P-values given in Table 1. Boxplots represent the median (middle line), the mean (+ sign),
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25 25th and 75th percentiles (box) and the top and bottom values (whiskers).

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31 Our next objective was to compare electrophysiological phenotypes for GABAergic
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33 neurons in control conditions (CTRL), in purified cultures (PUR) with no glial cells and in PUR
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35 cultures supplemented with oligodendrocyte conditioned medium (OCM). We found nodal pro-
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37 teins were clustered on GABAergic axons in CTRL but not in PUR cultures (Sup. Fig1D).
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39 Adding OCM to PUR cultures induced prenodule formation as previously shown (Sup. Fig1D;
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41 Freeman et al. 2015; Dubessy et al. 2019). We also found some electrophysiological parameters
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43 of GABAergic neurons changed when glial cells were absent, and were partially restored by
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45 OCM treatment (Fig. 1, 2 and Table 1). The mean resting membrane potential of GABAergic
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47 neurons did not change significantly (Fig. 1F, CTRL, -55 ± 5 mV; PUR, -49 ± 11 mV; OCM, $-$
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49 54 ± 7 mV). Input resistance increased in PUR cultures (Fig. 1G, PUR, 144 ± 46 M Ω , GABA
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51 CTRL, 74 ± 53 M Ω) and was reduced back towards control values by OCM addition (110 ± 104
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53 M Ω). Tau did not change significantly (Fig. 2C, PUR, 15 ± 7 ms; OCM, 14 ± 6 ms). Sag ratio
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3 decreased significantly in PUR (Fig. 2D, PUR, 1.17 ± 0.10 ; OCM, 1.33 ± 0.20), as did the rheo-
4 base current (2E, PUR, 169 ± 121 pA; OCM, 347 ± 276 pA. Mean firing rate induced by 200 pA
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6 base current injection increased in PUR (Fig. 2F, PUR, 21 ± 23 Hz; OCM, 7 ± 12 Hz). The slope
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8 of input-output curves did not change (Fig. 2G, PUR, 188 ± 139 Hz/pA; OCM, 113 ± 115 Hz/pA).
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10 Mean AP threshold (Fig. 2H) was -31.8 ± 5.7 mV in PUR, and -35.3 ± 2.9 mV in OCM. AP width
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12 increased in PUR cultures (Fig. 2I, PUR, 0.96 ± 0.60 ms; OCM, 0.74 ± 0.50 ms), while AHP am-
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14 plitude decreased (Fig. 2J, PUR, -23.8 ± 3.2 mV; OCM, -29.4 ± 7.3 mV). AP rising amplitude
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16 was significantly higher in OCM than in PUR cultures (Fig. 2K, PUR, 56 ± 13 mV; OCM, 68 ± 8
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18 mV). Both the AP depolarization rate (Fig. 2L, PUR, 192 ± 105 V/s; OCM, 327 ± 103 V/s) and
19
20 maximal repolarization rate were slower (Fig. 2M, PUR, -91 ± 57 V/s; OCM, -119 ± 51 V/s) in
21
22 PUR culture compared to CTRL and OCM cultures. AP onset latency at rheobase was shorter
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24 in PUR conditions than in CTRL (Fig. 2N, PUR, 28 ± 24 ms; OCM, 64 ± 86 ms).
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32 These data show that factors of the OCM have significant effects on the input resistance,
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34 rheobase current, and AP and AHP amplitudes of GABAergic neurons. These effects partially
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36 reverse changes induced by switching from a mixed culture of neurons, oligodendrocytes, and
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38 other glial cells, to a purified neuronal culture.
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44 **Impact of OCM on hippocampal GABAergic neuron morphology**

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46 We next asked whether factors secreted by oligodendrocyte exert trophic effects on GA-
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48 BAergic neuron anatomy. Biocytin-filled GABAergic neurons from CTRL, PUR, and OCM
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50 cultures were reconstructed and axonal and dendritic lengths were measured (Fig. 3A-C). The
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52 absence of glial cells had no significant effect on total axonal length (CTRL, 1179 ± 427 μ m,
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54 $n=6$; PUR, 1929 ± 1305 μ m, $n=5$; Fig. 3B) or total dendritic length (CTRL, 4405 ± 983 μ m,
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56 $n=6$; PUR, 4794 ± 1621 μ m, $n=5$; Fig. 3C). Scholl analysis of dendritic arbors revealed slight
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58 differences (Fig. 3D). However, in OCM cultures, total axonal length (OCM, 6451 ± 4793 μ m,
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n=8) was significantly increased compared to CTRL ($p=0.0148$) and mid-dendritic arbors were significantly more complex at distances of 260-700 μm from the soma compared to CTRL and PUR (Fig. 3B, D). Thus, oligodendrocyte derived factors exert effects on axons and dendrites of GABAergic neurons, which were not apparent on switching from CTRL to PUR cultures.

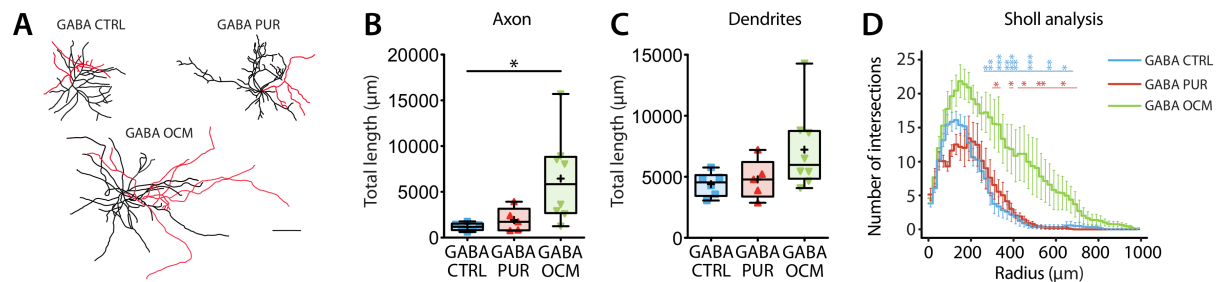


Figure 3: Axo-dendritic morphologies of biocytin filled GABAergic neurons. (A) Reconstruction of biocytin-filled GABAergic neurons at 17 DIV in different culture conditions. Axons shown in red, dendrites in black. Scale bar: 100 μm . (B) Total axonal and (C) dendritic lengths of GABAergic neurons in different conditions (Kruskal-Wallis followed by Dunn's *post hoc*). Boxplots represent the median (middle line), the mean (+ sign), 25th and 75th percentiles (box) and the top and bottom values (whiskers). (D) Sholl analysis showing for each condition the number of dendrites intersecting increasing radii (20-1000 μm from the soma at interval 20 μm). The two segmented lines above the plot indicate significant differences between GABA OCM and CTRL (blue) and between GABA OCM and PUR (red). There were no significant differences between GABA CTRL and PUR. LMM and Type II Wald chi-square tests followed by *post-hoc* analyses using Tukey's method. Mean \pm SEM is represented. ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$).

Single-cell transcriptomic analysis of electrophysiologically characterized neurons

We used single cell RNA-sequencing (scRNA-seq) of the cytoplasmic contents of GABAergic neurons to pursue the identity of protein targets underlying changes in their phenotype induced by OCM. When patch-clamp recordings were completed, the same pipette was used to harvest neuronal cytosolic contents (n=64). [Sup. Fig. 3A, B](#) illustrates the experimental workflow and bioinformatics pipeline. We noted a strong correlation ($R=0.79$) between the number of expressed genes and the number of aligned reads suggesting that increasing reads could improve transcript detection (Fig. 4-1C). RNA-seq data was filtered to exclude samples of poor RNA quality where fewer than 2000 transcripts were detected. We also excluded samples which expressed glial cell specific genes, such as *Mog* or *Gfap*, as likely contaminated. Samples from 21 neurons passed these two controls.

Principal component analysis (PCA) of transcriptomic profiles captured 22% of explained variance with the first two principal components, PC1 and PC2 (Fig. 4A). Pyramidal cells and GABAergic neurons were clearly segregated in this two-dimensional space. GABAergic neurons from PUR cultures were separated from GABAergic neurons in CTRL cultures. Transcriptomes of GABAergic neurons from OCM cultures overlapped with those of CTRL cultures.

We investigated transcriptomic differences between hippocampal neuron types and the transcriptional response to glial factors in GABAergic neurons. The heat map of Fig. 4B shows in red up-regulated genes and in blue genes that were down-regulated with respect to mean expression in all three conditions. High, deep sequencing detected up to 5,700 expressed genes in single neurons. Hierarchical clustering of samples from different cells in the heat map segregated 4 out of 5 pyramidal neurons from GABAergic neurons. GABAergic neurons from purified cultures (PUR) were also grouped together in the dendrogram while GABAergic neurons sampled in CTRL and OCM cultures overlapped in a large branch (Fig. 4B).

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3 As a step towards validation of these results, we searched for the presence of known
4 pyramidal and GABAergic neuron markers in genes from different samples. All samples ex-
5 pressed the neuronal marker *Snap25*. Only samples from non-fluorescent pyramidal cells ex-
6 pressed the vesicular glutamate transporter1 (vGlut1, *Slc17a7*), while the vesicular GABA
7 transporter (VGAT; *Slc32a1*) and GAD67 (*Gad1*) were only detected in samples obtained from
8 fluorescent GABAergic neurons (Fig. 4C). Subclasses of hippocampal GABAergic neurons
9 express neuropeptides and Ca²⁺-binding proteins. Searching for neuropeptide (Somatostatin
10 (*Sst*), Neuropeptide Y (*Npy*), Cholecystokinin (*Cck*), Vasoactive intestinal peptide (*Vip*), Prota-
11 chykinin (*Tac1*), Prepronociceptin (*Pnoc*)) and Ca²⁺-binding protein (Parvalbumin (*Pvalb*),
12 Calbindin-1 (*Calb1*), Calbindin-2 (*Calb2*) genes revealed a diversity of expression. Most GA-
13 BAergic neurons expressed *Pnoc* (87%), *Sst* (81%) and *Npy* (57%). Samples from 56% of cells
14 expressed both *Sst* and *Npy*, or combinations of *Sst* and *Calb1* (37%) and/or *Sst* and *Cck* (25%)
15 and/or *Sst* and *Pvalb* (19%, Fig. 4D). GABAergic neurons expressing *Pnoc*, *Npy* and *Sst* neu-
16 ropeptide genes were found in all culture conditions (CTRL, PUR and OCM). *Calb-1* was less
17 frequently expressed in PUR cultures. Genes for other interneuron markers detected in GA-
18 BAergic neurons included the transcription factors *Satb1* and *Nkx-2.1*, the post-synaptic protein
19 *Elfn1*, the serotonin receptor *Htr3a*, KCC2 the potassium chloride cotransporter 2, *Slc12a5*, the
20 kinase *ErbB4* and the protease reelin, *Reln*. We note that some molecular markers examined
21 here are not entirely specific to GABAergic neurons, and were also detected in samples from 1
22 or 2 pyramidal cells (*Slc12a5*, *Calb1*, *Satb1*, *Reln*, *Sst*, *Npy*, *Elfn1* and *Cck*). Furthermore, no
23 samples from either pyramidal or GABAergic neurons expressed *Vip*, *Calb2* or *Nos1* (Fig. 4D).
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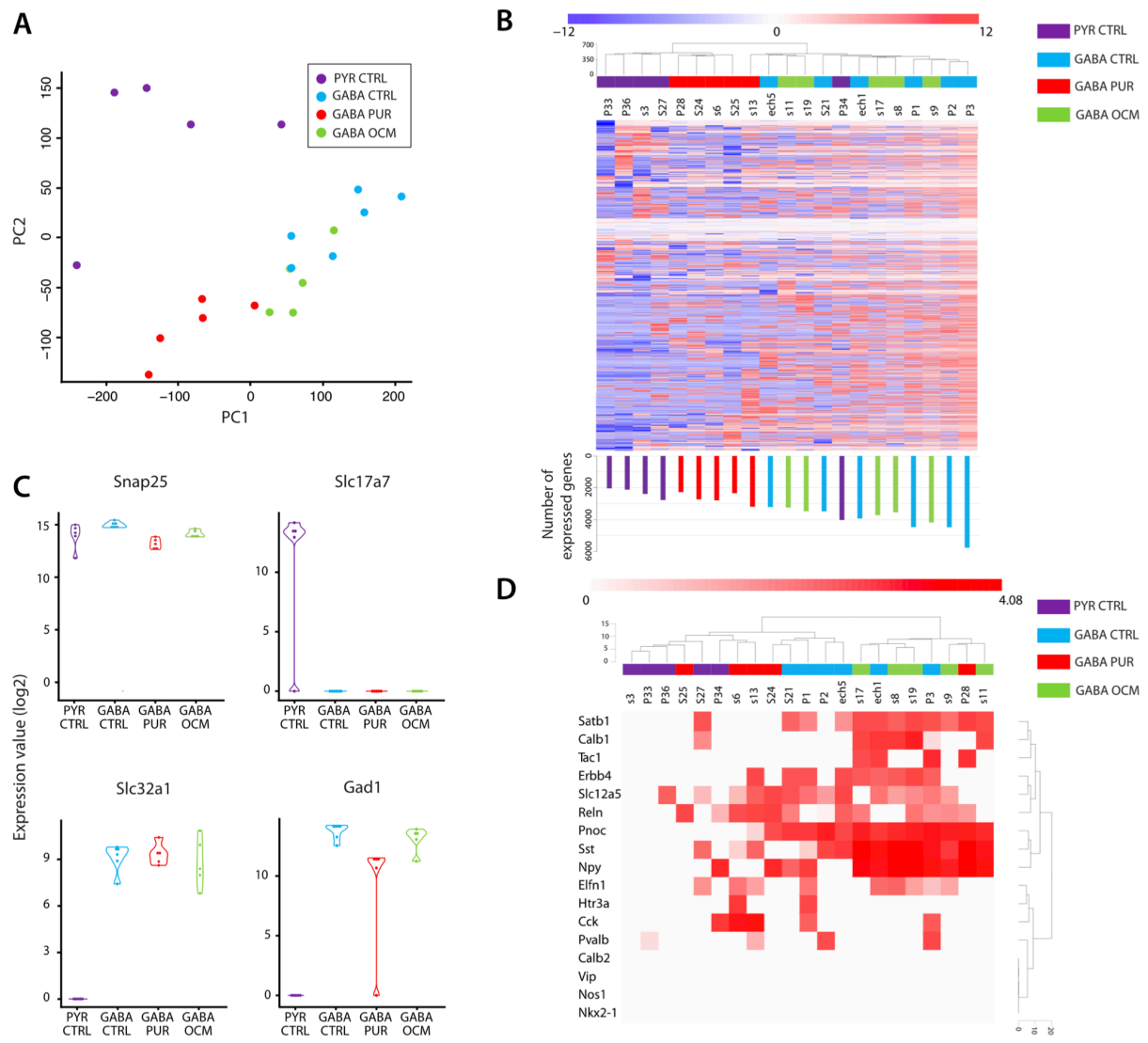


Figure 4: Gene expression analysis of the content of pyramidal or GABAergic neuron cytoplasm in the presence or absence of glial cells or oligodendrocyte secreted factors. (A) Principal component analysis showing clustering of validated neurons by culture conditions on single-cell data. PC1 and PC2 explain 14.9 % and 6.6 % of the variance, respectively. (B) Heatmap summarizing unsupervised analysis of mRNAs from validated neurons in different culture conditions. Rows represent genes and columns different neurons. Colors indicate gene expression (blue, low – red, high) normalized by row. Barplots (below) show the number of genes expressed by each neuron. 5391 genes (out of 35 152) are represented in the heatmap and only genes detected in at least 20% of neurons are included. C) Expression levels for markers for

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3 neurons (*Snap25*), excitatory neurons (*Slc17a7*) and GABAergic neurons (*Slc32a1* and *Gad1*)
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5 in different culture conditions. (D) Differential expression of genes associated with subtypes of
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7 GABAergic neuron. Rows represent gene expression and columns represent different neurons
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9 under different culture conditions. Color intensity represents gene expression level. In A-D,
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11 data from pyramidal neurons under CTRL conditions are shown in purple, GABAergic neurons
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13 in CTRL conditions in blue, GABAergic neurons in purified neuron cultures in red and GA-
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15 BAergic neurons in purified cultures treated with OCM in green.
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23 **Ion channel and transmitter receptor gene expression in single hippocampal neurons**

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25 The cellular and synaptic physiology of neurons depends on the expression of genes
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27 coding for ion channels, transporters and neurotransmitter receptors. We examined quantitative
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29 expression of these genes in samples from each neuron in our RNAseq data set (Fig. 5A, B).
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31 Different neurons expressed different levels of *Atp1a, b* genes coding for Na⁺/K⁺-transporting
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33 ATPase subunits and *Clcn3-7* genes coding for Cl⁻/H⁺ exchangers, which contribute to stabilize
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35 membrane potential. The depolarization phase of action potentials is due to opening of voltage-
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37 gated sodium channels, which consist of an α -subunit forming pore (*Scn1a-9a*) and auxiliary β
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39 subunits (*Scn1b-4b*). Almost all neurons expressed high levels of *Scn2a* (encodes Nav1.2). In
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41 contrast, only GABAergic neurons in CTRL cultures with glial cells or with oligodendroglial
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43 factors (OCM) expressed *Scn1a* (Nav1.1) and few expressed *Scn8a* (Nav1.6). The Na⁺ channel
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45 modifier 1 (*Scnm1*), which governs alternative splicing of pre-mRNAs, was detected in samples
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47 from some GABAergic neurons but not from pyramidal cells.
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54 Various potassium channels are crucial for action potential repolarization, generate the
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56 AHP and contribute to maintenance of membrane potential. Voltage-gated K⁺ channels differ
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58 in structure, biophysics and pharmacology from voltage independent, two-pore-domain (K2P)
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60 channels which support leak-type K⁺ conductances. We found that distinct neurons express

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3 specific combinations of K⁺ channel α (*Kcn a to v*) and auxiliary subunits (*Kcnab1-2*) as well
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5 as K2P channels (*Kcnk1-10*). We also examined Ca²⁺ channels, Ca²⁺-activated K⁺ channels and
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7 hyperpolarization-activated, cyclic nucleotide gated, K⁺/Na⁺ permeable 'h' channels (HCN).
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10 Fig. 5B shows genes encoding ionotropic glutamate receptors, expressed at excitatory
11 synapses, and including AMPA receptors (*Gria1-4*), NMDA receptors (*Grin1-3*) and kainate
12 receptors (*Grik1-5*). Genes encoding GABA_A receptors (*Gabra-g*), which mediate fast inhibi-
13 tory neurotransmission and are assembled as heteropentameric chloride channels, are also in-
14 dicated as are detected genes which code for subunits of nicotinic cholinergic receptors (*Chrna-*
15 *b*), serotonin receptor (*Htr3a*) and glycine receptor (*Gla2*). Fig. 5C shows genes coding for G-
16 protein linked receptors including metabotropic glutamate (*Grm2, 5*) and GABA_B (*Gabbr1, 2*)
17 receptors.
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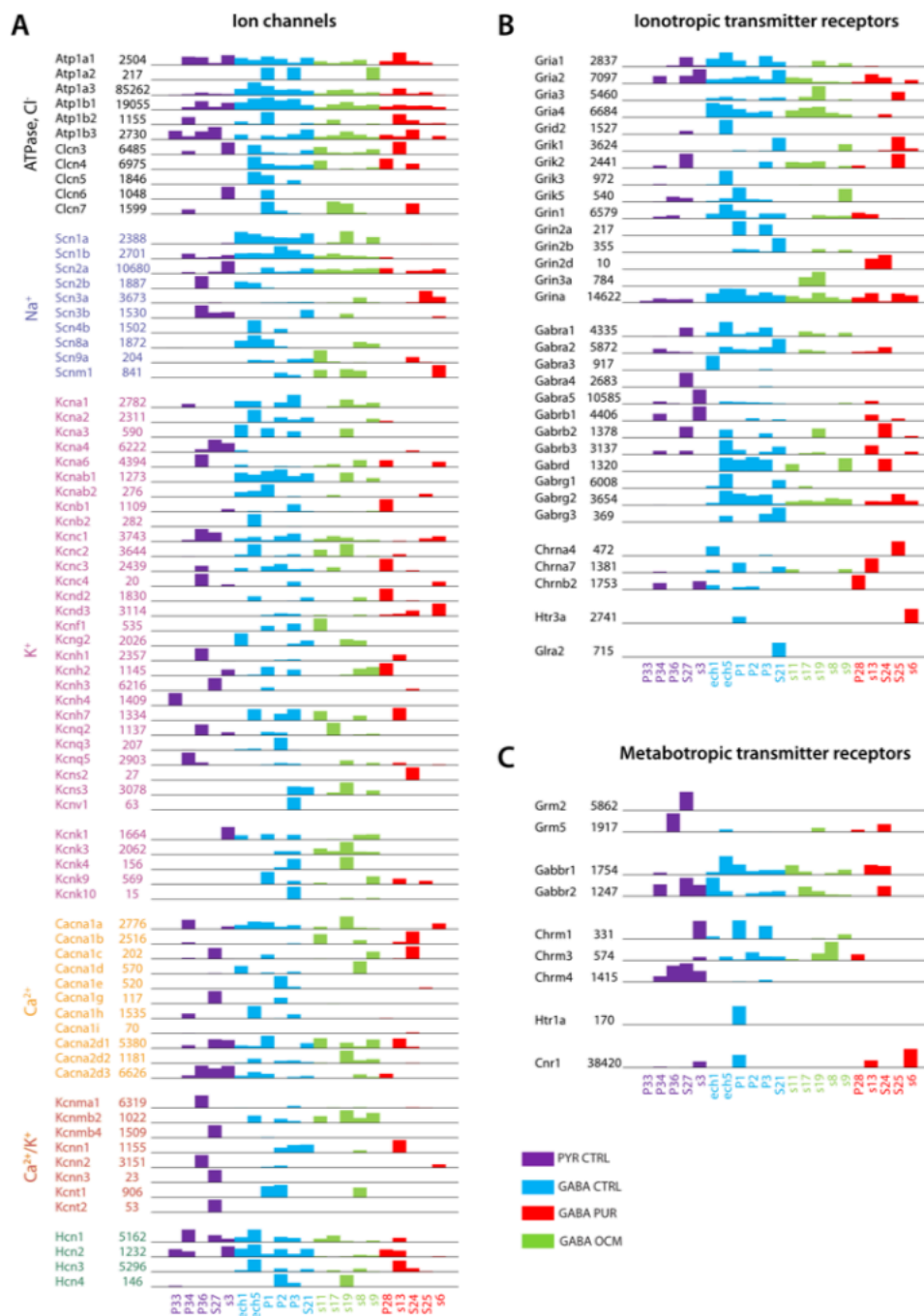


Figure 5: Cell-type specific expression of mRNAs coding for ion channel and receptors. (A) Ion channel, (B) ionotropic transmitter receptor and (C) metabotropic transmitter receptor mRNAs in different culture conditions. Maximal expression from all samples is indicated. Number of reads normalized from pyramidal neurons in CTRL conditions is shown in purple, GABAergic neurons in CTRL conditions in blue, GABAergic neurons in purified cultures in red and GABAergic neurons in purified cultures treated with OCM in green.

Correlation-based approach

These scPatch-seq data permit quantitative assays of transcriptomic features. We attempted to relate them to intrinsic neuronal electrophysiology by searching for correlations between values from transcriptomic samples and different electrophysiological parameters. Fig. 6 plots genes coding for ion channels, transporters and synaptic receptors for which a correlation (p-value <0.05) with electrophysiological parameters was detected. The analysis was based on all neurons with complete electrical and transcriptomic datasets and on cells from all culture conditions. Genes were clustered based on their relations with electrophysiological parameters. One cluster coding for $\alpha 1$, $\beta 1$ and $\alpha 3$ subunits of the Na^+ , K^+ -ATPase (*Atp1a1*, *Atp1b1* and *Atp1a3*), was correlated with neuronal input resistance, *Atp1b1* was also correlated with time constant, tau and AP width. The Na^+ channel subunit *Scn2a* (coding for Nav1.2) was correlated with the time constant tau and with AP threshold, neuronal input resistance and AP width. A larger cluster, consisting of several K-channel linked genes (*Kcnc2*, coding for Kv3.2; *Kcnk3*, Task-1; *Kcnip1*, K^+ channel modulatory protein), as well as two Zn transporters (*Slc30a3*, ZnT3; *Slc30a4*, ZnT4) was strongly correlated with the Sag ratio, the AP threshold and the after-hyperpolarization amplitude (AP AHP).

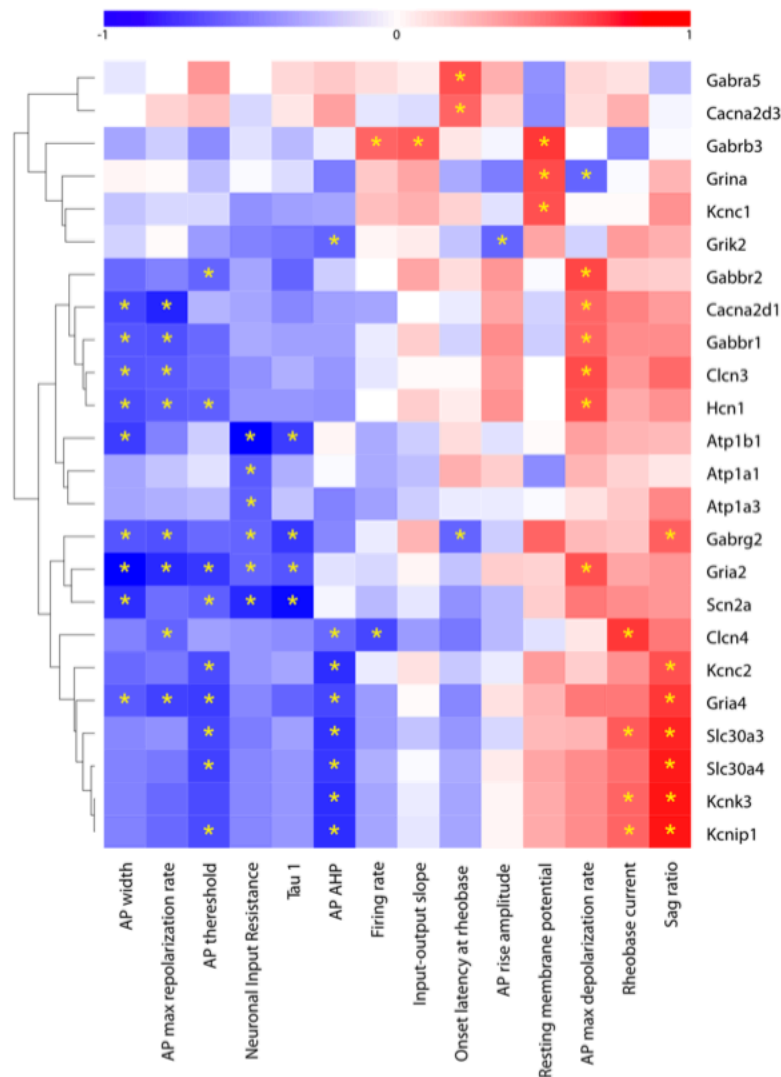
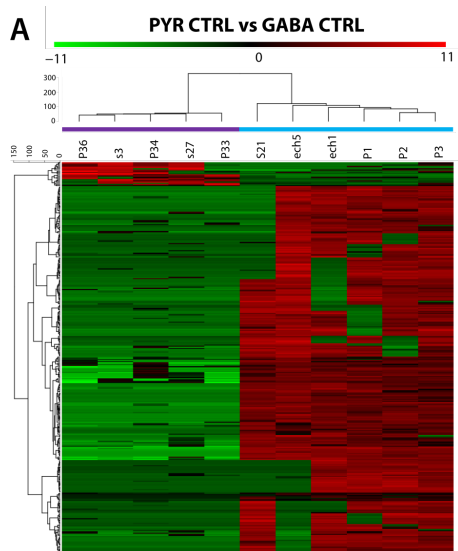


Figure 6: Pearson correlation between scRNASeq data and electrophysiological parameters. Ion channel and synapse related genes significantly correlated ($p < 0.05$) with at least one parameter are shown. Color intensity represents correlation coefficient. Blue indicates negative correlation; expression decreases as the parameter increases. Red indicates positive correlation; both increase together. Significant positive or negative correlations with coefficient > 0.6 and p -value < 0.05 are marked with a yellow star.

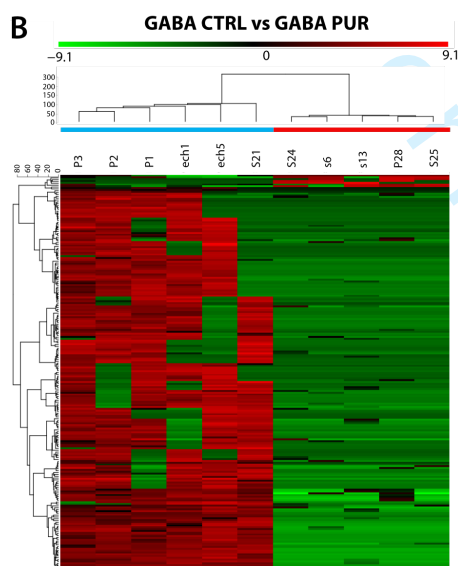
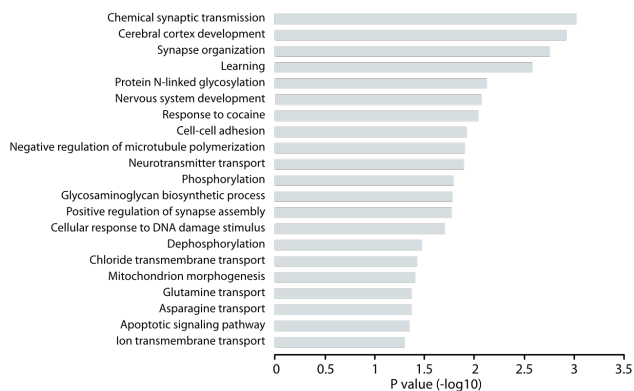
Transcriptomic patterns across groups of neurons in relation to biological processes

Gene Ontology (GO) analysis let us estimate biological processes underlying differential expression of groups of genes in different neurons or in different culture conditions. For

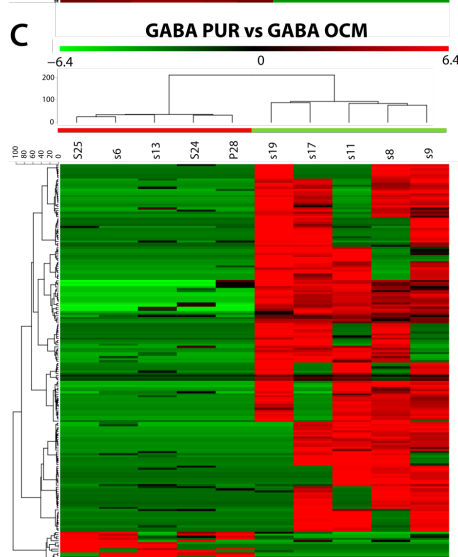
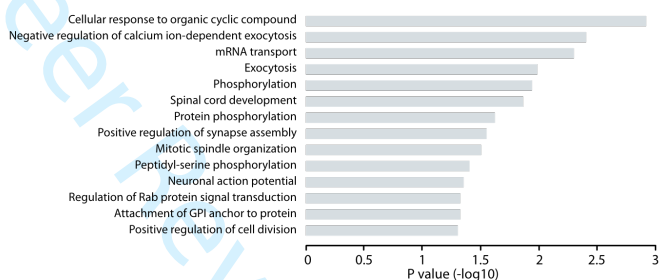
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3 instance, 326 genes were differentially expressed in GABAergic neurons and pyramidal neu-
4 rons in CTRL cultures (Fig. 7A, [Sup. Fig5](#)). GO process terms derived from the identity of the
5 genes were related to synaptic transmission, organization and transmitter transport as well as
6 cortical development. Comparing GABAergic neurons in CTRL and PUR cultures we found
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8 219 genes were differentially expressed, mostly down-regulated in PUR conditions (Fig. 7B,
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10 [Sup. Fig5](#)). Inversely, comparing GABAergic neurons in PUR and OCM cultures, 192 genes
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12 were differentially expressed, mostly up-regulated in OCM conditions (Fig. 7C, [Sup. Fig5](#)).
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14 Many genes were down-regulated in one comparison and up-regulated in the other. GO process
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16 terms identified from their identity regulate neuronal action potential, synapse assembly, Ca²⁺-
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18 dependent exocytosis, protein phosphorylation, kinase signaling and cell division (Fig. 7B, C).
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20 GO-analysis further suggested that genes coding for proteins involved in transmembrane
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22 transport of K⁺ were up-regulated by OCM treatment (Fig. 7C).
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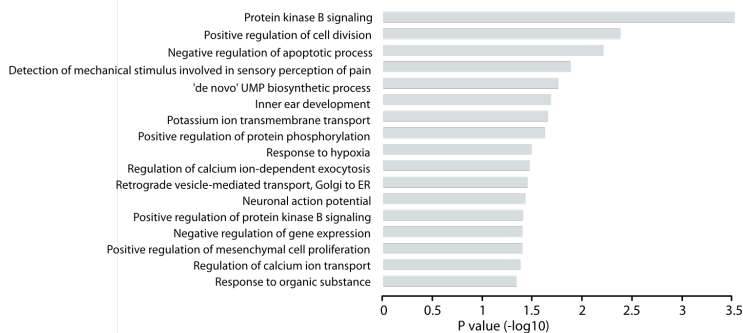
Biological processes



Biological processes



Biological processes



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3 **Figure 7:** Heatmap of genes expressed differentially between conditions. (A) Differences be-
4 tween pyramidal and GABAergic neurons in CTRL culture conditions. (B) Differences be-
5 tween GABAergic neurons in CTRL and PUR cultures. (C) Effects of OCM on GABAergic
6 neurons in PUR cultures. Rows represent genes and columns represent neurons in different
7 conditions. Color intensity is mean centered expression. At the right, gene ontology analysis of
8 biological processes for differentially expressed genes. Differences between pyramidal and
9 GABAergic neurons in CTRL conditions (upper). Differences between GABAergic neurons in
10 PUR cultures and CTRL. Effects of OCM on GABAergic neurons in PUR cultures (lower).

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22 Further insights into processes affected by oligodendrocyte factors were obtained by
23 grouping genes with similar profiles of changes. RNA-seq data from GABAergic neurons in
24 different culture conditions was normalized with respect to expression of each gene in pyrami-
25 dal cells (Fig. 8A, B and [Sup. Fig6](#)). A total of 241 genes were identified as differentially ex-
26 pressed between pyramidal and GABAergic neurons in CTRL cultures and were mostly insen-
27 sitive to PUR or OCM culture conditions ([Sup. Fig6](#)).

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36 We found a significant difference in the group of genes that were reduced in PUR cultures and
37 restored in OCM cultures. For one group of these genes, expression in GABAergic and pyram-
38 idal neurons in CTRL conditions were comparable (Fig. 8A; n=137). Another second group of
39 genes differed in that expression in GABAergic neurons was systematically higher than in py-
40 ramidal cells in CTRL cultures (Fig. 8B; n=120). GO term analysis of the identities of the first
41 group of genes (Fig. 8a') linked them to processes including negative regulation of protein
42 kinase activity and apoptosis signaling pathways. In contrast, the identities of the second group
43 of genes (Fig. 8b') evoked biological processes including the membrane transport of zinc, K⁺
44 channels, regulation of membrane potential and action potential and G-protein coupled receptor
45 signaling pathways.

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60 Finally, we present target genes whose expression was affected by the absence of glial cells in

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3 PUR cultures and inversely by OCM and which are linked to GABAergic cell physiology.
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5 These target transcripts code for ion channels, transporters, synaptic markers, vesicle traffick-
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7 ing, cytoskeleton remodeling, cell adhesion molecules, growth factors and signaling (Fig. 8C)
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9 and were mostly up-regulated in CTRL and OCM neurons. They included Na⁺ channels, *Scn1a*
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11 (Nav1.1) and *Scn1b* (β1Nav) and K⁺ channels, *Kcna1* (Kv1.1), *Kcnab1* (β1Kv), *Kcnk3* (Task-
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13 1), *Kcnipl* (KChip-1, a K⁺ channel modulatory protein). Genes encoding zinc transporters
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15 (*Slc39a11*, *Slc30a4* and *Slc30a3*), were upregulated by OCM, while a Na⁺/K⁺/Ca²⁺ exchanger
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17 (*Slc24a2*) was one of the few transcripts downregulated by OCM. Among genes coding for
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19 signaling molecules, growth factors and receptors, the kinases *Nek7*, *Pak1* and *Akt1*, and growth
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21 factors *Vegfb*, *Pdffa*, *Fgf9* and *Rara* were up-regulated in OCM culture conditions. Only the
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23 protein kinase C binding protein *Nell2* and the neuropeptide hormone Proenkephalin (*Penk*)
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25 were downregulated by OCM. To address possible coordinated changes, we also analyzed path-
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27 ways of regulated genes between OCM and PUR, or CTRL and PUR. We found that the MAPK,
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29 AMPc and PI3K-Akt signal transduction pathways are significantly up-regulated by glial cells
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31 and OCM, respectively (Fig. 8D, E).
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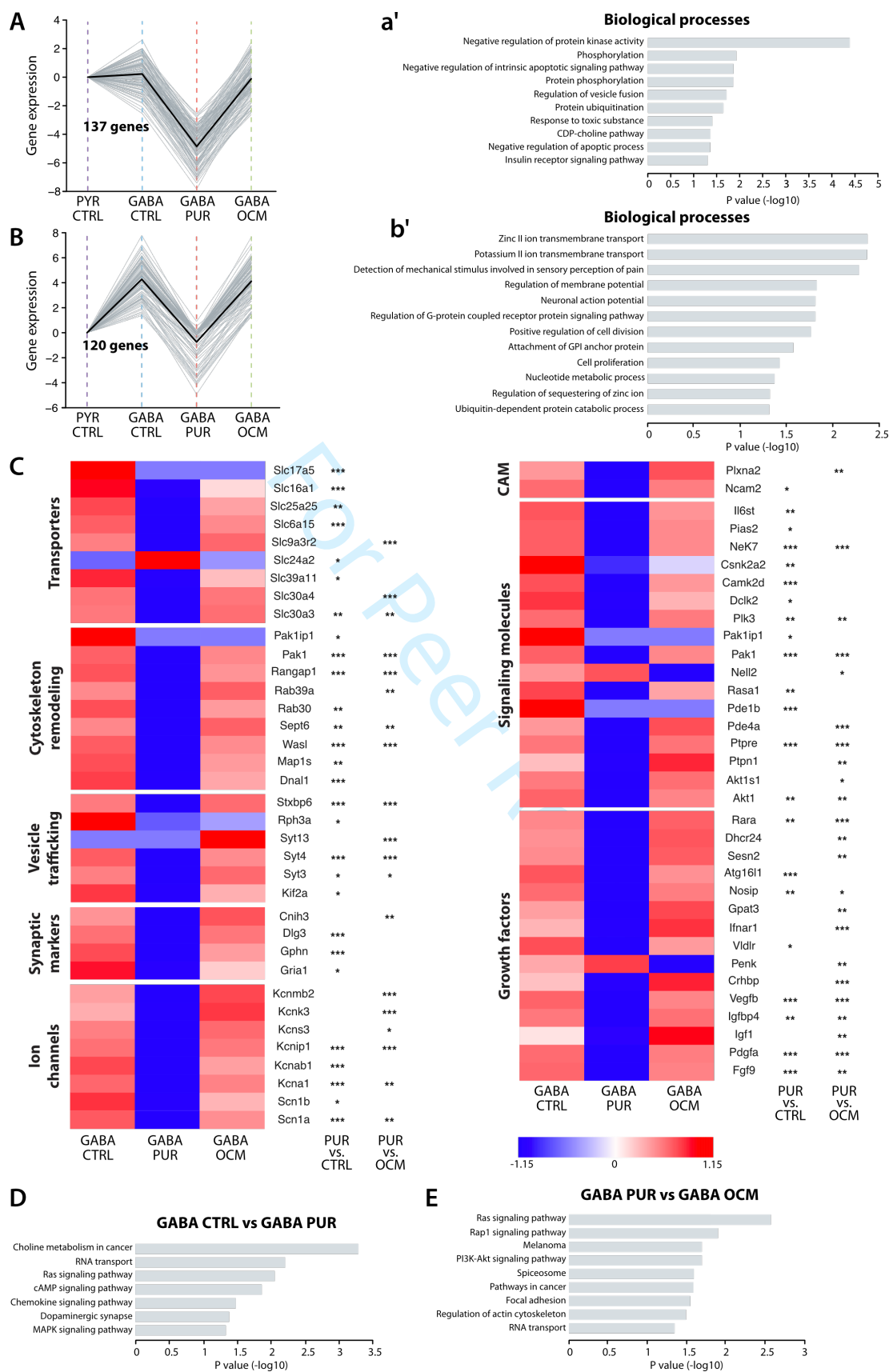


Figure 8: Gene ontology analysis of regulated genes. (A, B) Expression within clusters with a

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3 similar expression pattern in different culture conditions. Gene expression was normalized to
4 that of pyramidal cells in control conditions. Cluster A and B comprise 137 and 120 genes,
5 respectively. The continuous black line shows the mean of mRNA expression in different con-
6 ditions. (a', b') Gene ontology analysis of biological processes for genes of clusters A and B.
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12 (C) Heatmap of mRNAs expressed differentially in different conditions for different classes of
13 coded protein. ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$). Color intensity shows the Z-score for
14 differential expression. (D, E) KEGG pathway analysis on regulated genes between GABA
15 PUR versus GABA CTRL (D), and GABA PUR versus GABA OCM (E).
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25 DISCUSSION

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27 Data presented here suggests that factors released by oligodendrocytes modulate the transcrip-
28 tome, electrical phenotype and morphology of GABAergic neurons. The absence of glial cells
29 from purified neuron cultures reduced synaptic activity and action potential firing of GABAer-
30 gic neurons and many genes were downregulated. Processes linked to these changes included
31 synapse assembly, action potential generation and transmembrane ion transport. Our results
32 should help identify some of the molecular targets by which oligodendrocytes modulate GA-
33 BAergic neuron excitability and synaptic function.
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47 **A hippocampal culture model permits investigation of regulation of interneuron morphol-** 48 **ogy, excitability and firing properties by oligodendroglial factors**

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52 This study was based on dissociated hippocampal cell cultures. Recordings were made
53 from (i) glutamatergic and GABAergic neurons in the presence of glial cells (CTRL), (ii) GA-
54 BAergic neurons in the absence of glial cells (PUR) and (iii), GABAergic neurons in cultures
55 without glial cells but with added oligodendrocyte conditioned medium (OCM). Our data
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3 showed (Fig. 2) GABAergic neurons in culture conserved properties, including a relatively de-
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5 polarized resting potential, and action potentials of short duration followed by a prominent
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7 AHP, which distinguish them from hippocampal pyramidal cells (Spruston and Johnston 1992;
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9 Fricker et al. 1999; Staff et al. 2000; Hu et al. 2014; Prestigio et al. 2019).

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13 The frequency of excitatory synaptic events impinging on hippocampal GABAergic
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15 neurons was strongly reduced in the absence of glial cells. This is consistent with data showing
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17 that glutamatergic synaptic transmission is enhanced by factors secreted by glia (Turko et al.
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19 2019) including astrocytes (Baldwin and Eroglu 2017). Here we demonstrate that oligodendro-
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21 cytes regulate synaptic excitation of GABAergic interneurons. Adding OCM to PUR cultures
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23 partly restored EPSC frequencies. Additional effects of OPC or astrocyte - released factors, as
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25 well as cell-cell contacts in CTRL culture may explain differences with OCM effect.
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30 Anatomical analysis revealed that oligodendrocyte secreted factors (OCM) enhanced
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32 the complexity of dendritic arbors, although dendritic length differed little between cultures
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34 that did (CTRL) or did not (PUR) contain glial cells. Novel synapses formed on more complex
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36 dendrites in OCM cultures may contribute to the increased EPSC frequency in these conditions.
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39 We found similar electrophysiological properties for GABAergic neurons grown in CTRL and
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41 OCM cultures, notably a low input resistance and high rheobase. Rheobase was reduced and
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43 AP firing frequency significantly depressed in PUR cultures. The PUR condition may be similar
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45 to a lack of maturation in some respect (Okaty et al., 2009) and our study may suggest that the
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47 maturation process depend on oligodendrocyte secreted factors. The phenotype of low intrinsic
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49 excitability corresponds to mature neurons expressing a large array of voltage dependent or
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51 independent ion channels. We show (see Figure 8C-E) that numerous transcripts coding for ion
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53 channels (notably Kv1.1, Nav1.1, Task-1) and also signaling factors belonging to the PI3K-Akt
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55 signaling pathway are up-regulated by oligodendrocyte released factors. Underlying molecular
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3 mechanisms may rely on an indirect effect through glutamatergic neurotransmission via down-
4 stream signaling pathways (Sakry et al. 2014; Birey et al. 2015, Jang et al. 2019), and/or a cell
5 autonomous mechanism (Favuzzi et al. 2017). Oligodendroglial factors may operate homeo-
6 statically so that neurons adapt their intrinsic excitability and spontaneous firing activity in
7 cultures with dense synaptic connections (Desai et al. 1999).
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15 We did not attempt to identify factors released by oligodendrocytes, and their precursor
16 cells, which mediated the effects of OCM on GABAergic neurons. Candidate molecules may
17 include the proteoglycan NG2 (Sakry et al. 2014), FGF2 (Birey et al. 2015), or BDNF (Jang et
18 al. 2019) which modulate glutamatergic neurotransmission on pyramidal cells but their effects
19 on GABAergic neurons are not known. Multiple glial factors could affect optimal survival and
20 maturation of CNS neurons, although the precise identity and combination of factors may differ
21 depending on neuronal type and age (Meyer-Franke et al., 1995; Goldberg and Barres, 2000;
22 Wilkins et al., 2003). We previously showed that Contactin-1 together with Phosphacan or
23 Tenascin-R secreted by oligodendrocytes mediate early formation of prenodal clusters along
24 hippocampal GABAergic axons likely through a direct clustering effect (Dubessy et al., 2019).
25 In addition to its role in prenodal clustering, Contactin-1 also plays important role in the hippo-
26 campus, in synaptic plasticity, neurogenesis, and memory in adult mice (Murai et al., 2002;
27 Puzzo D et al., 2013). It would be worth examining the role of Contactin-1 in regulating specific
28 gene expression in GABAergic neurons. Cell adhesion molecules and extracellular matrix pro-
29 teins secreted by oligodendrocytes also form perinodal and perineuronal complexes that trans-
30 mit signals to neurons which could influence their physiology and connectivity (Favuzzi et al.
31 2017; Fawcett, Oohashi and Pizzorusso 2019).
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Technical points

This work combined patch clamp recordings with single neuron RNA-seq analysis. Relatively few studies have demonstrated strong correlations between single-neuron transcriptomic profiles and electrophysiological phenotypes (Cadwell et al. 2016; Földy et al. 2016; Fuzik et al. 2016; Muñoz-Manchado et al. 2018; Scala et al. 2019). We took several steps to ensure and verify the validity of our results. The duration of patch electrode recordings was deliberately limited to ~10 min in order to minimize perturbation of the transcriptome (Fuzik et al. 2016). When possible, patch electrodes targeted isolated neuronal somata to reduce possible mRNA contamination from adjacent cells (Tripathy et al. 2017).

As for previously published single-cell RNAseq datasets, the number of sequenced reads per cell was found to be positively correlated with detected transcript counts and did not reach a plateau (Cadwell et al. 2016; Tasic et al. 2016; Tripathy et al. 2017). We attempted to validate our data by cross-correlating transcripts detected for recorded pyramidal and inhibitory neurons with expected profiles for these cell types. Most GABAergic neurons expressed molecular markers, including peptides and Ca-binding proteins, specific to known subclasses of these cells (Zeisel et al. 2015; Gouwens et al. 2020). Larger numbers of sequenced cells would have permitted enhanced statistics to assure data quality even if links between specific transcripts and identified cell types tends to support our approach.

Single neuron transcriptomes obtained in this way helped us define a global view of processes initiated by oligodendrocyte conditioned medium. They showed glial factors modify the transcriptome of GABAergic neurons to change intrinsic electrophysiological properties, AP generation, EPSC frequencies and dendritic anatomy.

Gene expression in hippocampal neuron types

Transcriptomic data are defining the classification of cortical neurons (Zeisel et al. 2015; Cembrowski et al. 2016; Harris et al. 2018; Sugino et al. 2019; Yuste et al. 2020). A recent study based on Patch-seq data from several 1000s of cells may offer the best current correspondence between transcriptomic, anatomical and electrophysiological data for GABAergic mouse cortical neurons (Gouwens et al. 2020). Our data can be interpreted in the light of those studies. Most GABAergic neurons studied in the hippocampal cultures studied here expressed Somatostatin (SST) associated with other peptide markers. Several subtypes of hippocampal inhibitory cells express SST including long-range inhibitory neurons which possess myelinated axons (and also express *Calbindin* and *Npy*), oriens-lacunosum moleculare (O-LM) interneurons (also *Elfn1* and *Pnoc*), or oriens-bistratified neurons (also *Tac1*, *Npy*, *Satb1* and *ErbB4*) (Somogyi and Klausberger 2005; Jinno 2009; Harris et al. 2018). We found some cells expressed genes for *Sst*, *Pnoc* and *Pvalb* (Jinno and Kosaka 2000; Jinno 2009; Harris et al. 2018). A minority of GABAergic neurons expressed genes for *Reelin* and *NPY* as do neurogliaform cells (Pelkey et al., 2017).

GABAergic neuron data revealed genes coding for proteins relevant to specific aspects of inhibitory cell physiology. They included Nav1.1 (*Scn1a*), Kv3.2 (*Kcnc2*) and Task-1 (*Kcnk3*) in neurons with PV and/or SST genes (Chow et al. 1999; Torborg et al. 2006; Lorincz and Nusser 2008). Kv3 channels with fast kinetics curtail action potentials permitting sustained firing at high frequencies (Rudy and McBain 2001; Gu et al. 2018; Hu et al. 2018). Task-1 forms K⁺ permeable leak channels which contribute to resting potential and membrane resistance (Okaty et al. 2009). We found high levels of genes for the zinc transporters, ZnT3 (*Slc30a3*) and ZnT4 (*Slc30a4*), which are found in SST-containing interneurons (Paul et al. 2017). ZnT3 is a vesicular transporter which may contribute to the co-release of zinc in synaptic vesicles with GABA (McAllister and Dyck 2017).

Correlation between gene expression and electrophysiological parameters

We attempted to link expression of genes for ion channels and neurotransmitter receptors with elements of electrophysiological phenotypes using a correlation-based analysis on data from different cell types and culture conditions. The analysis suggests genes for $\alpha 1$, $\beta 1$ and $\alpha 3$ subunits of the Na^+ , K^+ -ATPase, *Atp1a1*, *Atp1b1* and *Atp1a3*, are linked to neuronal input resistance. The Na^+/K^+ -ATPase maintains transmembrane ionic gradients and resting membrane thus affecting neuronal excitability (Larsen et al. 2016). The Na-channel subunit *Scn2a* (Nav1.2) was found to be correlated with action potential width, neuronal input resistance, and the membrane time constant, tau. A cluster including several K^+ channels (*Kcnc2*, *Kcnk3* and *Kcnipl*) and two Zinc transporters (*Slc30a3* and *Slc30a*), was expressed selectively in GABAergic neurons, and correlated with AP threshold, sag ratio and the after-hyperpolarization amplitude. We should note that these correlations do not imply causality and caution that class-driven correlations are an important confound in our dataset. Some within-cell-type correlations may have been missed (Bomkamp et al. 2019).

Biological processes affected by glial cells and oligodendroglial secreted factors

Clustering genes with similar patterns of altered expression revealed GO process terms regulated by factors in OCM. Processes identified in this way matched quite efficiently with changes in GABAergic neuron phenotype inferred from electrophysiological and anatomical observations. Enriched processes included synapse assembly, action potential generation, transmembrane transport of ions specifically zinc, and kinase signaling. They derived from differential expression of K^+ channel genes, including *Kcna1* (Kv1.1), *Kcnab1* (Kv $\beta 1$ chain), *Kcnipl* (KChIP) and *Kcnk3* (Task-1), and Na^+ channel genes, including *Scn1a* (Nav1.1) and *Scn1b* (Nav $\beta 1$ chain). We found two kinases which were upregulated in OCM. *Nek7* is involved in microtubule polymerization during the formation of PV⁺ interneuron connections (Hinojosa et

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3 al. 2018). In addition, we found that the PI3K-Akt, MAPK and AMPc signal transduction path-
4 ways are significantly up-regulated by OCM and glial cells. These signaling pathways control
5 gene expression by phosphorylating a number of transcription factors and thus regulating their
6 transcriptional activity. Previous studies have shown that these pathways are activated by oli-
7 godendrocytes secreted factors to exert their neuromodulatory functions on cultured neurons
8 (Meyer-Franke et al. 1995; Wilkins et al. 2003). PIP3-Akt1-mTOR activation is critical for
9 neuronal development, and notably for hippocampal function (Wang et al. 2003; Lai et al. 2006;
10 Goebbels et al. 2017; Balu et al. 2012). It increases the caliber of axons and the expression of
11 numerous genes encoding regulatory proteins, which might be sufficient to trigger all steps of
12 myelination (Goebbels et al. 2017).

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26 In conclusion, our study provides new insights into communication between glial cells and
27 neurons showing that factors secreted by oligodendrocytes induce transcriptomic changes
28 which may modulate the physiology and anatomy of hippocampal GABAergic neurons. Further
29 study analyzing OCM effect on purified GABAergic neurons would allow to discriminate in-
30 direct effect via glutamatergic neurotransmission and cell-autonomous effect. In addition, it is
31 now established that PV⁺ neurons as well as some Sst⁺ neurons with long range projections
32 through the hippocampus and more distant regions are frequently myelinated (Jinno et al. 2007;
33 Micheva et al. 2016; Stedehouder et al. 2017). It is fundamental to understand how OPCs and
34 oligodendrocytes feedback to neurons and contribute to the assembly, maturation and mye-
35 lination of cortical circuits during post-natal development. Moreover, CNS demyelination
36 likely results in altered neuron-oligodendrocyte interactions, and this disruption might influ-
37 ence neuronal function and myelin repair capacity in demyelinating diseases such as multiple
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Acknowledgements

We thank Marie-Stéphane Aigrot and Loane Wallon, Claire Lovo from ICM Quant, Yannick Marie and Emeline Mundwiller from iGenSeq, and François-Xavier Lejeune from iCONICS, for technical support. We thank Bernard Zalc, Richard Miles and Anne Desmazieres for discussion and critical reading of the manuscript. This work was supported by the French MS research foundation ARSEP (Aide à la Recherche sur la Sclérose en Plaques), Bouvet-Labruyère prize to NSF, and Biogen funding to EM.

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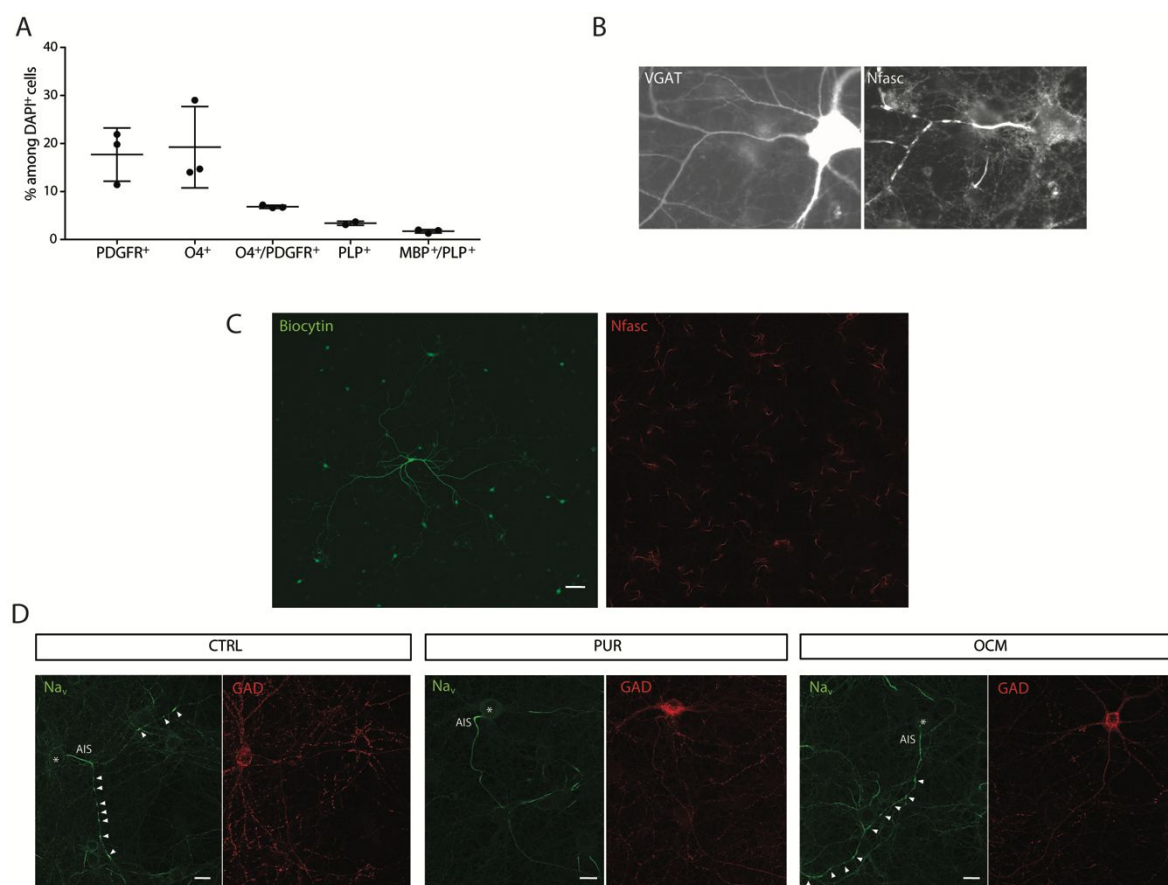
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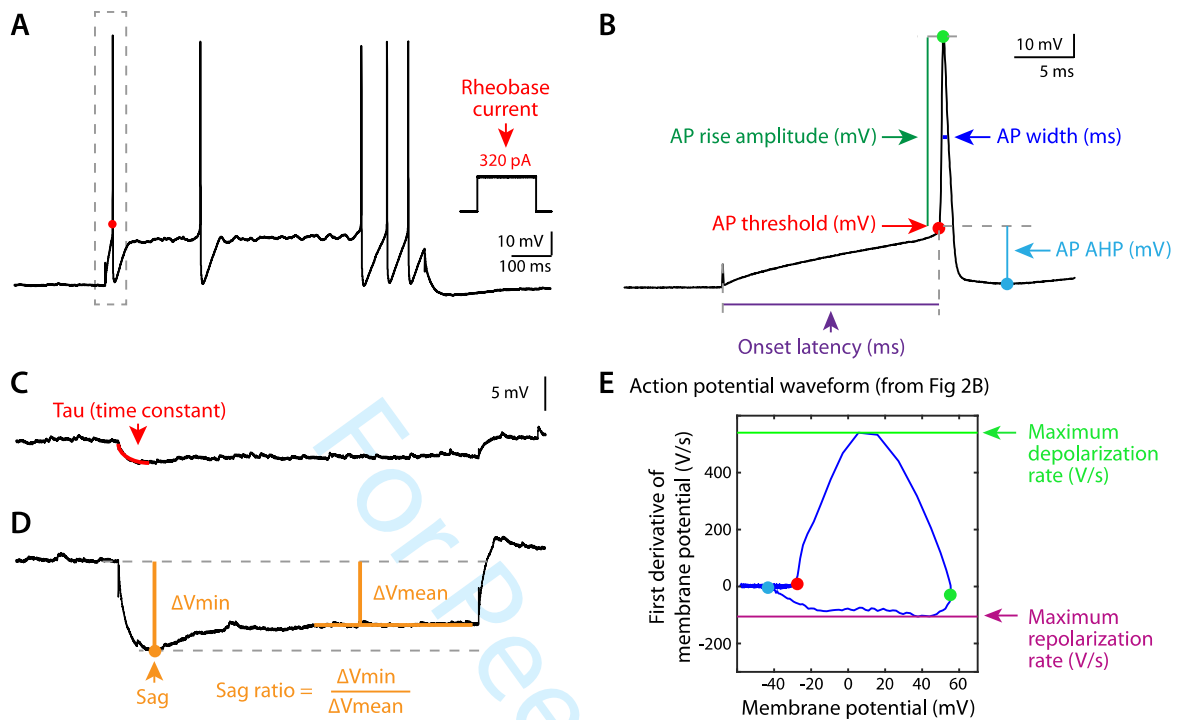
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Supplementary material



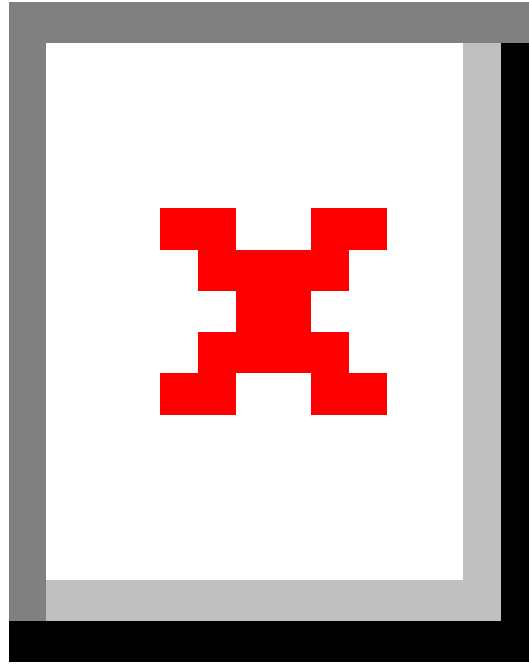
Sup. Figure 1: (A) Quantification of oligodendroglial cell phenotype in CTRL hippocampal cultures depending on positivity of PDGFR, O4, PLP and MBP. n=3 different cultures; mean \pm SEM; between 1,500 to 2,000 cells were counted on acquired images for each staining and in each experiment. (B) Image from OCM culture, incubated with Nfasc Ab directly coupled with Alexa594, before patch-clamp recordings. Fluorescent GABAergic neuron (VGAT-venus) with Nfasc staining showing axon initial segment and prenodal clusters along axon. (C) Nfasc staining (in red) on fixed OCM culture, corresponding to reconstruction of neuronal morphology of a biocytin injected neuron (in green). Scale bar: 100 μ m (D) Immunostainings of mixed hippocampal neurons (CTRL) and purified neurons in the absence (PUR) or presence of OCM (OCM), at 17 DIV. Na_v is in green and GAD67 in red. Nav clusters (indicated by

arrows) are formed along hippocampal GABAergic axons (identified by the presence of the axon initial segment (AIS)) in CTRL and OCM cultures. Scale bar: 20 μm



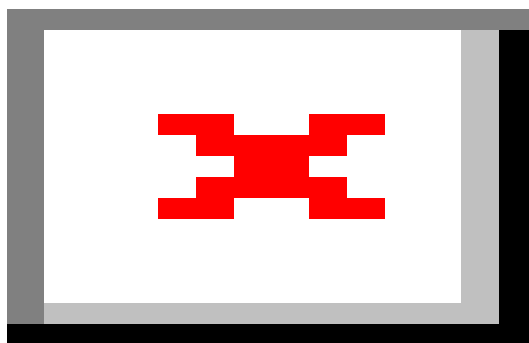
Sup. Figure 2: (A) Voltage response of an inhibitory cell to rheobase injected current, the minimal intensity needed to initiate an action potential (AP). In this example, rheobase is 320 pA. The AP voltage threshold is defined as the point at the foot of the first AP where dV/dt exceeds 30 mV/ms, indicated by a red dot. (B) The first AP at rheobase (dashed grey area from A). The following measures of active neuronal properties presented in Fig. 1 and 2 are derived from analysis of this waveform: Onset latency (purple line), AP threshold (red dot), AP rise amplitude (green line), AP width (dark blue line), AP afterhyperpolarization (AHP, light blue dot and line). Green point represents AP peak. (C) The membrane time constant (Tau) is the shorter time constant determined by fitting a double exponential function to a membrane response (-10 mV from baseline) to a small hyperpolarizing current. (D) Sag ratio is related to the I_h current. Measures of the ratio between ΔV_{min} and ΔV_{mean} were made on three consecutive traces where the steady state voltage during the second half of the hyperpolarizing

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3 pulse was close to -100mV . ΔV_{min} is the difference between the minimal potential reached
4 during of the first part of the hyperpolarizing step and the baseline (ΔV_{min}). ΔV_{mean} is the
5 difference between the mean potential during the second part of the step and the baseline
6 (ΔV_{mean}). **(E)** Phase plot representation of the first action potential at rheobase, as the first
7 derivative of membrane potential against membrane potential. Dots indicate membrane
8 potential parameters as in **(B)**: the derivative increases from the threshold (red dot) to maximum
9 depolarization rate (maximum slope of AP depolarization, green line) and then decreases to the
10 AP peak (green dot). After peak, the derivative decreases to reach the maximum repolarization
11 rate (maximum slope of AP repolarization) and then further to AP AHP (blue dot), the most
12 negative voltage point of the AP waveform.
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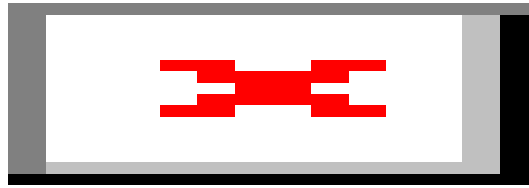
Sup. Figure 3: (A) Overview of transcript library preparation. Cytosol content was extracted from hippocampal neurons by a patch pipette. SMART-Seq v4 technology was used for mRNA capture, reverse transcription and cDNA amplification. Full-length cDNA was processed with the Nextera XT DNA Library Preparation Kit from Illumina to generate multiplex sequencing libraries. Next-generation sequencing was used to produce libraries with the Illumina NextSeq500 after a 2x75bp paired end sequencing. (B) Bioinformatic pipeline of scRNASeq data treatment. Each step is shown (left column) together with the tool used (right column). (C)

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3 Number of expressed genes plotted against the number of uniquely mapped reads. ($R^2=0.79$ all
4 samples, $R^2= 0.57$, selected samples). Black symbols represent cells that passed quality control
5 and grey symbols cells which failed quality control. Circles represent pyramidal neurons under
6 CTRL conditions, squares GABAergic neurons under CTRL conditions. GABAergic neurons
7 in purified neuron cultures are shown in red and in purified neuron cultures treated with OCM
8 in green. **(D)** Mapping statistics of reads for each sample (top, quality control passed, bottom,
9 quality control failed). **(E)** Distribution of reads of transcripts with different origins for each
10 sample (top, quality control passed, bottom, quality control failed).



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43 **Sup. Figure 4:** Comparison of distributions for genes expressed (representative example,
44 sample 34, PYR) within noncoding regions (intergenic, black) and coding regions. Genes were
45 not detected when their expression fell within 98% of intergenic regions. In this case, *Scn1b*
46 and *Kcnc1* were considered to be expressed while *Bsn* was not.

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55 **Sup. Figure 5:** Lists of regulated genes in the different comparisons, PYR vs GABA CTRL
56 (1), GABA PUR vs GABA CTRL (2), GABA PUR vs GABA OCM (3), GABA OCM vs
57 GABA CTRL (4)
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Sup. Figure 6: Expression of genes in a cluster with similar expression pattern in different culture conditions. Gene expression was normalized to that of pyramidal cells in control conditions. The number of genes for each cluster is indicated. The continuous black line shows the mean gene expression in different culture conditions.

For Peer Review

List of the 326 Regulated Genes (Fold-change ≥ 1 ,

| FAST DB STABLE ID | Gene Symbol | Regulation | Fold-Change |
|-------------------|-------------|------------|-------------|
| GSRG0000560 | Slc17a7 | up | 16918.32 |
| GSRG0002948 | Prkcg | up | 4642.46 |
| GSRG0026715 | Nfkbia | up | 2981.33 |
| GSRG0002531 | Sgk1 | up | 922.89 |
| GSRG0013623 | Spry4 | up | 423.62 |
| GSRG0015016 | Spata2L | up | 203.79 |
| GSRG0017766 | Cd24 | up | 138.50 |
| GSRG0022848 | Neurod6 | up | 97.83 |
| GSRG0025424 | Nasp | up | 86.28 |
| GSRG0012842 | Hist1h4b | up | 75.27 |
| GSRG0024955 | Slc24a2 | up | 52.13 |
| GSRG0013303 | -- | up | 51.72 |
| GSRG0009687 | Zfp238 | up | 44.96 |
| GSRG0019546 | -- | up | 41.11 |
| GSRG0022863 | Snca | up | 40.84 |
| GSRG0015022 | Ccsap | up | 35.58 |
| GSRG0024940 | -- | up | 28.64 |
| GSRG0009994 | Rgs4 | up | 21.49 |
| GSRG0013681 | Rbm22 | up | 20.40 |
| GSRG0023849 | Rpl7 | up | 4.92 |
| GSRG0018804 | Gad1 | down | 16727.68 |
| GSRG0033108 | Dner | down | 5724.64 |
| GSRG0034492 | Uba1 | down | 4160.43 |
| GSRG0015557 | Sv2a | down | 3253.04 |
| GSRG0012231 | Spock3 | down | 3071.60 |
| GSRG0022680 | -- | down | 2324.87 |
| GSRG0006308 | Kcnip1 | down | 2234.85 |
| GSRG0007991 | Pom121 | down | 2018.75 |
| GSRG0020026 | Slc32a1 | down | 1852.63 |
| GSRG0036252 | Brix1 | down | 1841.54 |
| GSRG0032304 | Nabp1 | down | 1658.96 |
| GSRG0013772 | Neto1 | down | 1625.89 |
| GSRG0011717 | Pnoc | down | 1609.67 |
| GSRG0021375 | Nxph1 | down | 1478.22 |
| GSRG0036488 | Deaf1 | down | 1396.69 |
| GSRG0015089 | Ankrd34b | down | 1394.61 |
| GSRG0020659 | Pdhx | down | 1319.10 |
| GSRG0004821 | Vegfb | down | 1306.99 |
| GSRG0023056 | Sfxn5 | down | 1283.91 |
| GSRG0015402 | Kcnab1 | down | 1270.91 |
| GSRG0005815 | Igfbp4 | down | 1057.25 |

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| 1 | | | | |
| 2 | GSRG0015667 | Extl2 | down | 987.69 |
| 3 | GSRG0028182 | Csdc2 | down | 973.27 |
| 4 | GSRG0029722 | Slc38a1 | down | 968.97 |
| 5 | GSRG0031867 | Slc17a5 | down | 953.13 |
| 6 | GSRG0002264 | Smc3 | down | 936.04 |
| 7 | GSRG0000412 | Atp5sl | down | 922.17 |
| 8 | GSRG0026695 | Stxbp6 | down | 877.20 |
| 9 | GSRG0009858 | Nek7 | down | 870.48 |
| 10 | GSRG0010407 | Vstm2a | down | 839.95 |
| 11 | GSRG0029946 | -- | down | 821.59 |
| 12 | GSRG0006796 | Ormdl3 | down | 818.47 |
| 13 | GSRG0015289 | Usp13 | down | 806.73 |
| 14 | GSRG0030658 | Gria4 | down | 791.02 |
| 15 | GSRG0024321 | Meaf6 | down | 746.53 |
| 16 | GSRG0024467 | Casp9 | down | 746.17 |
| 17 | GSRG0023359 | Wnt7a | down | 723.15 |
| 18 | GSRG0023969 | Nfx1 | down | 710.03 |
| 19 | GSRG0014272 | Fam210a | down | 694.05 |
| 20 | GSRG0012763 | Sirt5 | down | 629.95 |
| 21 | GSRG0024969 | Elavl2 | down | 617.75 |
| 22 | GSRG0015701 | Camk2d | down | 609.79 |
| 23 | GSRG0028286 | Letmd1 | down | 580.97 |
| 24 | GSRG0034591 | Ap1s2 | down | 574.99 |
| 25 | GSRG0022888 | Tgoln2 | down | 569.64 |
| 26 | GSRG0029330 | Lynx1 | down | 550.47 |
| 27 | GSRG0011067 | Med4 | down | 543.22 |
| 28 | GSRG0021798 | Slc6a1 | down | 522.99 |
| 29 | GSRG0009613 | Creg1 | down | 518.93 |
| 30 | GSRG0033044 | Lancl1 | down | 518.67 |
| 31 | GSRG0011989 | Tenm3 | down | 503.97 |
| 32 | GSRG0006834 | Nt5c3b | down | 495.39 |
| 33 | GSRG0010011 | Pcp4l1 | down | 485.28 |
| 34 | GSRG0011506 | Zfp385d | down | 457.15 |
| 35 | GSRG0006857 | Aarsd1 | down | 446.91 |
| 36 | GSRG0001759 | Ubfd1 | down | 431.53 |
| 37 | GSRG0032453 | Neu2 | down | 418.98 |
| 38 | GSRG0029596 | Rps19bp1 | down | 411.93 |
| 39 | GSRG0014616 | Cntnap4 | down | 406.45 |
| 40 | GSRG0005831 | Tubg2 | down | 406.34 |
| 41 | GSRG0024218 | Rab3b | down | 399.77 |
| 42 | GSRG0000359 | Pnmal2 | down | 391.86 |
| 43 | GSRG0016396 | Glrb | down | 388.02 |
| 44 | GSRG0024704 | Tstd3 | down | 383.90 |
| 45 | GSRG0015615 | Slc16a1 | down | 368.12 |
| 46 | GSRG0024749 | -- | down | 357.24 |
| 47 | GSRG0010809 | Pno1 | down | 353.48 |
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|----|-------------|------------|------|--------|
| 1 | | | | |
| 2 | GSRG0025990 | Ap4s1 | down | 352.86 |
| 3 | GSRG0008103 | Rnf10 | down | 352.55 |
| 4 | GSRG0029606 | Rangap1 | down | 350.02 |
| 5 | GSRG0021638 | LRRTM1 | down | 347.45 |
| 6 | GSRG0020416 | -- | down | 347.38 |
| 7 | GSRG0012470 | Lman2 | down | 345.79 |
| 8 | GSRG0029369 | MGC94207 | down | 343.91 |
| 9 | GSRG0023833 | Amn1 | down | 339.41 |
| 10 | GSRG0025855 | Lbh | down | 326.88 |
| 11 | GSRG0027460 | Mbd3 | down | 325.80 |
| 12 | GSRG0000256 | Tfpt | down | 325.69 |
| 13 | GSRG0002201 | -- | down | 323.84 |
| 14 | GSRG0003572 | -- | down | 319.24 |
| 15 | GSRG0004950 | Ranbp6 | down | 316.28 |
| 16 | GSRG0020147 | Zgpat | down | 313.15 |
| 17 | GSRG0010749 | Drg1 | down | 305.45 |
| 18 | GSRG0007852 | Mcoln1 | down | 305.15 |
| 19 | GSRG0012440 | Agtpbp1 | down | 305.05 |
| 20 | GSRG0032457 | Dgkd | down | 297.20 |
| 21 | GSRG0004958 | Sgms1 | down | 274.55 |
| 22 | GSRG0034043 | Arx | down | 273.79 |
| 23 | GSRG0008042 | Abcb9 | down | 272.04 |
| 24 | GSRG0032237 | Ccdc115 | down | 268.62 |
| 25 | GSRG0013915 | Cep120 | down | 266.68 |
| 26 | GSRG0014676 | Cdk10 | down | 265.50 |
| 27 | GSRG0034650 | Eif2s3 | down | 253.31 |
| 28 | GSRG0023848 | Stau2 | down | 247.94 |
| 29 | GSRG0030119 | Bace1 | down | 245.66 |
| 30 | GSRG0004927 | Fam189a2 | down | 245.13 |
| 31 | GSRG0029709 | Slc2a13 | down | 241.64 |
| 32 | GSRG0036721 | Tes | down | 230.92 |
| 33 | GSRG0031432 | RGD1309779 | down | 222.68 |
| 34 | GSRG0030208 | Rpp25 | down | 219.90 |
| 35 | GSRG0035015 | -- | down | 215.07 |
| 36 | GSRG0025896 | -- | down | 212.86 |
| 37 | GSRG0034875 | Zdhhc9 | down | 209.94 |
| 38 | GSRG0022886 | Elmod3 | down | 208.22 |
| 39 | GSRG0012951 | Plxdc2 | down | 207.09 |
| 40 | GSRG0032869 | -- | down | 199.78 |
| 41 | GSRG0015813 | Rasa1 | down | 197.87 |
| 42 | GSRG0031919 | Pxylp1 | down | 197.81 |
| 43 | GSRG0013521 | RGD1311805 | down | 195.11 |
| 44 | GSRG0033974 | Clcn4 | down | 194.41 |
| 45 | GSRG0011557 | Ttc5 | down | 191.17 |
| 46 | GSRG0000476 | Dpf1 | down | 189.93 |
| 47 | GSRG0020273 | Slc25a25 | down | 189.76 |

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|----|-------------|---------|------|--------|
| 1 | | | | |
| 2 | GSRG0029609 | Phf5a | down | 188.98 |
| 3 | GSRG0016022 | Zc2hc1a | down | 183.74 |
| 4 | GSRG0030501 | Tmem115 | down | 181.28 |
| 5 | GSRG0007362 | Pi4ka | down | 180.47 |
| 6 | GSRG0028688 | Actr6 | down | 177.91 |
| 7 | GSRG0030674 | Endod1 | down | 175.88 |
| 8 | GSRG0036082 | Fam13b | down | 174.11 |
| 9 | GSRG0015955 | Mrps30 | down | 170.52 |
| 10 | GSRG0025787 | Cptp | down | 170.26 |
| 11 | GSRG0034878 | Aifm1 | down | 169.88 |
| 12 | GSRG0006168 | Nubp1 | down | 166.62 |
| 13 | GSRG0036211 | Zfp148 | down | 166.42 |
| 14 | GSRG0002170 | Hectd2 | down | 162.89 |
| 15 | GSRG0020281 | Slc2a8 | down | 162.64 |
| 16 | GSRG0000549 | Nup62 | down | 160.38 |
| 17 | GSRG0012893 | Pitrm1 | down | 160.02 |
| 18 | GSRG0032105 | -- | down | 159.76 |
| 19 | GSRG0022959 | Mrpl19 | down | 158.59 |
| 20 | GSRG0036591 | Akap2 | down | 152.88 |
| 21 | GSRG0006992 | Acox1 | down | 152.41 |
| 22 | GSRG0009710 | Cnih4 | down | 151.46 |
| 23 | GSRG0021258 | Samd10 | down | 149.25 |
| 24 | GSRG0024488 | Dffa | down | 144.68 |
| 25 | GSRG0013012 | B4galt7 | down | 143.26 |
| 26 | GSRG0024281 | Foxj3 | down | 140.02 |
| 27 | GSRG0016443 | Hcn3 | down | 139.28 |
| 28 | GSRG0022691 | Bmt2 | down | 136.95 |
| 29 | GSRG0031938 | Slc35g2 | down | 134.69 |
| 30 | GSRG0015143 | Il6st | down | 132.58 |
| 31 | GSRG0007589 | Ccdc50 | down | 129.26 |
| 32 | GSRG0002006 | Rasgrp2 | down | 128.07 |
| 33 | GSRG0020342 | Ppp6c | down | 127.75 |
| 34 | GSRG0013719 | Preli3a | down | 125.53 |
| 35 | GSRG0018533 | Fam229b | down | 124.61 |
| 36 | GSRG0022878 | Ptcd3 | down | 121.96 |
| 37 | GSRG0006325 | Gabrg2 | down | 121.50 |
| 38 | GSRG0032163 | Ppp2r5d | down | 115.86 |
| 39 | GSRG0006071 | Mrps7 | down | 112.91 |
| 40 | GSRG0030101 | Slc37a4 | down | 112.80 |
| 41 | GSRG0008075 | Rph3a | down | 110.97 |
| 42 | GSRG0021118 | Ahcy | down | 110.76 |
| 43 | GSRG0015217 | Ctnnd2 | down | 109.57 |
| 44 | GSRG0037062 | -- | down | 109.41 |
| 45 | GSRG0015248 | Pex2 | down | 108.50 |
| 46 | GSRG0036688 | Ift52 | down | 108.41 |
| 47 | GSRG0004218 | Man2a2 | down | 106.12 |

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|----|-------------|-----------|------|--------|
| 1 | | | | |
| 2 | GSRG0028415 | Matk | down | 103.47 |
| 3 | GSRG0032367 | Atic | down | 101.21 |
| 4 | GSRG0010329 | LOC680039 | down | 100.90 |
| 5 | GSRG0011981 | Galntf6 | down | 100.29 |
| 6 | GSRG0004243 | Arnt2 | down | 99.74 |
| 7 | GSRG0022835 | Hibadh | down | 96.86 |
| 8 | GSRG0011901 | Fam213a | down | 96.06 |
| 9 | GSRG0006957 | Slc39a11 | down | 95.70 |
| 10 | GSRG0001710 | Ipo7 | down | 95.56 |
| 11 | GSRG0028151 | Mgat3 | down | 95.47 |
| 12 | GSRG0004194 | Slco3a1 | down | 95.41 |
| 13 | GSRG0032455 | Atg16l1 | down | 95.36 |
| 14 | GSRG0019759 | Cds2 | down | 93.84 |
| 15 | GSRG0027443 | Gng7 | down | 93.10 |
| 16 | GSRG0010385 | Dbnl | down | 92.42 |
| 17 | GSRG0034674 | Slc7a3 | down | 92.08 |
| 18 | GSRG0016839 | Atf6b | down | 91.97 |
| 19 | GSRG0036603 | Elavl4 | down | 91.86 |
| 20 | GSRG0014809 | Rad23a | down | 91.42 |
| 21 | GSRG0001503 | Hddc3 | down | 90.39 |
| 22 | GSRG0014694 | Gnpat | down | 90.38 |
| 23 | GSRG0010962 | Thtpa | down | 88.71 |
| 24 | GSRG0012881 | -- | down | 87.57 |
| 25 | GSRG0026745 | Vcpkmt | down | 85.59 |
| 26 | GSRG0010288 | Lgi2 | down | 85.51 |
| 27 | GSRG0009616 | Tada1 | down | 84.89 |
| 28 | GSRG0024362 | Pef1 | down | 82.43 |
| 29 | GSRG0012481 | Thoc3 | down | 82.21 |
| 30 | GSRG0021352 | Cldn12 | down | 81.70 |
| 31 | GSRG0012237 | Mfap3l | down | 81.51 |
| 32 | GSRG0028788 | Cpsf6 | down | 80.75 |
| 33 | GSRG0033071 | Abcb6 | down | 79.77 |
| 34 | GSRG0003204 | Fam98c | down | 79.50 |
| 35 | GSRG0007942 | Zfp68 | down | 78.65 |
| 36 | GSRG0006141 | Tbcd | down | 77.32 |
| 37 | GSRG0036538 | Tigar | down | 76.54 |
| 38 | GSRG0011694 | Nefm | down | 73.74 |
| 39 | GSRG0010307 | Fbxl5 | down | 73.71 |
| 40 | GSRG0005641 | Poldip2 | down | 72.91 |
| 41 | GSRG0026364 | Golga5 | down | 71.80 |
| 42 | GSRG0014644 | Mlycd | down | 70.33 |
| 43 | GSRG0014332 | Slc38a7 | down | 70.27 |
| 44 | GSRG0007023 | Aatk | down | 66.75 |
| 45 | GSRG0005828 | Coasy | down | 65.78 |
| 46 | GSRG0015633 | Kcna2 | down | 65.06 |
| 47 | GSRG0023361 | Xpc | down | 64.11 |

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|----|-------------|------------|------|-------|
| 1 | | | | |
| 2 | GSRG0029746 | Ddx23 | down | 63.76 |
| 3 | GSRG0007430 | Gart | down | 63.68 |
| 4 | GSRG0018818 | Rapgef4 | down | 63.22 |
| 5 | GSRG0005300 | Rnf145 | down | 62.79 |
| 6 | GSRG0032295 | Asnsd1 | down | 62.09 |
| 7 | GSRG0013699 | St8sia3 | down | 59.77 |
| 8 | GSRG0032472 | Ube2f | down | 59.69 |
| 9 | GSRG0015568 | Pex11b | down | 59.18 |
| 10 | GSRG0012252 | Aga | down | 59.08 |
| 11 | GSRG0024240 | Atpaf1 | down | 58.97 |
| 12 | GSRG0015476 | Rit1 | down | 58.66 |
| 13 | GSRG0034325 | -- | down | 58.33 |
| 14 | GSRG0010671 | Smim20 | down | 56.64 |
| 15 | GSRG0023923 | Ccnc | down | 56.29 |
| 16 | GSRG0020103 | Cstf1 | down | 56.01 |
| 17 | GSRG0010760 | Mtfp1 | down | 55.81 |
| 18 | GSRG0012821 | Nrsn1 | down | 55.12 |
| 19 | GSRG0009744 | Lpgat1 | down | 54.92 |
| 20 | GSRG0033045 | Erbp4 | down | 53.73 |
| 21 | GSRG0034459 | Naa10 | down | 53.00 |
| 22 | GSRG0026671 | Bcap29 | down | 52.23 |
| 23 | GSRG0015121 | Sgtb | down | 51.77 |
| 24 | GSRG0037008 | LOC317456 | down | 51.43 |
| 25 | GSRG0023726 | Chtop | down | 51.10 |
| 26 | GSRG0019739 | Ptpn11 | down | 49.63 |
| 27 | GSRG0023914 | Mmp16 | down | 49.38 |
| 28 | GSRG0032551 | Ppip5k2 | down | 49.08 |
| 29 | GSRG0021152 | Mafb | down | 48.92 |
| 30 | GSRG0007034 | Alyref | down | 48.83 |
| 31 | GSRG0025892 | Adcy3 | down | 48.58 |
| 32 | GSRG0013593 | Slc35a4 | down | 48.40 |
| 33 | GSRG0003080 | Bckdha | down | 46.49 |
| 34 | GSRG0023441 | Erc1 | down | 45.02 |
| 35 | GSRG0020405 | Stk39 | down | 42.85 |
| 36 | GSRG0005277 | -- | down | 42.78 |
| 37 | GSRG0008980 | -- | down | 42.77 |
| 38 | GSRG0022727 | Impdh1 | down | 42.42 |
| 39 | GSRG0004240 | Cemip | down | 42.30 |
| 40 | GSRG0032964 | Rnf149 | down | 41.80 |
| 41 | GSRG0003380 | Bax | down | 40.71 |
| 42 | GSRG0025741 | -- | down | 40.12 |
| 43 | GSRG0024724 | RGD1359108 | down | 39.32 |
| 44 | GSRG0036716 | Sdhaf3 | down | 37.94 |
| 45 | GSRG0022895 | Ctnna2 | down | 37.62 |
| 46 | GSRG0014508 | Farsa | down | 37.41 |
| 47 | GSRG0026023 | Mgat2 | down | 37.19 |

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|----|-------------|------------|------|-------|
| 1 | | | | |
| 2 | GSRG0021713 | Tpra1 | down | 37.11 |
| 3 | GSRG0030373 | Ccp1 | down | 36.72 |
| 4 | GSRG0006092 | Mgat5b | down | 36.70 |
| 5 | GSRG0030404 | Irak1bp1 | down | 35.29 |
| 6 | GSRG0033905 | RGD1565685 | down | 35.19 |
| 7 | GSRG0006292 | Mpg | down | 34.11 |
| 8 | GSRG0008961 | Tpst1 | down | 33.96 |
| 9 | GSRG0034071 | Nlgn3 | down | 33.55 |
| 10 | GSRG0030592 | Glb1 | down | 33.27 |
| 11 | GSRG0009332 | Chfr | down | 32.72 |
| 12 | GSRG0012257 | Rwdd4 | down | 32.61 |
| 13 | GSRG0020043 | Gdap111 | down | 32.49 |
| 14 | GSRG0022971 | Dguok | down | 31.45 |
| 15 | GSRG0001760 | -- | down | 31.35 |
| 16 | GSRG0022860 | Nap1l5 | down | 31.03 |
| 17 | GSRG0027274 | Itpk1 | down | 30.88 |
| 18 | GSRG0010446 | Pnpt1 | down | 30.13 |
| 19 | GSRG0026166 | Nrxn3 | down | 29.89 |
| 20 | GSRG0020851 | -- | down | 29.71 |
| 21 | GSRG0019760 | -- | down | 29.55 |
| 22 | GSRG0012962 | Gad2 | down | 29.41 |
| 23 | GSRG0025780 | Gabrd | down | 29.38 |
| 24 | GSRG0015761 | Ddah1 | down | 29.12 |
| 25 | GSRG0024731 | Topors | down | 28.92 |
| 26 | GSRG0030754 | Herpud2 | down | 28.45 |
| 27 | GSRG0016680 | Ap1ar | down | 28.29 |
| 28 | GSRG0010470 | Rpl5 | down | 28.28 |
| 29 | GSRG0020402 | Scn1a | down | 27.06 |
| 30 | GSRG0037033 | -- | down | 24.95 |
| 31 | GSRG0016679 | -- | down | 24.65 |
| 32 | GSRG0019734 | Nop56 | down | 24.47 |
| 33 | GSRG0006408 | Anxa6 | down | 23.95 |
| 34 | GSRG0028835 | Lrp1 | down | 23.54 |
| 35 | GSRG0025742 | -- | down | 23.40 |
| 36 | GSRG0036181 | Sst | down | 23.13 |
| 37 | GSRG0001513 | Tm6sf1 | down | 22.57 |
| 38 | GSRG0006876 | Hdac5 | down | 22.53 |
| 39 | GSRG0014269 | Spire1 | down | 22.04 |
| 40 | GSRG0008871 | -- | down | 21.58 |
| 41 | GSRG0015487 | -- | down | 21.25 |
| 42 | GSRG0006976 | Gga3 | down | 21.14 |
| 43 | GSRG0018613 | Fam69b | down | 19.11 |
| 44 | GSRG0021660 | Bola3 | down | 17.10 |
| 45 | GSRG0010144 | Fam69a | down | 17.00 |
| 46 | GSRG0009573 | Astn1 | down | 16.08 |
| 47 | GSRG0029871 | Dcun1d5 | down | 14.98 |

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| GSRG0032125 | -- | down | 13.65 |
| GSRG0036853 | -- | down | 11.11 |
| GSRG0034667 | -- | down | 10.93 |
| GSRG0019586 | Disp2 | down | 10.62 |
| GSRG0010140 | Cplx1 | down | 9.95 |
| GSRG0008872 | Vgf | down | 9.34 |
| GSRG0013844 | Reep5 | down | 8.57 |
| GSRG0004774 | Klc2 | down | 7.79 |
| GSRG0003068 | Atp1a3 | down | 4.87 |

For Peer Review

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4 **,5; P-Value \leq 0,05) - P)**
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| P-Value | Adjusted P-Value |
|----------|------------------|
| 4.36E-09 | 3.21E-06 |
| 1.22E-06 | 2.72E-04 |
| 2.53E-06 | 5.04E-04 |
| 1.04E-05 | 1.39E-03 |
| 1.97E-04 | 1.04E-02 |
| 1.28E-03 | 3.40E-02 |
| 3.05E-03 | 5.74E-02 |
| 5.64E-03 | 7.88E-02 |
| 9.19E-03 | 1.05E-01 |
| 1.22E-02 | 1.25E-01 |
| 7.09E-03 | 9.02E-02 |
| 2.30E-02 | 1.87E-01 |
| 1.81E-02 | 1.60E-01 |
| 1.26E-02 | 1.28E-01 |
| 2.91E-02 | 2.16E-01 |
| 3.40E-02 | 2.39E-01 |
| 2.92E-02 | 2.16E-01 |
| 4.32E-02 | 2.76E-01 |
| 4.42E-02 | 2.80E-01 |
| 4.10E-02 | 2.67E-01 |
| 9.44E-18 | 6.95E-14 |
| 7.67E-14 | 2.82E-10 |
| 6.67E-12 | 9.83E-09 |
| 1.56E-10 | 1.44E-07 |
| 1.63E-12 | 3.01E-09 |
| 9.87E-12 | 1.21E-08 |
| 1.36E-08 | 7.14E-06 |
| 1.21E-08 | 7.14E-06 |
| 1.51E-11 | 1.59E-08 |
| 6.34E-06 | 1.02E-03 |
| 6.76E-06 | 1.04E-03 |
| 9.47E-13 | 2.32E-09 |
| 1.51E-08 | 7.41E-06 |
| 3.63E-08 | 1.57E-05 |
| 7.85E-09 | 5.25E-06 |
| 6.08E-07 | 1.72E-04 |
| 1.33E-08 | 7.14E-06 |
| 3.75E-07 | 1.26E-04 |
| 8.24E-07 | 2.09E-04 |
| 1.07E-06 | 2.54E-04 |
| 9.52E-07 | 2.34E-04 |

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| 1 | | |
| 2 | 1.99E-07 | 7.00E-05 |
| 3 | 3.54E-08 | 1.57E-05 |
| 4 | 7.79E-08 | 3.19E-05 |
| 5 | | |
| 6 | 6.54E-05 | 4.92E-03 |
| 7 | 7.06E-05 | 5.20E-03 |
| 8 | 3.64E-06 | 6.87E-04 |
| 9 | | |
| 10 | 3.63E-06 | 6.87E-04 |
| 11 | 4.38E-06 | 7.68E-04 |
| 12 | 4.42E-07 | 1.41E-04 |
| 13 | | |
| 14 | 3.89E-05 | 3.58E-03 |
| 15 | 5.29E-05 | 4.38E-03 |
| 16 | | |
| 17 | 2.74E-05 | 2.92E-03 |
| 18 | 1.93E-06 | 4.19E-04 |
| 19 | 1.50E-07 | 5.82E-05 |
| 20 | 1.20E-04 | 7.41E-03 |
| 21 | | |
| 22 | 1.13E-06 | 2.59E-04 |
| 23 | 1.33E-05 | 1.66E-03 |
| 24 | 1.48E-04 | 8.57E-03 |
| 25 | | |
| 26 | 8.03E-07 | 2.09E-04 |
| 27 | 2.51E-06 | 5.04E-04 |
| 28 | 3.47E-05 | 3.32E-03 |
| 29 | | |
| 30 | 2.85E-05 | 2.95E-03 |
| 31 | 4.05E-06 | 7.31E-04 |
| 32 | 4.07E-06 | 7.31E-04 |
| 33 | | |
| 34 | 1.23E-05 | 1.57E-03 |
| 35 | 2.07E-06 | 4.35E-04 |
| 36 | 1.22E-09 | 1.00E-06 |
| 37 | | |
| 38 | 7.10E-06 | 1.07E-03 |
| 39 | 8.68E-06 | 1.19E-03 |
| 40 | 1.21E-05 | 1.56E-03 |
| 41 | | |
| 42 | 5.06E-05 | 4.24E-03 |
| 43 | 4.83E-05 | 4.09E-03 |
| 44 | 1.52E-05 | 1.83E-03 |
| 45 | 1.09E-05 | 1.44E-03 |
| 46 | 1.51E-05 | 1.83E-03 |
| 47 | 1.29E-04 | 7.74E-03 |
| 48 | | |
| 49 | 5.75E-07 | 1.69E-04 |
| 50 | | |
| 51 | 4.17E-05 | 3.78E-03 |
| 52 | 2.23E-05 | 2.52E-03 |
| 53 | 7.91E-06 | 1.16E-03 |
| 54 | | |
| 55 | 8.55E-06 | 1.19E-03 |
| 56 | 5.77E-05 | 4.57E-03 |
| 57 | 2.88E-05 | 2.95E-03 |
| 58 | 3.58E-04 | 1.53E-02 |
| 59 | 5.91E-06 | 9.79E-04 |
| 60 | 3.13E-04 | 1.42E-02 |

Peer Review

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| 2.65E-05 | 2.87E-03 |
| 8.17E-06 | 1.18E-03 |
| 7.42E-07 | 2.02E-04 |
| 6.06E-05 | 4.70E-03 |
| 1.75E-05 | 2.04E-03 |
| 2.81E-04 | 1.35E-02 |
| 4.57E-05 | 3.99E-03 |
| 2.82E-05 | 2.95E-03 |
| 3.10E-05 | 3.05E-03 |
| 3.45E-05 | 3.32E-03 |
| 1.55E-04 | 8.78E-03 |
| 6.81E-05 | 5.07E-03 |
| 2.21E-04 | 1.13E-02 |
| 8.83E-05 | 5.86E-03 |
| 6.75E-04 | 2.23E-02 |
| 6.35E-05 | 4.87E-03 |
| 5.42E-05 | 4.41E-03 |
| 7.83E-05 | 5.55E-03 |
| 7.44E-05 | 5.32E-03 |
| 7.79E-04 | 2.46E-02 |
| 5.35E-07 | 1.64E-04 |
| 8.03E-05 | 5.63E-03 |
| 5.80E-04 | 2.00E-02 |
| 5.55E-04 | 1.96E-02 |
| 3.23E-04 | 1.45E-02 |
| 3.54E-04 | 1.53E-02 |
| 8.50E-05 | 5.75E-03 |
| 6.48E-04 | 2.15E-02 |
| 5.97E-04 | 2.02E-02 |
| 3.15E-04 | 1.42E-02 |
| 5.20E-04 | 1.87E-02 |
| 8.17E-04 | 2.52E-02 |
| 6.32E-04 | 2.11E-02 |
| 1.36E-03 | 3.52E-02 |
| 1.21E-04 | 7.42E-03 |
| 3.66E-04 | 1.54E-02 |
| 1.23E-03 | 3.29E-02 |
| 1.13E-03 | 3.14E-02 |
| 1.65E-04 | 9.23E-03 |
| 1.60E-03 | 3.92E-02 |
| 2.04E-03 | 4.52E-02 |
| 1.20E-03 | 3.24E-02 |
| 4.36E-04 | 1.68E-02 |
| 3.93E-04 | 1.61E-02 |
| 1.84E-04 | 1.00E-02 |
| 1.73E-03 | 4.12E-02 |

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| 2 | 1.09E-03 | 3.05E-02 |
| 3 | 3.77E-04 | 1.58E-02 |
| 4 | 4.30E-04 | 1.67E-02 |
| 5 | 5.98E-06 | 9.79E-04 |
| 6 | 4.19E-04 | 1.65E-02 |
| 7 | 1.53E-04 | 8.72E-03 |
| 8 | 2.04E-03 | 4.52E-02 |
| 9 | 5.75E-04 | 1.99E-02 |
| 10 | 8.85E-04 | 2.67E-02 |
| 11 | 1.46E-03 | 3.70E-02 |
| 12 | 4.94E-04 | 1.86E-02 |
| 13 | 5.12E-04 | 1.87E-02 |
| 14 | 9.31E-04 | 2.78E-02 |
| 15 | 5.58E-04 | 1.96E-02 |
| 16 | 2.01E-03 | 4.50E-02 |
| 17 | 5.73E-04 | 1.99E-02 |
| 18 | 1.06E-03 | 3.01E-02 |
| 19 | 1.58E-03 | 3.91E-02 |
| 20 | 2.90E-03 | 5.63E-02 |
| 21 | 2.69E-03 | 5.36E-02 |
| 22 | 1.14E-03 | 3.14E-02 |
| 23 | 5.46E-04 | 1.94E-02 |
| 24 | 1.18E-03 | 3.22E-02 |
| 25 | 8.48E-04 | 2.60E-02 |
| 26 | 3.25E-03 | 5.93E-02 |
| 27 | 2.40E-04 | 1.20E-02 |
| 28 | 3.48E-03 | 6.08E-02 |
| 29 | 1.32E-03 | 3.46E-02 |
| 30 | 3.39E-03 | 5.99E-02 |
| 31 | 8.67E-04 | 2.63E-02 |
| 32 | 7.92E-04 | 2.48E-02 |
| 33 | 9.32E-04 | 2.78E-02 |
| 34 | 1.02E-03 | 2.96E-02 |
| 35 | 3.80E-03 | 6.43E-02 |
| 36 | 1.77E-03 | 4.19E-02 |
| 37 | 3.07E-05 | 3.05E-03 |
| 38 | 4.81E-06 | 8.24E-04 |
| 39 | 1.90E-03 | 4.36E-02 |
| 40 | 2.17E-03 | 4.73E-02 |
| 41 | 2.98E-04 | 1.40E-02 |
| 42 | 5.15E-03 | 7.53E-02 |
| 43 | 3.77E-03 | 6.42E-02 |
| 44 | 2.16E-03 | 4.73E-02 |
| 45 | 6.46E-03 | 8.47E-02 |
| 46 | 4.39E-03 | 6.77E-02 |
| 47 | 3.42E-03 | 6.00E-02 |
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| 4.96E-03 | 7.34E-02 |
| 4.13E-03 | 6.58E-02 |
| 4.77E-03 | 7.21E-02 |
| 4.03E-03 | 6.54E-02 |
| 3.98E-03 | 6.53E-02 |
| 3.39E-03 | 5.99E-02 |
| 4.08E-03 | 6.55E-02 |
| 7.45E-03 | 9.30E-02 |
| 4.97E-03 | 7.34E-02 |
| 2.19E-03 | 4.75E-02 |
| 5.47E-03 | 7.76E-02 |
| 3.29E-03 | 5.93E-02 |
| 8.39E-03 | 9.96E-02 |
| 6.06E-03 | 8.19E-02 |
| 3.27E-03 | 5.93E-02 |
| 3.12E-03 | 5.81E-02 |
| 3.40E-03 | 5.99E-02 |
| 3.49E-03 | 6.08E-02 |
| 3.19E-03 | 5.90E-02 |
| 6.70E-03 | 8.71E-02 |
| 3.89E-03 | 6.51E-02 |
| 5.86E-03 | 8.06E-02 |
| 7.07E-03 | 9.02E-02 |
| 5.70E-03 | 7.91E-02 |
| 2.76E-03 | 5.44E-02 |
| 1.02E-02 | 1.10E-01 |
| 4.10E-03 | 6.55E-02 |
| 1.06E-02 | 1.13E-01 |
| 6.21E-03 | 8.33E-02 |
| 1.09E-02 | 1.16E-01 |
| 2.21E-03 | 4.75E-02 |
| 4.29E-03 | 6.69E-02 |
| 4.15E-03 | 6.59E-02 |
| 7.19E-03 | 9.10E-02 |
| 8.09E-03 | 9.82E-02 |
| 5.86E-03 | 8.06E-02 |
| 6.02E-05 | 4.70E-03 |
| 6.40E-03 | 8.44E-02 |
| 5.93E-04 | 2.01E-02 |
| 8.21E-03 | 9.90E-02 |
| 9.78E-03 | 1.07E-01 |
| 6.41E-03 | 8.44E-02 |
| 1.13E-02 | 1.19E-01 |
| 8.97E-03 | 1.03E-01 |
| 1.41E-02 | 1.37E-01 |
| 1.65E-02 | 1.52E-01 |

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| 2 | 9.04E-03 | 1.04E-01 |
| 3 | 1.63E-02 | 1.51E-01 |
| 4 | 8.50E-03 | 1.00E-01 |
| 5 | 4.27E-03 | 6.69E-02 |
| 6 | 8.86E-03 | 1.03E-01 |
| 7 | 1.78E-02 | 1.59E-01 |
| 8 | 1.10E-02 | 1.16E-01 |
| 9 | 1.08E-02 | 1.15E-01 |
| 10 | 1.46E-02 | 1.40E-01 |
| 11 | 1.60E-02 | 1.49E-01 |
| 12 | 1.15E-02 | 1.20E-01 |
| 13 | 1.74E-05 | 2.04E-03 |
| 14 | 1.20E-02 | 1.24E-01 |
| 15 | 1.24E-02 | 1.26E-01 |
| 16 | 1.58E-02 | 1.49E-01 |
| 17 | 9.82E-03 | 1.08E-01 |
| 18 | 1.60E-02 | 1.49E-01 |
| 19 | 5.68E-03 | 7.91E-02 |
| 20 | 1.38E-02 | 1.35E-01 |
| 21 | 1.61E-02 | 1.50E-01 |
| 22 | 1.10E-02 | 1.17E-01 |
| 23 | 1.29E-02 | 1.30E-01 |
| 24 | 1.72E-02 | 1.55E-01 |
| 25 | 2.29E-03 | 4.86E-02 |
| 26 | 1.38E-03 | 3.56E-02 |
| 27 | 1.60E-02 | 1.49E-01 |
| 28 | 1.99E-02 | 1.71E-01 |
| 29 | 1.96E-02 | 1.69E-01 |
| 30 | 7.27E-03 | 9.15E-02 |
| 31 | 1.66E-02 | 1.52E-01 |
| 32 | 1.83E-02 | 1.61E-01 |
| 33 | 2.10E-02 | 1.76E-01 |
| 34 | 2.56E-02 | 1.99E-01 |
| 35 | 2.06E-02 | 1.75E-01 |
| 36 | 8.94E-03 | -- |
| 37 | 1.89E-02 | 1.65E-01 |
| 38 | 2.51E-02 | 1.96E-01 |
| 39 | 2.07E-02 | 1.75E-01 |
| 40 | 2.58E-02 | 2.00E-01 |
| 41 | 2.45E-02 | 1.94E-01 |
| 42 | 8.81E-03 | 1.03E-01 |
| 43 | 1.81E-02 | 1.60E-01 |
| 44 | 2.15E-02 | 1.79E-01 |
| 45 | 1.82E-02 | 1.60E-01 |
| 46 | 2.46E-02 | 1.94E-01 |
| 47 | 2.53E-02 | 1.97E-01 |

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| 3.09E-02 | 2.25E-01 |
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| 3.18E-02 | 2.30E-01 |
| 1.69E-02 | 1.54E-01 |
| 3.69E-02 | 2.51E-01 |
| 3.24E-02 | 2.33E-01 |
| 4.07E-02 | 2.66E-01 |
| 8.90E-03 | 1.03E-01 |
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| 3.68E-02 | 2.51E-01 |
| 4.13E-02 | 2.68E-01 |
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| 1.11E-03 | 3.08E-02 |
| 1.75E-02 | 1.56E-01 |
| 4.55E-02 | 2.85E-01 |
| 4.70E-02 | 2.92E-01 |
| 2.85E-03 | 5.56E-02 |
| 2.42E-02 | 1.92E-01 |
| 3.32E-02 | 2.36E-01 |
| 2.38E-02 | 1.90E-01 |
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| 2 | 3.59E-02 | 2.47E-01 |
| 3 | 4.08E-02 | 2.66E-01 |
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For Peer Review

YR CTRL vs GABA CTRL

| Gene Name |
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| solute carrier family 17 member 7 |
| protein kinase C, gamma |
| NFKB inhibitor alpha |
| serum/glucocorticoid regulated kinase 1 |
| sprouty RTK signaling antagonist 4 |
| spermatogenesis associated 2-like |
| CD24 molecule |
| neuronal differentiation 6 |
| nuclear autoantigenic sperm protein |
| histone cluster 1, H4b |
| solute carrier family 24 member 2 |
| -- |
| zinc finger protein 238 |
| -- |
| synuclein alpha |
| centriole, cilia and spindle-associated protein |
| -- |
| regulator of G-protein signaling 4 |
| RNA binding motif protein 22 |
| ribosomal protein L7 |
| glutamate decarboxylase 1 |
| delta/notch-like EGF repeat containing |
| ubiquitin-like modifier activating enzyme 1 |
| synaptic vesicle glycoprotein 2a |
| SPARC/osteonectin, cwcv and kazal like domains proteoglycan 3 |
| -- |
| potassium voltage-gated channel interacting protein 1 |
| POM121 transmembrane nucleoporin |
| solute carrier family 32 member 1 |
| BRX1, biogenesis of ribosomes |
| nucleic acid binding protein 1 |
| neuropilin and tolloid like 1 |
| prepronociceptin |
| neurexophilin 1 |
| DEAF1 transcription factor |
| ankyrin repeat domain 34B |
| pyruvate dehydrogenase complex, component X |
| vascular endothelial growth factor B |
| sideroflexin 5 |
| potassium voltage-gated channel subfamily A member regulatory beta subunit 1 |
| insulin-like growth factor binding protein 4 |

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| 1 | |
| 2 | exostosin-like glycosyltransferase 2 |
| 3 | cold shock domain containing C2 |
| 4 | solute carrier family 38, member 1 |
| 5 | solute carrier family 17 member 5 |
| 6 | structural maintenance of chromosomes 3 |
| 7 | ATP5S-like |
| 8 | syntaxin binding protein 6 |
| 9 | NIMA-related kinase 7 |
| 10 | V-set and transmembrane domain containing 2A |
| 11 | -- |
| 12 | ORMDL sphingolipid biosynthesis regulator 3 |
| 13 | ubiquitin specific peptidase 13 |
| 14 | glutamate ionotropic receptor AMPA type subunit 4 |
| 15 | MYST/Esa1-associated factor 6 |
| 16 | caspase 9 |
| 17 | wingless-type MMTV integration site family, member 7A |
| 18 | nuclear transcription factor, X-box binding 1 |
| 19 | family with sequence similarity 210, member A |
| 20 | sirtuin 5 |
| 21 | ELAV like RNA binding protein 2 |
| 22 | calcium/calmodulin-dependent protein kinase II delta |
| 23 | LETM1 domain containing 1 |
| 24 | adaptor-related protein complex 1, sigma 2 subunit |
| 25 | trans-golgi network protein 2 |
| 26 | Ly6/neurotoxin 1 |
| 27 | mediator complex subunit 4 |
| 28 | solute carrier family 6 member 1 |
| 29 | cellular repressor of E1A-stimulated genes 1 |
| 30 | LanC like 1 |
| 31 | teneurin transmembrane protein 3 |
| 32 | 5'-nucleotidase, cytosolic IIIB |
| 33 | Purkinje cell protein 4-like 1 |
| 34 | zinc finger protein 385D |
| 35 | alanyl-tRNA synthetase domain containing 1 |
| 36 | ubiquitin family domain containing 1 |
| 37 | neuraminidase 2 |
| 38 | ribosomal protein S19 binding protein 1 |
| 39 | contactin associated protein-like 4 |
| 40 | tubulin, gamma 2 |
| 41 | RAB3B, member RAS oncogene family |
| 42 | paraneoplastic Ma antigen family-like 2 |
| 43 | glycine receptor, beta |
| 44 | thiosulfate sulfurtransferase (rhodanese)-like domain containing 3 |
| 45 | solute carrier family 16 member 1 |
| 46 | -- |
| 47 | partner of NOB1 homolog |
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| adaptor-related protein complex 4, sigma 1 subunit |
| ring finger protein 10 |
| RAN GTPase activating protein 1 |
| leucine rich repeat transmembrane neuronal 1 |
| -- |
| lectin, mannose-binding 2 |
| similar to RIKEN cDNA C030006K11 |
| antagonist of mitotic exit network 1 homolog |
| limb bud and heart development |
| methyl-CpG binding domain protein 3 |
| TCF3 (E2A) fusion partner |
| -- |
| -- |
| RAN binding protein 6 |
| zinc finger CCCH-type and G-patch domain containing |
| developmentally regulated GTP binding protein 1 |
| mucoilin 1 |
| ATP/GTP binding protein 1 |
| diacylglycerol kinase, delta |
| sphingomyelin synthase 1 |
| aristaless related homeobox |
| ATP binding cassette subfamily B member 9 |
| coiled-coil domain containing 115 |
| centrosomal protein 120 |
| cyclin-dependent kinase 10 |
| eukaryotic translation initiation factor 2 subunit gamma |
| staufen double-stranded RNA binding protein 2 |
| beta-secretase 1 |
| family with sequence similarity 189, member A2 |
| solute carrier family 2 member 13 |
| testin LIM domain protein |
| similar to ENSANGP00000021391 |
| ribonuclease P/MRP 25 subunit |
| -- |
| -- |
| zinc finger, DHHC-type containing 9 |
| ELMO domain containing 3 |
| plexin domain containing 2 |
| -- |
| RAS p21 protein activator 1 |
| 2-phosphoxylose phosphatase 1 |
| similar to RIKEN cDNA 2400010D15 |
| chloride voltage-gated channel 4 |
| tetratricopeptide repeat domain 5 |
| double PHD fingers 1 |
| solute carrier family 25 member 25 |

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| 1 | |
| 2 | PHD finger protein 5A |
| 3 | zinc finger, C2HC-type containing 1A |
| 4 | transmembrane protein 115 |
| 5 | phosphatidylinositol 4-kinase alpha |
| 6 | ARP6 actin-related protein 6 homolog |
| 7 | endonuclease domain containing 1 |
| 8 | family with sequence similarity 13, member B |
| 9 | mitochondrial ribosomal protein S30 |
| 10 | ceramide-1-phosphate transfer protein |
| 11 | apoptosis inducing factor, mitochondria associated 1 |
| 12 | nucleotide binding protein 1 |
| 13 | zinc finger protein 148 |
| 14 | HECT domain E3 ubiquitin protein ligase 2 |
| 15 | solute carrier family 2 member 8 |
| 16 | nucleoporin 62 |
| 17 | pitrilysin metalloproteinase 1 |
| 18 | -- |
| 19 | mitochondrial ribosomal protein L19 |
| 20 | A-kinase anchoring protein 2 |
| 21 | acyl-CoA oxidase 1 |
| 22 | cornichon family AMPA receptor auxiliary protein 4 |
| 23 | sterile alpha motif domain containing 10 |
| 24 | DNA fragmentation factor subunit alpha |
| 25 | beta-1, 4-galactosyltransferase 7 |
| 26 | forkhead box J3 |
| 27 | hyperpolarization-activated cyclic nucleotide-gated potassium channel 3 |
| 28 | base methyltransferase of 25S rRNA 2 homolog |
| 29 | solute carrier family 35, member G2 |
| 30 | interleukin 6 signal transducer |
| 31 | coiled-coil domain containing 50 |
| 32 | RAS guanyl releasing protein 2 |
| 33 | protein phosphatase 6, catalytic subunit |
| 34 | PRELI domain containing 3A |
| 35 | family with sequence similarity 229, member B |
| 36 | Pentatricopeptide repeat domain 3 |
| 37 | gamma-aminobutyric acid type A receptor gamma 2 subunit |
| 38 | protein phosphatase 2, regulatory subunit B', delta |
| 39 | mitochondrial ribosomal protein S7 |
| 40 | solute carrier family 37 member 4 |
| 41 | rabphilin 3A |
| 42 | adenosylhomocysteinase |
| 43 | catenin delta 2 |
| 44 | -- |
| 45 | peroxisomal biogenesis factor 2 |
| 46 | intraflagellar transport 52 |
| 47 | mannosidase, alpha, class 2A, member 2 |

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| megakaryocyte-associated tyrosine kinase |
| 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase |
| hypothetical protein LOC680039 |
| polypeptide N-acetylgalactosaminyltransferase-like 6 |
| aryl hydrocarbon receptor nuclear translocator 2 |
| 3-hydroxyisobutyrate dehydrogenase |
| family with sequence similarity 213, member A |
| solute carrier family 39, member 11 |
| importin 7 |
| mannosyl (beta-1, 4-)-glycoprotein beta-1, 4-N-acetylglucosaminyltransferase |
| solute carrier organic anion transporter family, member 3a1 |
| autophagy related 16-like 1 |
| CDP-diacylglycerol synthase 2 |
| G protein subunit gamma 7 |
| drebrin-like |
| solute carrier family 7 member 3 |
| activating transcription factor 6 beta |
| ELAV like RNA binding protein 4 |
| RAD23 homolog A, nucleotide excision repair protein |
| HD domain containing 3 |
| glyceronephosphate O-acyltransferase |
| thiamine triphosphatase |
| -- |
| valosin containing protein lysine methyltransferase |
| leucine-rich repeat LGI family, member 2 |
| transcriptional adaptor 1 |
| penta-EF hand domain containing 1 |
| THO complex 3 |
| claudin 12 |
| microfibrillar-associated protein 3-like |
| cleavage and polyadenylation specific factor 6 |
| ATP-binding cassette, subfamily B (MDR/TAP), member 6 |
| family with sequence similarity 98, member C |
| zinc finger protein 68 |
| tubulin folding cofactor D |
| TP53 induced glycolysis regulatory phosphatase |
| neurofilament, medium polypeptide |
| F-box and leucine-rich repeat protein 5 |
| DNA polymerase delta interacting protein 2 |
| golgin A5 |
| malonyl-CoA decarboxylase |
| solute carrier family 38, member 7 |
| apoptosis-associated tyrosine kinase |
| Coenzyme A synthase |
| potassium voltage-gated channel subfamily A member 2 |
| XPC complex subunit, DNA damage recognition and repair factor |

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|----|---|
| 1 | |
| 2 | DEAD-box helicase 23 |
| 3 | phosphoribosylglycinamide formyltransferase |
| 4 | Rap guanine nucleotide exchange factor 4 |
| 5 | ring finger protein 145 |
| 6 | asparagine synthetase domain containing 1 |
| 7 | ST8 alpha-N-acetyl-neuraminide alpha-2, 8-sialyltransferase 3 |
| 8 | ubiquitin-conjugating enzyme E2F (putative) |
| 9 | peroxisomal biogenesis factor 11 beta |
| 10 | aspartylglucosaminidase |
| 11 | ATP synthase mitochondrial F1 complex assembly factor 1 |
| 12 | Ras-like without CAAX 1 |
| 13 | -- |
| 14 | small integral membrane protein 20 |
| 15 | cyclin C |
| 16 | cleavage stimulation factor subunit 1 |
| 17 | mitochondrial fission process 1 |
| 18 | neurensin 1 |
| 19 | lysophosphatidylglycerol acyltransferase 1 |
| 20 | erb-b2 receptor tyrosine kinase 4 |
| 21 | N(alpha)-acetyltransferase 10, NatA catalytic subunit |
| 22 | B-cell receptor-associated protein 29 |
| 23 | small glutamine rich tetratricopeptide repeat containing beta |
| 24 | hypothetical LOC317456 |
| 25 | chromatin target of PRMT1 |
| 26 | protein tyrosine phosphatase, receptor type, A |
| 27 | matrix metalloproteinase 16 |
| 28 | diphosphoinositol pentakisphosphate kinase 2 |
| 29 | MAF bZIP transcription factor B |
| 30 | Aly/REF export factor |
| 31 | adenylate cyclase 3 |
| 32 | solute carrier family 35, member A4 |
| 33 | branched chain ketoacid dehydrogenase E1, alpha polypeptide |
| 34 | ELKS/RAB6-interacting/CAST family member 1 |
| 35 | serine threonine kinase 39 |
| 36 | -- |
| 37 | -- |
| 38 | inosine monophosphate dehydrogenase 1 |
| 39 | cell migration-inducing hyaluronan binding protein |
| 40 | ring finger protein 149 |
| 41 | BCL2 associated X, apoptosis regulator |
| 42 | -- |
| 43 | similar to RIKEN cDNA 3110043O21 |
| 44 | succinate dehydrogenase complex assembly factor 3 |
| 45 | catenin alpha 2 |
| 46 | phenylalanyl-tRNA synthetase, alpha subunit |
| 47 | mannosyl (alpha-1, 6-)-glycoprotein beta-1, 2-N-acetylglucosaminyltransferase |

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| transmembrane protein adipocyte associated 1 |
| cell cycle progression 1 |
| mannosyl (alpha-1, 6-)-glycoprotein beta-1, 6-N-acetyl-glucosaminyltransferase, isozyme B |
| interleukin-1 receptor-associated kinase 1 binding protein 1 |
| similar to RIKEN cDNA 1810030O07 |
| N-methylpurine-DNA glycosylase |
| tyrosylprotein sulfotransferase 1 |
| neuroligin 3 |
| galactosidase, beta 1 |
| checkpoint with forkhead and ring finger domains |
| RWD domain containing 4 |
| ganglioside-induced differentiation-associated protein 1-like 1 |
| deoxyguanosine kinase |
| -- |
| nucleosome assembly protein 1-like 5 |
| inositol-tetrakisphosphate 1-kinase |
| polyribonucleotide nucleotidyltransferase 1 |
| neurexin 3 |
| -- |
| -- |
| glutamate decarboxylase 2 |
| gamma-aminobutyric acid type A receptor delta subunit |
| dimethylarginine dimethylaminohydrolase 1 |
| TOP1 binding arginine/serine rich protein |
| HERPUD family member 2 |
| adaptor-related protein complex 1 associated regulatory protein |
| ribosomal protein L5 |
| sodium voltage-gated channel alpha subunit 1 |
| -- |
| -- |
| NOP56 ribonucleoprotein |
| annexin A6 |
| LDL receptor related protein 1 |
| -- |
| somatostatin |
| transmembrane 6 superfamily member 1 |
| histone deacetylase 5 |
| spire-type actin nucleation factor 1 |
| -- |
| -- |
| golgi associated, gamma adaptin ear containing, ARF binding protein 3 |
| family with sequence similarity 69, member B |
| bolA family member 3 |
| family with sequence similarity 69, member A |
| astrotactin 1 |
| defective in cullin neddylation 1 domain containing 5 |

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| 1 | |
| 2 | -- |
| 3 | -- |
| 4 | -- |
| 5 | -- |
| 6 | dispatched RND transporter family member 2 |
| 7 | complexin 1 |
| 8 | VGF nerve growth factor inducible |
| 9 | receptor accessory protein 5 |
| 10 | receptor accessory protein 5 |
| 11 | kinesin light chain 2 |
| 12 | kinesin light chain 2 |
| 13 | ATPase Na ⁺ /K ⁺ transporting subunit alpha 3 |
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For Peer Review

List of the 219 Regulated Genes (Fold-change ≥ 1 ,

| FAST DB STABLE ID | Gene Symbol | Regulation | Fold-Change |
|-------------------|-------------|------------|-------------|
| GSRG0021091 | Nrsn2 | up | 1022.12 |
| GSRG0025694 | Igsf21 | up | 40.67 |
| GSRG0016369 | Lxn | up | 39.79 |
| GSRG0006002 | Arf2 | up | 37.47 |
| GSRG0024955 | Slc24a2 | up | 24.11 |
| GSRG0024695 | Maged2 | up | 22.83 |
| GSRG0003565 | -- | up | 11.61 |
| GSRG0008871 | -- | down | 2563.68 |
| GSRG0006308 | Kcnip1 | down | 2147.92 |
| GSRG0036252 | Brix1 | down | 1735.13 |
| GSRG0032304 | Nabp1 | down | 1532.74 |
| GSRG0013907 | Tmed7 | down | 1420.91 |
| GSRG0023056 | Sfxn5 | down | 1281.68 |
| GSRG0015402 | Kcnab1 | down | 1273.14 |
| GSRG0029606 | Rangap1 | down | 1223.71 |
| GSRG0026087 | Gphn | down | 1005.02 |
| GSRG0000412 | Atp5sl | down | 924.05 |
| GSRG0031867 | Slc17a5 | down | 921.18 |
| GSRG0002264 | Smc3 | down | 907.22 |
| GSRG0026695 | Stxbp6 | down | 877.43 |
| GSRG0009858 | Nek7 | down | 874.10 |
| GSRG0015289 | Usp13 | down | 827.85 |
| GSRG0006796 | Ormdl3 | down | 747.37 |
| GSRG0024467 | Casp9 | down | 713.66 |
| GSRG0001557 | Pak1 | down | 669.55 |
| GSRG0023378 | Tmf1 | down | 667.03 |
| GSRG0014272 | Fam210a | down | 664.42 |
| GSRG0015089 | Ankrd34b | down | 637.92 |
| GSRG0013826 | Syt4 | down | 636.29 |
| GSRG0006408 | Anxa6 | down | 623.90 |
| GSRG0015701 | Camk2d | down | 617.64 |
| GSRG0020611 | Madd | down | 602.83 |
| GSRG0019603 | Rtf1 | down | 598.47 |
| GSRG0028286 | Letmd1 | down | 591.24 |
| GSRG0026756 | Trim9 | down | 571.23 |
| GSRG0034068 | Dlg3 | down | 541.81 |
| GSRG0006834 | Nt5c3b | down | 500.57 |
| GSRG0006333 | Ublcp1 | down | 496.12 |
| GSRG0002210 | Cnnm1 | down | 418.62 |
| GSRG0029946 | -- | down | 415.29 |
| GSRG0003193 | Mrps12 | down | 393.42 |

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|----|-------------|------------|------|--------|
| 1 | | | | |
| 2 | GSRG0007941 | Pdgfa | down | 385.80 |
| 3 | GSRG0015615 | Slc16a1 | down | 376.89 |
| 4 | GSRG0010809 | Pno1 | down | 362.70 |
| 5 | GSRG0032455 | Atg16l1 | down | 360.38 |
| 6 | GSRG0012470 | Lman2 | down | 354.73 |
| 7 | GSRG0018406 | LOC294154 | down | 354.12 |
| 8 | GSRG0021713 | Tpra1 | down | 349.96 |
| 9 | GSRG0022714 | Wasl | down | 341.04 |
| 10 | GSRG0003572 | -- | down | 323.93 |
| 11 | GSRG0020828 | Pcna | down | 302.49 |
| 12 | GSRG0010144 | Fam69a | down | 292.68 |
| 13 | GSRG0026692 | Lrrn3 | down | 292.38 |
| 14 | GSRG0026548 | Fbxo11 | down | 289.98 |
| 15 | GSRG0028324 | Pde1b | down | 285.84 |
| 16 | GSRG0005300 | Rnf145 | down | 284.77 |
| 17 | GSRG0026127 | Dnal1 | down | 282.98 |
| 18 | GSRG0005807 | Casc3 | down | 282.65 |
| 19 | GSRG0004958 | Sgms1 | down | 281.14 |
| 20 | GSRG0024716 | Pnrc1 | down | 278.81 |
| 21 | GSRG0032237 | Ccdc115 | down | 275.44 |
| 22 | GSRG0013915 | Cep120 | down | 273.05 |
| 23 | GSRG0005434 | Gid4 | down | 267.63 |
| 24 | GSRG0030255 | Pdcd7 | down | 261.25 |
| 25 | GSRG0004821 | Vegfb | down | 258.33 |
| 26 | GSRG0034650 | Eif2s3 | down | 256.91 |
| 27 | GSRG0012479 | Nop16 | down | 254.91 |
| 28 | GSRG0004927 | Fam189a2 | down | 251.86 |
| 29 | GSRG0026146 | Eif2b2 | down | 251.26 |
| 30 | GSRG0030119 | Bace1 | down | 250.51 |
| 31 | GSRG0024519 | Cep104 | down | 244.42 |
| 32 | GSRG0005298 | Pwwp2a | down | 242.45 |
| 33 | GSRG0013170 | Gadd45g | down | 236.92 |
| 34 | GSRG0004850 | Asrgl1 | down | 235.95 |
| 35 | GSRG0001855 | Ptpre | down | 235.52 |
| 36 | GSRG0014470 | Brd7 | down | 235.43 |
| 37 | GSRG0027665 | Slc6a15 | down | 233.04 |
| 38 | GSRG0010351 | Slbp | down | 229.80 |
| 39 | GSRG0004860 | Dagla | down | 227.58 |
| 40 | GSRG0008011 | Sbds | down | 227.44 |
| 41 | GSRG0031432 | RGD1309779 | down | 227.29 |
| 42 | GSRG0008817 | Kdelr2 | down | 226.12 |
| 43 | GSRG0010061 | Adss | down | 223.40 |
| 44 | GSRG0035015 | -- | down | 219.17 |
| 45 | GSRG0032126 | -- | down | 209.91 |
| 46 | GSRG0015813 | Rasa1 | down | 202.09 |
| 47 | GSRG0013521 | RGD1311805 | down | 200.19 |

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|----|-------------|------------|------|--------|
| 1 | | | | |
| 2 | GSRG0024724 | RGD1359108 | down | 195.18 |
| 3 | GSRG0026028 | Atf1 | down | 194.67 |
| 4 | GSRG0011004 | Fgf9 | down | 194.30 |
| 5 | GSRG0020273 | Slc25a25 | down | 194.00 |
| 6 | GSRG0026364 | Golga5 | down | 192.29 |
| 7 | GSRG0029609 | Phf5a | down | 192.09 |
| 8 | GSRG0019511 | Chst1 | down | 190.79 |
| 9 | GSRG0025971 | Dgkb | down | 188.90 |
| 10 | GSRG0000549 | Nup62 | down | 187.53 |
| 11 | GSRG0023498 | Kcna1 | down | 185.65 |
| 12 | GSRG0018780 | Slc4a10 | down | 184.78 |
| 13 | GSRG0021290 | Actr3b | down | 178.53 |
| 14 | GSRG0013015 | Prr7 | down | 178.51 |
| 15 | GSRG0036082 | Fam13b | down | 178.06 |
| 16 | GSRG0020402 | Scn1a | down | 178.03 |
| 17 | GSRG0015143 | Il6st | down | 177.77 |
| 18 | GSRG0013016 | Grk6 | down | 177.47 |
| 19 | GSRG0001944 | Chka | down | 174.57 |
| 20 | GSRG0034878 | Aifm1 | down | 174.32 |
| 21 | GSRG0029295 | Fam49b | down | 167.07 |
| 22 | GSRG0018818 | Rapgef4 | down | 166.62 |
| 23 | GSRG0014335 | Csnk2a2 | down | 165.63 |
| 24 | GSRG0004194 | Slco3a1 | down | 165.07 |
| 25 | GSRG0009020 | -- | down | 163.99 |
| 26 | GSRG0022959 | Mrpl19 | down | 162.48 |
| 27 | GSRG0009785 | Insig2 | down | 160.15 |
| 28 | GSRG0005047 | Slit1 | down | 157.60 |
| 29 | GSRG0006992 | Acox1 | down | 155.77 |
| 30 | GSRG0036591 | Akap2 | down | 154.70 |
| 31 | GSRG0020103 | Cstf1 | down | 152.08 |
| 32 | GSRG0020147 | Zgpat | down | 151.97 |
| 33 | GSRG0012186 | Map1s | down | 151.54 |
| 34 | GSRG0004212 | Ap3s2 | down | 142.31 |
| 35 | GSRG0022691 | Bmt2 | down | 140.13 |
| 36 | GSRG0034712 | Taf9b | down | 137.16 |
| 37 | GSRG0029711 | Yaf2 | down | 135.13 |
| 38 | GSRG0012252 | Aga | down | 132.61 |
| 39 | GSRG0027340 | Akt1 | down | 129.95 |
| 40 | GSRG0001542 | Rab30 | down | 129.84 |
| 41 | GSRG0028164 | Sgsm3 | down | 129.60 |
| 42 | GSRG0029703 | Chkb | down | 125.36 |
| 43 | GSRG0011756 | Gtf2f2 | down | 122.78 |
| 44 | GSRG0007154 | Cmss1 | down | 116.84 |
| 45 | GSRG0015802 | Nr2f1 | down | 116.33 |
| 46 | GSRG0031919 | Pxylp1 | down | 112.54 |
| 47 | GSRG0011159 | Pcca | down | 111.90 |

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| 1 | | | | |
| 2 | GSRG0034673 | Pdzd11 | down | 109.42 |
| 3 | GSRG0005814 | Rara | down | 105.12 |
| 4 | GSRG0005237 | Gng13 | down | 102.58 |
| 5 | GSRG0006464 | Tom1l2 | down | 101.53 |
| 6 | GSRG0001964 | mrpl11 | down | 99.93 |
| 7 | GSRG0006465 | Atpaf2 | down | 98.56 |
| 8 | GSRG0029944 | Icam5 | down | 96.81 |
| 9 | GSRG0012881 | -- | down | 92.98 |
| 10 | GSRG0003583 | -- | down | 91.01 |
| 11 | GSRG0032238 | Bend6 | down | 90.99 |
| 12 | GSRG0005137 | -- | down | 90.49 |
| 13 | GSRG0017318 | Pdxk | down | 90.44 |
| 14 | GSRG0009616 | Tada1 | down | 86.62 |
| 15 | GSRG0009893 | Smg7 | down | 79.67 |
| 16 | GSRG0008780 | Rasl11a | down | 77.64 |
| 17 | GSRG0005815 | Igfbp4 | down | 74.00 |
| 18 | GSRG0036647 | Nosip | down | 73.65 |
| 19 | GSRG0034327 | Bhlhb9 | down | 72.67 |
| 20 | GSRG0025396 | Prpf38a | down | 72.15 |
| 21 | GSRG0013285 | Pak1ip1 | down | 71.70 |
| 22 | GSRG0021769 | Thumpd3 | down | 70.38 |
| 23 | GSRG0016414 | Dclk2 | down | 69.13 |
| 24 | GSRG0025430 | Plk3 | down | 68.09 |
| 25 | GSRG0022886 | Elmod3 | down | 66.80 |
| 26 | GSRG0034842 | Sept6 | down | 66.00 |
| 27 | GSRG0012489 | -- | down | 64.35 |
| 28 | GSRG0032175 | Polr1c | down | 63.12 |
| 29 | GSRG0002132 | Vldlr | down | 61.87 |
| 30 | GSRG0024721 | Smim8 | down | 61.56 |
| 31 | GSRG0009488 | Ivns1abp | down | 61.03 |
| 32 | GSRG0021376 | Phf14 | down | 61.00 |
| 33 | GSRG0008927 | Bcl7b | down | 60.65 |
| 34 | GSRG0006229 | Pdpk1 | down | 58.94 |
| 35 | GSRG0025868 | Slc30a3 | down | 56.58 |
| 36 | GSRG0032334 | Abi2 | down | 55.42 |
| 37 | GSRG0011056 | Lgi3 | down | 55.22 |
| 38 | GSRG0012042 | Brf2 | down | 54.53 |
| 39 | GSRG0006957 | Slc39a11 | down | 52.76 |
| 40 | GSRG0026573 | Galnt14 | down | 52.55 |
| 41 | GSRG0002105 | -- | down | 50.44 |
| 42 | GSRG0025906 | Pum2 | down | 50.09 |
| 43 | GSRG0002539 | Ccdc127 | down | 48.96 |
| 44 | GSRG0013947 | Fech | down | 48.66 |
| 45 | GSRG0024731 | Topors | down | 48.46 |
| 46 | GSRG0021119 | Pigu | down | 48.26 |
| 47 | GSRG0010906 | Fbxo34 | down | 46.96 |

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|----|-------------|----------|------|-------|
| 1 | | | | |
| 2 | GSRG0028792 | Rap1b | down | 43.78 |
| 3 | GSRG0000541 | Syt3 | down | 43.16 |
| 4 | GSRG0001487 | Aen | down | 42.54 |
| 5 | GSRG0028309 | Pcbp2 | down | 41.90 |
| 6 | GSRG0004453 | Btbd10 | down | 41.75 |
| 7 | GSRG0000414 | Exosc5 | down | 41.61 |
| 8 | GSRG0020224 | Fam163b | down | 41.27 |
| 9 | GSRG0013662 | Csnk1g3 | down | 40.80 |
| 10 | GSRG0021118 | Ahcy | down | 39.94 |
| 11 | GSRG0005277 | -- | down | 39.61 |
| 12 | GSRG0026808 | Dhrs7 | down | 39.57 |
| 13 | GSRG0032934 | Fam168b | down | 37.19 |
| 14 | GSRG0030373 | Ccp1 | down | 37.02 |
| 15 | GSRG0026659 | Trappc12 | down | 36.28 |
| 16 | GSRG0020063 | Dnttip1 | down | 35.11 |
| 17 | GSRG0025607 | -- | down | 34.58 |
| 18 | GSRG0021286 | Ube3c | down | 33.34 |
| 19 | GSRG0028144 | Cby1 | down | 31.86 |
| 20 | GSRG0017401 | Lrrtm3 | down | 31.37 |
| 21 | GSRG0031993 | -- | down | 30.61 |
| 22 | GSRG0013749 | Pias2 | down | 30.38 |
| 23 | GSRG0003276 | Uri1 | down | 29.78 |
| 24 | GSRG0029611 | Polr3h | down | 29.76 |
| 25 | GSRG0008019 | Psph | down | 29.54 |
| 26 | GSRG0036721 | Tes | down | 29.18 |
| 27 | GSRG0031922 | Clstn2 | down | 29.18 |
| 28 | GSRG0019760 | -- | down | 28.83 |
| 29 | GSRG0030208 | Rpp25 | down | 26.98 |
| 30 | GSRG0012951 | Plxdc2 | down | 26.15 |
| 31 | GSRG0007991 | Pom121 | down | 25.35 |
| 32 | GSRG0023827 | Pthlh | down | 24.98 |
| 33 | GSRG0010011 | Pcp4l1 | down | 21.85 |
| 34 | GSRG0008075 | Rph3a | down | 21.10 |
| 35 | GSRG0005383 | Gria1 | down | 20.98 |
| 36 | GSRG0005636 | Pigs | down | 19.72 |
| 37 | GSRG0015889 | Kif2a | down | 17.61 |
| 38 | GSRG0003245 | Scn1b | down | 14.98 |
| 39 | GSRG0000359 | Pnmal2 | down | 14.82 |
| 40 | GSRG0036149 | Ncam2 | down | 14.75 |
| 41 | GSRG0028182 | Csdc2 | down | 13.52 |
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4 **,5; P-Value ≤ 0,05) - G/**
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| P-Value | Adjusted P-Value |
|----------|------------------|
| 7.94E-05 | 1.21E-02 |
| 3.62E-02 | 2.71E-01 |
| 3.83E-02 | 2.79E-01 |
| 1.90E-02 | 1.90E-01 |
| 3.02E-02 | 2.46E-01 |
| 3.36E-02 | 2.61E-01 |
| 2.11E-02 | 2.00E-01 |
| 1.39E-09 | 1.03E-05 |
| 2.58E-08 | 4.79E-05 |
| 9.29E-06 | 3.45E-03 |
| 1.10E-05 | 3.87E-03 |
| 1.80E-08 | 4.45E-05 |
| 9.55E-07 | 1.01E-03 |
| 1.25E-06 | 1.16E-03 |
| 5.56E-09 | 2.06E-05 |
| 2.79E-07 | 4.15E-04 |
| 3.61E-06 | 1.93E-03 |
| 8.06E-05 | 1.21E-02 |
| 8.59E-05 | 1.23E-02 |
| 3.85E-06 | 1.93E-03 |
| 4.95E-06 | 2.30E-03 |
| 2.49E-05 | 6.84E-03 |
| 8.29E-05 | 1.21E-02 |
| 1.49E-04 | 1.68E-02 |
| 3.91E-06 | 1.93E-03 |
| 2.57E-06 | 1.91E-03 |
| 1.83E-04 | 1.86E-02 |
| 5.51E-06 | 2.41E-03 |
| 7.58E-07 | 9.38E-04 |
| 7.20E-06 | 2.81E-03 |
| 3.31E-05 | 7.92E-03 |
| 1.36E-05 | 4.60E-03 |
| 2.28E-06 | 1.88E-03 |
| 3.11E-05 | 7.92E-03 |
| 3.91E-06 | 1.93E-03 |
| 6.75E-06 | 2.78E-03 |
| 4.87E-05 | 9.27E-03 |
| 3.80E-06 | 1.93E-03 |
| 7.41E-05 | 1.20E-02 |
| 1.85E-04 | 1.86E-02 |
| 2.33E-05 | 6.65E-03 |

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| 1.97E-05 | 6.10E-03 |
| 3.34E-04 | 2.56E-02 |
| 2.90E-04 | 2.46E-02 |
| 1.68E-04 | 1.80E-02 |
| 2.60E-04 | 2.27E-02 |
| 3.92E-05 | 8.09E-03 |
| 6.20E-04 | 3.13E-02 |
| 3.88E-05 | 8.09E-03 |
| 2.11E-04 | 2.01E-02 |
| 4.10E-05 | 8.22E-03 |
| 5.94E-05 | 1.00E-02 |
| 6.68E-05 | 1.10E-02 |
| 4.77E-05 | 9.27E-03 |
| 6.42E-04 | 3.20E-02 |
| 1.20E-04 | 1.50E-02 |
| 2.47E-04 | 2.21E-02 |
| 1.84E-04 | 1.86E-02 |
| 7.29E-04 | 3.43E-02 |
| 5.60E-05 | 9.66E-03 |
| 5.39E-04 | 3.01E-02 |
| 5.18E-04 | 2.93E-02 |
| 5.15E-04 | 2.93E-02 |
| 2.42E-04 | 2.21E-02 |
| 3.77E-05 | 8.09E-03 |
| 3.38E-04 | 2.56E-02 |
| 2.09E-05 | 6.21E-03 |
| 5.52E-04 | 3.03E-02 |
| 4.59E-04 | 2.79E-02 |
| 6.12E-04 | 3.13E-02 |
| 1.83E-04 | 1.86E-02 |
| 7.81E-04 | 3.51E-02 |
| 5.18E-05 | 9.61E-03 |
| 3.27E-04 | 2.56E-02 |
| 1.20E-04 | 1.50E-02 |
| 3.00E-04 | 2.46E-02 |
| 1.44E-04 | 1.65E-02 |
| 1.21E-04 | 1.50E-02 |
| 2.47E-04 | 2.21E-02 |
| 2.33E-04 | 2.16E-02 |
| 7.70E-04 | 3.50E-02 |
| 1.42E-04 | 1.64E-02 |
| 2.50E-04 | 2.21E-02 |
| 1.29E-03 | 4.52E-02 |
| 3.96E-04 | 2.63E-02 |
| 1.51E-03 | 4.81E-02 |
| 1.12E-03 | 4.16E-02 |

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| 1 | | |
| 2 | 7.16E-04 | 3.41E-02 |
| 3 | 6.04E-04 | 3.13E-02 |
| 4 | 5.93E-04 | 3.13E-02 |
| 5 | 1.63E-03 | 5.00E-02 |
| 6 | 1.20E-03 | 4.31E-02 |
| 7 | 1.04E-03 | 4.12E-02 |
| 8 | 3.53E-04 | 2.62E-02 |
| 9 | 2.98E-04 | 2.46E-02 |
| 10 | 1.46E-03 | 4.76E-02 |
| 11 | 6.33E-04 | 3.18E-02 |
| 12 | 4.07E-04 | 2.63E-02 |
| 13 | 6.56E-04 | 3.25E-02 |
| 14 | 2.77E-04 | 2.39E-02 |
| 15 | 1.93E-03 | 5.50E-02 |
| 16 | 2.01E-04 | 1.96E-02 |
| 17 | 1.90E-03 | 5.50E-02 |
| 18 | 6.08E-04 | 3.13E-02 |
| 19 | 3.85E-04 | 2.63E-02 |
| 20 | 1.36E-03 | 4.59E-02 |
| 21 | 4.97E-04 | 2.88E-02 |
| 22 | 1.32E-03 | 4.57E-02 |
| 23 | 1.25E-03 | 4.42E-02 |
| 24 | 1.93E-03 | 5.50E-02 |
| 25 | 1.35E-03 | 4.57E-02 |
| 26 | 1.48E-03 | 4.79E-02 |
| 27 | 7.67E-04 | 3.50E-02 |
| 28 | 1.35E-03 | 4.57E-02 |
| 29 | 2.55E-03 | 6.05E-02 |
| 30 | 2.82E-03 | 6.36E-02 |
| 31 | 2.64E-03 | 6.14E-02 |
| 32 | 2.68E-03 | 6.18E-02 |
| 33 | 1.12E-03 | 4.16E-02 |
| 34 | 1.08E-03 | 4.16E-02 |
| 35 | 3.30E-03 | 6.95E-02 |
| 36 | 1.09E-03 | 4.16E-02 |
| 37 | 1.34E-03 | 4.57E-02 |
| 38 | 3.50E-03 | 7.14E-02 |
| 39 | 1.16E-03 | 4.27E-02 |
| 40 | 1.94E-03 | 5.50E-02 |
| 41 | 1.18E-03 | 4.29E-02 |
| 42 | 2.31E-03 | 5.82E-02 |
| 43 | 4.99E-03 | 8.63E-02 |
| 44 | 4.51E-03 | 8.13E-02 |
| 45 | 3.17E-03 | 6.77E-02 |
| 46 | 5.71E-03 | 9.16E-02 |
| 47 | 1.97E-03 | 5.50E-02 |
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| 3.09E-03 | 6.68E-02 |
| 1.39E-03 | 4.61E-02 |
| 2.43E-03 | 5.92E-02 |
| 3.48E-03 | 7.13E-02 |
| 2.73E-03 | 6.22E-02 |
| 3.82E-03 | 7.53E-02 |
| 3.35E-03 | 6.98E-02 |
| 6.87E-03 | 1.04E-01 |
| 4.52E-03 | 8.13E-02 |
| 1.62E-03 | 5.00E-02 |
| 3.75E-03 | 7.47E-02 |
| 4.68E-03 | 8.28E-02 |
| 9.75E-03 | 1.28E-01 |
| 1.00E-02 | 1.30E-01 |
| 4.51E-03 | 8.13E-02 |
| 1.98E-03 | 5.50E-02 |
| 5.74E-03 | 9.19E-02 |
| 7.47E-03 | 1.09E-01 |
| 7.07E-03 | 1.06E-01 |
| 1.36E-02 | 1.54E-01 |
| 4.46E-03 | 8.11E-02 |
| 1.08E-02 | 1.36E-01 |
| 5.52E-03 | 9.04E-02 |
| 9.95E-03 | 1.30E-01 |
| 6.22E-03 | 9.76E-02 |
| 2.54E-03 | 6.05E-02 |
| 1.67E-02 | 1.75E-01 |
| 1.14E-02 | 1.42E-01 |
| 8.57E-03 | 1.20E-01 |
| 7.51E-03 | 1.10E-01 |
| 5.39E-03 | 9.00E-02 |
| 1.07E-02 | 1.36E-01 |
| 1.28E-02 | 1.52E-01 |
| 5.45E-03 | 9.01E-02 |
| 1.80E-02 | 1.85E-01 |
| 1.77E-02 | 1.83E-01 |
| 2.17E-02 | 2.02E-01 |
| 1.92E-02 | 1.90E-01 |
| 1.46E-02 | 1.62E-01 |
| 1.57E-02 | 1.70E-01 |
| 1.19E-02 | 1.46E-01 |
| 1.60E-02 | 1.71E-01 |
| 2.14E-02 | 2.01E-01 |
| 1.32E-02 | 1.53E-01 |
| 2.29E-02 | 2.07E-01 |
| 1.34E-02 | 1.54E-01 |

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| 1 | | |
| 2 | 2.03E-02 | 1.95E-01 |
| 3 | 1.89E-02 | 1.90E-01 |
| 4 | 2.69E-02 | 2.29E-01 |
| 5 | 2.05E-02 | 1.97E-01 |
| 6 | 2.12E-02 | 2.01E-01 |
| 7 | 2.40E-02 | 2.12E-01 |
| 8 | 2.55E-02 | 2.22E-01 |
| 9 | 1.31E-02 | 1.53E-01 |
| 10 | 2.77E-02 | 2.34E-01 |
| 11 | 1.33E-02 | 1.54E-01 |
| 12 | 2.32E-02 | 2.08E-01 |
| 13 | 3.51E-02 | 2.67E-01 |
| 14 | 2.79E-02 | 2.35E-01 |
| 15 | 3.33E-02 | 2.60E-01 |
| 16 | 3.34E-02 | 2.60E-01 |
| 17 | 3.38E-02 | 2.62E-01 |
| 18 | 3.53E-02 | 2.67E-01 |
| 19 | 4.22E-02 | 2.91E-01 |
| 20 | 3.65E-02 | 2.72E-01 |
| 21 | 2.45E-02 | 2.16E-01 |
| 22 | 3.71E-02 | 2.74E-01 |
| 23 | 4.35E-02 | 2.97E-01 |
| 24 | 3.86E-02 | 2.80E-01 |
| 25 | 4.13E-02 | 2.88E-01 |
| 26 | 3.03E-02 | 2.46E-01 |
| 27 | 3.91E-02 | 2.80E-01 |
| 28 | 3.52E-02 | 2.67E-01 |
| 29 | 3.44E-02 | 2.64E-01 |
| 30 | 4.58E-02 | 3.06E-01 |
| 31 | 9.82E-03 | 1.29E-01 |
| 32 | 3.49E-02 | 2.66E-01 |
| 33 | 4.14E-02 | 2.88E-01 |
| 34 | 1.75E-02 | 1.82E-01 |
| 35 | 2.20E-02 | 2.03E-01 |
| 36 | 3.53E-02 | 2.67E-01 |
| 37 | 4.74E-02 | 3.12E-01 |
| 38 | 2.44E-02 | 2.15E-01 |
| 39 | 4.15E-02 | 2.88E-01 |
| 40 | 4.96E-02 | 3.21E-01 |
| 41 | 3.52E-02 | 2.67E-01 |
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Peer Review

ABA PUR vs GABA CTRL

| Gene Name |
|--|
| neurensin 2 |
| immunoglobulin superfamily, member 21 |
| latexin |
| ADP-ribosylation factor 2 |
| solute carrier family 24 member 2 |
| MAGE family member D2 |
| -- |
| -- |
| potassium voltage-gated channel interacting protein 1 |
| BRX1, biogenesis of ribosomes |
| nucleic acid binding protein 1 |
| transmembrane p24 trafficking protein 7 |
| sideroflexin 5 |
| potassium voltage-gated channel subfamily A member regulatory beta subunit 1 |
| RAN GTPase activating protein 1 |
| gephyrin |
| ATP5S-like |
| solute carrier family 17 member 5 |
| structural maintenance of chromosomes 3 |
| syntaxin binding protein 6 |
| NIMA-related kinase 7 |
| ubiquitin specific peptidase 13 |
| ORMDL sphingolipid biosynthesis regulator 3 |
| caspase 9 |
| p21 (RAC1) activated kinase 1 |
| TATA element modulatory factor 1 |
| family with sequence similarity 210, member A |
| ankyrin repeat domain 34B |
| synaptotagmin 4 |
| annexin A6 |
| calcium/calmodulin-dependent protein kinase II delta |
| MAP-kinase activating death domain |
| Rtf1, Paf1/RNA polymerase II complex component, homolog (S. cerevisiae) |
| LETM1 domain containing 1 |
| tripartite motif-containing 9 |
| discs large MAGUK scaffold protein 3 |
| 5'-nucleotidase, cytosolic IIIB |
| ubiquitin-like domain containing CTD phosphatase 1 |
| cyclin and CBS domain divalent metal cation transport mediator 1 |
| -- |
| mitochondrial ribosomal protein S12 |

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|----|---|
| 1 | |
| 2 | platelet derived growth factor subunit A |
| 3 | solute carrier family 16 member 1 |
| 4 | partner of NOB1 homolog |
| 5 | autophagy related 16-like 1 |
| 6 | lectin, mannose-binding 2 |
| 7 | similar to chromosome 6 open reading frame 106 isoform a |
| 8 | transmembrane protein adipocyte associated 1 |
| 9 | Wiskott-Aldrich syndrome-like |
| 10 | -- |
| 11 | proliferating cell nuclear antigen |
| 12 | family with sequence similarity 69, member A |
| 13 | leucine rich repeat neuronal 3 |
| 14 | F-box protein 11 |
| 15 | phosphodiesterase 1B |
| 16 | ring finger protein 145 |
| 17 | dynein, axonemal, light chain 1 |
| 18 | cancer susceptibility candidate 3 |
| 19 | sphingomyelin synthase 1 |
| 20 | proline-rich nuclear receptor coactivator 1 |
| 21 | coiled-coil domain containing 115 |
| 22 | centrosomal protein 120 |
| 23 | GID complex subunit 4 |
| 24 | programmed cell death 7 |
| 25 | vascular endothelial growth factor B |
| 26 | eukaryotic translation initiation factor 2 subunit gamma |
| 27 | NOP16 nucleolar protein |
| 28 | family with sequence similarity 189, member A2 |
| 29 | eukaryotic translation initiation factor 2B subunit beta |
| 30 | beta-secretase 1 |
| 31 | centrosomal protein 104 |
| 32 | PWWP domain containing 2A |
| 33 | growth arrest and DNA-damage-inducible, gamma |
| 34 | asparaginase like 1 |
| 35 | protein tyrosine phosphatase, receptor type, E |
| 36 | bromodomain containing 7 |
| 37 | solute carrier family 6 member 15 |
| 38 | stem-loop binding protein |
| 39 | diacylglycerol lipase, alpha |
| 40 | SBDS ribosome assembly guanine nucleotide exchange factor |
| 41 | similar to ENSANGP00000021391 |
| 42 | KDEL endoplasmic reticulum protein retention receptor 2 |
| 43 | adenylosuccinate synthase |
| 44 | -- |
| 45 | -- |
| 46 | RAS p21 protein activator 1 |
| 47 | similar to RIKEN cDNA 2400010D15 |

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| similar to RIKEN cDNA 3110043O21 |
| atlastin GTPase 1 |
| fibroblast growth factor 9 |
| solute carrier family 25 member 25 |
| golgin A5 |
| PHD finger protein 5A |
| carbohydrate sulfotransferase 1 |
| diacylglycerol kinase, beta |
| nucleoporin 62 |
| potassium voltage-gated channel subfamily A member 1 |
| solute carrier family 4 member 10 |
| ARP3 actin related protein 3 homolog B |
| proline rich 7 (synaptic) |
| family with sequence similarity 13, member B |
| sodium voltage-gated channel alpha subunit 1 |
| interleukin 6 signal transducer |
| G protein-coupled receptor kinase 6 |
| choline kinase alpha |
| apoptosis inducing factor, mitochondria associated 1 |
| family with sequence similarity 49, member B |
| Rap guanine nucleotide exchange factor 4 |
| casein kinase 2 alpha 2 |
| solute carrier organic anion transporter family, member 3a1 |
| -- |
| mitochondrial ribosomal protein L19 |
| insulin induced gene 2 |
| slit guidance ligand 1 |
| acyl-CoA oxidase 1 |
| A-kinase anchoring protein 2 |
| cleavage stimulation factor subunit 1 |
| zinc finger CCCH-type and G-patch domain containing |
| microtubule-associated protein 1S |
| adaptor-related protein complex 3, sigma 2 subunit |
| base methyltransferase of 25S rRNA 2 homolog |
| TATA-box binding protein associated factor 9b |
| YY1 associated factor 2 |
| aspartylglucosaminidase |
| AKT serine/threonine kinase 1 |
| RAB30, member RAS oncogene family |
| small G protein signaling modulator 3 |
| choline kinase beta |
| general transcription factor IIF subunit 2 |
| cms1 ribosomal small subunit homolog (yeast) |
| nuclear receptor subfamily 2, group F, member 1 |
| 2-phosphoxylose phosphatase 1 |
| propionyl-CoA carboxylase alpha subunit |

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|----|---|
| 1 | |
| 2 | PDZ domain containing 11 |
| 3 | retinoic acid receptor, alpha |
| 4 | G protein subunit gamma 13 |
| 5 | target of myb1 like 2 membrane trafficking protein |
| 6 | mitochondrial ribosomal protein L11 |
| 7 | ATP synthase mitochondrial F1 complex assembly factor 2 |
| 8 | intercellular adhesion molecule 5 |
| 9 | -- |
| 10 | -- |
| 11 | BEN domain containing 6 |
| 12 | -- |
| 13 | pyridoxal (pyridoxine, vitamin B6) kinase |
| 14 | transcriptional adaptor 1 |
| 15 | SMG7 nonsense mediated mRNA decay factor |
| 16 | RAS-like family 11 member A |
| 17 | insulin-like growth factor binding protein 4 |
| 18 | nitric oxide synthase interacting protein |
| 19 | basic helix-loop-helix domain containing, class B, 9 |
| 20 | pre-mRNA processing factor 38A |
| 21 | PAK1 interacting protein 1 |
| 22 | THUMP domain containing 3 |
| 23 | doublecortin-like kinase 2 |
| 24 | polo-like kinase 3 |
| 25 | ELMO domain containing 3 |
| 26 | septin 6 |
| 27 | -- |
| 28 | RNA polymerase I subunit C |
| 29 | very low density lipoprotein receptor |
| 30 | small integral membrane protein 8 |
| 31 | influenza virus NS1A binding protein |
| 32 | PHD finger protein 14 |
| 33 | BCL tumor suppressor 7B |
| 34 | 3-phosphoinositide dependent protein kinase-1 |
| 35 | solute carrier family 30 member 3 |
| 36 | abl-interactor 2 |
| 37 | leucine-rich repeat LGI family, member 3 |
| 38 | BRF2, RNA polymerase III transcription initiation factor 50 subunit |
| 39 | solute carrier family 39, member 11 |
| 40 | polypeptide N-acetylgalactosaminyltransferase 14 |
| 41 | -- |
| 42 | pumilio RNA-binding family member 2 |
| 43 | coiled-coil domain containing 127 |
| 44 | ferrochelatase |
| 45 | TOP1 binding arginine/serine rich protein |
| 46 | phosphatidylinositol glycan anchor biosynthesis, class U |
| 47 | F-box protein 34 |

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| RAP1B, member of RAS oncogene family |
| synaptotagmin 3 |
| apoptosis enhancing nuclease |
| poly(rC) binding protein 2 |
| BTB domain containing 10 |
| exosome component 5 |
| family with sequence similarity 163, member B |
| casein kinase 1, gamma 3 |
| adenosylhomocysteinase |
| -- |
| dehydrogenase/reductase 7 |
| family with sequence similarity 168, member B |
| cell cycle progression 1 |
| trafficking protein particle complex 12 |
| deoxynucleotidyltransferase, terminal, interacting protein 1 |
| -- |
| ubiquitin protein ligase E3C |
| chibby family member 1, beta catenin antagonist |
| leucine rich repeat transmembrane neuronal 3 |
| -- |
| protein inhibitor of activated STAT, 2 |
| URI1, prefoldin-like chaperone |
| RNA polymerase III subunit H |
| phosphoserine phosphatase |
| testin LIM domain protein |
| calsyntenin 2 |
| -- |
| ribonuclease P/MRP 25 subunit |
| plexin domain containing 2 |
| POM121 transmembrane nucleoporin |
| parathyroid hormone-like hormone |
| Purkinje cell protein 4-like 1 |
| rabphilin 3A |
| glutamate ionotropic receptor AMPA type subunit 1 |
| phosphatidylinositol glycan anchor biosynthesis, class S |
| kinesin family member 2A |
| sodium voltage-gated channel beta subunit 1 |
| paraneoplastic Ma antigen family-like 2 |
| neural cell adhesion molecule 2 |
| cold shock domain containing C2 |

List of the 192 Regulated Genes (Fold-change ≥ 1 ,

| FAST DB STABLE ID | Gene Symbol | Regulation | Fold-Change |
|-------------------|-------------|------------|-------------|
| GSRG0000256 | Tfpt | up | 782.96 |
| GSRG0021091 | Nrsn2 | up | 776.48 |
| GSRG0022737 | Zc3hc1 | up | 284.58 |
| GSRG0031980 | Gnai2 | up | 260.06 |
| GSRG0024597 | Penk | up | 237.43 |
| GSRG0009861 | RGD1566099 | up | 123.61 |
| GSRG0015292 | Sox2 | up | 84.59 |
| GSRG0023366 | Rbsn | up | 75.16 |
| GSRG0015759 | Znhit6 | up | 51.74 |
| GSRG0013452 | Ankrd16 | up | 49.20 |
| GSRG0002031 | Stx5 | up | 48.74 |
| GSRG0028880 | Rad21 | up | 45.27 |
| GSRG0027470 | Med16 | up | 28.23 |
| GSRG0029718 | Nell2 | up | 21.86 |
| GSRG0006308 | Kcnip1 | down | 1791.25 |
| GSRG0008871 | -- | down | 1715.09 |
| GSRG0000412 | Atp5sl | down | 1057.61 |
| GSRG0026695 | Stxbp6 | down | 1005.73 |
| GSRG0013907 | Tmed7 | down | 937.91 |
| GSRG0019514 | Syt13 | down | 823.69 |
| GSRG0023056 | Sfxn5 | down | 633.01 |
| GSRG0013170 | Gadd45g | down | 555.62 |
| GSRG0015282 | Kcnmb2 | down | 550.92 |
| GSRG0006333 | Ublcp1 | down | 537.82 |
| GSRG0026603 | Kcnk3 | down | 488.98 |
| GSRG0023378 | Tmf1 | down | 481.94 |
| GSRG0007094 | Ifnar1 | down | 480.88 |
| GSRG0009858 | Nek7 | down | 475.02 |
| GSRG0029606 | Rangap1 | down | 468.15 |
| GSRG0006834 | Nt5c3b | down | 461.79 |
| GSRG0015089 | Ankrd34b | down | 428.12 |
| GSRG0026020 | Fancm | down | 417.05 |
| GSRG0013258 | lars | down | 401.60 |
| GSRG0002284 | Fam160b1 | down | 394.67 |
| GSRG0010351 | Slbp | down | 381.96 |
| GSRG0020767 | Slc30a4 | down | 380.31 |
| GSRG0010144 | Fam69a | down | 379.33 |
| GSRG0026692 | Lrrn3 | down | 378.07 |
| GSRG0001557 | Pak1 | down | 368.09 |
| GSRG0015833 | Crhbp | down | 361.58 |
| GSRG0008817 | Kdelr2 | down | 360.12 |

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|----|-------------|------------|------|--------|
| 1 | | | | |
| 2 | GSRG0022959 | Mrpl19 | down | 332.49 |
| 3 | GSRG0026756 | Trim9 | down | 318.30 |
| 4 | GSRG0013826 | Syt4 | down | 315.98 |
| 5 | GSRG0007941 | Pdgfa | down | 301.72 |
| 6 | GSRG0008011 | Sbds | down | 297.43 |
| 7 | GSRG0020657 | Fjx1 | down | 289.60 |
| 8 | GSRG0004927 | Fam189a2 | down | 269.01 |
| 9 | GSRG0006244 | Slc9a3r2 | down | 254.74 |
| 10 | GSRG0003390 | Sult2b1 | down | 253.09 |
| 11 | GSRG0003193 | Mrps12 | down | 247.47 |
| 12 | GSRG0029945 | Pde4a | down | 244.94 |
| 13 | GSRG0013566 | Apc | down | 243.03 |
| 14 | GSRG0001855 | Ptpre | down | 238.09 |
| 15 | GSRG0007979 | Prkrip1 | down | 221.80 |
| 16 | GSRG0012479 | Nop16 | down | 215.81 |
| 17 | GSRG0029609 | Phf5a | down | 207.82 |
| 18 | GSRG0006093 | Sec14l1 | down | 206.08 |
| 19 | GSRG0027609 | Igf1 | down | 200.12 |
| 20 | GSRG0013015 | Prr7 | down | 200.04 |
| 21 | GSRG0032466 | Ackr3 | down | 193.94 |
| 22 | GSRG0004212 | Ap3s2 | down | 187.88 |
| 23 | GSRG0010509 | Gpat3 | down | 187.41 |
| 24 | GSRG0024716 | Pnrc1 | down | 182.26 |
| 25 | GSRG0022714 | Wasl | down | 180.47 |
| 26 | GSRG0014684 | -- | down | 175.74 |
| 27 | GSRG0007041 | Myadml2 | down | 175.40 |
| 28 | GSRG0015365 | Trpc4 | down | 171.84 |
| 29 | GSRG0024434 | Eif4g3 | down | 169.02 |
| 30 | GSRG0028697 | Snrpf | down | 168.93 |
| 31 | GSRG0011159 | Pcca | down | 164.14 |
| 32 | GSRG0020828 | Pcna | down | 163.81 |
| 33 | GSRG0004821 | Vegfb | down | 162.67 |
| 34 | GSRG0028103 | Mfsd3 | down | 161.91 |
| 35 | GSRG0019546 | -- | down | 157.63 |
| 36 | GSRG0028796 | Lemd3 | down | 156.94 |
| 37 | GSRG0025610 | Sesn2 | down | 154.60 |
| 38 | GSRG0031432 | RGD1309779 | down | 154.45 |
| 39 | GSRG0032308 | Coq10b | down | 149.67 |
| 40 | GSRG0024196 | Dhcr24 | down | 149.28 |
| 41 | GSRG0017769 | Rtn4ip1 | down | 147.39 |
| 42 | GSRG0005814 | Rara | down | 147.20 |
| 43 | GSRG0021260 | Rgs19 | down | 142.93 |
| 44 | GSRG0031845 | Tex9 | down | 142.23 |
| 45 | GSRG0012470 | Lman2 | down | 141.93 |
| 46 | GSRG0010061 | Adss | down | 140.33 |
| 47 | GSRG0025995 | Akap6 | down | 138.94 |

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|----|-------------|----------|------|--------|
| 1 | | | | |
| 2 | GSRG0009785 | Insig2 | down | 134.66 |
| 3 | GSRG0001551 | Alg8 | down | 132.63 |
| 4 | GSRG0030976 | Rab39a | down | 131.89 |
| 5 | GSRG0014604 | Dhodh | down | 129.45 |
| 6 | GSRG0011004 | Fgf9 | down | 125.03 |
| 7 | GSRG0023498 | Kcna1 | down | 124.16 |
| 8 | GSRG0009711 | Cnih3 | down | 121.46 |
| 9 | GSRG0020093 | Ptpn1 | down | 120.18 |
| 10 | GSRG0012489 | -- | down | 116.61 |
| 11 | GSRG0030402 | Senp6 | down | 116.58 |
| 12 | GSRG0005807 | Casc3 | down | 108.06 |
| 13 | GSRG0029295 | Fam49b | down | 106.79 |
| 14 | GSRG0023977 | Phf24 | down | 105.30 |
| 15 | GSRG0032998 | Tyw5 | down | 104.01 |
| 16 | GSRG0009488 | Ivns1abp | down | 101.91 |
| 17 | GSRG0021544 | Mpp6 | down | 101.46 |
| 18 | GSRG0034842 | Sept6 | down | 100.51 |
| 19 | GSRG0009754 | Plxna2 | down | 98.57 |
| 20 | GSRG0005239 | Narfl | down | 97.69 |
| 21 | GSRG0010843 | Chac2 | down | 93.76 |
| 22 | GSRG0004850 | Asrgl1 | down | 93.03 |
| 23 | GSRG0020402 | Scn1a | down | 90.53 |
| 24 | GSRG0026589 | Snx17 | down | 88.81 |
| 25 | GSRG0025396 | Prpf38a | down | 88.01 |
| 26 | GSRG0005137 | -- | down | 87.77 |
| 27 | GSRG0027340 | Akt1 | down | 84.54 |
| 28 | GSRG0029711 | Yaf2 | down | 83.17 |
| 29 | GSRG0021769 | Thumpd3 | down | 77.71 |
| 30 | GSRG0036155 | Gfm1 | down | 75.70 |
| 31 | GSRG0005815 | Igfbp4 | down | 74.81 |
| 32 | GSRG0014547 | Nol3 | down | 74.01 |
| 33 | GSRG0025999 | Srp54a | down | 72.14 |
| 34 | GSRG0001964 | mrpl11 | down | 72.02 |
| 35 | GSRG0006506 | Rangrf | down | 71.73 |
| 36 | GSRG0032315 | Spats2l | down | 71.64 |
| 37 | GSRG0005237 | Gng13 | down | 71.49 |
| 38 | GSRG0022586 | Ccdc91 | down | 70.86 |
| 39 | GSRG0015523 | Them4 | down | 70.60 |
| 40 | GSRG0021290 | Actr3b | down | 69.06 |
| 41 | GSRG0020088 | Ddx27 | down | 65.44 |
| 42 | GSRG0026736 | Mdga2 | down | 63.18 |
| 43 | GSRG0025353 | Caap1 | down | 62.82 |
| 44 | GSRG0003253 | Lsm14a | down | 61.41 |
| 45 | GSRG0026565 | Clip4 | down | 60.83 |
| 46 | GSRG0018780 | Slc4a10 | down | 60.66 |
| 47 | GSRG0025868 | Slc30a3 | down | 60.55 |
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|----|-------------|----------|------|-------|
| 1 | | | | |
| 2 | GSRG0007885 | Rnf6 | down | 59.48 |
| 3 | GSRG0024306 | Mycbp | down | 58.18 |
| 4 | GSRG0036839 | Arhgap5 | down | 57.66 |
| 5 | GSRG0028164 | Sgsm3 | down | 57.56 |
| 6 | GSRG0036647 | Nosip | down | 57.29 |
| 7 | GSRG0013400 | Mplkip | down | 57.16 |
| 8 | GSRG0023059 | Egr4 | down | 57.06 |
| 9 | GSRG0004287 | Uvrage | down | 55.94 |
| 10 | GSRG0025430 | Plk3 | down | 55.60 |
| 11 | GSRG0002105 | -- | down | 55.51 |
| 12 | GSRG0025810 | Morn2 | down | 55.44 |
| 13 | GSRG0036313 | -- | down | 55.25 |
| 14 | GSRG0036814 | Kcns3 | down | 55.18 |
| 15 | GSRG0032238 | Bend6 | down | 53.38 |
| 16 | GSRG0000541 | Syt3 | down | 53.25 |
| 17 | GSRG0011737 | Fam160b2 | down | 52.22 |
| 18 | GSRG0024580 | Rb1cc1 | down | 50.68 |
| 19 | GSRG0007220 | Umps | down | 50.33 |
| 20 | GSRG0006659 | Wsb1 | down | 49.76 |
| 21 | GSRG0000551 | Akt1s1 | down | 48.78 |
| 22 | GSRG0026076 | Mthfd1 | down | 47.86 |
| 23 | GSRG0006193 | Naa60 | down | 47.55 |
| 24 | GSRG0010956 | Bcl2l2 | down | 47.25 |
| 25 | GSRG0021593 | Ppm1k | down | 45.89 |
| 26 | GSRG0029819 | -- | down | 45.66 |
| 27 | GSRG0013466 | Phyh | down | 44.86 |
| 28 | GSRG0008398 | N4bp2l2 | down | 44.75 |
| 29 | GSRG0034565 | Tspyl2 | down | 43.77 |
| 30 | GSRG0024721 | Smim8 | down | 43.50 |
| 31 | GSRG0005692 | Pthr2 | down | 43.27 |
| 32 | GSRG0027325 | Cinp | down | 42.88 |
| 33 | GSRG0022729 | Tnpo3 | down | 42.27 |
| 34 | GSRG0008019 | Psph | down | 40.84 |
| 35 | GSRG0030416 | Mrap2 | down | 40.74 |
| 36 | GSRG0031930 | Mras | down | 40.57 |
| 37 | GSRG0007986 | Tmem120a | down | 39.83 |
| 38 | GSRG0025945 | Fam150b | down | 38.86 |
| 39 | GSRG0032822 | -- | down | 38.22 |
| 40 | GSRG0021184 | Acot8 | down | 36.29 |
| 41 | GSRG0014672 | Spg7 | down | 36.24 |
| 42 | GSRG0013662 | Csnk1g3 | down | 35.37 |
| 43 | GSRG0017921 | Ppil1 | down | 35.22 |
| 44 | GSRG0011525 | Rpp14 | down | 34.00 |
| 45 | GSRG0010557 | Utp3 | down | 33.56 |
| 46 | GSRG0029818 | -- | down | 33.46 |
| 47 | GSRG0023398 | Crbn | down | 31.92 |

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|-------------|---------|------|-------|
| GSRG0010246 | Lnx1 | down | 31.12 |
| GSRG0015013 | -- | down | 30.36 |
| GSRG0028271 | Spats2 | down | 28.44 |
| GSRG0011976 | Tll1 | down | 27.80 |
| GSRG0000492 | U2af1l4 | down | 27.47 |
| GSRG0004453 | Btbd10 | down | 27.37 |
| GSRG0005277 | -- | down | 24.23 |
| GSRG0024007 | Nans | down | 22.85 |
| GSRG0021895 | Mrpl51 | down | 19.43 |
| GSRG0024183 | Sgip1 | down | 19.31 |
| GSRG0005636 | Pigs | down | 18.31 |
| GSRG0015202 | Golph3 | down | 15.35 |
| GSRG0021248 | Eef1a2 | down | 11.54 |

For Peer Review

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4 **,5; P-Value \leq 0,05) - G/**
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| P-Value | Adjusted P-Value |
|----------|------------------|
| 1.67E-05 | 9.27E-03 |
| 1.86E-04 | 3.30E-02 |
| 8.06E-04 | 6.86E-02 |
| 3.02E-04 | 4.11E-02 |
| 1.46E-03 | 9.48E-02 |
| 3.84E-03 | 1.51E-01 |
| 1.71E-03 | 1.00E-01 |
| 1.20E-02 | 2.64E-01 |
| 2.29E-02 | 3.56E-01 |
| 2.50E-02 | 3.62E-01 |
| 2.42E-02 | 3.60E-01 |
| 6.55E-03 | 1.92E-01 |
| 3.04E-02 | 3.93E-01 |
| 2.98E-02 | 3.90E-01 |
| 1.10E-07 | 3.99E-04 |
| 2.31E-08 | 1.67E-04 |
| 4.04E-06 | 4.91E-03 |
| 4.24E-06 | 4.91E-03 |
| 2.55E-07 | 6.14E-04 |
| 1.87E-04 | 3.30E-02 |
| 1.61E-05 | 9.27E-03 |
| 5.44E-06 | 4.91E-03 |
| 6.79E-05 | 1.76E-02 |
| 5.35E-06 | 4.91E-03 |
| 1.48E-04 | 2.97E-02 |
| 1.40E-05 | 9.27E-03 |
| 1.64E-04 | 3.21E-02 |
| 4.93E-05 | 1.60E-02 |
| 1.00E-06 | 1.81E-03 |
| 9.01E-05 | 2.10E-02 |
| 3.36E-05 | 1.60E-02 |
| 7.94E-04 | 6.83E-02 |
| 1.37E-04 | 2.90E-02 |
| 2.57E-04 | 3.95E-02 |
| 4.38E-05 | 1.60E-02 |
| 1.01E-04 | 2.28E-02 |
| 4.46E-05 | 1.60E-02 |
| 5.07E-05 | 1.60E-02 |
| 4.58E-05 | 1.60E-02 |
| 5.75E-04 | 6.02E-02 |
| 5.86E-05 | 1.69E-02 |

Peer Review

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| 1 | | |
| 2 | 3.90E-04 | 4.77E-02 |
| 3 | 4.67E-05 | 1.60E-02 |
| 4 | | |
| 5 | 1.89E-05 | 9.75E-03 |
| 6 | 6.80E-05 | 1.76E-02 |
| 7 | 1.69E-04 | 3.21E-02 |
| 8 | | |
| 9 | 5.09E-04 | 5.59E-02 |
| 10 | 6.29E-04 | 6.23E-02 |
| 11 | 7.12E-04 | 6.76E-02 |
| 12 | | |
| 13 | 8.40E-04 | 6.90E-02 |
| 14 | 1.47E-04 | 2.97E-02 |
| 15 | 5.38E-04 | 5.71E-02 |
| 16 | 6.21E-04 | 6.23E-02 |
| 17 | 1.78E-04 | 3.30E-02 |
| 18 | | |
| 19 | 4.28E-04 | 4.99E-02 |
| 20 | 6.29E-05 | 1.75E-02 |
| 21 | | |
| 22 | 1.12E-03 | 7.88E-02 |
| 23 | 2.81E-04 | 4.11E-02 |
| 24 | | |
| 25 | 2.56E-03 | 1.19E-01 |
| 26 | 2.98E-04 | 4.11E-02 |
| 27 | 2.31E-03 | 1.14E-01 |
| 28 | 7.63E-04 | 6.76E-02 |
| 29 | | |
| 30 | 2.12E-03 | 1.11E-01 |
| 31 | 2.93E-04 | 4.11E-02 |
| 32 | 3.63E-04 | 4.68E-02 |
| 33 | | |
| 34 | 3.83E-03 | 1.51E-01 |
| 35 | 2.41E-03 | 1.17E-01 |
| 36 | 3.28E-03 | 1.38E-01 |
| 37 | | |
| 38 | 3.15E-04 | 4.22E-02 |
| 39 | 4.05E-04 | 4.79E-02 |
| 40 | 1.10E-03 | 7.88E-02 |
| 41 | | |
| 42 | 3.69E-04 | 4.68E-02 |
| 43 | 2.44E-04 | 3.84E-02 |
| 44 | 1.59E-03 | 9.71E-02 |
| 45 | 1.05E-03 | 7.74E-02 |
| 46 | | |
| 47 | 2.82E-03 | 1.25E-01 |
| 48 | 2.59E-03 | 1.19E-01 |
| 49 | | |
| 50 | 2.23E-03 | 1.12E-01 |
| 51 | 3.46E-03 | 1.42E-01 |
| 52 | 3.48E-03 | 1.42E-01 |
| 53 | 3.31E-03 | 1.39E-01 |
| 54 | | |
| 55 | 8.30E-04 | 6.90E-02 |
| 56 | 2.25E-03 | 1.12E-01 |
| 57 | 4.47E-03 | 1.60E-01 |
| 58 | 2.56E-03 | 1.19E-01 |
| 59 | | |
| 60 | 1.12E-03 | 7.88E-02 |
| | 2.22E-03 | 1.12E-01 |

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| 1.53E-03 | 9.65E-02 |
| 5.56E-03 | 1.78E-01 |
| 4.27E-03 | 1.59E-01 |
| 5.66E-03 | 1.78E-01 |
| 2.14E-03 | 1.11E-01 |
| 2.10E-03 | 1.11E-01 |
| 5.05E-03 | 1.65E-01 |
| 1.93E-03 | 1.10E-01 |
| 7.47E-04 | 6.76E-02 |
| 2.60E-03 | 1.19E-01 |
| 2.49E-03 | 1.19E-01 |
| 1.98E-03 | 1.11E-01 |
| 4.50E-03 | 1.60E-01 |
| 8.35E-03 | 2.14E-01 |
| 3.36E-03 | 1.39E-01 |
| 1.79E-03 | 1.04E-01 |
| 3.32E-03 | 1.39E-01 |
| 7.63E-03 | 2.04E-01 |
| 7.31E-03 | 2.02E-01 |
| 1.15E-02 | 2.57E-01 |
| 3.65E-03 | 1.47E-01 |
| 1.69E-03 | 9.99E-02 |
| 4.50E-03 | 1.60E-01 |
| 5.89E-03 | 1.79E-01 |
| 4.96E-03 | 1.65E-01 |
| 3.90E-03 | 1.51E-01 |
| 4.83E-03 | 1.65E-01 |
| 4.59E-03 | 1.61E-01 |
| 1.05E-02 | 2.44E-01 |
| 2.59E-03 | 1.19E-01 |
| 8.54E-03 | 2.17E-01 |
| 1.57E-02 | 2.97E-01 |
| 6.63E-03 | 1.92E-01 |
| 1.51E-02 | 2.91E-01 |
| 7.12E-03 | 1.98E-01 |
| 6.40E-03 | 1.90E-01 |
| 9.90E-03 | 2.38E-01 |
| 9.96E-03 | 2.38E-01 |
| 6.63E-03 | 1.92E-01 |
| 1.23E-02 | 2.67E-01 |
| 1.37E-02 | 2.82E-01 |
| 2.16E-02 | 3.45E-01 |
| 2.12E-02 | 3.41E-01 |
| 1.42E-02 | 2.87E-01 |
| 6.77E-03 | 1.95E-01 |
| 5.97E-03 | 1.81E-01 |

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|----|----------|----------|
| 1 | | |
| 2 | 1.11E-03 | 7.88E-02 |
| 3 | 1.22E-02 | 2.66E-01 |
| 4 | 1.13E-02 | 2.54E-01 |
| 5 | 8.48E-03 | 2.16E-01 |
| 6 | 1.11E-02 | 2.52E-01 |
| 7 | 2.40E-02 | 3.58E-01 |
| 8 | 1.04E-02 | 2.44E-01 |
| 9 | 2.36E-02 | 3.57E-01 |
| 10 | 1.00E-02 | 2.38E-01 |
| 11 | 1.55E-02 | 2.96E-01 |
| 12 | 2.18E-02 | 3.45E-01 |
| 13 | 1.40E-02 | 2.84E-01 |
| 14 | 2.42E-02 | 3.60E-01 |
| 15 | 6.90E-03 | 1.97E-01 |
| 16 | 1.54E-02 | 2.96E-01 |
| 17 | 1.98E-02 | 3.32E-01 |
| 18 | 2.12E-02 | 3.41E-01 |
| 19 | 2.38E-02 | 3.57E-01 |
| 20 | 1.92E-02 | 3.26E-01 |
| 21 | 1.86E-02 | 3.23E-01 |
| 22 | 2.87E-02 | 3.82E-01 |
| 23 | 1.76E-02 | 3.14E-01 |
| 24 | 2.34E-02 | 3.57E-01 |
| 25 | 3.11E-02 | 3.96E-01 |
| 26 | 2.40E-02 | 3.58E-01 |
| 27 | 3.15E-02 | 3.96E-01 |
| 28 | 2.01E-02 | 3.34E-01 |
| 29 | 1.20E-02 | 2.65E-01 |
| 30 | 1.88E-02 | 3.25E-01 |
| 31 | 2.87E-02 | 3.82E-01 |
| 32 | 2.68E-02 | 3.76E-01 |
| 33 | 2.32E-02 | 3.56E-01 |
| 34 | 2.85E-02 | 3.82E-01 |
| 35 | 3.05E-02 | 3.93E-01 |
| 36 | 2.81E-02 | 3.80E-01 |
| 37 | 3.88E-02 | 4.41E-01 |
| 38 | 3.82E-02 | 4.39E-01 |
| 39 | 4.38E-02 | 4.60E-01 |
| 40 | 3.10E-02 | 3.96E-01 |
| 41 | 3.49E-02 | 4.19E-01 |
| 42 | 2.01E-02 | 3.34E-01 |
| 43 | 3.49E-02 | 4.19E-01 |
| 44 | 3.04E-02 | 3.93E-01 |
| 45 | 5.00E-02 | 4.93E-01 |
| 46 | 3.84E-02 | -- |
| 47 | 2.26E-02 | 3.53E-01 |
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| 1 | | |
| 2 | 4.43E-02 | 4.64E-01 |
| 3 | 2.67E-02 | 3.76E-01 |
| 4 | | |
| 5 | 2.68E-02 | 3.76E-01 |
| 6 | 4.88E-02 | 4.89E-01 |
| 7 | 2.87E-02 | 3.82E-01 |
| 8 | 4.56E-02 | 4.71E-01 |
| 9 | | |
| 10 | 3.56E-02 | -- |
| 11 | 4.02E-02 | 4.44E-01 |
| 12 | | |
| 13 | 3.95E-02 | 4.42E-01 |
| 14 | 4.06E-02 | 4.45E-01 |
| 15 | 4.61E-02 | 4.75E-01 |
| 16 | | |
| 17 | 3.09E-02 | 3.96E-01 |
| 18 | 3.53E-02 | 4.21E-01 |
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For Peer Review

ABA PUR vs GABA OCM

| Gene Name |
|---|
| TCF3 (E2A) fusion partner |
| neurensin 2 |
| zinc finger, C3HC-type containing 1 |
| G protein subunit alpha i2 |
| proenkephalin |
| similar to novel protein |
| SRY box 2 |
| rabenosyn, RAB effector |
| zinc finger, HIT-type containing 6 |
| ankyrin repeat domain 16 |
| syntaxin 5 |
| RAD21 cohesin complex component |
| mediator complex subunit 16 |
| neural EGFL like 2 |
| potassium voltage-gated channel interacting protein 1 |
| -- |
| ATP5S-like |
| syntaxin binding protein 6 |
| transmembrane p24 trafficking protein 7 |
| synaptotagmin 13 |
| sideroflexin 5 |
| growth arrest and DNA-damage-inducible, gamma |
| potassium calcium-activated channel subfamily M regulatory beta subunit 2 |
| ubiquitin-like domain containing CTD phosphatase 1 |
| potassium two pore domain channel subfamily K member 3 |
| TATA element modulatory factor 1 |
| interferon alpha and beta receptor subunit 1 |
| NIMA-related kinase 7 |
| RAN GTPase activating protein 1 |
| 5'-nucleotidase, cytosolic IIIB |
| ankyrin repeat domain 34B |
| Fanconi anemia, complementation group M |
| isoleucyl-tRNA synthetase |
| family with sequence similarity 160, member B1 |
| stem-loop binding protein |
| solute carrier family 30 member 4 |
| family with sequence similarity 69, member A |
| leucine rich repeat neuronal 3 |
| p21 (RAC1) activated kinase 1 |
| corticotropin releasing hormone binding protein |
| KDEL endoplasmic reticulum protein retention receptor 2 |

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| mitochondrial ribosomal protein L19 |
| tripartite motif-containing 9 |
| synaptotagmin 4 |
| platelet derived growth factor subunit A |
| SBDS ribosome assembly guanine nucleotide exchange factor |
| four jointed box 1 |
| family with sequence similarity 189, member A2 |
| SLC9A3 regulator 2 |
| sulfotransferase family 2B member 1 |
| mitochondrial ribosomal protein S12 |
| phosphodiesterase 4A |
| APC, WNT signaling pathway regulator |
| protein tyrosine phosphatase, receptor type, E |
| Prkr interacting protein 1 (IL11 inducible) |
| NOP16 nucleolar protein |
| PHD finger protein 5A |
| SEC14-like lipid binding 1 |
| insulin-like growth factor 1 |
| proline rich 7 (synaptic) |
| atypical chemokine receptor 3 |
| adaptor-related protein complex 3, sigma 2 subunit |
| glycerol-3-phosphate acyltransferase 3 |
| proline-rich nuclear receptor coactivator 1 |
| Wiskott-Aldrich syndrome-like |
| -- |
| myeloid-associated differentiation marker-like 2 |
| transient receptor potential cation channel, subfamily C, member 4 |
| eukaryotic translation initiation factor 4 gamma, 3 |
| small nuclear ribonucleoprotein polypeptide F |
| propionyl-CoA carboxylase alpha subunit |
| proliferating cell nuclear antigen |
| vascular endothelial growth factor B |
| major facilitator superfamily domain containing 3 |
| -- |
| LEM domain containing 3 |
| sestrin 2 |
| similar to ENSANGP00000021391 |
| coenzyme Q10B |
| 24-dehydrocholesterol reductase |
| reticulon 4 interacting protein 1 |
| retinoic acid receptor, alpha |
| regulator of G-protein signaling 19 |
| testis expressed 9 |
| lectin, mannose-binding 2 |
| adenylosuccinate synthase |
| A-kinase anchoring protein 6 |

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| 1 | |
| 2 | insulin induced gene 2 |
| 3 | ALG8, alpha-1, 3-glycosyltransferase |
| 4 | RAB39A, member RAS oncogene family |
| 5 | dihydroorotate dehydrogenase (quinone) |
| 6 | fibroblast growth factor 9 |
| 7 | potassium voltage-gated channel subfamily A member 1 |
| 8 | cornichon family AMPA receptor auxiliary protein 3 |
| 9 | protein tyrosine phosphatase, non-receptor type 1 |
| 10 | -- |
| 11 | SUMO1/sentrin specific peptidase 6 |
| 12 | cancer susceptibility candidate 3 |
| 13 | family with sequence similarity 49, member B |
| 14 | PHD finger protein 24 |
| 15 | tRNA-yW synthesizing protein 5 |
| 16 | influenza virus NS1A binding protein |
| 17 | membrane palmitoylated protein 6 |
| 18 | septin 6 |
| 19 | plexin A2 |
| 20 | nuclear prelamin A recognition factor-like |
| 21 | ChaC cation transport regulator 2 |
| 22 | asparaginase like 1 |
| 23 | sodium voltage-gated channel alpha subunit 1 |
| 24 | sorting nexin 17 |
| 25 | pre-mRNA processing factor 38A |
| 26 | -- |
| 27 | AKT serine/threonine kinase 1 |
| 28 | YY1 associated factor 2 |
| 29 | THUMP domain containing 3 |
| 30 | G elongation factor, mitochondrial 1 |
| 31 | insulin-like growth factor binding protein 4 |
| 32 | nucleolar protein 3 |
| 33 | signal recognition particle 54A |
| 34 | mitochondrial ribosomal protein L11 |
| 35 | RAN guanine nucleotide release factor |
| 36 | spermatogenesis associated, serine-rich 2-like |
| 37 | G protein subunit gamma 13 |
| 38 | coiled-coil domain containing 91 |
| 39 | thioesterase superfamily member 4 |
| 40 | ARP3 actin related protein 3 homolog B |
| 41 | DEAD-box helicase 27 |
| 42 | MAM domain containing glycosylphosphatidylinositol anchor 2 |
| 43 | caspase activity and apoptosis inhibitor 1 |
| 44 | LSM14A mRNA processing body assembly factor |
| 45 | CAP-GLY domain containing linker protein family, member 4 |
| 46 | solute carrier family 4 member 10 |
| 47 | solute carrier family 30 member 3 |
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| ring finger protein 6 |
| Myc binding protein |
| Rho GTPase activating protein 5 |
| small G protein signaling modulator 3 |
| nitric oxide synthase interacting protein |
| M-phase specific PLK1 interacting protein |
| early growth response 4 |
| UV radiation resistance associated |
| polo-like kinase 3 |
| -- |
| MORN repeat containing 2 |
| -- |
| potassium voltage-gated channel, modifier subfamily S, member 3 |
| BEN domain containing 6 |
| synaptotagmin 3 |
| family with sequence similarity 160, member B2 |
| RB1-inducible coiled-coil 1 |
| uridine monophosphate synthetase |
| WD repeat and SOCS box-containing 1 |
| AKT1 substrate 1 |
| methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1 |
| N(alpha)-acetyltransferase 60, NatF catalytic subunit |
| Bcl2-like 2 |
| protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent, 1K |
| -- |
| phytanoyl-CoA 2-hydroxylase |
| NEDD4 binding protein 2-like 2 |
| TSPY-like 2 |
| small integral membrane protein 8 |
| peptidyl-tRNA hydrolase 2 |
| cyclin-dependent kinase 2-interacting protein |
| transportin 3 |
| phosphoserine phosphatase |
| melanocortin 2 receptor accessory protein 2 |
| muscle RAS oncogene homolog |
| transmembrane protein 120A |
| family with sequence similarity 150, member B |
| -- |
| acyl-CoA thioesterase 8 |
| SPG7, paraplegin matrix AAA peptidase subunit |
| casein kinase 1, gamma 3 |
| peptidylprolyl isomerase like 1 |
| ribonuclease P/MRP 14 subunit |
| UTP3, small subunit processome component homolog (S. cerevisiae) |
| -- |
| cereblon |

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| 1 | |
| 2 | ligand of numb-protein X 1 |
| 3 | -- |
| 4 | spermatogenesis associated, serine-rich 2 |
| 5 | tolloid-like 1 |
| 6 | U2 small nuclear RNA auxiliary factor 1-like 4 |
| 7 | BTB domain containing 10 |
| 8 | -- |
| 9 | N-acetylneuraminase |
| 10 | mitochondrial ribosomal protein L51 |
| 11 | SH3-domain GRB2-like (endophilin) interacting protein 1 |
| 12 | phosphatidylinositol glycan anchor biosynthesis, class S |
| 13 | golgi phosphoprotein 3 |
| 14 | eukaryotic translation elongation factor 1 alpha 2 |
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For Peer Review

List of the 68 Regulated Genes (Fold-change $\geq 1,5$)

| FAST DB STABLE ID | Gene Symbol | Regulation | Fold-Change |
|-------------------|-------------|------------|-------------|
| GSRG0019514 | Syt13 | up | 1354.01 |
| GSRG0026020 | Fancm | up | 697.69 |
| GSRG0014684 | -- | up | 269.65 |
| GSRG0032466 | Ackr3 | up | 260.39 |
| GSRG0018539 | Rpf2 | up | 246.51 |
| GSRG0008967 | Sumf2 | up | 171.63 |
| GSRG0006423 | Zfp672 | up | 140.68 |
| GSRG0013466 | Phyh | up | 123.50 |
| GSRG0032824 | -- | up | 101.57 |
| GSRG0025810 | Morn2 | up | 86.95 |
| GSRG0013400 | Mplkip | up | 85.10 |
| GSRG0005486 | Ctc1 | up | 80.08 |
| GSRG0020417 | Dlx2 | up | 67.45 |
| GSRG0005145 | Zc3h7a | up | 65.77 |
| GSRG0027614 | Igf1 | up | 50.77 |
| GSRG0016423 | Rrnad1 | up | 24.49 |
| GSRG0036252 | Brix1 | down | 2378.19 |
| GSRG0032304 | Nabp1 | down | 2147.97 |
| GSRG0031867 | Slc17a5 | down | 1200.98 |
| GSRG0002264 | Smc3 | down | 1177.14 |
| GSRG0006796 | Ormdl3 | down | 1045.74 |
| GSRG0024467 | Casp9 | down | 941.28 |
| GSRG0014272 | Fam210a | down | 872.64 |
| GSRG0000256 | Tfpt | down | 447.27 |
| GSRG0021713 | Tpra1 | down | 420.12 |
| GSRG0032453 | Neu2 | down | 405.72 |
| GSRG0005434 | Gid4 | down | 319.67 |
| GSRG0028324 | Pde1b | down | 310.69 |
| GSRG0023969 | Nfx1 | down | 278.21 |
| GSRG0026146 | Eif2b2 | down | 226.38 |
| GSRG0005298 | Pwwp2a | down | 212.66 |
| GSRG0015283 | Pik3ca | down | 157.31 |
| GSRG0018533 | Fam229b | down | 141.26 |
| GSRG0011756 | Gtf2f2 | down | 140.97 |
| GSRG0007154 | Cmss1 | down | 123.22 |
| GSRG0015248 | Pex2 | down | 117.17 |
| GSRG0019759 | Cds2 | down | 102.19 |
| GSRG0036688 | Ift52 | down | 92.76 |
| GSRG0012481 | Thoc3 | down | 89.71 |
| GSRG0013699 | St8sia3 | down | 88.57 |
| GSRG0015952 | Pelo | down | 87.03 |

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|----|-------------|----------|------|-------|
| 1 | | | | |
| 2 | GSRG0012237 | Mfap3l | down | 86.89 |
| 3 | GSRG0024281 | Foxj3 | down | 82.16 |
| 4 | GSRG0002210 | Cnnm1 | down | 78.40 |
| 5 | GSRG0034928 | Slitrk4 | down | 74.64 |
| 6 | GSRG0006754 | Pdk2 | down | 74.57 |
| 7 | GSRG0013285 | Pak1ip1 | down | 74.42 |
| 8 | GSRG0007430 | Gart | down | 66.47 |
| 9 | GSRG0023361 | Xpc | down | 65.78 |
| 10 | GSRG0032175 | Polr1c | down | 65.14 |
| 11 | GSRG0001503 | Hddc3 | down | 64.52 |
| 12 | GSRG0020830 | Gpcpd1 | down | 61.82 |
| 13 | GSRG0029946 | -- | down | 56.27 |
| 14 | GSRG0012042 | Brf2 | down | 55.74 |
| 15 | GSRG0028761 | Ppp1r12a | down | 48.75 |
| 16 | GSRG0024746 | Ubap2 | down | 47.89 |
| 17 | GSRG0011023 | Stmn4 | down | 42.19 |
| 18 | GSRG0020147 | Zgpat | down | 35.00 |
| 19 | GSRG0010043 | Cadm3 | down | 31.66 |
| 20 | GSRG0005300 | Rnf145 | down | 31.08 |
| 21 | GSRG0002156 | Pten | down | 30.19 |
| 22 | GSRG0021308 | Tmub1 | down | 30.09 |
| 23 | GSRG0014335 | Csnk2a2 | down | 23.80 |
| 24 | GSRG0020611 | Madd | down | 21.49 |
| 25 | GSRG0027470 | Med16 | down | 20.20 |
| 26 | GSRG0008075 | Rph3a | down | 12.96 |
| 27 | GSRG0032016 | Arpp19 | down | 11.17 |
| 28 | GSRG0006987 | Wbp2 | down | 9.65 |
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3 **); P-Value ≤ 0,05) - GA**
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| P-Value | Adjusted P-Value |
|----------|------------------|
| 4.13E-05 | 2.98E-02 |
| 1.96E-04 | 6.12E-02 |
| 1.44E-03 | 9.70E-02 |
| 1.03E-03 | 8.90E-02 |
| 7.86E-04 | 8.36E-02 |
| 2.81E-03 | 1.27E-01 |
| 4.98E-03 | 1.61E-01 |
| 5.65E-03 | 1.70E-01 |
| 8.61E-03 | 2.12E-01 |
| 9.36E-03 | 2.23E-01 |
| 1.18E-02 | 2.57E-01 |
| 1.23E-02 | 2.64E-01 |
| 1.67E-02 | 3.24E-01 |
| 1.73E-02 | 3.32E-01 |
| 2.66E-02 | 4.33E-01 |
| 3.50E-02 | 5.09E-01 |
| 2.63E-06 | 1.15E-02 |
| 2.88E-06 | 1.15E-02 |
| 3.34E-05 | 2.98E-02 |
| 3.65E-05 | 2.98E-02 |
| 2.78E-05 | 2.98E-02 |
| 6.22E-05 | 2.98E-02 |
| 7.84E-05 | 3.29E-02 |
| 5.34E-05 | 2.98E-02 |
| 3.66E-04 | 6.69E-02 |
| 1.22E-04 | 4.47E-02 |
| 3.00E-04 | 6.12E-02 |
| 5.05E-04 | 7.45E-02 |
| 1.23E-04 | 4.47E-02 |
| 5.21E-04 | 7.45E-02 |
| 9.31E-04 | 8.63E-02 |
| 2.16E-03 | 1.16E-01 |
| 2.81E-03 | 1.27E-01 |
| 3.63E-03 | 1.41E-01 |
| 3.99E-03 | 1.47E-01 |
| 5.46E-03 | 1.67E-01 |
| 7.01E-03 | 1.92E-01 |
| 5.56E-03 | 1.69E-01 |
| 8.86E-03 | 2.16E-01 |
| 9.35E-03 | 2.23E-01 |
| 4.55E-03 | 1.54E-01 |

Peer Review

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| 2 | 9.54E-03 | 2.26E-01 |
| 3 | 8.52E-03 | 2.12E-01 |
| 4 | 3.27E-03 | 1.34E-01 |
| 5 | 7.49E-03 | 1.99E-01 |
| 6 | 8.89E-03 | 2.16E-01 |
| 7 | 1.26E-02 | 2.67E-01 |
| 8 | 1.50E-02 | 3.04E-01 |
| 9 | 1.58E-02 | 3.13E-01 |
| 10 | 1.57E-02 | 3.13E-01 |
| 11 | 1.18E-02 | 2.57E-01 |
| 12 | 1.15E-02 | 2.55E-01 |
| 13 | 1.15E-02 | 2.55E-01 |
| 14 | 2.09E-02 | 3.79E-01 |
| 15 | 1.42E-02 | 2.92E-01 |
| 16 | 1.62E-02 | 3.19E-01 |
| 17 | 2.48E-02 | 4.20E-01 |
| 18 | 3.22E-02 | 4.87E-01 |
| 19 | 2.05E-02 | 3.75E-01 |
| 20 | 1.72E-02 | 3.31E-01 |
| 21 | 1.60E-02 | 3.16E-01 |
| 22 | 2.48E-02 | 4.20E-01 |
| 23 | 4.31E-02 | 5.75E-01 |
| 24 | 3.51E-02 | 5.09E-01 |
| 25 | 4.55E-02 | 5.99E-01 |
| 26 | 4.54E-02 | 5.98E-01 |
| 27 | 2.20E-02 | 3.89E-01 |
| 28 | 2.97E-03 | 1.29E-01 |
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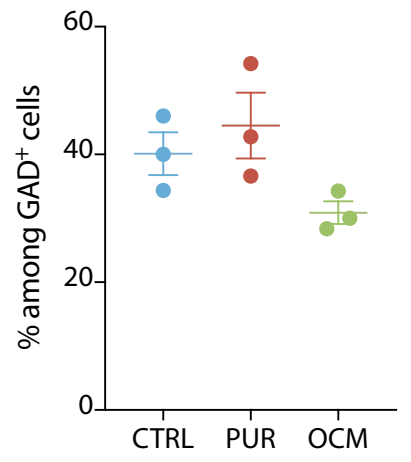
Peer Review

BA OCM vs GABA CTRL

| Gene Name |
|--|
| synaptotagmin 13 |
| Fanconi anemia, complementation group M |
| -- |
| atypical chemokine receptor 3 |
| ribosome production factor 2 homolog |
| sulfatase modifying factor 2 |
| zinc finger protein 672 |
| phytanoyl-CoA 2-hydroxylase |
| -- |
| MORN repeat containing 2 |
| M-phase specific PLK1 interacting protein |
| CST telomere replication complex component 1 |
| distal-less homeobox 2 |
| zinc finger CCCH type containing 7 A |
| insulin-like growth factor 1 |
| ribosomal RNA adenine dimethylase domain containing 1 |
| BRX1, biogenesis of ribosomes |
| nucleic acid binding protein 1 |
| solute carrier family 17 member 5 |
| structural maintenance of chromosomes 3 |
| ORMDL sphingolipid biosynthesis regulator 3 |
| caspase 9 |
| family with sequence similarity 210, member A |
| TCF3 (E2A) fusion partner |
| transmembrane protein adipocyte associated 1 |
| neuraminidase 2 |
| GID complex subunit 4 |
| phosphodiesterase 1B |
| nuclear transcription factor, X-box binding 1 |
| eukaryotic translation initiation factor 2B subunit beta |
| PWWP domain containing 2A |
| phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha |
| family with sequence similarity 229, member B |
| general transcription factor IIF subunit 2 |
| cms1 ribosomal small subunit homolog (yeast) |
| peroxisomal biogenesis factor 2 |
| CDP-diacylglycerol synthase 2 |
| intraflagellar transport 52 |
| THO complex 3 |
| ST8 alpha-N-acetyl-neuraminide alpha-2, 8-sialyltransferase 3 |
| pelota homolog (Drosophila) |

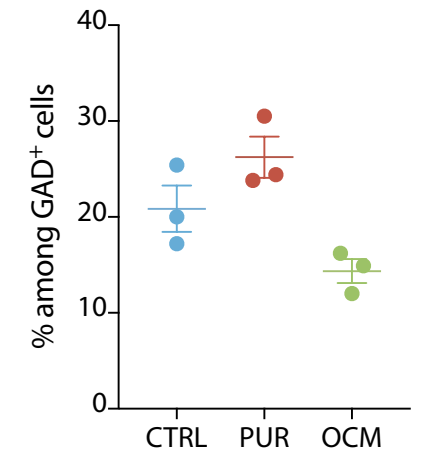
| | |
|----|---|
| 1 | |
| 2 | microfibrillar-associated protein 3-like |
| 3 | forkhead box J3 |
| 4 | cyclin and CBS domain divalent metal cation transport mediator 1 |
| 5 | SLIT and NTRK-like family, member 4 |
| 6 | pyruvate dehydrogenase kinase 2 |
| 7 | PAK1 interacting protein 1 |
| 8 | phosphoribosylglycinamide formyltransferase |
| 9 | XPC complex subunit, DNA damage recognition and repair factor |
| 10 | RNA polymerase I subunit C |
| 11 | HD domain containing 3 |
| 12 | glycerophosphocholine phosphodiesterase 1 |
| 13 | -- |
| 14 | BRF2, RNA polymerase III transcription initiation factor 50 subunit |
| 15 | protein phosphatase 1, regulatory subunit 12A |
| 16 | ubiquitin-associated protein 2 |
| 17 | stathmin 4 |
| 18 | zinc finger CCCH-type and G-patch domain containing |
| 19 | cell adhesion molecule 3 |
| 20 | ring finger protein 145 |
| 21 | phosphatase and tensin homolog |
| 22 | transmembrane and ubiquitin-like domain containing 1 |
| 23 | casein kinase 2 alpha 2 |
| 24 | MAP-kinase activating death domain |
| 25 | mediator complex subunit 16 |
| 26 | rabphilin 3A |
| 27 | cAMP-regulated phosphoprotein 19 |
| 28 | WW domain binding protein 2 |
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Total of SST⁺ cells

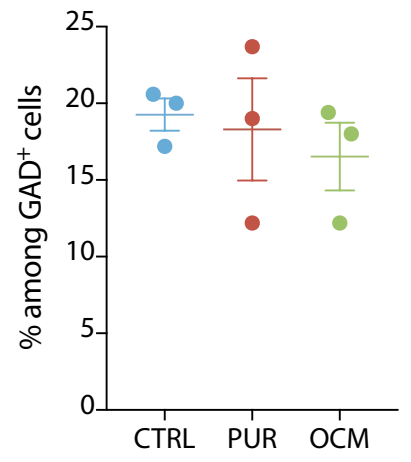


SST⁺/PV⁻ cells

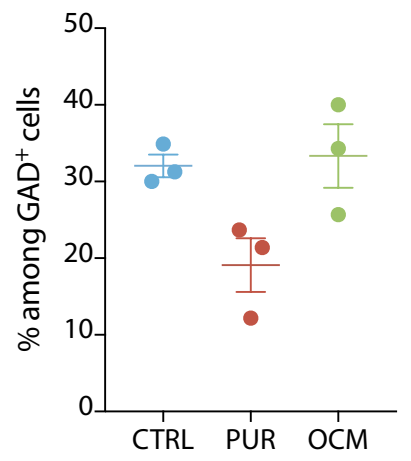
Cerebral Cortex



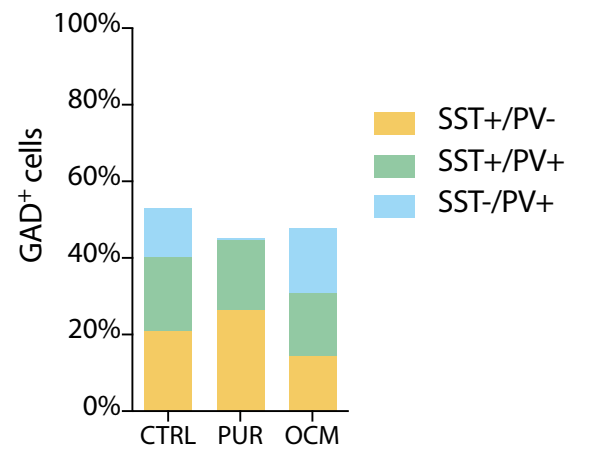
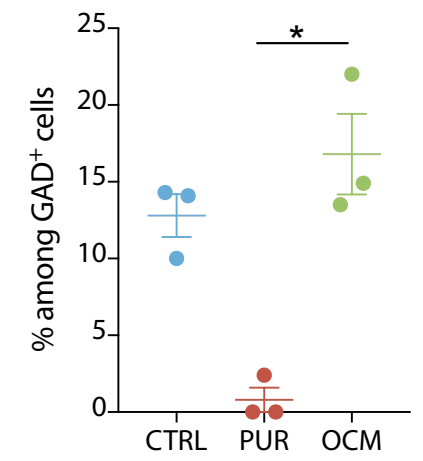
PV⁺/SST⁺ cells



Total of PV⁺ cells



PV⁺/SST⁻ cells



* p<0.05; Kruskal-Wallis test

Quantification of GABAergic neurons (GAD⁺) expressing PV, SST or both in CTRL, PUR and OCM hippocampal cultures. n=3 different cultures; mean ±SEM; about 70 to 100 GAD⁺ neurons were counted on acquired images in each experiment.

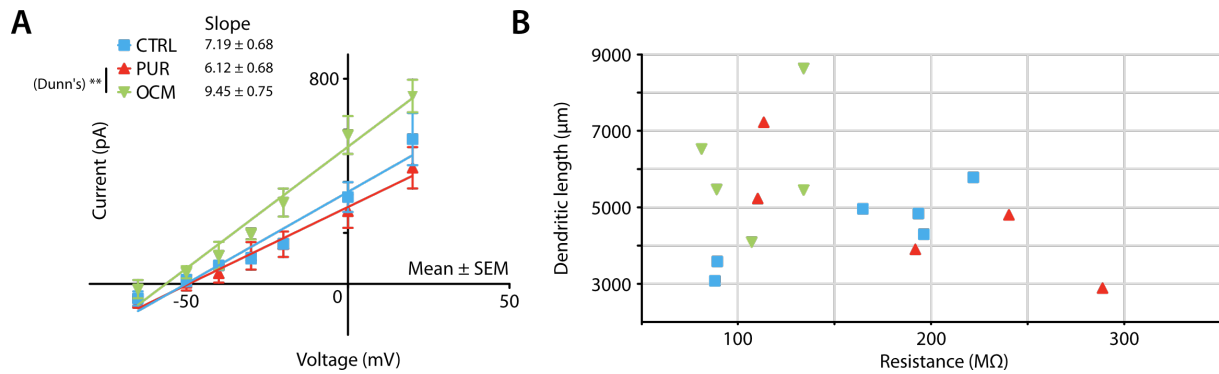
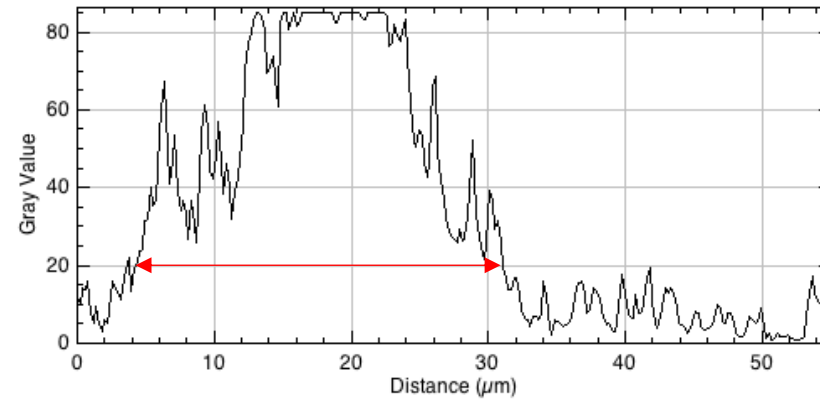
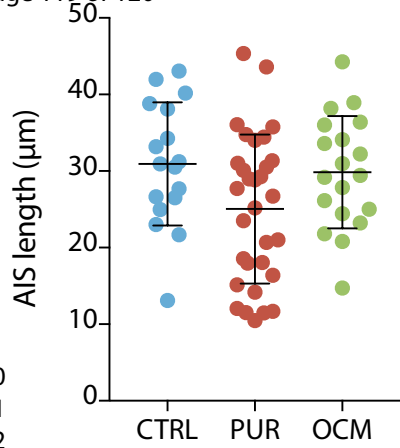
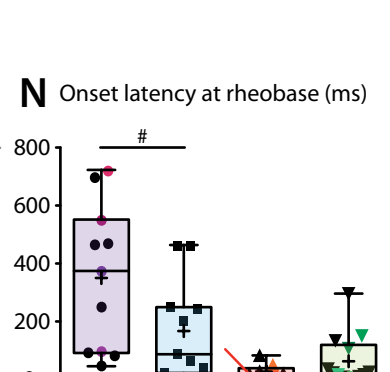
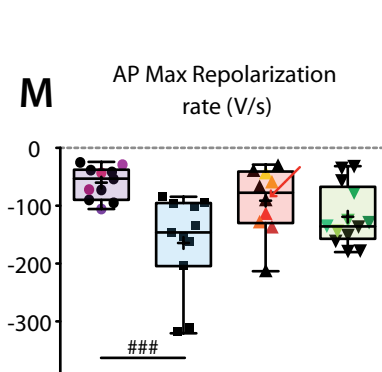
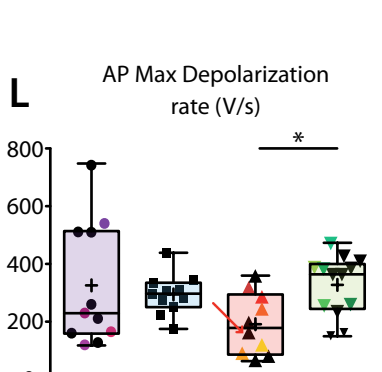
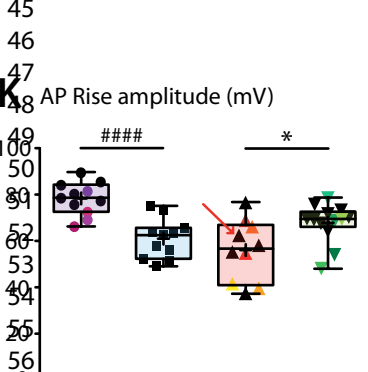
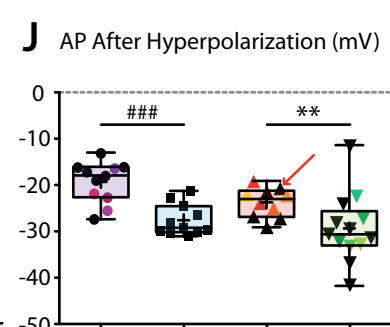
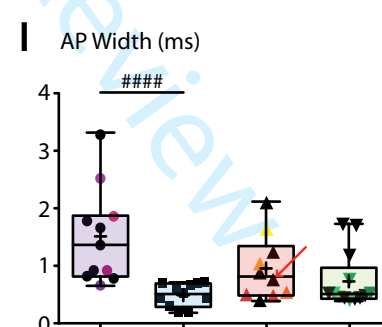
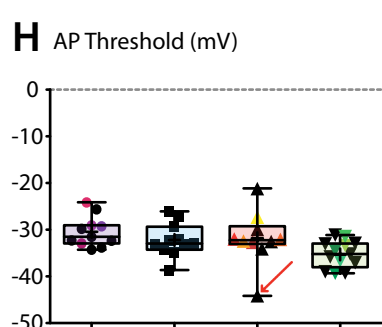
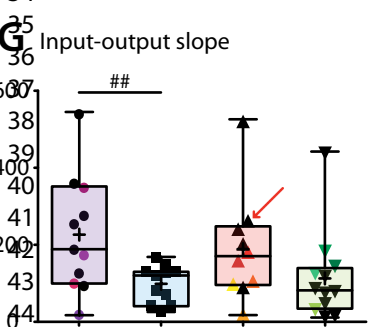
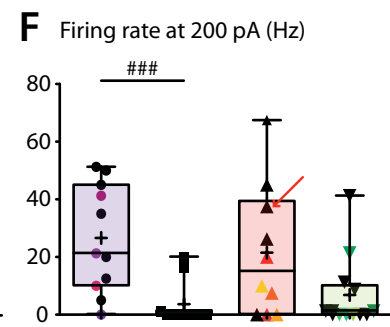
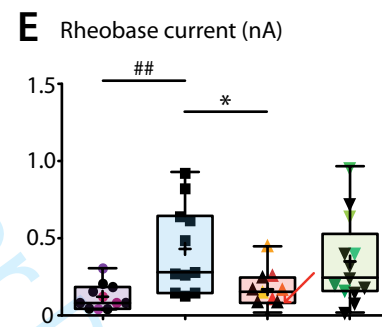
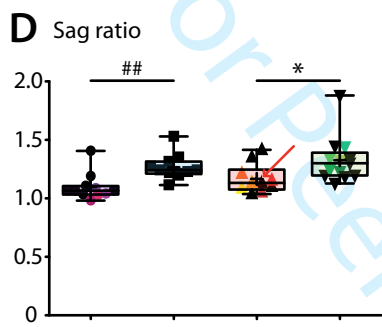
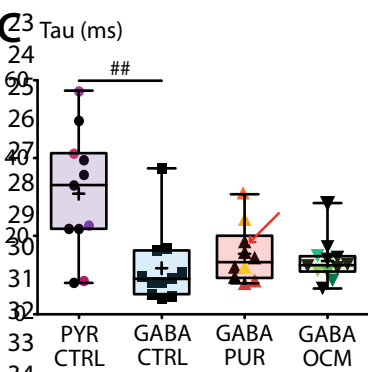
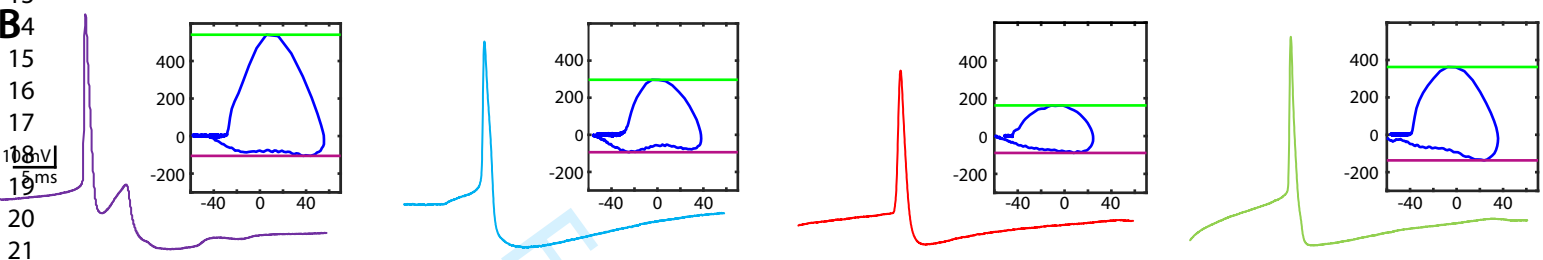
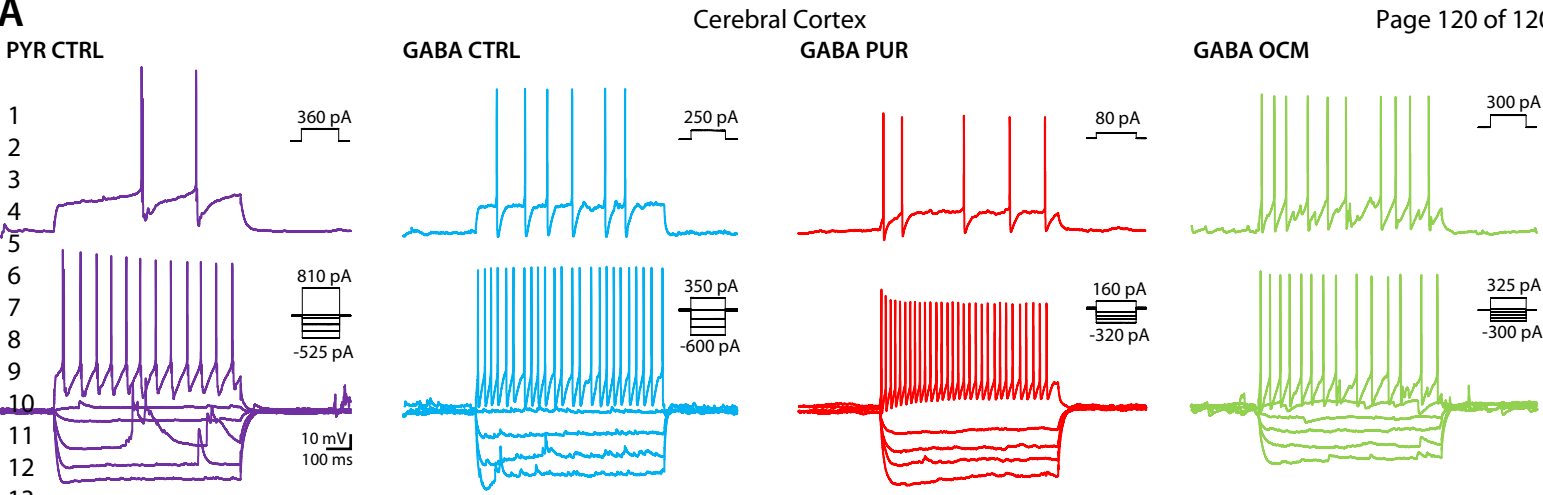


Figure for Reviewer 3. Correlating dendritic length and resistance. (A) I-V curves of GABAergic neurons for the three culture conditions: CTRL $n = 5$, PUR $n = 6$, OCM $n = 5$. I-V curves were obtained for a set of reconstructed neurons (from Figure 3) recorded with Cesium-based internal solution. Cs-based solution was composed of (in mM): CsGluc 125, QX-314 Cl 5, HEPES 10, MgCl₂ 2, EGTA 0.2, MgATP 2H₂O 4, Na₃-GFTP 2H₂O, Na₂-phosphocreatine 10. Biocytin was added to the solution as in the Materials and Methods. Cells were recorded in voltage clamp at holding potentials ranging from -65mV to +20mV. For each potential, an average on 5s of the corresponding steady-state current was measured. The graph gives the mean \pm SEM of currents for each condition. The slopes of these curves were obtained from linear fits. PUR and OCM were significantly different ($p < 0.01$, Dunn's multiple comparison test) indicating that GABAergic cells from OCM cultures had lower resistance than GABAergic cells from PUR ones. (B) Dendritic length as a function of resistance plotted for each cell. GABAergic cells from OCM cultures tended to have lower resistance and greater dendritic length.



Measure of AIS lengths on plot profile of Na_v intensity from acquired images after Na_v and GAD immunostainings of mixed hippocampal neurons (CTRL) and purified neurons in the absence (PUR) or presence of OCM (OCM), at 17 DIV. Data represent mean \pm SD.

Cerebral Cortex



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