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Transcriptomic evidence for alterations in astrocytes and parvalbumin interneurons in bipolar disorder and schizophrenia subjects

Lilah Toker[1,2], **Burak Ogan Mancarci**[1,2,3], **Shreejoy Tripathy**[1,2], and **Paul Pavlidis**[1,2]

[1]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

[2]Michael Smith Laboratories, University of British Columbia, Vancouver, BC, Canada

[3]Graduate Program in Bioinformatics, University of British Columbia, Vancouver, BC, Canada

Abstract

Background: High-throughput expression analyses of post-mortem brain tissue have been widely used to study bipolar disorder and schizophrenia. However, despite the extensive efforts, no consensus has emerged as to the functional interpretation of the findings. We hypothesized that incorporating information on cell type-specific expression would provide new insights.

Methods: We re-analysed 15 publicly available bulk-tissue expression datasets on schizophrenia and bipolar disorder, representing various brain regions from eight different cohorts of subjects (unique subjects: 332 controls, 129 bipolar disorder, 341 schizophrenia). We studied changes in the expression profiles of cell type marker-genes, and evaluated whether these expression profiles could serve as surrogates for relative abundance of their corresponding cells.

Results: In both disorders, we consistently observed an increase in the expression profiles of cortical astrocytes and a decrease in the expression profiles of fast-spiking parvalbumin interneurons. No changes in astrocyte expression profiles were observed in subcortical regions. Furthermore, we found that many of the genes previously identified as differentially expressed in schizophrenia are highly correlated with the expression profiles of astrocytes or fast-spiking parvalbumin interneurons.

Conclusions: Our results indicate convergence of transcriptome studies of schizophrenia and bipolar disorder on changes in cortical astrocytes and fast-spiking parvalbumin interneurons, providing a unified interpretation of numerous studies. We suggest that these changes can be attributed to alterations in the relative abundance of the cells and are important for understanding the pathophysiology of the disorders.

Corresponding author: Paul Pavlidis, paul@msl.ubc.ca, +1-6048274157, 177 Michael Smith Laboratories, 2185 East Mall, Vancouver, BC, V6T 1Z4, Canada.

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Keywords

Gene expression; psychiatric disorders; cell types; cortex; meta-analysis; mitochondria

Introduction

Despite extensive research, a comprehensive understanding of the etiology and pathophysiology of bipolar disorder (BP) and schizophrenia (SCZ) has yet to emerge. The involvement of several biological systems and mechanisms have been proposed, including the immune system, epigenetics, and excitatory-inhibitory balance (1–10). However, the causality, the pathological impact, as well as the crosstalk between these systems remains to be resolved.

Transcriptomics analyses of post-mortem brain tissue have been widely applied in the study of both disorders. In broad strokes, the goal of these analyses is to answer two major questions: Which genes or gene modules are affected by the disease? What is their functional relevance to the disease, if any? Unfortunately, definitive answers have been elusive. The specific genes reported by individual studies rarely overlap (11, 12) even for studies based on the same cohorts of subjects (12, 13). Some level of agreement can be observed at the gene-set level using enrichment analyses based on resources such as the Gene Ontology (GO) (11, 14, 15) or cell type-specific genes (15–19) . In both disorders, downregulated transcripts were repeatedly reported to be enriched in genes related to mitochondrial function (12, 14, 17, 20–22) or being over-expressed in neurons (17–19). Yet, the interpretation of these findings has remained speculative.

In a parallel line of research, numerous studies have evaluated changes in the abundance of specific brain cell types in psychiatric patients using experimental cell counting methods (2, 23–29). As with transcriptome studies, these have yielded conflicting results. The discrepancies among the findings have been previously discussed (2, 30) and attributed to biological factors such as cohort differences, subject variability and different cortical regions analyzed, as well as technical or methodological factors, including relying on a single marker to identify the cells of interest.

It has been previously suggested that some of the transcriptional signal captured from brain tissue of psychiatric patients might represent differences in the number of cells expressing these genes rather than alterations in transcript levels within the cells (18, 31). Thus, while the question of changes in the abundance of specific cell types in psychiatric patients remains open, it would seem sensible to address potential variation in cell numbers in transcriptome studies. However, obtaining counts of cell types is technically difficult and is not available for the existing transcriptomic studies of brain tissue.

Fluctuations in cell type abundance can be directly inferred from bulk tissue transcriptomics data (32–37). These approaches have been successfully ap plied to various tissues, including the brain (35, 36, 38, 39). However, due to the scarcity of reliable markers for brain cell types, to date brain studies have been limited to a small number of relatively broad cell types such as “neurons” (34, 38, 39).

Recently, our group has extended the repertoire of cellular markers for 36 cell types brain-wide using Neuro (40) Expresso, a database of brain cell type expression profiles based on publicly available single- and pooled-cell data (40). We have further demonstrated that summarised expression of these markers (referred to as a Marker Gene Profile, MGP) can be used to infer changes in the abundance of specific cell types across samples (40). While MGPs are not direct measures of cell numbers, they have several advantages in that: 1) they are based on multiple markers for each cell type and thus are less likely to be adversely affected by artifacts or noise in individual genes, 2) They allow assessment of multiple cell types simultaneously, and 3) they provide information on relative cellular abundance in a sample, based on the same data used to evaluate its gene expression levels.

In the current work, our goal was to address two major questions: First, is there consistent evidence for alterations in the abundance of specific brain cell types in BP and SCZ subjects? Second, can alterations in cellular abundance provide a more parsimonious interpretation of previous findings based on traditional differential expression analyses? To address these questions, we re-analyzed 15 publicly available datasets, representing seven different cohorts of subjects. Our results indicate a decrease in neocortical fast spiking parvalbumin-positive interneurons (fsPV) and an increase in astrocytes, in all of the cohorts studied. In addition, we show that many genes previously reported to be differentially expressed in SCZ can be attributed to relative abundance changes in these two cell types. Our results provide a unifying interpretation for multiple transcriptomic studies, and emphasize the need for future studies to incorporate changes related to cellular composition into analysis and interpretation of their observations.

Methods and Materials

Detailed descriptions of the methods are provided in the supplement. Except where noted, analyses were conducted in R version 3.3.2 (41). Scripts and data files underlying the analyses are available through https://github.com/ltoker/CellularChangesPsychiatry .

Datasets

Table S1 contains full information on the datasets analysed. Data from Stanley Medical Research Institute (SMRI) were downloaded from https://www.stanleygenomics.org/stanley. Data for datasets GSE17806, GSE53987, GSE35978, GSE13564, GSE80655 and GSE25219 were downloaded from the Gene Expression Omnibus (GEO) https://www.ncbi.nlm.nih.gov/geo. The McLean dataset was obtained from the Harvard Brain Tissue Resource Center (http://national_databank.mclean.harvard.edu/, accessed in 2004). Information regarding the brain pH and the exact age of the samples in McLean dataset was obtained from an earlier study based on the same cohort of subjects (42).

Data pre-processing

Microarray data were pre-processed and normalized with the “rma” function of the “oligo” or “affy” R packages (43). Probeset to gene annotation s were obtained from Gemma (44) (http://gemma.msl.ubc.ca/). RNAseq data pre-processing is described in supplementary

methods. The data were batch corrected using the “ComBat” function from the “sva” R package (45).

Sex-specific genes (*XIST*, *KDM5D*, *RPS4Y1*) were used to identify misannotated samples (46) and to define the noise threshold. Supplementary table S1 contains the number of misannotated samples and the noise threshold for each of the datasets analysed.

Estimation of marker gene profiles

The general approach for estimation of marker gene profiles was previously described (40). Briefly, marker gene-sets were obtained from NeuroExpresso via neuroexpresso.org (supplementary table S2). Human orthologues were defined using HomoloGene (ftp://ftp.ncbi.nih.gov/pub/HomoloGene/build68/homologene.data) (47). MGPs were calculated for each cell type separately, based on the corresponding marker gene-sets, using Principal component analysis (PCA) (40). To reduce the impact of outlier samples, PCA was repeated 100 times on subsampled data, containing equal number of subjects per group, and the mean score for each sample was used for downstream analyses. QC assessment of MGP analysis outcome are described in supplementary methods.

Statistical analysis of MGPs

For each dataset, a two-sided Wilcoxon rank-sum test was used to compare MGPs between diagnostic groups. Mixed-models were used to pool MGPs across the datasets. For visualization purposes, scores were normalized to the range 0–1.

Gene-MGP correlation

Spearman’s correlation between genes and MGPs of each of the cortical cell types was calculated separately for each of the datasets analysed. List of probesets with altered expression in the cortex of SCZ subjects was obtained from supplementary table 2 in Mistry et al. 2013 (11).

Developmentally regulated genes in fsPV interneurons

Data from a time course of mouse developing fsPV cells (48) was downloaded from GEO (GSE17806). The effect of age on each of the genes on the microarray platform was evaluated using linear models, treating the age of the animals as an ordered factor. Developmentally regulated genes were defined as genes selected while controlling the FDR at 0.01.

Gene expression in human brain cell types

The expression level of top genes correlated with fsPV and astrocyte MGPs in human cell types was evaluated based on single-cell expression data from Darmanis et al. (GSE67835) (40, 49). Only cells purified from adult subjects and classified as astrocytes, endothelial cells, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs) or neurons were used.

Raw cell count data

Raw cell counts from Beasley et al. (27) were downloaded from the Stanley Neuropathology database (http://sncid.stanleyresearch.org/Data/RawData.aspx). For visualization purposes the raw values were normalized to the range 0–1.

Functional enrichment of cortical cell type transcriptomes

Mouse cell type-specific expression profiles were downloaded from the NeuroExpresso database (40). Gene signals were z-transformed and summarised at the cell type level by taking the average of all samples representing the same cell type (normalized scores). The functional role of the overexpressed genes was assessed based on GO annotations using the precision-recall method implemented in ErmineJ (50, 51).

Results

The focus of this paper is analysis of brain cell type marker-gene expression profiles (MGPs) in subjects with BP, SCZ and controls. The MGP analysis assesses coordinated changes in the expression levels of cell type-specific marker genes across samples from bulk tissue. These relative changes can be cautiously interpreted as surrogates of relative abundance of the corresponding cell types (40).

We initially analysed 13 publicly-available expression datasets from multiple brain regions, representing six independent cohorts of subjects. 11/13 datasets included samples from the neocortex (Table 1, supplementary table S1). Our key result is an increase in astrocyte and a decrease in fast-spiking parvalbumin-positive interneuron (fsPV) MGPs in neocortex of both psychiatric groups (Fig. 1–2, supplementary Fig. S3, S11–12). The changes replicated across the individual datasets, with the exception of a single dataset, indicating a decrease in astrocyte MGPs in the BP group (same discrepancy was not observed in two additional datasets from the same cohort of subjects) (Fig. 1–2). For both cell types, the effect sizes were larger in the SCZ than in BP group (median effect difference SCZ *vs.* BP|: Astrocytes 0.053, fsPV cells: −0.052, Fig. 1–2). We confirmed these findings with an alternative cell type profile estimation method (32) (supplementary Fig. S18–20).

To assess the data in aggregate, for each neocortical cell type we performed a “mega-analysis” of all relevant datasets, by fitting a linear mixed-effects model treating subject and study as random effects, while adjusting for the effects of sex, age, PMI and pH. This analysis confirmed the dataset-specific observations, namely, increase in astrocyte MGPs [effect size (95%CI): BP: 0.08(0.04, 0.14); SCZ: 0.11(0.06, 0.15), Fig. 1] and decrease in fsPV MGPs [BP: −0.1(−0.14, - 0.05); SCZ: −0.09(−0.14, −0.05), Fig. 2]. The mega-analysis additionally suggested a reduction in total microglia MGPs in BP subjects and a change in the activation profile of these cells, in both disorders (Fig. 1–2; supplementary Fig. S3). However, these effects were not consistent across individual datasets (Fig. 2). To further assess the reproducibility of our findings, we performed MGP analysis in independent cohorts of subjects from the CommonMind and the PsychEncode Consortia (two additional data sets; supplementary data). These data corroborated our findings (see supplement).

The remainder of the paper is focused on assessing the interpretation and implication of the most consistent findings, related to fsPV and astrocyte cells.

Consistency between MGPs and cell count data

An obvious question is how well changes in MGPs correspond to changes in cell type proportions. In the case of fsPV cells, for two neocortical datasets we had access to raw cell count data based on the same cohort of subjects (27). from two Brodmann areas (BA) - BA46 and BA9. As shown in supplementary Fig. S1, there was an agreement between MGPs and cell counts both at the group and at the sample level (Spearman's correlation: 0.33–0.56). For reference, the correlation between the two experimental cell count data sets was 0.73 (supplementary Fig. S1B). In addition, in both hippocampal datasets we observed a decrease in somatostatin positive interneuron (GabaSSTReln) MGPs, with a stronger effect observed in the SCZ group (supplementary Fig. S2A-B), corroborating experimental cell counts in two independent cohorts of subjects (52–54).

The decrease in fsPV MGPs is not likely to represent immaturity

It was previously proposed that immaturity of fsPV interneurons might be involved in the pathophysiology of both disorders (55, 56). This raises the question of whether our observed changes in the fsPV MGP reflect decreased maturation stage (associated with loss of marker expression), rather than lower cell numbers. To be consistent with a change in maturation, genes downregulated during fsPV development should be negatively correlated with the MGP, while those upregulated should be positively correlated. We first confirmed that this pattern is indeed observed in datasets representing development time-courses (Table 1, Fig. 3A-C). In contrast we found no relation between MGP and the fsPV maturation-related genes in any of our psychiatry datasets, (Fig. 3D, supplementary Fig. S5). Thus, our observation of decreased fsPV MGPs in psychiatric patients is more consistent with a change in the proportions of these cells, than a change in their maturation state.

fsPV cells exhibit enriched expression of genes related to mitochondrial function

One of the more consistent findings from SZ and BP transcriptomic studies is enrichment of mitochondria-related GO terms among the downregulated genes (12, 14, 17, 20–22). Because fsPV cells are considered especially metabolically active (57–61), we hypothesized that the expression level of mitochondria-related transcripts is specifically high in this cell type. If this is true, the decreased abundance of fsPV cells in psychiatric patients would be reflected in a decreased level of multiple mitochondria-related genes in the bulk tissue transcriptome.

We tested our hypothesis by performing enrichment analysis on the NeuroExpresso cell type transcriptomes (see supplementary methods). We observed that mitochondria-related GO terms are the only terms significantly enriched among genes overexpressed in fsPV cells (supplementary tables S5–6). GO terms related to myelination and immune response were enriched in oligodendrocyte and microglia cells, respectively, validating our approach (62) (Supplementary tables S5–6). This suggested that the reported enrichment of mitochondrial terms among the downregulated genes in SCZ and BP might be driven by a decrease in the proportion of fsPV cells. We further performed a differential expression analysis with or

without inclusion of MGPs as covariates in the model, followed by enrichment analysis of the under-expressed genes (supplementary methods). Without MGP adjustment, mitochondria-related terms were highly enriched among the down-regulated genes in both disorders (Fig. 5A, supplementary data files 2–3). In contrast, none of the mitochondria-related GO terms was enriched after adjusting for MGPs (supplementary Fig. S21, supplementary data file 4).

Increase in Astrocyte MGPs in bipolar disorder and schizophrenia is region specific

We analyzed samples from subcortical regions to examine the cortex specificity of our findings. Out of the five subcortical datasets analyzed (Table 1), an increase in the astrocyte MGP was only observed in thalamic samples (supplementary Fig. S6). This region specificity was observed both for MGPs of region-specific astrocyte marker genes and MGPs of cortical astrocyte marker genes (see Methods, supplementary Fig. S6).

A majority of genes differentially expressed in cortical samples of schizophrenic subjects are correlated with astrocyte or fsPV MGPs.

A final question we wished to address was whether our previously reported changes in expression in SCZ (11) were consistent with our new findings. In Mistry et al. (2013), we used a meta-analysis approach to identify genes differentially expressed in SCZ. Using the cell type-specific expression resources available at the time, we had identified a possible downregulation of neuron-associated genes (11) and in a follow-up report, subtle effects on the coexpression of astrocyte-associated genes (17). Here we consider whether MGP analysis can provide a more complete explanation of these earlier observations. In particular, we hypothesised that changes in the expression of some of the genes reported in Mistry et al. (11) might be better explained by changes in cellular abundance as opposed to global regulatory changes.

To test this hypothesis, we assessed the correlation between genes identified in Mistry et al. with the astrocyte and fsPV MGPs calculated here. We made use of the idea that expression of genes that are enriched in specific cell-types should be correlated with their respective MGPs. For example, expression of *PVALB*, a marker of fsPV cells should be highly correlated with fSPV MGP (Fig. 4A). Similar relation can be expected for genes that for various reasons were not considered as markers in our analysis, but are enriched in these cells (see Methods and supplementary Fig. S7-S9). As hypothesised, the vast majority of genes over-expressed in Mistry et al. (11) were positively correlated with astrocyte MGPs, while most of the under-expressed genes were positively correlated with fsPV MGPs (Fig. 4F-D, supplementary Fig. S12-S13).

Discussion

Our main contribution in this paper is a synthesis of many years of study of transcriptomes in the brains of individuals with SCZ and BD in terms of cell type-specific effects. We suggest that the most prominent transcriptomic effects observed from neocortical samples of these subjects can be understood as being driven by changes in two cell types (fsPV interneurons and astrocytes), most readily explained by changes in their abundance

(decrease and increase, respectively). Our results replicate in numerous datasets representing eight different cohorts of subjects. The robustness of our findings is particularly striking given that these datasets have been extensively analysed in previous studies, with little consensus found among differentially expressed genes. Our analysis also indicates that the changes in astrocyte MGPs are region specific, as they were not observed in datasets from hippocampus, striatum and cerebellum of the same subjects.

It is important to note that alterations in these cell types have been previously suggested based on transcriptomic (17, 18) and non-transcriptomic (24 26, 63, 64) data. However, these reports have been accompanied by numerous other findings and claims, partially fed by the apparent inconsistency of the results. We now make a stronger claim: there is a clear transcriptomic signal indicating cell type-specific changes in SCZ and BD, weakening the alternative interpretations such as a general down-regulation of mitochondrial-associated genes or immaturity of interneurons. This is not to say that there are no caveats to our study, nor a lack of room for additional phenomena to be occurring in these disorders, and our discussion attempts to address some of these.

We stress that MGPs are not calibrated against cellular abundance, and thus should not be directly translated to changes in cellular counts (i.e., a 50% decrease in an MGP is not equivalent to 50% reduction in the number of the corresponding cells). Considering the small changes in expression at the gene level (fold change < 1.5) it is clear that any change in proportions must be fairly small. Indeed, the changes reported from experimental cell counts in (26) and (27) are ~33% and 18%, respectively.

MGPs as surrogates for cellular abundance

The idea that levels of cell type-specific marker genes can be used to infer cellular abundance in bulk samples has been used by numerous studies (32, 35, 38), but it is obviously an indirect measure and could be questioned. We feel it is the most likely explanation for several reasons. First, there is no doubt that transcriptomes in bulk tissue change can reflect cell type proportions; this has been validated extensively by ourselves and others. This does not prove that such changes are present in any particular case, but there are reasons to favour this explanation in our study on the grounds of parsimony. For example, the genes most correlated with astrocyte and fsPV MGPs in our study are highly enriched in human astrocytes and neurons, respectively (supplementary Fig S7-S9). This indicates that MGPs are representing not just the behavior of the selected marker genes, but rather of all genes highly expressed in these cell types. Second, multiple effects observed in our analysis at the MGP level corroborate previous studies:

- **a.** Cell type-specific effects of age and sex identified in our analysis (supplementary Fig. S4, supplementary table S3) corroborate findings from previous experimental and computational studies (supplementary table S3).
- **b.** The decrease in fsPV MGPs corroborate cell count studies based on the same cohort of subjects and similar cortical brain region (26, 27).
- **c.** The decrease in hippocampal SST interneuron MGPs corroborate cell counts studies based on different cohorts of subjects.

While in our opinion cell type proportions are the most likely explanation for our findings, we cannot rule out the scenario in which numerous marker genes are coordinately dysregulated, changing the identity phenotype of the cell. Thus, a more conservative interpretation of MGP changes might be a change in the “functional abundance” of these cells.

Integration with previous findings

As mentioned, our findings are in agreement with reports of alterations in fsPV cells (3, 26, 60) in BP and SCZ. Of note, despite the reports of alterations in fsPV cells in psychiatric disorders, the nature of these alterations remains unclear. It was previously argued that reduced PV immunoreactivity in SCZ indicates reduced expression of the protein rather cellular loss (28). However, a microarray study of isolated fsPV cells did not identify changes in the expression level of parvalbumin or any other marker of these cells in SCZ (65). Rather, the authors reported enrichment in apoptosis- and cell-cycle-related pathways, suggesting that at least in some subjects cellular loss might be occurring (65).

Our observation of enrichment in mitochondria-related GO terms among genes overexpressed in fsPV cells is in line with the high metabolic demand of these cells, making them particularly vulnerable to impairments in mitochondrial respiration (57–61, 66). Interestingly, one of the most consistent observations in BD and SCZ are signs of mitochondrial dysfunction, linked to oxidative stress (3, 60, 63, 67–72), providing a plausible etiology for the observed impairment in fsPV circuits. While this observation is supported by numerous direct measurements such as mitochondrial morphology, metabolites and oxidative stress markers, the term “mitochondrial dysfunction” has also been used to describe the observed downregulation of mitochondria related genes in bulk tissue transcriptomics (discussed in (73)). We note that while oxidative stress and mitochondrial dysfunction are related (namely, oxidative stress can result in damaged mitochondria and aberrant mitochondrial function can induce oxidative stress) (74) to our knowledge direct experimental evidence for oxidative stress-induced downregulation of mitochondrial genes is lacking. Thus, our suggestion that the observed downregulation of mitochondria-related genes is a readout of a decrease in fsPV cells does not contradict studies indicating involvement of oxidative stress and mitochondrial dysfunction in psychiatric disorders. Instead, we are suggesting that the bulk tissue transcriptome is not a clear source of evidence for mitochondrial dysfunction or oxidative stress.

Our findings of increased astrocyte MGPs are in line with some but not all experimental studies of astrocyte marker levels and cell counts (2, 23, 67, 75, 76). We note that many of the studies conflicting with our findings are based on the same single cohort of subjects – the Stanley Consortium cohort (for example (67, 75, 77, 78)) , for which both decreased and increased levels of the astrocyte marker GFAP were reported in different Brodmann areas of BP and SCZ subjects (79). This cohort is represented by three datasets in our analysis (Table 1). Of these three datasets, Study2AltarC is an outlier, exhibiting changes in multiple MGPs, and showing a trend for decreased astrocyte MGP (Fig. 2). While multiple reasons were previously suggested to explain the conflicting results (2, 30), one possibility is that changes in astrocytes are region specific.

Implication of alterations in fsPV and astrocyte MGPs

Our results indicate an emerging consensus pointing to effects specific to cortical fsPV cells and astrocytes in SZ and BP. Therefore, we advise that these cell type-specific changes be carefully considered in future studies. Our results also emphasize the need to move from bulk tissue analyses to targeted analyses of specific cell types in order to unequivocally differentiate between alterations taking place at the tissue level (such as changes in cell type proportions) and alterations occurring inside individual cells.

While we provide a revised and unified interpretation for transcriptomic changes previously reported from BP and SCZ subjects, the clinical implication of our findings remains unclear. First, it remains to be determined whether these are mere consequences of the disorders (e.g. due to medication or lifestyle), rather than factors directly involved in their pathophysiology. Next, the considerable overlaps in the calculated MGPs between controls and affected individuals as well as the overlap between BB and SCZ suggest that alterations in these cells represent endophenotypes shared between subgroups of BP and SCZ subjects, rather than disease-specific phenotypes. Finally, endophenotypes do not necessarily mediate between the disease etiology and phenotype (80) and thus, it is important to differentiate whether alterations in astrocytes and fsPV cells are mediators or biomarkers of BP and SCZ pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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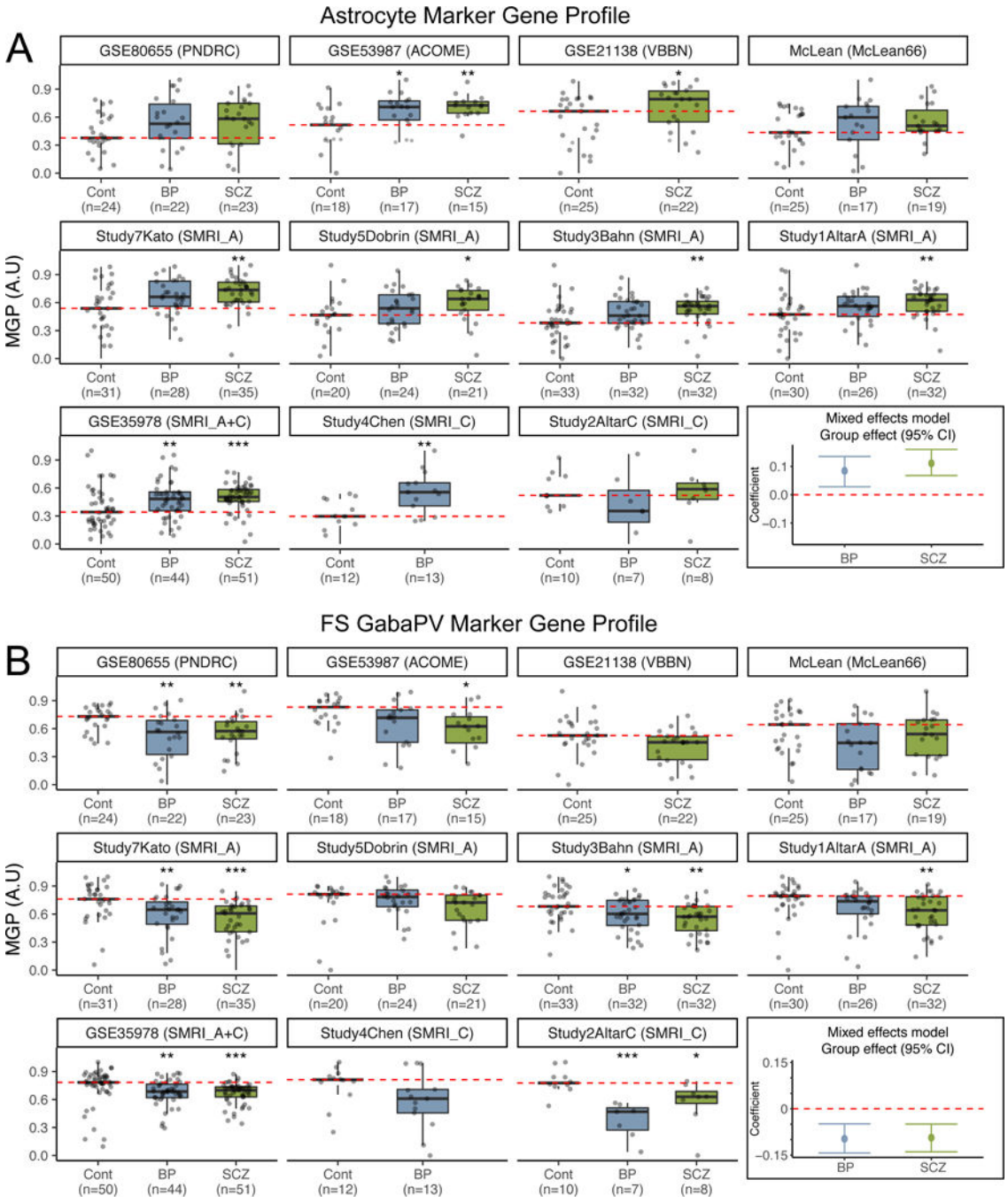

Figure 1: Changes in astrocyte and fsPV MGPs are consistent across cortical datasets from six cohorts

Astrocyte **(A)** and fsPV **(B)** MGPs organized by cohort, dataset and diagnostic group. Each point represents a single sample. Red dashed line indicates the median MGP in the control group. The last plot in each of A and B shows the 95% confidence intervals for the group effects based on linear mixed model analysis. * - Wilcoxon ranked sum p for comparison to controls < 0.05, ** - p < 0.01, *** - p < 0.001.

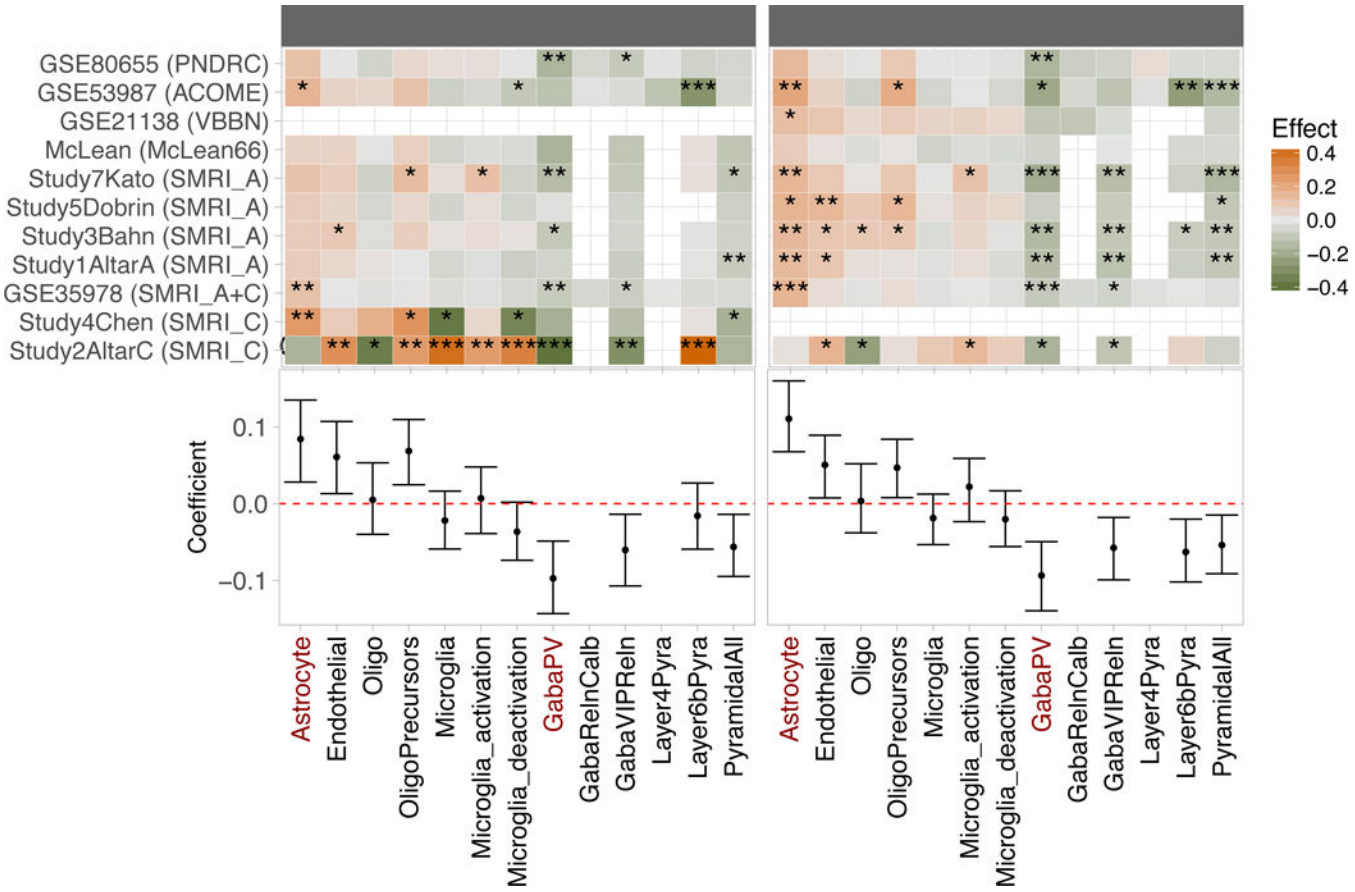

Figure 2: Summary of MGP analysis for all thirteen cell types considered.

Upper panel: Heatmap summarizing shifts in MGPs estiated for each study separately based on the Wilcoxon signed ranked test as in Figure 1. Gaps indicate missing or insufficient data. Datasets and cohorts are indicated as provided in Table 1. * - Wilcoxon p < 0.05, ** - p < 0.01, - p < 0.001. **Lower panel:** Coefficients (95%CI) for fitted linear mixed model. Effects were not calculated for MGPs that could not be estimated for the majority of the studies. Cell types included in the analysis are indicated at the bottom of the figure. Astrocyte and fsPV MGPs are highlighted in red. OPC: Oligodendrocyte precursors; Microglia_act: Microglia_activation; Microglia_deact: Microglia_deactivation; Pyr: pyramidal cells. Refer to supplementary table S2 for detailed description of the cell types.

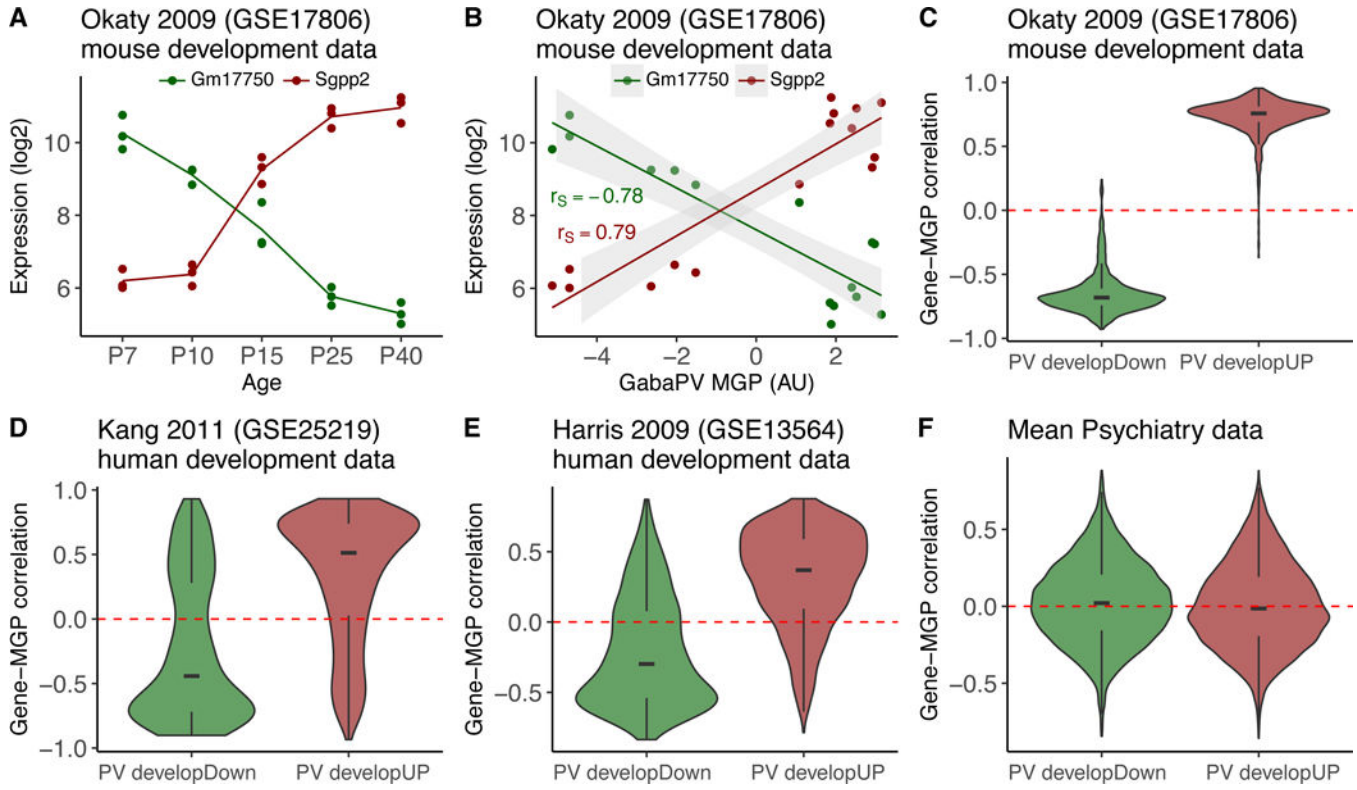

Figure 3: Decreased fsPV MGPs in bipolar disorder and schizophrenia are not likely to represent immature state of these cells.

A,B Illustration of the relation between transcriptomic changes related to maturation of fsPV cells and fsPV MGP, in a mouse dataset representing different developmental stages of these cells. **(A)** Expression levels of *Gm17750* (downregulated) and *Sgpp2* (upregulated) in five developmental ages of fsPV cells. Data are from GSE178206. **(B)** Relation between the expression levels in **A** and the calculated fsPV MGP. The fsPV MGP is positively correlated with *Sgpp2* and negatively correlated with *Gm17750*, as expected (r_s: Spearman correlation). **C-F** Distributions of Spearman correlations with the MGP of all genes downregulated (green; PV developDown) and upregulated (red; PV developUP) during fsPV maturation; dashed red line indicates zero. **C.** Mouse development data (same source of data in A and B) **D.** Human cortex development data (prenatal week 8 – 42 years) **E.** Human cortex development data (ages 2–50) **F.** Mean Gene-MGP correlations aggregated across the psychiatry datasets analysed. Note that correlations of both up- and down-regulated genes is similarly distributes around zero. Correlation plots for individual studies are shown in supplementary figure S5.

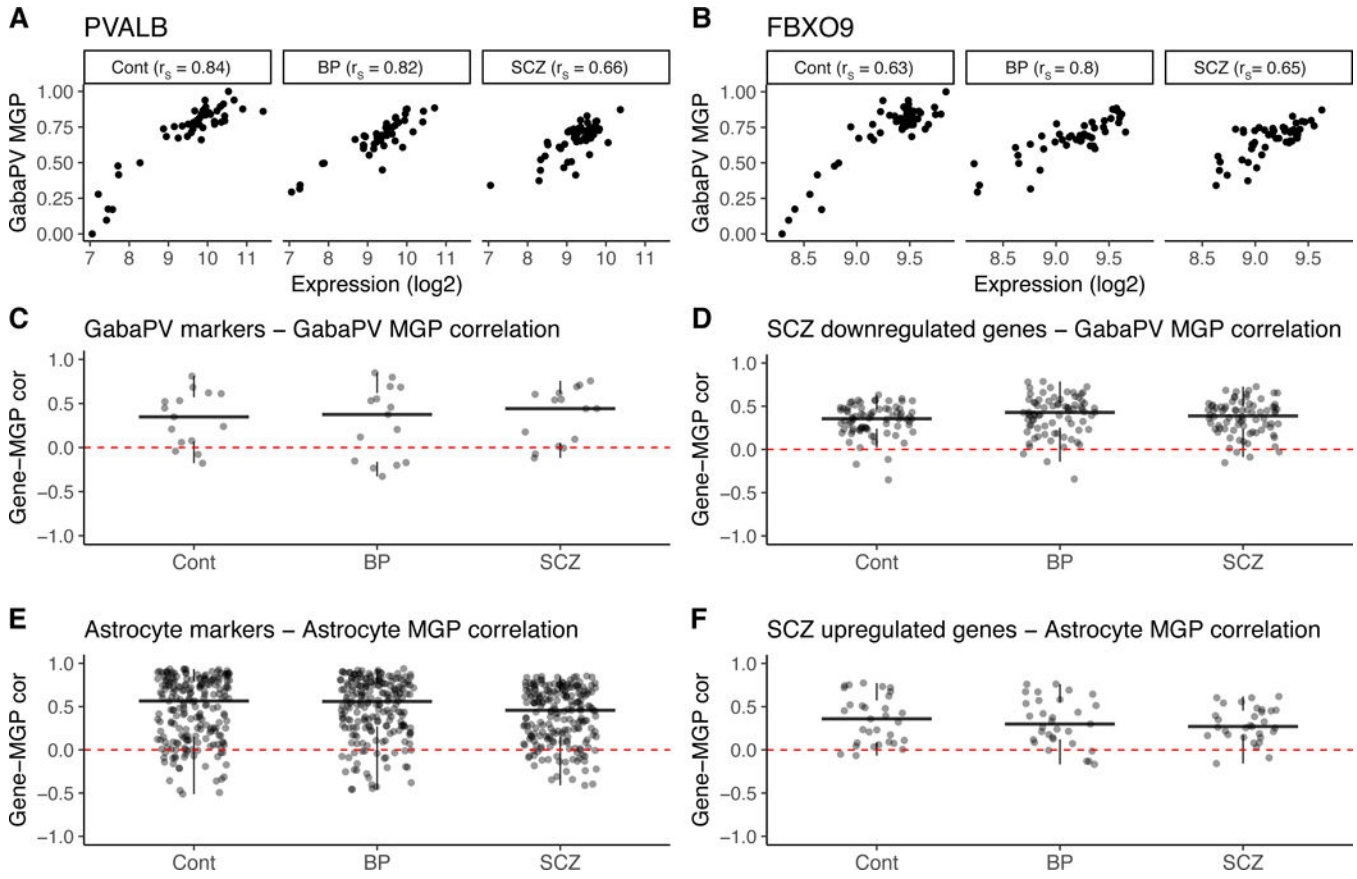

Figure 4: Genes with altered expression in a schizophrenia meta-analysis are highly correlated with astrocyte and fsPV MGPs

A,B. Examples of relations between expression level of individual genes and fsPV MGPs in a representative dataset (GSE35978). **(A)** Relation between the expression level of PVALB, a marker of fsPV cells included in MGP calculation and MGP of these cells. As expected, the two measurements are strongly correlated **(B)** A similar relation is observed for FBXO9, a gene reported by Mistry et al. (11) as downregulated in SCZ (B). r_s – Spearman correlation. **C-F** Correlation of all fsPV and astrocyte markers (**C, E**) or genes reported in Mistry et al. (**D, F**) with fsPV (**C, D**) or astrocyte (**E, F**) MGPs. Each point represents a single gene. Genes above the red dashed line (indicating zero correlation value) are positively correlated with the MGP indicated on the y axis label. Correlations were calculated for each dataset separately; values plotted are means across the 10 cortical datasets analysed in the current study. Data for each study are shown in supplementary figures S12, S13.

Table 1

Dataset	Cohort	Region	Reference	Description
Psychiatry datasets				
GSE21138	VBBN	DLPC (BA46)	(81)	Human bulk tissue
GSE53987	ACOME	DLPC (BA46) Hippocampus Striatum	(82)	Human bulk tissue
McLean	McLean66	DLPC (BA9)	NA	Human bulk tissue
GSE35978	SMRI (A+C)	Parietal cortex, cerebellum	(83)	Human bulk tissue
Study17Laeng	SMRI (A)	Hippocampus	NA	Human bulk tissue
Study1AltarA	SMRI (A)	DLPFC (BA46)	NA	Human bulk tissue
Study3Bahn	SMRI (A)	DLPFC (BA46)	(84)	Human bulk tissue
Study5Dobrin	SMRI (A)	DLPFC (BA46)	NA	Human bulk tissue
Study7Kato	SMRI (A)	DLPFC (BA46)	(21)	Human bulk tissue
Study16Kemether	SMRI (C)	Thalamus	NA	Human bulk tissue
Study2AltarC	SMRI (C)	DLPFC (BA46/BA10)	NA	Human bulk tissue
Study4Chen	SMRI (C)	PFC (BA6)	NA	Human bulk tissue
GSE80655	PNDRC	DLPFC	(18)	Human bulk tissue
PsychEncode	*	DLPFC (BA46)	NA	Human bulk tissue
CommonMind	*	DLPFC (BA9)	NA	Human bulk tissue
Development datasets				
GSE13564	UMBB	PFC	(85)	Human bulk tissue
GSE25219	DNYU	DLPFC	(86)	Human bulk tissue
GSE17806	-----	Cortical fsPV cells	(48)	Pooled mouse cells
Other				
GSE67835	-----	Cortex	(49)	Human single cell

Datasets analyzed in the current study.

VBBN – Victorian Brain Bank Network; ACOME – Allegheny County Office of the Medical Examiner (Pittsburgh, PA); McLean66 – McLean66 coll ection, Harvard Brain Tissue Resource Center, SMRI (A) – Stanley Medical Research institute, Array collection; SMRI (C) – Stanley Medical Research institute, Consortium collection; PNDRC - Pritzker Neuropsychiatric Disorders Research Consortium; UMBB - National Child Health and Human Development Brain and Tissue Bank for Developmental Disorders at the University of Maryland; DNYU - Department of Neurobiology at Yale University School of Medicine. DLPFC – dorsolateral prefrontal cortex; PFC – prefrontal cortex. NA – un published. Reference indicates the publication that first reported the data.

*Details are provided in the supplement.