Cell-Type Specific Reductions in Interneuron Gene Expression within Subregions of the Anterior and Posterior Cingulate Gyrus of Schizophrenia and Bipolar Disorder Subjects

David M. Krolewski [1*], Maria Waselus [1*], Blynn G. Bunney [2], Richard M. Myers [3], Jack D. Barchas [4], Francis S.Y. Lee [4], Alan F. Schatzberg [5], William E. Bunney [2], Huda Akil [1], Stanley J. Watson, Jr. [1]

[1] Michigan Neuroscience Institute, University of Michigan, Ann Arbor, MI, United States of America

[2] University of California-Irvine, Irvine, CA, United States of America

[3] HudsonAlpha Institute for Biotechnology, Huntsville, AL, United States of America

[4] Cornell University, New York, NY, United States of America

[5] Stanford University, Palo Alto, CA, United States of America

*Shared first authorship

Correspondence:

Dr. David M. Krolewski

205 Zina Pitcher Place, Ann Arbor, MI 48109

dkrolews@umich.edu

734-936-2046

Abstract

Schizophrenia (SZ) and bipolar disorder (BP) patients share overlapping and distinct neurocognitive deficits. Neuroimaging of these patients and postmortem gene expression analyses suggest that compromised cingulate gyrus GABA-ergic interneurons may contribute to cognitive impairments in SZ and BP. Therefore, we investigated potential gene expression signatures for SZ and BP using interneuron cell-type specific markers including glutamic acid decarboxylase (GAD67), parvalbumin (PV), somatostatin (SST), and vasoactive intestinal peptide (VIP) within cingulate Brodmann's areas (BA). We report reduced GAD67 mRNA in anterior midcingulate cortex (aMCC) of SZ and BP subjects with BA24c' being most dysregulated across disorders, demonstrating reduced PV (SZ), SST (BP), and VIP mRNA (SZ and BP). Dorsal posterior cingulate (dPCC) displayed decreased SST (BP) whereas retrosplenial cortex (RSC) showed reduced PV (SZ and BP) and SST mRNA (BP). Our results show shared and unique transcription signatures of two disorders in specific cingulate gyrus regions and cell types. SZ and BP show a similar profile of aMCC gene expression reductions suggesting subregional dysregulation within areas associated with error/action monitoring and the saliency network. In dPCC/RSC, transcriptional changes are associated with disease-specific gene/subregion signatures, possibly underlying differential effects on allocation of attentional resources and visuospatial memory processing unique to each disorder.

Introduction

The cingulate gyrus is a functionally heterogeneous cortical structure that mediates various forms of neurocognition including motor control, attention, and memory processing (1,2) which are reported to be compromised in schizophrenia (SZ) and bipolar disorder (BP) (3,4). Coordination of cognitive domains is achieved via cytoarchitecturally parcellated subdivisions, or Brodmann's areas (BA) (5). These include the anterior midcingulate cortex (aMCC; BA32', 24'), dorsal posterior cingulate cortex (dPCC; BAd31, d23), and retrosplenial cortex (RSC; BA30, 29). Often described as dorsal ACC in literature, aMCC mediates error processing, action monitoring, and evaluative learning from action-outcomes concerning reward engagement and pain/fear avoidance behaviors (6,7). dPCC is linked to recognition memory processing and attention set shifting (8,9). RSC is associated with spatial navigation and memory retrieval (10,11).

Despite being highly interconnected (1,2), imaging studies demonstrate integration of aMCC, dPCC, and RSC modular operations through distinct hubs within different resting-state large-scale neurocognitive networks (12,13). dPCC/RSC are components of the default mode network (DMN) characterized by its heightened metabolic status during internally directed attention in the absence of stimulus-driven tasks (14-16). DMN activation drives self-referential constructs including mentalizing, future planning, and autobiographic/episodic memory (17,18). The aMCC-anchored saliency network (SAN) directs attention toward pertinent stimuli, attenuating DMN activity and thereby limiting self-referentiality in favor of filtering interoceptive-autonomic, emotion, and reward processing information (12,19). Higher order goal-directed tasks, e.g., involving working memory, recruit the dorsal lateral prefrontal cortex (DLPFC)-driven central executive network (CEN) which has capacity to bridge with the SAN, co-acting to maintain physiological and stimulus saliency (12,19). According to the triple network model of psychopathology, task information processing is facilitated by SN-mediated switching between the DMN and CEN based upon cognitive demand (12) whereas aberrant inter/intra-network

functional connectivity (FC) is associated with cognitive impairments in SZ and BP patients (20,21).

Evidence suggests that dysfunction of aMCC inhibitory gamma aminobutyric acid (GABA)-ergic interneurons may disrupt local and large-scale networks potentially lending to the neurocognitive manifestations of psychiatric illness. Meta-analyses show that patients with SZ consistently display decreased aMCC GABA levels (22,23). Functional imaging studies demonstrate abnormal associations between aMCC GABA and, as part of the SAN, FC with DMN/CEN nodes in SZ (24-26). Elucidating the pathological underpinnings of proposed dysregulation of cingulate GABA-ergic neurocircuits in SZ has been aided by examination of discrete interneuron subpopulations. Three largely separate GABA-ergic cell-types concordantly producing the GABA synthesizing enzyme glutamic acid decarboxylase (GAD67) with either the calcium-binding protein parvalbumin (PV), neuropeptide somatostatin (SST), or vasoactive intestinal peptide (VIP), exhibit differential synaptic connectivity and collectively coordinate excitatory pyramidal neuron activity (27). As a result, compromised function of any single specific cell-type may reshape corticocortical communication. Indeed, aligned with an aberrant SAN, postmortem gene expression analyses in aMCC of SZ subjects reveal diminished GAD67, PV, and SST mRNA (28,29), suggesting that alteration of both local inhibitory neurocircuits and corresponding pyramidal cell output may contribute to associated neurocognitive deficits.

Notwithstanding compelling evidence connecting aMCC GABA-ergic interneurons to the psychopathology of SZ, there is a clear need for further assessment of the posterior cingulate gyrus in SZ. There is also a dearth of evidence around the dysregulation in BP overall. Thus, we conducted the present in situ hybridization study to evaluate GAD67, PV, SST, and VIP gene expression within distinct BAs of the anterior and posterior cingulate gyrus in SZ and BP postmortem subjects. The results shed further light on the potential mechanisms underlying features of neurocognitive impairment in two psychiatric disorders.

Materials and Methods

Sample collection

Postmortem brain tissue from a total of 72 subjects diagnosed as normal CTR, SZ, or BP were obtained from the Pritzker Brain Bank at the University of California, Irvine (UCI). All studies were approved by the Institutional Review Board of UCI and the University of Michigan. All subjects had zero agonal factors with postmortem interval of <37 hours and pH above 6.5 to ensure mRNA preservation (30,31) (see summaries **Table 1**, also comprehensive demographics **Tables S1 and S2**).

Brain dissection and in situ hybridization (ISH)

Slabs containing the aMCC and dPCC/RSC/ectosplenial (ESC) regions were visually identified with respect to gross anatomical landmarks and subdissected (see Supplemental Methods and **Fig. S1** for representative sagittal brain schematic illustrating gross cingulate dissection locations). Tissue processing methods have been previously described (32). Briefly, following brain removal, coronal slabs of ~0.8 cm were cut, flash-frozen, and stored at -80°C. Blocks were sectioned at 10 µm in a cryostat, thaw mounted onto Superfrost™ Plus glass slides (Fisher Scientific, Pittsburgh, PA), and stored at -80°C. ^{35}S-labeled ISH was performed utilizing gene-specific [^{35}S]UTP and [^{35}S]ATP-labeled cRNA riboprobes for GAD67, PV, SST, and VIP. Slides containing the sections were exposed to film and developed at which point digitized images were quantified with ImageJ software (NIH) to measure signal intensity for each gene. Additional details regarding ISH, quantitative assessment, and image preparation/manipulation are included in Supplemental Methods.

Statistical analysis

Statistical analyses were completed using IBM SPSS Statistics (Version 27) and graphs prepared using GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). Demographic variables of age, pH, and PMI were analyzed using a one-way ANOVA. Gene expression in control subjects was examined using a two-way

ANOVA where anatomical subregion and gene were included as factors. A linear mixed effects model was used to evaluate whether diagnosis of SZ or BP resulted in gene expression changes in aMCC or dPCC/RSC/ESC subregions. The dependent variable, o.d., was stratified by the fixed effects of diagnosis, cingulate subregion, and gene. Subject was included as a random effect and pH as a covariate. For all described analyses, Bonferroni post-hoc correction was used when appropriate. All results were considered statistically significant at $p<0.05$.

Results

Demographic variables

Subject demographics included age, pH, and PMI. Comparisons between CTR, SZ, and BP subject groups in the aMCC and dPCC/RSC/ESC (see **Table 1**, also **Tables S1** and **S2**) indicated that brain pH was significantly different between groups in the aMCC (**Fig. S2B**; $F(2,57)=4.804$, $p=0.012$), with lower brain pH found in BP (pH=6.79) vs. CTR (pH=6.9) subjects (BP < CTR; $p=0.020$). Consequently, pH was included as a covariant in subsequent statistical analyses.

Gene Expression in Control Subjects

Visual inspection of ISH signal demonstrated anticipated distributions for each gene, along with PV gradients in the aMCC and dPCC/RSC/ESC regions of control CTR subjects **(Figs. 1,2)**. The distribution of PV appeared to be more intense in the dorsal aspects of the aMCC (**Fig. 1C,D**) and stronger ventrally within the posterior regions (**Fig. 2C,E**), particularly within the RSC/ESC. In the aMCC, these observations were supported by a significant gene x subregion interaction in CTR ($F(6,208) = 2.965$, $p=0.008$) which indicated that PV expression differed by aMCC subregion ($F(2,208) = 8.019$, $p<0.001$). PV expression was lower in BA24ab' compared to BA32' (**Fig. 1G**; $p<0.001$) and BA24c' (**Fig. 1G**; $p=0.018$). Similarly, the interaction between gene and subregion in the dPCC/RSC/ESC of CTR subjects was significant (F(15,366) =15,366) =20.640, $p<0.001$), and only PV expression varied across dPCC/RSC/ESC subregions ($F(5,366) = 74.664$, $p<0.001$). In the dPCC/RSC/ESC, there was dorsoventral and mediolateral gradient of PV expression, with the lowest PV levels measured dorsally in BAd23c and BAd23b **(Fig. 2C,E,F, Table S3)**.

Ventrally, PV intensity in BAd23a was higher vs. BAd23c and BAd23b (**Fig. 2C,E,F, Table S3;** $p<0.05$). RSC BA30 demonstrated elevated PV vs. BAd23c, BAd23b, and BAd23a (**Fig. 2C,E,F, Table S3;** $p<0.001$). Lastly, BA29 and BA26 were similar ($p>0.05$), expressing the highest PV o.d. compared to all other regions (**Fig. 2C,E,F, Table S3;** $p<0.001$). No variations in GAD67, SST, or VIP o.d. were found between subregions in the aMCC (**Fig. S3 A,C,E**) or dPCC/RSC/ESC of CTRs (**Fig. S3 B,D,F**).

Diagnosis-specific aMCC gene expression

We first determined if aMCC gene expression was different between the CTR, SZ and BP groups. The effect of diagnosis was significant ($F(2,79.312) = 5.872$, $p=0.004$) and indicated interneuron o.d. measurements were lower in SZ ($p=0.020$) and BP ($p=0.009$) groups versus CTR (data not shown). To determine whether the effect of diagnosis was specific to a particular gene, we looked at the interaction between diagnosis and gene and determined that it was significant ($F(9, 169.658) = 92.920$, $p<0.001$). GAD67 ($F(2, 171.706) = 4.307$, $p=0.015$), SST ($F(2,166.427) = 5.272$, $p=0.006$), and VIP ($F(2,58.233) = 3.994$, $p=0.024$) expression all differed by diagnosis, with both SZ (GAD67: $p=0.020$; SST: $p=0.002$, VIP: $p=0.038$) and BP (GAD67: $p=0.009$; SST: $p=0.043$; VIP: $p=0.010$) subjects exhibiting lower mRNA expression than CTR. Differences in PV expression between CTR, SZ and BP groups was not significant ($F(2,124.406) = 3.000$, $p=0.053$).

When examining potential differences in specific genes and their subregional restriction within the aMCC, a significant 3-way interaction was found (diagnosis x gene x subregion; $F(18,90.961) = 3.387$, $p<0.001$). This indicated that aMCC subregions exhibited diagnosis-associated differences in o.d. for each gene. Differences in PV and SST expression were identified exclusively in BA24c' (PV: $F(2,89.262) = 3.094$, $p=0.05$ and SST: $F(2,79.678) = 4.715$, $p=0.012$), where relative to CTR, PV o.d. was decreased in SZ **(Fig. 1H:** 24c' $p=0.022$) while SST expression was lower in BP (**Fig. 1I**: BA24c' $p=0.003$) subjects. For VIP, diagnosis was associated with expression differences in all aMCC subdivisions (BA32': $F(2, 60.790) = 4.191$, $p=0.020$; BA24c': $F(2,57.245) = 4.251$, $p=0.019$; BA24ab': $F(2,71.101) = 3.245$, $p=0.045$). VIP o.d. was lower in SZ compared to CTR in all aMCC regions (**Fig. 1J**: BA32' $p=0.011$; **Fig. 1K**; BA24c'

p=0.010; **Fig. 1L:** BA24ab' p=0.015) and decreased in BP BA32' (**Fig. 1J**: p=0.024) and BA24c' (**Fig. 1K**: p=0.026) vs. CTR. Differences in GAD67 expression between control and diagnosis when the aMCC was broken down by subregion did not reach significance (data not shown). Anatomical localization of aMCC mRNA alterations is schematically summarized in **Fig. S2**.

Diagnosis-specific dPCC/RSC/ESC gene expression

Fixed effects of diagnosis along with gene and/or subregion were examined in the dPCC/RSC/ESC as described for the aMCC. Diagnosis was associated with differences in dPCC/RSC/ESC gene expression (F(2,67.248) = 5.031, p=0.009) showing that gene expression was reduced in SZ (p=0.027) and BP (p=0.020) groups vs. CTR. The significant diagnosis x gene interaction (F(9,325.498) = 106.480, p<0.001) revealed that SST (F(2,104.140) = 6.767, p=0.002) and PV (F(2, 149.348) = 8.989, p<0.001) expression changed with diagnosis. Relative to CTR, SST and PV expression was decreased in SZ (SST: p=0.018, PV: p<0.001) and BP (SST: p<0.001, PV: p=0.008) subjects. The interaction between diagnosis and gene was not significant for either GAD67 or VIP expression in the dPCC/RSC/ESC (p>0.05).

Ultimately, the significant interaction of diagnosis within each combination of gene x subregion (F(45,140)=8.474, p<0.001) indicated diagnosis-specific effects on interneuron genes within dPCC/RSC/ESC subregions. Diagnosis-related differences in SST expression were found in the dPCC (BAd23c: F(2,91.098) = 3.179, p=0.046 and BAd23b: F(2,70.106) = 3.310, p=0.042) as well as in the RSC (BA30: F(2,67.366) = 3.284, p=0.044 and BA29: F(2,68.626) = 3.483, p=0.036). As in the aMCC, SST o.d. was decreased only in BP subjects in the dPCC (**Fig. 2G:** BAd23c p=0.014; **Fig. 2H**: BAd23b p=0.013) and RSC (**Fig. 2I**: BA30 p=0.014; **Fig. 2J:** BA29 p=0.016) vs. CTR. PV expression was significantly different between diagnoses, exclusively in the RSC (BA30: F(2,65.233) = 4.533, p=0.014; BA29: F(2,56.969 = 8.217, p=0.001) and ESC (BA26: F(2,56.523) = 6.704, p=0.002), where PV expression was reduced in SZ vs. both CTR and BP in region BA30 (**Fig. 2K**, vs. CTR p=0.005; vs. BP p=0.034) and vs. CTR in BA29 (**Fig. 2L**, p<0.001), and BA26 (**Fig. 2M**, p=0.001). BP subjects also had lower PV o.d. compared to CTR in BA29 (**Fig. 2L**, p=0.013) and BA26 (**Fig. 2M**, p=0.009). Differences in the expression of

GAD67 and VIP between diagnoses were not found in any dPCC/RSC/ESC subregion ($p>0.05$, data not shown). Anatomical localization of dPCC/RSC/ESC mRNA alterations is schematically summarized in **Fig. S2**.

Discussion

The current study was conducted to enhance the understanding of potential GABA-ergic circuit dysfunction in the cingulate gyrus in two disorders, schizophrenia, and bipolar disorder, with both common and distinct clinical features. Employing neuroanatomical specificity, we report consistent subregional reductions in interneuron-related gene expression in the anterior and posterior cingulate gyrus. Decreased GAD67 and VIP gene expression was exclusive to aMCC and shared by both SZ and BP subjects. However, within aMCC, BA24c' displayed diagnosis-dependent changes showing differentially reduced PV and SST mRNA in SZ and BP, respectively. In the caudal cingulate gyrus, PV reductions were shared by both SZ and BP subjects in RSC whereas SST changes, like those in aMCC, were BP-specific in dPCC and RSC.

Here we discuss the potential functional implications of these local cingulate dysregulations, using as a framework the previously proposed alterations in dynamic shifting between large-scale neurocognitive networks (DMN, SAN, and CEN) in accordance with the triple network of psychopathology.

GAD67 Expression

Our finding of reduced aMCC GAD67 expression in SZ largely agrees with and extends two previous postmortem analyses in this region. Utilizing qPCR, Hashimoto et al. (28) showed downregulated aMCC GAD67 mRNA where its expression was not significantly altered intrinsically, but rather similarly decreased when considered along with expression in DLPFC, primary motor, and visual cortices of SZ subjects. Similar assessment of SZ subjects by Ramaker et al. (29) detected both reduced aMCC GAD67 mRNA and GABA. Taken together with the current analysis, these findings agree with SZ meta-analyses of basal aMCC GABA measurements showing a general reduction (22,23). Disruption of rostral cingulate GABA-ergic

mechanisms is likely not limited to aMCC as prior findings within the anatomically adjacent pregenual ACC (pACC), a DMN hub better attuned to affective responses versus goal-directed behaviors of aMCC (1,2), highlight cortical layer II density deficits of GAD67 mRNA expressing neurons in SZ subjects (33).

Our data revealing reduced aMCC GAD67 in BP is more novel. Ramaker et al. (29), despite examining an overlapping subject cohort with the current investigation, did not uncover reduced aMCC GAD67 mRNA in BP. However, in contrast to several previous aMCC imaging analyses examining BP patients collectively demonstrating non-significant change in that region (23,34), reduced GABA was reported (29) which parallels our GAD67 results. Interestingly, in pACC, dysregulation of GABA-ergic interneurons is better associated with mood. For example, BP subjects exhibit reduced layer II GAD67 mRNA, similar to SZ (33), but also significant density decreases in non-pyramidal, presumably GABA-ergic neurons, in BP and schizoaffective disorder along with consistent albeit non-significant reductions in SZ (35,36). In contrast, comparable investigation in aMCC shows a general increase in non-specific layer VI neurons amongst both BP and SZ subjects (37).

Much of what is known regarding the potential clinical implications of altered cingulate gyrus GABA-ergic systems centers around functional analyses examining the aMCC. Concomitant with glutamate, aMCC GABA encodes evaluative feedback from conflict-driven action-outcomes and that information is subsequently used for future decision-making involving alternative actions (38,39). aMCC-mediated error processing and action monitoring is neurophysiologically assessed by the error-related negativity (ERN) corresponding to local activity in response to incorrect choices and ensuing behavioral correction (40,41). Patients with SZ, psychotic bipolar (42-44) and eurythmic BP, when controlling for depressive symptoms (45), exhibit an attenuated ERN which is connected to poor real-world functioning, negative symptom severity, and compromised executive function in psychotic disorders (43,44).

While reducing aMCC activity via GABAA receptor agonists in healthy subjects is associated with diminished ERN and action monitoring (46), lower aMCC/dPCC GABA levels are correlated with worse executive function in patients with mild cognitive impairment (47). In accord, compared to controls, first-episode psychosis patients (SZ and schizoaffective disorder) display negative correlation between aMCC GABA and total score on the Repeatable Battery for the Assessment of Neuropsychological Status, particularly in the immediate memory and language categories (48). Notably, higher aMCC GABA in first-episode psychosis patients is associated with increased local activity and Stroop task reaction time (response to incongruent and congruent stimuli) (27,28) which agrees with aMCC hyperactivation during working memory tasks in SZ (49). In sum, it is plausible that reduced aMCC GAD67 gene expression in SZ and BP subjects reflects compromised GABA-ergic neurotransmission at rest as well as stimulation of an insufficient cingulate GABA-eric signaling system associated with cognitive deficits. It would therefore be reasonable to hypothesize that reduced GABA-ergic function in this region may contribute to some of the key clinical features seen in both disorders.

Dysregulation of aMCC GABA has also been linked to aberrant large-scale neurocognitive network interactions, particularly concerning the basal ganglia. Meta-analysis demonstrates a strikingly common reduction in aMCC-caudate FC across first-episode psychosis, BP, and psychotic-bipolar patients (50). Compared to controls, reduced aMCC GABA is found in SZ spectrum disorders (22,23) and predicts a more negative FC with the caudate and putamen (26), which are SAN and CEN nodes, respectively, in first-episode psychosis (19). In psychotic bipolar disorder, aMCC-caudate FC is negatively correlated with acuteness of negative symptoms, psychopathology, and Positive and Negative Syndrome Scale (50). In addition, reduced fear perception in BP subjects is paired with decreased activation of the aMCC, caudate, and putamen (51). Of clinical significance, diminished aMCC-caudate FC also serves as a biomarker for SZ spectrum disorders as evidenced by lower strength of FC associated with better response antipsychotic drug treatment (52). Together with a SZ-related loss of correlation between aMCC

GABA and FC with ventral PCC (vPCC) (53), a DMN node involved in visuospatial mnemonic processes (9), aMCC GAD67 mRNA deficits in SZ and BP subjects may contribute to psychomotor deficits through aberrant corticostriatal circuits as well blunted error processing and action monitoring, thereby supporting the triple network hypothesis of psychopathology.

Parvalbumin Expression

Functional relevance of decreased PV gene expression in aMCC BA24c' of SZ subjects and RSC/ectosplenial cortex (ESC) BA30/29/26 in SZ and BP can be posited from the neurophysiological properties of PV cells along with neuroanatomical and functional connectivity. Most PV interneurons are fast-spiking basket cells which utilize perisomal synapses for feedforward and feedback inhibition and generation of gamma band oscillations for synchronizing activity of pyramidal cell assemblies (27,54). Convincing arguments have been made for connecting reduced PV gene expression and GABA-ergic inhibition of DLPFC pyramidal cells to altered gamma oscillatory activity and cognitive deficits in SZ (54). Our results combined with other work showing a trend toward decreased aMCC PV mRNA in SZ (28) alludes to potentially similar deleterious effects of dysregulated BA24c' gamma oscillatory activity on cognition. However, such alterations are probably not locally limited. Several SZ studies examining PV interneurons in BA24c, which corresponds to pACC, indicate reduced somal size and dendritic tree extent as well as increased axonal cartridges and layer V PV+ cell count (55-57). Nevertheless, although the latter concurs with heightened aMCC layer VI neuronal density in SZ (37), our results imply an overall hypofunction of BA24c' PV interneurons, potentially affecting local gamma band oscillatory activity.

Functional imaging studies often show that BA24c' activation associated with cognitive motor control overlaps with BA32', thus acquiring the collective term dorsal aMCC (daMCC) as reviewed by Vogt et al (7). The functional capacity of daMCC is expansive with its activity implicated in divided attention, movement anticipation, and action initiation while also serving as the cingulate region engaged in the monitoring of ongoing action-outcomes (7) and producing

ERN responses (58). Upper primate studies indicate BA24c' function is mediated by reciprocal connections with DLPFC and premotor/supplementary motor cortex in concert with cingulospinal projections (59-62). DLPFC has been hypothesized to mediate resolve of daMCC-detected error responses (6,42) whereas DLPFC lesions alter ERN and associated corrective behavior (64). Given that DLPFC exhibits particularly strong FC with daMCC (67) and classifies as both a SAN node and CEN hub (19), it is tempting to speculate that decreased BA24c' PV expression may point to desynchronization of aMCC-DLPFC gamma oscillatory activity during cognitive motor control tasks in SZ. However, the latter remains unclear.

More implicit evidence for daMCC-mediated cognitive motor control derives from electrical stimulation and blood flow analyses in humans showing its activation linked to body-directed arm movement, head/eye movement, and speech/speech arrest (65,66). Intertwined with this, daMCC interconnection with the insular cortex, another SAN hub, also facilitates emotional salience processing. (67). This is supported by evidence suggesting daMCC encodes value of action-outcomes for valence and arousal (68). In SZ, diminished daMCC activity is associated with impaired processing of affective asymmetry stimuli (69), anticipation of stimulus response (70), self-processing versus others (71), and executive function during N-back, go-no-go, and Stroop tasks (72). Taken together, we speculate downregulation of BA24c' PV mRNA in SZ could be related to affective and cognitive motor control deficits. If so, aberrant daMCC communications with SAN/CEN circuits involving the insular cortex and DLPFC likely play a key role.

Within the caudal cingulate gyrus, RSC/ESC displayed the highest PV gene expression in controls while exhibiting significant BA30/29/26 reductions in SZ and BP. Importantly, interpretating these results within context of previous RSC analyses is made challenging due to potential confounds regarding various past neuroanatomical atlases/schematics incorrectly placing its location caudal to the corpus callosum splenium on the surface of the caudomedial lobule, which is actually vPCC as discussed by Vogt et al. (73). Our in situ hybridization assessment was conducted dorsal to the splenium within what we refer to as anterior RSC (aRSC)

(5,73). Careful attention to brain coordinates reveals aRSC shares functional similarities with its caudal counterpart where lesions induce impairment of visuospatial memory, impaired navigation, and episodic memory (10). Indeed, aRSC activation couples with location/action recollection (9,74), anticipatory allocation of spatial attention (75), autobiographical memory (17), and memory encoding (76). In contrast, while caudal RSC is an integrated node of the self-referential DMN known to be dysregulated in SZ and BP, the role of aRSC is less clear.

Our data suggests stronger PV mRNA reductions in SZ as mean expression values were consistently lower versus BP subjects and reaching significance in RSC BA30. These finding are conceptually in-line with overlapping neurocognitive deficits in SZ and BP where SZ patients are generally more affected. Compared to controls, SZ patients demonstrate increased aRSC activity during self-reflection (77), which is influenced by visuospatial attention (78), as well as enhanced FC with the lingual gyrus (79), suggesting heightened interaction with visual systems. Along these same lines, meta-analysis of patient groups, including SZ, demonstrates increased lingual gyrus activation when evaluated while experiencing visual hallucinations (80). In addition, SZ patients with persistent auditory/verbal hallucinations exhibit increased aRSC-DMN FC and decreased aRSC-hippocampal formation FC (81,82). Reminiscent of a dysfunctional DMN, less aRSC deactivation is observed during word generation in both SZ and BP patients (83). Collectively, lower aRSC PV gene expression points to the possibility of altered gamma oscillations contributing to positive and negative symptoms, particularly in SZ.

Positioned lateral to aRSC BA29 and dorsal to the hippocampal rudiment, also referred to as indusium griseum (73), downregulation of ESC BA26 PV gene expression in SZ and BP is more difficult to interpret. Precise ESC function is unknown due, in large part, to its diminutive size being less than ideal for functional imaging assessments (73). To our knowledge, the current study is the first quantitative gene expression effort in this region. Alongside uniform aRSC PV dysregulation in BA29/30, we hypothesize ESC in SZ and BP subjects may exhibit abnormal filtering of relatively more unrefined visuospatial memory-related information. The latter is likely

to be communicated to a dysfunctional aRSC in SZ and BP for further processing via ESC-BA29 interconnections.

Somatostatin Expression

Contrasting with SZ-associated PV mRNA decreases, cingulate gyrus SST gene expression changes were strongest in BP subjects. These findings agree with comparable SZ and BP studies in orbital frontal cortex and DLPFC showing, although non-significant, lower mean levels of SST mRNA in BP versus SZ (84). In the present report, reduced SST expression was apparent in BP aMCC BA24c', analogous to PV mRNA alterations in SZ, as well as dPCC BA23b/c where it represents the only transcriptional alteration for either diagnosis.

The differential synaptic patterns of SST+ interneuron upon pyramidal cells compared to PV+ cells dictate BA24c' information processing likely differs by diagnosis, creating speculation and potential insight to the less sever, but overlapping psychomotor impairments observed in BP versus SZ. SST+ cells are largely Martinotti type and synapse upon distal dendrites of pyramidal cells (29) which receive afferent input from thalamic, dopaminergic, and long-range cortical afferents (85). Since SST mRNA transcription is activity dependent (86), the altered ERN amplitude in response to action monitoring displayed by BP patients (42,45) may signify reduced ability of BA24c' SST/GABA to sharpen input from long-range cortical and subcortical inputs. SST+ neurons are important for synchronizing distant brain regions for optimal long-range cortical transmissions (29,87). More specifically, while SST interneurons have been linked to generation of theta oscillations (87,89), animal models demonstrate that disruption of SST+ cells also minimizes gamma oscillatory power in response to pharmacological and visual stimuli (89,90). Moreover, suppressing SST or PV gene transcription in medial prefrontal cortical (mPFC) produces similar SZ-like changes in social interaction and cognitive flexibility (91). Thus, similar to dysregulated BA24c' PV in SZ, potential alterations in gamma and/or theta band oscillatory activity due to SST+ cell dysfunction may disrupt local circuits and large-scale cognitive networks mediating error/action monitoring and salience detection.

Regarding reduced SST gene expression in BA23b/c, the more dorsal aspects of dPCC, several meta-analyses associate dPCC with recognition memory and decision-making (9,92,93). As discussed by Foster et al. (2023), as opposed to decision-making contributions based upon implicit value, dPCC more likely assesses environmental prospects by integrating prospective rewards with memory-based context (9). During a cognitively demanding task, the aMCC-anchored SAN suppresses dPCC/vPCC (DMN hubs) and directs switching to the CEN for reallocation of attentional resources (12). However, dPCC BA23b/c functionally differs versus more ventral aspects. When shifting from internally directed attention to conditions of broad-external focus, although still experiencing discernable deactivation, BA23b/c continues to exhibit appreciable activity and increases FC with the CEN (8). Not until a narrower external attentional focus is required that greater deactivation ensues and FC with the CEN and DMN decreases and increases, respectively (8).

In eurythmic cognitively impaired BP patients, increased hyperconnectivity within the DMN is associated with less BA23b/c anticorrelated FC to the CEN (94), suggesting disrupted large-scale neurocognitive network dynamics. In support, lower variability, or more rigidity, of BA23b/c FC to the pACC hub of the DMN is associated with slower psychomotor speed and decreased cognitive set shifting in BP (95). Furthermore, like aMCC BA24c' in BP, FC between dPCC and caudate is reduced (96). Altogether, our data indicate compromised BA23b/c SST+ interneurons may be connected to impairment of both motor control and allocation of attention resources needed for optimal decision-making in BP.

Vasoactive Intestinal Peptide Expression

Unlike all other transcripts examined, reduction of VIP gene expression was observed across all quantified aMCC subregions in SZ as well as daMCC (BA32'/24c') in BP. As a result, as determined by number of genes analyzed, the BA24c' portion of daMCC represents the region most affected within the current aMCC analysis. In addition, decreased VIP mRNA constitutes the only altered transcript in BA32' and BA24ab' irrespective of diagnosis. These findings in the

cingulate gyrus are novel. There are relatively few cortical studies investigating VIP expression in psychiatric illness, but two have reported reduced transcription in DLPFC and orbital frontal cortex of both SZ and BP (28) as well as the primary visual cortex node of the visuospatial working memory network in SZ subjects (97).

VIP+ GABA-ergic interneurons receive long-rang cortical afferent input and specialize in disinhibitory processes by primarily innervating dendrite-targeting SST+ cells thereby increasing the gain of excitatory pyramidal neurons (29). Elevating gain in BA24ab' may be of particular importance regarding avoidance/escape behaviors driven by daMCC (7) considering BA24ab' receives more appreciable input from the amydgala versus daMCC (59) and is uniquely activated by fear (7). Rodent studies show that deactivation of VIP+ interneurons in ACC or mPFC is associated with more time spent in open arms during elevated maze testing (98,99). However, upon further investigation in ACC, activity of VIP+ subpopulations preferentially increase, decrease, or remain neutral according to location in open or closed arms (99). Interestingly, the same environment-specific VIP+ cells do not stay stable over repeated trials as other specific subpopulations are replaced in later testing sessions (99).

In Humans, neuroimaging assessments reveal decreased BA24ab' activity in SZ versus control subjects at rest (100) while also exhibiting reduced deactivation during a facial emotion discrimination requiring matching/labeling of fear and anger depictions (101). Similar studies show patients diagnosed as having high negative schizotypy with anhedonia demonstrate reduced FC between BA24ab' and amygdala under fear and happy conditions (102). Furthermore, diminished FC between BA24ab' and putamen is positively and negatively associated with delusion score and antipsychotic treatment, respectively (103). Thus, decreased BA24ab' VIP expression in SZ subjects revealed here may point to the dysregulation of pyramidal cell gain control required for current and future avoidance behaviors related to fear in SZ patients.

Conclusion

In summary, the present study uncovered divergent and overlapping reductions in interneuron subtype-specific gene expression within the rostral and caudal cingulate gyrus of SZ and BP subjects. Similar aMCC mRNA downregulations, both by gene and subregion, raise the possibility of comparable information processing impairments which may lend to altered error /action monitoring and psychomotor behavior. Caudally, patterns of gene expression changes in SZ and BP are still overlapping, yet more segregated in comparison to the aMCC. This may potentially reflect disparate circuits affecting visuospatial memory processing and attention set shifting. These results shed further light on diagnosis-related alterations in the cingulate gyrus of SZ and BP subjects.

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Table 1: Demographic information for diagnostic groups studied in the aMCC and dPCC/RSC/ESC analyses

	Diagnosis	*Ns*	*Age*	*pH*	*PMI*	*Sex (m:f)*	*Cause of Death*	*Race*
aMCC	Control (CTR)	22	51 ± 13 *32-73*	6.90 ± 0.11 *6.67-7.07*	21.81 ± 6.64 *10.00-36.50*	19:3	Accident: 5 SMC: 16 LTMC: 1	Caucasian: 20 African American: 1 Pacific Islander: 1
	Schizophrenia (SZ)	17	42 ± 10 *24-58*	6.80 ± 0.13 *6.59-7.05*	20.49 ± 8.27 *6.25-34.00*	14:3	Accident: 3 SMC: 8 Suicide: 3 UD/AOD: 3	Caucasian: 17 African American: 1 Asian: 1 Other: 1
	Bipolar Disorder (BP)	21	50 ± 12 *25-70*	6.79 ± 0.15 *6.52-7.05*	22.05 ± 7.15 *9.20-36.00*	13:8	Accident: 5 SMC: 4 Suicide: 10 UD/AOD: 2	Caucasian: 20 Other: 1
dPCC/RSC/ESC	Control (CTR)	21	50 ± 13 *32-73*	6.92 ± 0.12 *6.67-7.10*	22.97 ± 6.65 *10.00-36.50*	19:2	Accident: 5 SMC: 15 LTMC: 1	Caucasian: 18 African American: 1 Asian: 1 Pacific Islander: 1
	Schizophrenia (SZ)	21	43 ± 11 *24-63*	6.80 ± 0.23 *6.19-7.21*	21.89 ± 9.31 *6.25-44.25*	18:3	Accident: 3 SMC: 11 Suicide: 4 UD/AOD: 3	Caucasian: 18 African American: 1 Asian: 1 Other: 1
	Bipolar Disorder (BP)	21	47 ± 13 *23-69*	6.81 ± 0.17 *6.52-7.12*	21.08 ± 7.53 *9.00-36.00*	13:8	Accident: 4 SMC: 4 Suicide: 11 UD/AOD: 2	Caucasian: 20 Other: 1

Table 1: Demographic information for diagnostic groups included in the aMCC and dPCC/RSC/ESC analyses

Summary values are listed for age, pH, and PMI (mean ± standard deviation) for the aMCC and dPCC/RSC/ESC regions by diagnosis, with the range of values for each group italicized below (when appropriate; also, see **Tables S1** and **S2** and **Fig. S2**). aMCC: anterior midcingulate cortex; dPCC: dorsal posterior cingulate cortex; RSC: retrosplenial cortex; ESC: ectosplenial cortex; n: number; m: male; f: female; SMC: sudden medical condition; UD/AOD: undetermined/accidental overdose; LTMC: long-term medical condition; PMI: postmortem interval

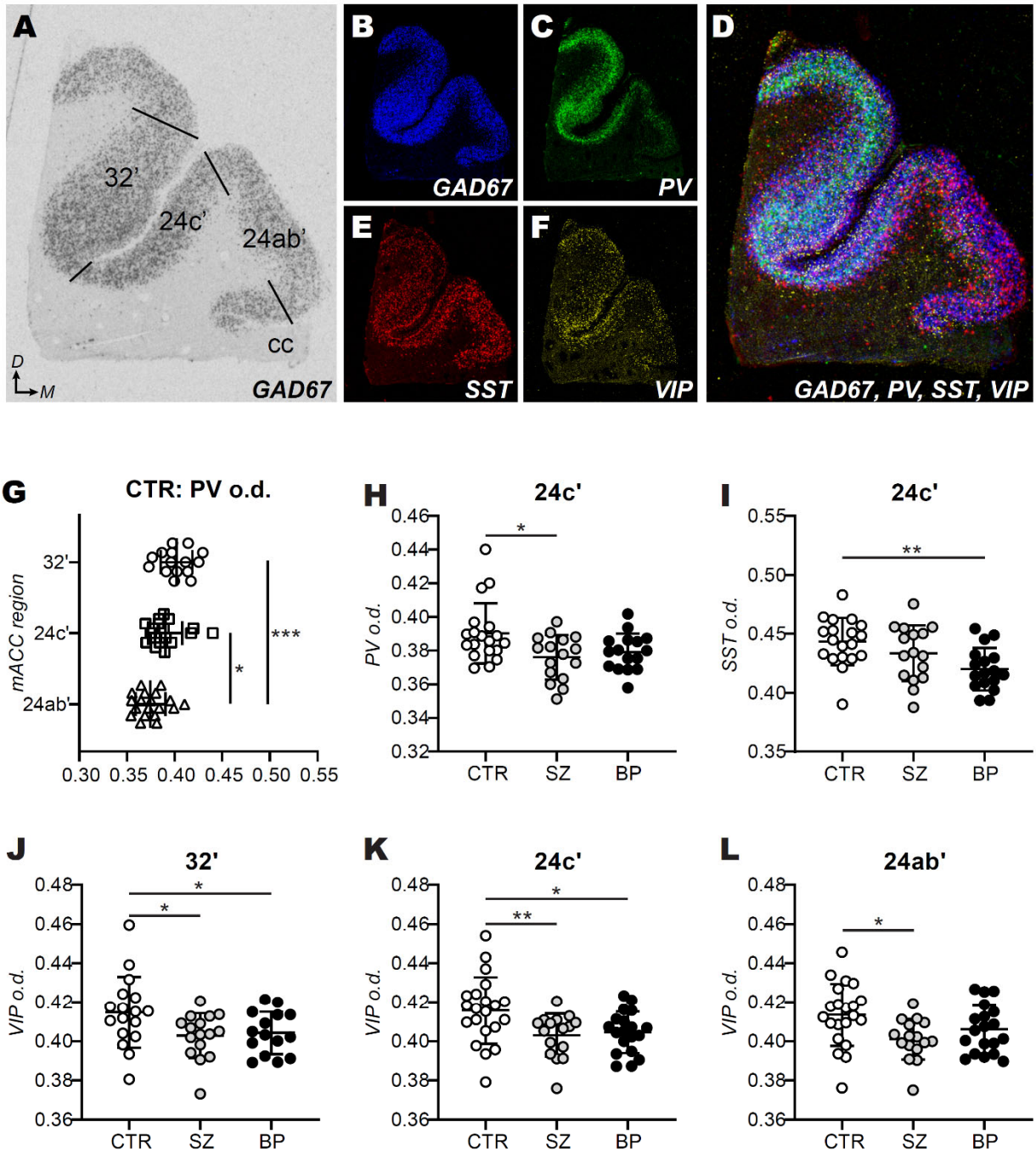

Figure 1 (anterior)
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Figure 1. Interneuron markers exhibit different distribution patterns in aMCC subregions as well as differences in gene expression between healthy control vs. psychiatric groups as revealed by radioactive in situ hybridization

A) GAD67 mRNA expression is shown in regions 32', 24c' and 24ab' of the aMCC. **B-E)** Monocolor images of adjacent in situ hybridization sections were pseudocolored, aligned and **F)** overlayed to examine the relative spatial distributions in gene expression as shown. Note that the distribution of PV within aMCC tissue sections was most varied across subregions (**C,D**). **G)** In healthy control subjects, the average aMCC PV mRNA expression was reduced in region 24ab' compared to region 32' ($p<0.001$) and 24c' ($p=0.018$). **H)** SZ subjects had reduced levels of PV vs. CTR, specifically in region 24c' ($p=0.022$). **I)** Reduced SST expression was also noted in 24c', where BP subjects had reduced expression vs CTR ($p=0.003$). **J-L)** VIP expression was lower in SZ subjects vs CTR in all examined aMCC subregions (**J**: $p=0.024$; **K**: $p=0.010$; **L**: $p=0.015$), while BP subjects also had reduced VIP mRNA in regions 32' (**J**: $p=0.011$) and 24c' (**K**: $p=0.026$) vs. CTR. Each dot (**G-L**) represents one subject. Data is presented as mean +/- standard deviation. ***$p<0.001$; **$p<0.01$; *$p<0.05$

aMCC: anterior midcingulate cortex; cc: corpus callosum; *D*: dorsal; GAD67: glutamic acid decarboxylase 67; *M*: medial; PV: parvalbumin; SST: somatostatin; VIP: vasoactive intestinal peptide

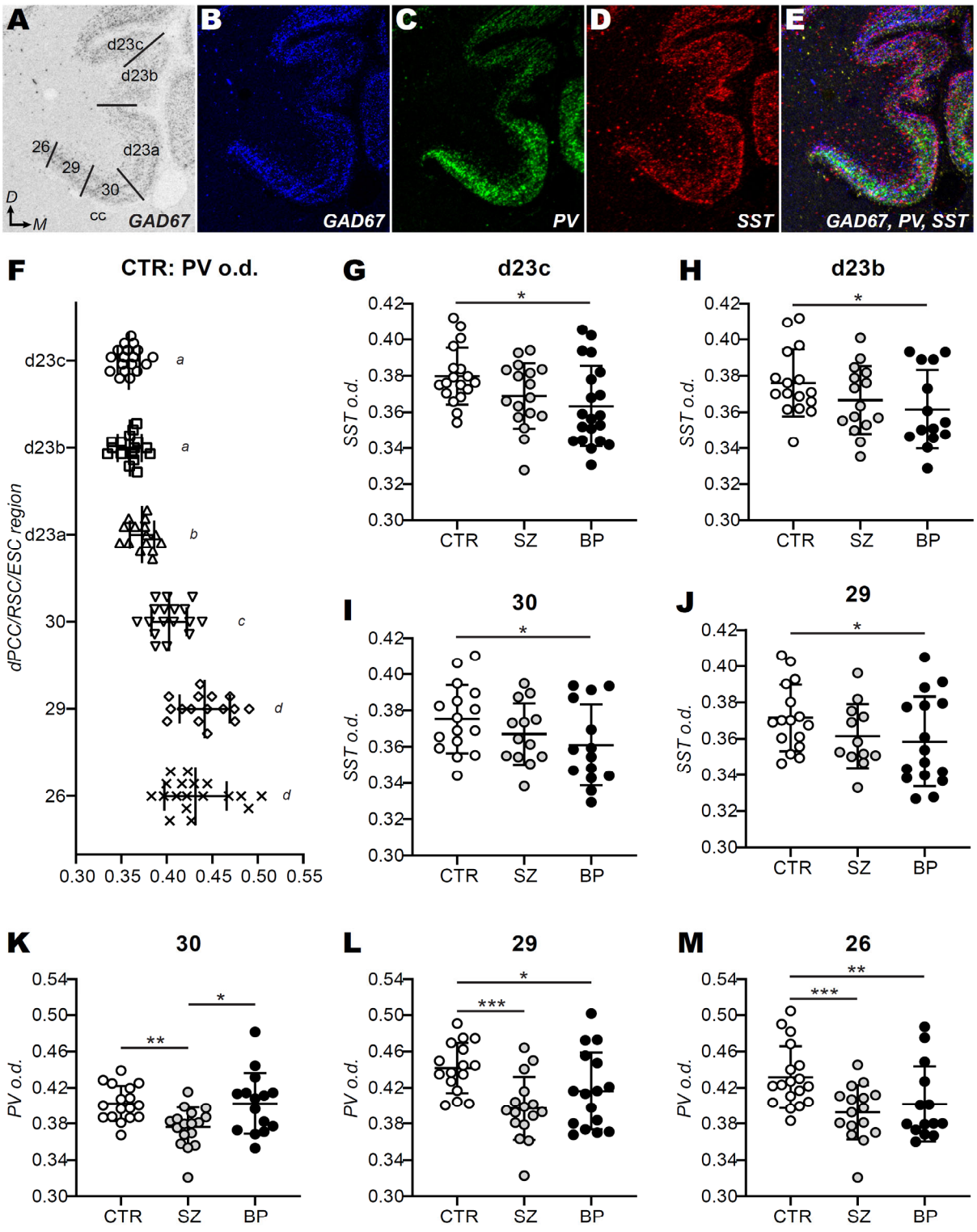

Figure 2 (posterior)
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Figure 2. Distribution and differential expression of interneuron marker genes within the dPCC/RSC/ESC of psychiatric and control subjects

A) GAD67 mRNA expression is shown in the dPCC (regions d23c, d23b, and d23a), the RSC (regions 30 and 29) and ESC (region 26). **B-D)** Monochrome images of adjacent tissues sections processed for in situ hybridization were pseudocolored, aligned and **E)** overlayed using Adobe Photoshop to visually examine the relative distribution of signal (VIP not shown). **F)** There was a gradient of PV expression in the dPCC/RSC/ESC, with regions d23c and d23b having the lowest (and comparable, "*a*") levels of PV expression and regions 29 and 26 exhibiting the most robust (and comparable, "*d*") expression (**C,E**). Significant differences in PV expression between dPCC/RSC/ESC subregions are indicated by different italicized letters (see **Table S3** for detailed group differences). **G-H)** In the dPCC, only SST expression differed significantly between diagnoses, where BP subjects exhibited reduced SST vs. CTRs in region d23c (**G**; p=0.014) and d23b (**H**; p=0.013). **I-J)** SST expression was also significantly reduced in BP vs. control subjects in the RSC (**I**: p=0.014; **J**: p=0.016). **K-M)** PV mRNA differed between diagnoses in the RSC and ESC, where SZ subjects had decreased PV in both the RSC (**K**: SZ vs. CTR: p=0.005; SZ vs. BP: p=0.034; and **L**: SZ vs. CTR: p<0.001) and ESC (**M**: p=0.001). PV expression was also decreased in BP subjects compared to CTRs in RSC region 29 (**L**: p=0.013) and ESC (**M**: p=0.009). Each dot represents one subject; data is presented as mean +/- standard deviation. ***p<0.001; **p<0.01; *p<0.05

BP: Bipolar Disorder subject group; cc: corpus callosum; CTR: non-psychiatric control subject group; *D*: dorsal; dPCC: dorsal posterior cingulate cortex; ESC: ectosplenial cortex; GAD67: glutamic acid decarboxylase 67; *M*: medial; PV: parvalbumin; RSC: retrosplenial cortex; SST: somatostatin; SZ: schizophrenia subject group

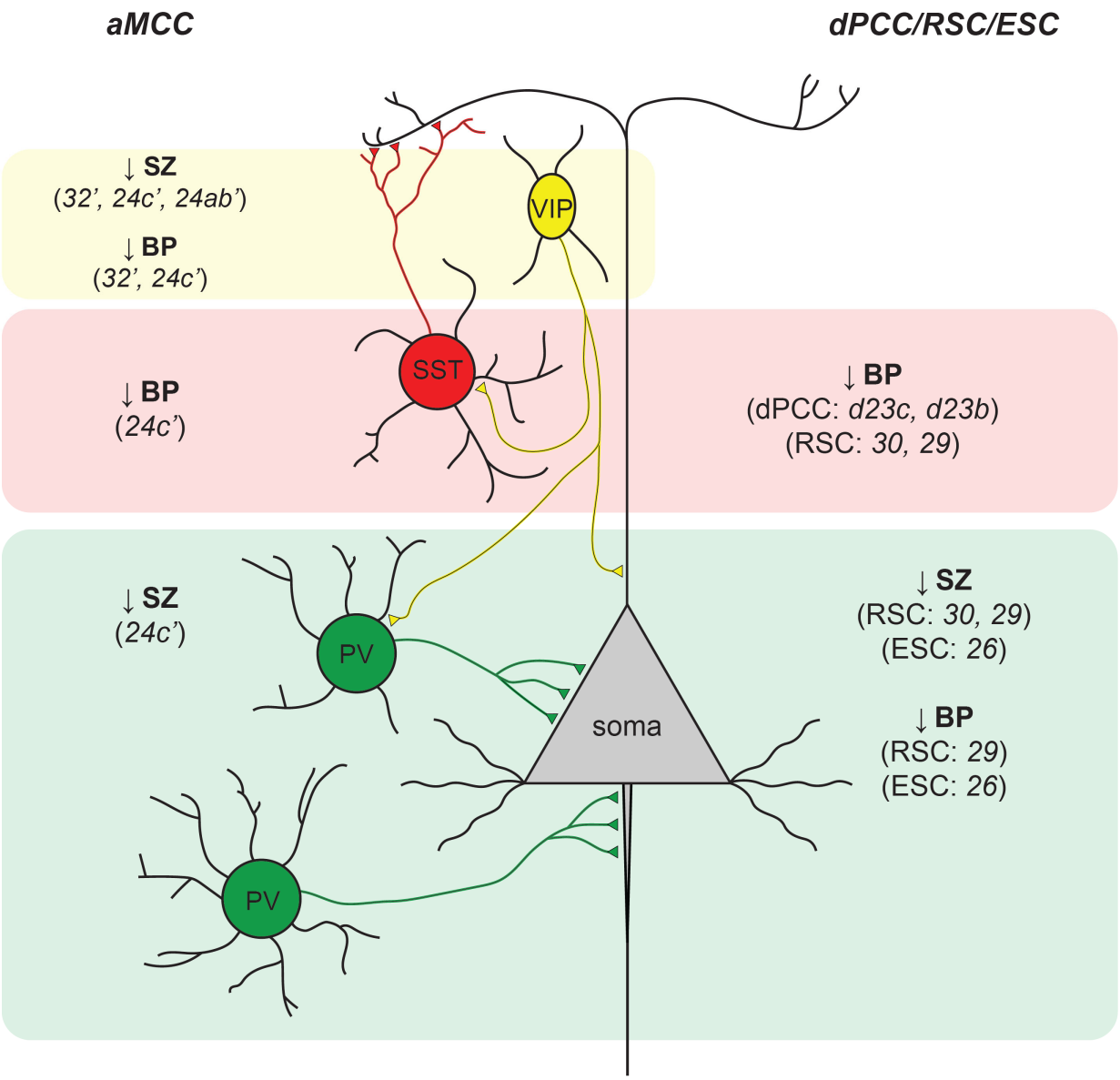

Figure 3
Krolewski and Waselus, et al.,

Figure 3. Summary of interneuron-related gene expression changes

Decreases in the expression of interneuron-related genes (top to bottom, VIP: yellow, SST: red; PV: green) are summarized for both the aMCC (left) and dPCC/RSC/ESC (right) cortical regions. In the aMCC, VIP expression was decreased in both SZ (32', 24c', and 24ab') and BP (regions 32' and 24c') subjects compared to CTR, presumably reflecting a disinhibition of cortical interneurons (e.g., SST and/or PV) as well as decreased inhibition at the apical dendrite of pyramidal neurons. Compared to CTRs, SST expression was decreased in BP subjects in the aMCC (24c') and both the dPCC (regions d23c and d23b) and RSC (regions 30 and 29). These decreases in SST likely occur in Martinotti cells, known to synapse onto the apical tufts of excitatory pyramidal neurons. Decreased PV expression (vs. CTRs) was found in SZ subjects in the aMCC (24c'), RSC (regions 30 and 29) and ESC (region 26) while decreased PV expression in BP subjects (vs CTRs) was only found in the RSC region 29 and ESC (region 26). PV expression is localized to both basket cells and chandelier cells of the aMCC and RSC/ESC where these neurons contact pyramidal neurons at the soma and initial axon segment, respectively.