Commentary

Toward Better Strategies for Understanding Disrupted Cortical Excitatory/Inhibitory Balance in Schizophrenia

Clare Paterson and Amanda J. Law

Cognitive impairment is a core feature of schizophrenia (SCZ) and a potential biomarker of functional outcome. Knowledge of the underlying molecular and neural network mechanisms has the potential to aid in the development of procognitive treatments to alleviate the burden of illness. While the pathophysiology is not well understood, impairments in executive function in SCZ are purported to result from abnormal intracortical connectivity and disruption of integrated information flow between neuroanatomical networks, in particular those involving the prefrontal and posterior parietal cortex (1,2). Consistently, neuroimaging studies in SCZ identify abnormal structural and functional patterns of connectivity across spatially distributed working memory networks (1,2). In the current issue of Biological Psychiatry, Hoftman et al. (3) provide novel evidence to support altered brain connectivity in SCZ at the molecular level.

It is known that efficient network connectivity in the brain requires homeostatic control of excitatory/inhibitory (E-I) balance, a process that is established early in brain development (4) and is maintained by a functional balance between the expression and activity of glutamatergic and gamma-aminobutyric acidergic (GABAergic) systems. Notably, the deregulation of E-I balance is associated with various human brain disorders, including epilepsy, autism spectrum disorder, and SCZ. Several postmortem human brain studies of SCZ provide support for transcriptional changes in both glutamatergic and GABAergic-related transcripts, most notably alterations in the expression of the principal enzyme responsible for cortical GABA synthesis, GAD67 (5), as well as ionotropic N-methyl-D-aspartate receptor subunits. To date, most of these studies have used homogenate approaches to the investigation of single brain regions, considered in isolation. Given that different cortical regions and cortical lamina are composed of diverse cell populations, it is likely that the E-I balance is differentially scaled in each region for optimal network function. In SCZ, deficits in cognitive function may be due, in part, to disrupted networks of gene expression across multiple cortical modalities and in specific cell populations.

To address this question, Hoftman et al. (3) performed quantitative gene expression profiling in human postmortem brain tissue for key markers of glutamate and GABA neurotransmission, exclusively in lamina 3 and across four cortical nodes, spanning rostral to caudal across the visuospatial working memory (vsWM) network, including the dorsolateral prefrontal cortex, posterior parietal cortex, association visual cortex, and primary visual cortex. Hoftman et al. (3) test the hypothesis that regional patterns of glutamate- and GABA-related gene expression are altered in SCZ within and across the vsWM network. To examine the spatial and gradient dynamics of gene expression in the vsWM network, the authors selected several representative transcripts of both neurotransmitter systems, including synthesis enzymes, transporters, and receptor subunits.

Using this approach, Hoftman et al. (3) demonstrate that in the vsWM network, unaffected individuals exhibit a pattern of increasing expression levels of glutamate transcripts vGLUT1, EAAT2, and GRIA2 from the caudal to rostral regions. Conversely, GABA transcripts GAD67, vGAT, and GABRG2 showed the opposite expression profile across these regions, with GABA-related markers being lower in the dorsolateral prefrontal cortex and higher in the visual cortex. These results of opposing interregional gradients are supportive of previous reports that key properties of neurons differ across cortical nodes. To further expand upon their findings, the authors conduct a well-designed study comparing 20 matched pairs of individuals with SCZ to unaffected individuals. Carefully controlling for confounding variables, the authors demonstrate that in a region-specific manner the pattern of GABA and glutamate markers is imbalanced in SCZ across the vsWM network. Specifically, for the glutamate-related transcript vGLUT1, expression was significantly decreased in SCZ across all regions of the vsWM network examined, while EAAT2 expression was selectively increased in visual cortices, and GRIN1 expression was increased in the primary visual cortex in patients; no expression changes were observed across the vsWM network for GLST1 or GRIA2. For GABA-related transcripts, the authors identified disease-associated decreased expression of vGAT specifically in the posterior parietal cortex but noted no significant changes in expression of GAD67, GAT1, or GABRG2. Because of the relatively small sample size and integration of both factors of diagnosis and region into the statistical analyses, the strength of statistical association of the individual gene expression findings was in some instances modest.

Notably, however, where the current study excels is that by systematically examining multiple transcripts of each neurotransmitter system across multiple nodes of the cortical vsWM network and in a specific lamina, the authors were able to compute “composite” measures of the gradient expression pattern of glutamate and GABA-signaling molecules. Remarkably, in SCZ, because of the transcript- and region-specific alterations

SEE CORRESPONDING ARTICLE ON PAGE 670
in individual transcript expression, the normally occurring rostral-to-caudal decreasing gradient of glutamate is blunted, whereas the normally occurring rostral-to-caudal increasing gradient of GABA is enhanced (Figure 1). Hoffman et al. (3) hypothesize that this shift in the balance of gene expression across the vsWM network may impair cortical microcircuitry and perhaps be responsible for the disruption in cortical oscillations observed in patients and subsequent working memory deficits.

Overall, the data presented by Hoffman et al. (3) demonstrate disease-related shifts in the balance between glutamatergic and GABAergic neurotransmission in lamina 3 of the vsWM network in SCZ. These findings represent an important advance and suggest that the relationship between cortical E-I balance is spatially complex and likely dependent upon specialized regional interactions and cellular composition. Furthermore, the work by Hoffman et al. (3) also highlights that global therapeutic targeting of GABA or glutamate neurotransmission may be ineffective for the treatment of working memory deficits in SCZ. Additional work replicating and expanding on the original data of Hoffman et al. (3) has the potential to establish the molecular correlates of cortical node dysconnectivity in SCZ.

Although not addressed in the current study, it is likely that the observed shifts in glutamate and GABA-related markers in SCZ originate during early development and are under genetic control. With regard to the vsWM network, the trajectory of maturation is protracted and consequently susceptible to insult during development (4,6). It is therefore possible that developmental malformation of the studied cortical nodes—i.e., misplacement, morphological maturation, or altered cellular number of either pyramidal neurons or interneurons during developmental periods preceding the onset of SCZ diagnosis—may be responsible for the observed disease-related shifts reported in the current study. Indeed, altered density, synaptic properties, and morphological features of neurons, particularly in lamina 3, have been previously reported in SCZ (7). In addition, previous topographical gene expression studies have demonstrated that in the human brain the greatest interareal differences in cortical gene expression are found prenatally (8). Moreover, expression trajectories of GABA-signaling molecules including GAD65, GAD67, and SLC12A2 (NKCC1) and SLC12A5 (KCC2) are temporally regulated across the lifespan and altered in SCZ (4). Finally, in agreement with the current study, an interregional, cross-cortical, coexpression network analysis identified that the normally occurring differential expression of GABA-related genes across cortical regions is enhanced in SCZ, whereas the normally occurring differential expression of glutamate-related genes, across regions, is diminished (9).

In addition to assessing the temporal dynamics of gradient changes, future studies exploring genetic determinants that drive the shift in GABA and glutamate gene expression are needed. Several glutamate- and GABA-related genes harbor risk-associated polymorphisms that predict altered cortical expression levels in SCZ (4); polymorphisms in glutamate-related genes have been identified in recent genome-wide association studies (10). As well as genetic determinants, epigenetic and environmental events in utero likely play critical roles in the patterning of E-I balance and warrant future investigation.

In summary, the research of Hoffman et al. (3) advances our understanding of the molecular correlates of altered E-I balance in SCZ and represents an important next step to refocusing post-mortem human brain studies to include systems-level analyses as an approach to better understand the neuropathophysiology of SCZ.

Acknowledgments and Disclosures

This work was supported by National Institute of Mental Health Grant No. R01MH103716 (to AJL). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Departments of Psychiatry (CP, AJL) and Cell and Developmental Biology (AJL), School of Medicine, University of Colorado, Aurora, Colorado. Address correspondence to Amanda J. Law, B.Sc. (Hons), M.Sc., Ph.D., Departments of Psychiatry and Cell and Developmental Biology, Nancy L. Gary Endowed Chair in Children’s Mental Disorders Research, Director, Neurodevelopmental and Neuropsychiatric Genetics Lab, University of Colorado, School of Medicine, 12700 East 19th Avenue, Mailstop 8619, RC2, Room 4100C, Aurora, CO 80045; E-mail: amanda.law@ucdenver.edu. Received Feb 21, 2018; accepted Feb 21, 2018.

References

GAD1 in cortical development and schizophrenia. J Neurosci 31:11088–11095.


