

Rebalancing Altered Computations: Considering the Role of Neural Excitation and Inhibition Balance Across the Psychiatric Spectrum

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A fundamental property of both local cortical and long-range neural computations involves a balanced communication between two principal neuronal populations—excitatory and inhibitory neurons. The precise mechanisms governing excitatory/inhibitory (E/I) balance across cortical circuits are complex and varied. Consequently, the number of possible ways by which this functional property could malfunction is similarly vast and multifaceted. For instance, malfunctions in E/I balance could involve architectural deficits in cell structure, dendritic arborization abnormalities, focal synaptic deficits on specific neuronal types, alterations in expression of proteins that form receptors on the cell surface, dysfunctional synthesis of specific neurotransmitters, or malfunction in long-range feedback and feedforward cortical-thalamic interactions. These examples, which are by no means an exhaustive list, highlight the emerging challenge faced by clinical neuroscience: while our understanding of basic neurobiology is pushing the field closer to mechanism, the number of causal upstream pathogenic mechanisms that could alter E/I balance and consequently lead to a downstream harmful behavioral dysfunction seems daunting. In other words, we are facing a many-to-one—or even many-to-many—mapping problem when attempting to link mechanisms governing E/I imbalance to behavior. More formally, E/I balance could malfunction in N ways owing to P mechanisms, which could in turn lead to R distinct neural features, which may exhibit a set of convergent neural pathways. To make matters more complex, the $N \times P$ mechanisms may vary over time owing to the time-dependent nature of neural development and gene expression.

Despite this massive computational complexity, it is encouraging that the field is continuously embracing neurobiologically grounded evidence needed for rational mapping of dysfunction via conceptual frameworks such as altered neural E/I balance. However, to circumvent the risk of “E/I imbalance” becoming a broad catch-all for cortical pathology, it is vital to concurrently refine the idea of E/I imbalance into a more mechanistically relevant set of experimentally testable hypotheses that can be applied across psychiatric spectrums. This Special Issue of *Biological Psychiatry* brings together reviews and commentaries that engage the idea of E/I balance as a central theme in clinical neuroscience research. The topics include translational, pharmacological, and neuroimaging perspectives on how E/I imbalance may be disrupted and play a role cross-diagnostically in schizophrenia, autism spectrum disorders (ASDs), and major depressive disorder.

First, Anticevic and Lisman (1) engage an unresolved tension in the field of schizophrenia research between two competing hypotheses concerning E/I imbalance: on one

hand, evidence supports the model that neuropathology affecting E/I balance may be present across the brain; on the other hand, focal dysfunction in a few key “hotspots” may drive the observed neuropathology in people diagnosed with schizophrenia. Next, building on this tension, Krystal *et al.* (2) review how consequences of impaired tuning of neural ensembles may underlie functional impairments resulting from the pathophysiology of schizophrenia. Their review takes on a translational and computational neuroscience perspective to consider how synaptic deficits that regulate E/I balance can ultimately lead to disrupted network regulation at the level of neural systems. In addition, the review discusses homeostatic time-dependent adaptations to network function that may stem from attempts of the circuits to “rebalance,” but with downstream functional consequences on optimal network tuning. Next, Heeger *et al.* (3) place the focus on the visual system as a translational and experimental test bed for putative E/I imbalance, particularly in ASDs. Hoftman *et al.* (4) engage the complexity of the current state-of-the-art evidence supporting cortical microcircuit alterations in schizophrenia. In particular, their review highlights three topics: 1) emerging evidence supporting cortical layer 3 circuit alterations in schizophrenia, 2) neurodevelopmental changes that sculpt the circuits needed for executive function and how E/I imbalance in layer 3 circuit alterations may relate to cognitive deficits in schizophrenia, and 3) how such E/I imbalance in cortical circuitry may stem from adverse environmental events. Tatti *et al.* (5) turn to a broader perspective on regulation and integration of E/I inputs in healthy neocortical circuits with the focus on how distinct insults to this E/I balance regulation could manifest cross-diagnostically across pathological phenotypes.

Building on the cross-diagnostic objectives of this Special Issue, Lener *et al.* (6) present a view for how altered E/I balance may contribute to neural and behavioral deficits in major depressive disorder. Specifically, they review therapeutic evidence supporting the roles of glutamate and gamma-aminobutyric acid systems in antidepressant responses to the *N*-methyl-D-aspartate receptor antagonist ketamine. This review in particular highlights the computational complexity of E/I balance and its cross-diagnostic relevance across disorders with putatively distinct pathophysiology (e.g., schizophrenia vs. major depressive disorder). Then Lee *et al.* (7) engage the literature on animal models of ASDs from the perspective of altered E/I balance. Finally, Foss-Feig *et al.* (8) build on this animal literature to consider the existing human neuroimaging evidence supporting existence of E/I imbalance in schizophrenia and ASDs. The review highlights both

converging and diverging evidence across a number of neuroimaging modalities that may map onto upstream deficits in E/I balance within each clinical syndrome.

Collectively, this Special Issue brings together a set of articles that engage and embrace the complex theoretical and experimental neurobiology of E/I imbalance across the psychiatric spectrum. This body of work jointly attempts to fine-tune what precisely is implied by “E/I imbalance,” how E/I balance could go awry in myriad ways across time in different disorders, and what emerging neural and behavioral biomarkers may present rich opportunities for testing cross-diagnostic hypotheses. We argue that the challenge facing the field, echoed throughout this Special Issue, is to refine the precise mechanisms contributing to altered computations that disrupt E/I balance across neocortical circuits. In turn, the goal is to tackle the putative many-to-many mapping problem by leveraging refined mechanistic insight regarding E/I imbalance to develop translational causal links across levels of analysis. The hope is that understanding of disease-specific E/I imbalance mechanisms could effectively accelerate the effort toward rational design of therapeutics targeting precise sources of E/I imbalance that contribute to the complex phenotypic expression across the psychiatric spectrum.

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References

1. Anticevic A, Lisman J (2017): How can global alteration of excitation/inhibition balance lead to the local dysfunctions that underlie schizophrenia? *Biol Psychiatry* 81:818–820.
2. Krystal JH, Anticevic A, Yang GJ, Dragoi G, Driesen NR, Wang X-J, Murray JD (2017): Impaired tuning of neural ensembles and the pathophysiology of schizophrenia: A translational and computational neuroscience perspective. *Biol Psychiatry* 81:874–885.
3. Heeger DJ, Behrmann M, Dinstein I (2017): Vision as a beachhead. *Biol Psychiatry* 81:832–837.
4. Hoftman GD, Datta D, Lewis DA (2017): Layer 3 excitatory and inhibitory circuitry in the prefrontal cortex: Developmental trajectories and alterations in schizophrenia. *Biol Psychiatry* 81:862–873.
5. Tatti R, Haley MS, Swanson OK, Tselha T, Maffei A (2017): Neurophysiology and regulation of the balance between excitation and inhibition in neocortical circuits. *Biol Psychiatry* 81:821–831.
6. Lener MS, Niciu MJ, Ballard ED, Park M, Park LT, Nugent AC, Zarate CA (2017): Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. *Biol Psychiatry* 81:886–897.
7. Lee E, Lee J, Kim E (2017): Excitation/inhibition imbalance in animal models of autism spectrum disorders. *Biol Psychiatry* 81:838–847.
8. Foss-Feig JH, Adkinson BD, Ji JL, Yang G, Srihari VH, McPartland JC, *et al.* (2017): Searching for cross-diagnostic convergence: Neural mechanisms governing excitation and inhibition balance in schizophrenia and autism spectrum disorders. *Biol Psychiatry* 81:848–861.