Review

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Searching for Cross-Diagnostic Convergence: Neural Mechanisms Governing Excitation and Inhibition Balance in Schizophrenia and Autism Spectrum Disorders

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ABSTRACT

Recent theoretical accounts have proposed excitation and inhibition (E/I) imbalance as a possible mechanistic, network-level hypothesis underlying neural and behavioral dysfunction across neurodevelopmental disorders, particularly autism spectrum disorder (ASD) and schizophrenia (SCZ). These two disorders share some overlap in their clinical presentation as well as convergence in their underlying genes and neurobiology. However, there are also clear points of dissociation in terms of phenotypes and putatively affected neural circuitry. We highlight emerging work from the clinical neuroscience literature examining neural correlates of E/I imbalance across children and adults with ASD and adults with both chronic and early-course SCZ. We discuss findings from diverse neuroimaging studies across distinct modalities, conducted with electroencephalography, magnetoencephalography, proton magnetic resonance spectroscopy, and functional magnetic resonance imaging, including effects observed both during task and at rest. Throughout this review, we discuss points of convergence and divergence in the ASD and SCZ literature, with a focus on disruptions in neural E/I balance. We also consider these findings in relation to predictions generated by theoretical neuroscience, particularly computational models predicting E/I imbalance across disorders. Finally, we discuss how human noninvasive neuroimaging can benefit from pharmacological challenge studies to reveal mechanisms in ASD and SCZ. Collectively, we attempt to shed light on shared and divergent neuroimaging effects across disorders with the goal of informing future research examining the mechanisms underlying the E/I imbalance hypothesis across neurodevelopmental disorders. We posit that such translational efforts are vital to facilitate development of neurobiologically informed treatment strategies across neuropsychiatric conditions.

Keywords: Autism, Computational modeling, E/I balance, Mechanism, Neuroimaging, Review, Schizophrenia

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Neural computations rely on balanced excitation and inhibition (E/I), predominantly driven by glutamatergic and gamma-aminobutyric acidergic (GABAergic) input, respectively. Without excitation, neurons would not fire. Without inhibition, the brain would become epileptogenic. Excitation allows neurons to respond to stimuli, while inhibition tunes their selectivity and enables precise neural representations (1,2). E/I balance is necessary for optimal neural signal formation, synchrony, and transmission, which in turn support information processing driving both simple and complex behaviors. Breakdowns in E/I balance can have profoundly disabling behavioral effects. Critically, clinical neuroimaging may offer in vivo measurement of E/I balance integrity arising from specific patterns of dysfunction (Table 1).

E/I imbalance has been hypothesized as one broad, microcircuit-based alteration underlying brain dysfunction across neurodevelopmental disorders, including autism spectrum disorder (ASD) and schizophrenia (SCZ) (see the Supplement for operationalization and commentary regarding this hypothesis) (3–6). Across disorders, the underlying assumption is that increased E/I ratio (i.e., increased excitation and/or decreased inhibition) drives core symptoms. In ASD, high epilepsy rates support this notion (7). In SCZ, the glutamate hypothesis predicts that *N*-methyl-D-aspartate (NMDA) receptor hypofunction on interneurons causes cortical hyperexcitation, contributing to disease symptoms (8–11). ASD and SCZ overlap in their clinical presentation (e.g., social dysfunction, sensory abnormalities) (12), genetics, and neurobiology (13,14) (Figure 1). However, clear dissociations in clinical phenotype (e.g., hallucinations in SCZ, hand flapping in ASD), neural alterations, and developmental timing of ASD and SCZ exist. Recently, Gao and Penzes (15) discussed overlapping genetic and molecular evidence implicating E/I imbalance across ASD and SCZ. They highlighted genetic, postmortem, and animal findings suggesting both glutamatergic and GABAergic circuit dysfunction across disorders. These emergent findings emphasize the importance of understanding cross-diagnostic mechanisms affecting E/I balance. A cross-diagnostic

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Table 1. Consequences of Elevated Versus Reduced E/I Ratio

Excitation	Inhibition	Predicted Neural Consequences
Adaptive	Adaptive	Balanced E/I ratio. There is moderate spontaneous baseline activity. Neurons are excitable in response to incoming input but also well tuned and capable of filtering out irrelevant input. Circuits are well organized and differentiated, capable of synchronization and signal transmission. Circuits are able to support information processing underlying both simple and complex behavior.
Increased or Adaptive	Adaptive or Reduced	Elevated E/I ratio. At baseline, circuits may exhibit high levels of random firing and be prone to seizure-like activity. Evoked responses to incoming stimuli can be difficult to obtain. When present, however, evoked responses may be exaggerated. Circuits are poorly tuned. They may respond to inappropriate stimuli. Functionally relevant macrocircuitry is hypothesized to be poorly organized, resulting in inefficient and ineffective signal transmission and information processing. Behaviorally, responses to sensory signals may be exaggerated and inappropriate, whereas more complex behavior will be impaired.
Adaptive	Increased	Reduced E/I ratio. Spontaneous baseline activity is low, and evoked responses to incoming stimuli are limited or blunted. Circuits will be narrowly tuned, to the extent that they are unable to respond to a full range of stimuli. Circuitry will be poorly organized and integrated owing to limited opportunities for tuning and synchronization among signals.

E/I, excitation and inhibition.

approach is consistent with the National Institute of Mental Health Research Domain Criteria initiative (16), which aims to identify neurobiological processes underlying symptom dimensions spanning psychiatric disorders and testable across analytic levels. Currently, testing within the Research Domain Criteria framework is limited by few studies incorporating multiple categorical diagnoses for direct comparisons and absence of transdiagnostic symptom ratings in single-disorder studies. In this article, we take a clinical neuroscience perspective, highlighting emerging evidence from human neuroimaging studies testing markers of E/I imbalance in cortical microcircuits. Though no studies have examined E/I balance cross-diagnostically, we evaluate evidence from parallel ASD and SCZ literatures in considering shared and divergent pathways. We discuss the problem whereby E/I imbalance becomes yet another overly general hypothesis, with minimal mechanistic precision or predictive power, for explaining diverse symptomatology (Supplement). To address this challenge, we highlight where E/I imbalance contributes to specific symptoms that may be constrained developmentally or neuroanatomically. Finally, we argue that refining the E/I imbalance hypothesis should occur cross-diagnostically with an ultimate goal of informing novel treatments targeting related pathways across neurodevelopmental disorders.

MAGNETIC RESONANCE SPECTROSCOPY

Proton magnetic resonance spectroscopy (^{1}H-MRS) measures total voxel metabolite levels (combined across multiple cellular and extracellular compartments) correlating with neural structure and metabolic alterations (17). Across ASD and SCZ, studies report diagnosis-related alterations in *N*-acetylaspartate, GABA, glutamate, and glutamine levels (normalized to water or creatine). Particular interest has developed in the glutamine/glutamate combination (Glx), as glutamate released during neurotransmission is taken up by glia and converted to glutamine (18). No uniform increase in Glx or decrease in GABA exists across all patients with ASD or SCZ. However, where present, metabolic alterations provide indirect support for cross-diagnostic E/I imbalance. Moreover, ^{1}H-MRS metabolite levels, particularly degree of hyperglutamatergia, correlate with symptoms, are affected by medication, and, in SCZ, change with illness progression.

In SCZ, increased glutamine in dorsal anterior cingulate cortex (ACC) is associated with more psychotic symptoms (19) and worse neuropsychological performance in patients with first-episode SCZ (20). Higher ACC glutamine/creatine ratio is associated with more negative symptoms in patients with early-course (EC) SCZ and correlates with reduced likelihood of remittance (21). Glutamate levels are consistently elevated across striatal (22), frontal, prefrontal, and ACC (23) regions in medication-naïve patients with first-episode SCZ, and medial prefrontal cortex (mPFC) Glx is elevated in unmedicated patients (24). Increased temporal and frontal Glx levels relate to particularly severe auditory hallucinations (25), while increased inferior parietal white matter Glx relates to symptom severity and psychotic exacerbations (26). Higher frontal Glx/creatinine ratio may predict poorer antipsychotic medication response (27). In medicated patients with SCZ, glutamate is decreased (28) or unchanged (19) in ACC, decreased in PFC (29), and possibly decreased in hippocampus (28,30). Glx is also reduced in ACC (31) and mPFC of patients with chronic SCZ but not patients with EC-SCZ or ultra-high-risk SCZ (32). Thus, measured glutamate and glutamine levels, while elevated early in illness, may normalize over illness progression, be sensitive to medication status, and specifically relate to clinical profiles and treatment response. However, possible confounds of long-term polypharmacy remain unresolved (33).

In ASD, less is known about metabolite changes over illness duration, in part because ASD onset occurs before the age when ^{1}H-MRS studies have been implemented. However, ACC Glx is increased in children with ASD (34) but reduced and predictive of greater symptom severity in adults with ASD (35). These findings point toward a possible progressive shift, as observed in SCZ. Overall, metabolic alterations may correlate with particular symptoms in ASD and be more regionally specific than in SCZ. For example, one study found that decreased ACC GABA/creatine ratio corresponded to more impaired social functioning (36), whereas another found no overall changes in ACC GABA but lower GABA/creatine ratio with more severe symptoms (37). Whereas reduced GABA characterizes auditory and motor regions (38,39), GABA/creatine ratios may be unaffected in visual regions yet aberrantly linked to visual performance (40). Glutamate is increased in ACC (41) and putamen (42) but decreased in medial temporal lobe (41) and unchanged in