Autism Spectrum Disorders and Schizophrenia Spectrum Disorders: Excitation/Inhibition Imbalance and Developmental Trajectories

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Autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) share clinical and genetic components that have long been recognized. The two disorders co-occur more frequently than would be predicted by their respective prevalence, suggesting that a complex, multifactor association is involved. However, DSM-5 maintains the distinction between ASD, with core social and communication impairments, and SSD, including schizophrenia (SCZ), with hallucinations, delusions, and thought disorder as essential features. ASD and SSD have common biological underpinnings that may emerge early in development and unfold over time. One of the hypotheses supporting the similarities in the social and cognitive disturbances of ASD and SSD relates to abnormalities in the ratio of excitatory to inhibitory cortical activity (E/I imbalance). E/I imbalance in neurodevelopmental disorders could be the consequence of abnormalities in genes coding for glutamatergic and GABAergic receptors or synaptic proteins followed by system derangements. SSD and ASD have been characterized as polygenic disorders in which the onset and progression of disease is triggered by interactions among multiple genes. Mammalian target of rapamycin signaling is under intense investigation as a convergent altered pathway in the two spectrum disorders. Current understanding of shared and divergent patterns between ASD and SSD from molecular to clinical aspects is still incomplete and may be implemented by the research domain criteria approach.

Keywords: autism spectrum disorders, schizophrenia spectrum disorders, psychosis, children and adolescents, excitation/inhibition imbalance

The clinical interplay and overlap between SSD and ASD have long been recognized as the two classes of disorder that share phenotypic and clinical features and a number of individuals diagnosed with ASD subsequently develop SSD symptoms (1). Currently, the relationship is further emphasized after controversies on the shared patterns and differences of the two disorders.

It has been demonstrated that the two types of disorder co-occur more frequently than would be that predicted by their respective prevalence. DSM-5 maintains a nosological distinction between ASD and schizophrenia (SCZ) in spite of overlapping in clinical characteristics. Examining the specific definition of core symptoms, there are two major criteria for ASD: "(1) persistent deficits in social communication, social interactions, social-emotional reciprocity and communicative behaviors and
restricted, repetitive patterns of behavior, interests or activities, including stereotyped or repetitive movements, behavioral rigidity, odd or intense interests,” and as an important additional criterion, abnormally high or low reactivity to sensory stimuli. On the other hand, the DSM-5 diagnostic criteria for SCZ specify that at least two of the following symptoms must be present: “hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms.” Furthermore, in DSM-5, the criteria have been reorganized to emphasize the variability in the severity of the psychopathology and the severity dimensions have been updated (2).

Childhood-onset schizophrenia (COS) is a subtype of SCZ defined by onset of psychotic symptoms before 13 years and the absence of any other neuropsychiatric diagnosis. Re-examination of the overlap between COS and ASD has highlighted the clinical and genetic commonalities. Remarkably, in almost half the cases of COS identified in the largest longitudinal study to date, a pervasive developmental disorder was present before the onset of psychosis (3). In contrast, and somewhat unexpectedly, prospective longitudinal studies following children with ASD into young adulthood rarely report the appearance of psychotic symptoms.

SSD includes SCZ, schizofreniform disorder, schizoaffective disorder, and schizotypal personality disorder. In ASD, it is not rare to detect unusual preoccupations, unusual perceptual experiences, odd thinking, and speech. Both the shared clinical features and frequent co-occurrence point to a close relationship between SSD and ASD. To further strengthen this relationship, it has been reported that about 30% of children and adolescents with COS had co-morbid ASD (4). In addition, the well-known difficulty to recognize social cues from the actions of others is tightly related to deficit in theory of mind that is a characteristic feature common to both SSD and ASD (5).

In this context, it is critically important to underscore that the negative symptoms of SSD are often more disabling and more resistant to treatment than the so-called positive ones, e.g., hallucinations and delusions (6). These negative symptoms include social avoidance and emotional flatness and might be regarded as closely linked to impairments in social communication and motivation. These so-called negative symptoms of SSD might be considered to fall within the same domain of social impairment as the social difficulties characteristic of ASD. Furthermore, the disorganized or abnormal behaviors characteristic of SSD include behaviors which would meet ASD Criterion B, e.g., repeated and stereotyped movements and verbal expressions, as to DSM-5. Other pathognomonic features common to both conditions include impairments in facial recognition and emotion processing (7, 8). Patients with both ASD and SSD have been shown to have significant difficulties in interpreting social cues associated with eye gaze and deficits on theory of mind tasks—one of the hallmarks of ASD.

Autism spectrum disorders and SSD share biological underpinnings that may emerge in early neural development and unfold during subsequent childhood development (9). Abnormal neural development has been ascertained in cortical projection neurons from different brain areas including prefrontal and somatosensory regions in ASD and dorsolateral/ventrolateral prefrontal regions in SSD. It has to be mentioned that neurodevelopmental disorders are associated with known genetic abnormalities both in ASD and SSD phenotypes, as detailed in Table 1. Furthermore, epigenetic effects and alterations in copy number variants (CNVs) have been reported to contribute to abnormalities of neural circuits associated with SSD and ASD (Table 2). The risk of both disorders is increased by advanced paternal age and maternal infection/immune activation during pregnancy (10, 11). These shared patterns suggest that the two spectra are likely to represent

### Table 1 | Candidate genes validated in autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD).

| Gene | Function | Other phenotypes |
|------|----------|------------------|
| RELN | Neuronal migration, polarization | Lissencephaly, Alzheimer’s disease |
| DISC1 | Neural development, synaptic plasticity, mammalian target of rapamycin (mTOR) regulation | Depressive, bipolar disorder |
| FOXP2 | Regulates DISC1, CTNAP2, language, and neural development | Developmental verbal dyspraxia |
| BDNF | Neurotrophic factor, regulates mTOR/AKT | Alzheimer’s disease, Huntington disease |
| MECP2 | Epigenetic regulator | Rett syndrome |
| UBE3A | Epigenetic regulator | Angelmann syndrome |
| NLGN3 | Postsynaptic component coupled with NRXN | Undefined |
| NLG4 | Postsynaptic component coupled with NRXN | ID |
| NRXN1 | Presynaptic component coupled with NXRN | Pitt–Hopkins phenotype |
| SHANK3 | Postsynaptic protein in glutamatergic neuron | Phelan–McDermid syndrome |
| CNTAP2 | Cell adhesion and differentiation | ID, epilepsy, language impairment |
| CNTAP4 | | ID, epilepsy |
| GRIK2B | NMDA receptor subunit | Bipolar disorder |
| NTGN1 | Axon guidance | Bipolar disorder |
| GABRB3 | GABA receptor subunits | | |
| GABRA5 | | | |
| GAD | Conversion of glutamate to GABA | Epilepsy |
| CACNA1C | Voltage-dependent calcium channel subunit | Bipolar disorder, Brugada, and Timothy syndromes |
| SLC25A12 | Mitochondrial membrane, solute channel protein | Mitochondrial disorders |
| OXTR/OXT | Oxytocin receptor/oxytocin gene | Undefined |
| ZNF804A | Transcription regulator of PRSS16, COMT | Bipolar disorders |

Modified by de Lacy and King (9).

**ID:** intellectual disability.
TABLE 2 | Copy number variants (CNVs) implicated in ASD and SSD.

| Region and type | Candidate genes | Phenotypes |
|----------------|-----------------|------------|
| 1q21.1 Del     | Unidentified    | SCZ, ASD, DD, ADHD, deficit IGE |
| 1q21.1 Dup     | Unidentified    | ASD, ID, ADHD |
| 2p16.3 Del     | NRXN1           | SCZ, ASD, ID |
| 3q29 Del       | PAK2            | ACZ, ID, ADHD |
| 3q29 Dup       | Unidentified    | ID |
| 15q11.2 Del    | CYF1P1          | ID, DD, SCZ, ASD, IGE, OCD, MDD |
| 15q11-13 Dup   | GABRA5, GABRB3, GABG3, and others | SCZ, ASD, ID, Ataxia |
| 15q13.3 Del    | CHRNA7          | SCZ, ASD, ID |
| 16p11.2 Del    | DOC2A, ERK1     | SCZ, ASD, ID, learning disorder |
| 16p11.2 Dup    | DOC2A, ERK1     | SCZ, ASD, ID, DD |
| 16p13.11 Del   | NDE1            | SCZ, ASD, ID |
| 16p13.11 Dup   | NDE1            | SCZ, ASD, ID, ADHD, IGE |
| 17q12          | Undefined       | SCZ, ASD, ID |
| 22q11.2        | PRRDH, COMT, DGCR6, TRX1 | SCZ, ASD, ID, epilepsy |
| 22q11.21       | SHANK3          | ID, DD, ASD, SCZ |

Modified by de Lacy and King (9).

ID, intellectual disability; ADHD, attention-deficit hyperactivity disorder; DD, developmental delay; OCD, obsessive–compulsive disorder; MMDD, major depressive disorder; IGE, immunoglobulin E deficit.

outcomes of common pathophysiological mechanisms. The next sections describe the E/I imbalance as a candidate mechanism possibly involved.

E/I IMBALANCE IN ASD AND SSD

An emerging hypothesis for the similarities in the social and cognitive disturbances associated with ASD and SSD is based on alterations in the ratio of excitatory to inhibitory cortical activity (E/I imbalance). Glutamate and GABA are, respectively, the two main neurotransmitters involved in excitatory and inhibitory signaling in the brain. Increased glutamatergic signaling alongside decreased GABAergic signaling would represent an E/I imbalance. Such imbalances may arise from disturbances in neural circuit formation or, abnormalities in the genes which code for proteins involved in these processes and linkage and association studies have been implicated in ASD and SSD (12). Postmortem studies have reported structural changes in both excitatory glutamatergic and inhibitory GABAergic circuits in individuals with ASD and SCZ (13–15).

In neurodevelopmental disorders, an E/I imbalance could arise directly through alterations in genes coding for glutamatergic receptors or synaptic proteins (16–18). The synapse organizers neurexins and their binding neuroligins are implicated in the formation and maintenance of excitatory and inhibitory synapses. Heterozygous deletions eliminating exons of the neurexin-1α gene in patients with ASD and SCZ have been detected and the functional significance of this recurrent deletion is still unclear. However, the availability of mice with deletion of the promoter and first exon of neurexin-1α provided evidence of the effects of neurexin-1α disruption on phenotypes relevant to ASD and SCZ and supported the role of neurexins in neurodevelopmental disorders (19, 20).

In addition to the synaptic dysfunction, there is increasing evidence that E/I balance is also modulated by glial mechanisms that regulate glutamate activity (21, 22). Abnormalities in astrocyte gene expression in both ASD and SCZ have been detected (23), and reduced numbers of oligodendrocytes, impaired cell maturation, and altered gene expression of myelin/oligodendrocyte-related genes have been ascertained in SCZ (24). In turn, an increased number of activated microglia cells in adults with ASD have been found (25). As a result, glia deserves specific attention in the evaluation of E/I imbalance in these conditions.

ASD AND E/I IMBALANCE

The net effect of changes in glutamatergic and GABAergic systems in ASD may be an overall increase in the ratio of excitation to inhibition (E/I). Such an increase is likely to be implicated in seizures, macrocephaly, and core ASD symptoms (26). The E–I ratio in neocortical structures is determined by pyramidal glutamatergic neurons and inhibitory GABAergic parvalbumin (PV)-positive interneurons that are modulated and fine-tuned by minicolumns (groups of functionally autonomous neurons whose afferent and efferent connections influence the functioning of microcircuits) which have been found to be abnormal in ASD (27, 28). There are a number of candidate mechanisms for glutamatergic hyperactivity-driven hyperexcitability. Neuroligins (NL1–4) and neurexins (Nrxns 1–3) have been linked with ASD via point mutations and truncations, and chromosomal rearrangements have been identified in the region of interest (29–31). SHANK1, SHANK2, and SHANK3 are scaffolding proteins which influence the postsynaptic density of glutamatergic synapses and are of primary importance in ASD. SHANK3 is reported to be involved in Phelan–McDermid syndrome a form of ASD associated with moderate to severe intellectual disability (ID) and poor language skills (32). Regarding SHANK2 and SHANK1, they were found altered in ASD associated with mild ID as well as in high functioning individuals (33). As to the mechanisms of GABAergic inhibitory dysfunction, the link with core ASD symptoms in humans is still under
investigation. Deficit in binocular rivalry, a visual function that is thought to rely on the balance of excitation/inhibition in visual cortex has been observed in ASD individuals. The link between GABA and binocular rivalry dynamics was found specifically absent in ASD pointing to an insufficient GABA inhibitory function (34). Postmortem studies have provided evidence of alterations in GABAergic circuits in ASD individuals; there have been reports of significantly reduced GAD65/GAD67 levels in the parietal cortex and cerebellum (35).

Induced pluripotent stem cells (iPSCs) have been used to investigate putative abnormalities in neural substrate of individuals with ASD. Even if no known underlying genomic mutation could be identified in a new study herein presented, interestingly, transcriptome and gene network analyses revealed upregulation of genes involved in cell proliferation, neuronal differentiation, and synaptic formation. The main finding was that overexpression of the transcription factor FOXG1 was responsible for the overproduction of GABAergic neurons, shifting the E/I balance toward inhibition (36).

SSD AND E/I IMBALANCE

Several postmortem studies detected lower levels of PV mRNA and GAD67, the principal synthesizing enzyme for GABA, in dorso-lateral-prefrontal cortex (DLPFC) PV neurons of patients with SCZ. Markers of GABA neurotransmission between chandelier neurons and their synaptic targets are altered in the DLPFC of subjects with SCZ (37, 38).

NMDA receptors are ionotropic glutamate receptors involved in synaptic regulation of E/I balance and there are multiple subtypes of NMDA receptor with different functions and distributions (39). Dysfunction of NMDARs has been documented in SCZ both in experimental models and human studies. In the NMDA-hypofunction model of the disease, changes in E/I balance and the resulting changes in behaviors have been hypothesized (40). Disrupted NMDAR function is implicated in altered neurodevelopment and may play a role in the progression of symptoms for SCZ especially for cognitive deficits (41–43). NMDA receptor hypofunction has been proposed in ASD as well and the NR2A, NR2B, and NR2C genes abnormalities have been associated with ASD (44).

Remarkably, two de novo mutations in the GRIN2A-coded subunit of NMDA receptors have been detected in patients with SCZ and one de novo mutation in GRIN2B-coded subunit in a patient with ASD. Truncating mutations in GRIN2C, GRIN3A, and GRIN3B were identified in both patients and controls, but no truncating mutations were found in the GRIN1, GRIN2A, GRIN2B, and GRIN2D genes (45).

NRG1 and ErbB4 genes deserve attention, are expressed at excitatory synapses, and regulate spine structure and function. ErbB4 deletion is associated with neurodevelopmental abnormalities that are consistent with SSD (46, 47). The disrupted in SCZ 1 gene (DISC1) is another important candidate gene implicated at different levels of neurodevelopment through a scaffolding protein and different mutations have been detected in SCZ emphasizing its role (48, 49).

E/I imbalance has been proposed as a mechanism for hallucinations, one of the main positive symptoms of SSD. Hallucinations have been linked to inhibitory deficits such as impaired GABA transmission unfolding in a series of abnormalities such as impaired NDMA receptor plasticity, reductions in gamma frequency oscillations, sensory cortical hyperactivity, and cognitive inhibition deficits. However, the mechanisms by which E/I dysfunctions at the cellular level might be linked to clinical symptoms and cognitive deficits remain unclear (50).

The 22q11 microdeletion syndrome is the most common CNV associated with SCZ as it is present in 1–2% of cases, further there is a very high association of the syndrome with SCZ, up to 30–40%. This elevated risk is not associated with any other neurogenetic syndrome. Social cognition is impaired in 22q11.2 deletion syndrome and remarkably this feature is correlated with psychotic symptoms. The role of this microdeletion as a potential contributor to E/I imbalance is undefined (51).

CONVERGENT PATHWAYS VS. DIVERGENT PHENOTYPE IN ASD AND SSD

Schizophrenia spectrum disorders and ASD have been described as polygenic disorders in which the onset and progression of disease are triggered by interactions among multiple susceptibility genes.

Overlaps of risk genes among ASD and SSD have been documented. Two lines of mutant mice with Shank3 mutations linked to ASD and SSD have been documented with shared and distinct synaptic and behavioral phenotypes. Mice with the ASD-linked InsG3680 mutation manifest striatal synaptic transmission defects before weaning age and impaired juvenile social interaction, coinciding with the early onset of ASD symptoms. On the other hand, adult mice carrying the SCZ-linked R1117X mutation demonstrated synaptic defects in prefrontal cortex and social dominance behavior. This is a paradigmatic example of different alleles of the same gene that have distinct phenotypes at molecular, synaptic, and circuit levels which may inform exploration of these divergences in human patients (52).

MAMMALIAN TARGET OF RAPAMYCIN (mTOR) SIGNALING IN ASD AND SSD

The mTOR pathway is directly involved in the physiological maintenance of the synaptic E/I ratio and is implicated in ASD by virtue of its role in upstream signaling and downstream regulatory mechanisms (12). Dysregulation of mTOR increases excitability and decreases inhibition thus contributing to E/I imbalance. mTOR activation is found in tuberous sclerosis complex mutations (TSC1/TSC2) occurring in tuberous sclerosis, which is frequently associated with ASD. Dysregulation of the mTOR pathway in these conditions provides clues to the molecular pathophysiology of ASD as the synaptic and cellular alterations involved may converge to produce the core social impairment of these disorders (53). In addition, mTOR...
inhibitor compounds have the potential to reverse many of the behavioral and neurophysiological abnormalities associated with ASD (54).

Recent investigations have linked SSD to the mTOR signaling cascade (55). Dysfunction of diverse upstream activators and environmental stressors, that have been previously implicated in SCZ, can lead to either over-activation or inhibition of the signaling pathway. Alterations in GABA signaling may be involved in the dysfunction of inhibitory circuits in SSD through the DISC1–Akt–mTOR pathway. As well, a putative depression of mTOR signaling with possible variation between and within brain regions affecting neuronal functioning in variable fashion has been proposed. Consistently, a preponderant decrease in glutamatergic activity with respect to GABAergic activity has been reported (56). In this functional and still undefined background, abnormal synaptic function may be related to positive and negative symptoms of SSD (57). Lastly, mTOR signaling undergoes variations as neurodevelopment unfold and environment plays a significant role especially through early life experiences that needs to be thoroughly considered (58).

**FINAL REMARKS AND FUTURE DIRECTIONS**

There is epidemiological, clinical, neurobiological, and genetic evidence for a close relationship between ASD and SSD, and significant overlap in symptoms is frequently observed; however, there are also differences in clinical presentation, behavioral phenotype, and developmental trajectory.

The complex pathways that control E/I balance provide a framework for understanding how different genetic alterations implicated in these two distinct disorders can interact to disrupt excitatory and inhibitory neuronal function, neuronal circuit organization thus eventually influence complex social and cognitive behaviors. Nonetheless, it has to be clearly stated that current knowledge of the mechanistic relationships between E/I imbalance and the two spectrum disorders is still exploratory and need further evidence. The ways in which these shared mechanisms contribute to specific phenotypes such as ASD and SSD are still largely unknown. There are a number of open questions that need to be addressed such as whether there is a critical period for an E/I imbalance that mediates ASD- and SSD-associated behavior, or whether the E/I imbalance is circuit specific. Furthermore, an E/I imbalance may arise not only from synaptic dysfunction but also from altered cell fate that can lead to abnormal proportions of inhibitory and excitatory cells.

Shedding light on the shared functions of candidate genes for involvement in ASD and SSD is the key to translating genetic findings into descriptions of developmental and clinical subtypes. As to neuronal dysfunction hypothesized, abnormalities might be specific affecting only a subset of synapses in a selective group of neurons responsible of distinct symptoms but all that is still an hypothesis as evidence on the brain circuits potentially involved is lacking.

Research domain criteria (RDoC) project seems particularly indicated to this scope as it is directed to implement all the above level of understanding. One of the main purpose is to investigate mental illness through the dimensional approach to the fundamental components of behavior, through individual symptoms or symptom clusters, that cut across diagnoses, in this case specifically in ASD and SSD domains (59). Aim and legacy of RDoC novel approach is to build a research perspective that reflects advances in genetics, neuroscience, and behavioral science to provide a foundation for precision diagnosis and treatment of complex mental disorders such as those herein examined. The details obtained by the use of RDoC matrix likely will help to shed light on ASD and SSD relationships as well as on the longitudinal monitoring of emerging convergent and divergent symptoms of the two spectra (60).

It should also be noted that there is a subset of individuals with complex neurodevelopmental disorders whose symptoms span multiple functional domains including cognition and social communication. These individuals do not fit under any of the current diagnostic labels listed under ASD and SSD and further research through an RDoC approach holds promise to describe the specific biobehavioral profiles and thus eventually establish the diagnostic category in which they should be included. Consistent developmental designs are awaited to capture changes in the underlying neural circuitry, molecular pathways including E/I balance, and other biological components in ASD and SSD, relating them to changes in their corresponding cognitive and affective determinants as they emerge over time and alter behavior under the influencing role of environment.

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RC and Mauro Pallagrosi equally participated in the substantial contribution to the conception or design of the work; drafted the work and revised it critically for important intellectual content; approved the final version to be published; and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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