EDITORIAL

Psychosis and autism spectrum disorder: a special issue of *Molecular Psychiatry*

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In this issue of *Molecular Psychiatry*, we have multiple articles that present exciting advances in psychosis and autism spectrum disorder (ASD). We start with interesting comments by Cohen & Ongur on the need for evidence-based updating of ICD and DSM models of psychotic and mood disorders [1] and by Tibrewal et al. on whether clozapine treats antipsychotic-induced behavioral supersensitivity through glutamate modulation within the striatum [2].

The subsequent several papers address schizophrenia, with Reviews by Zapata et al. covering the intriguing new finding of nuclear receptor 5A2 regulation of Agrp underlying olanzapine-induced hyperphagia [3] and by Howes & Onwordi on the synaptic hypothesis of schizophrenia [4]. Drawing upon empirical findings, Howes & Onword's intellectual construct argues that a confluence of genetic or environmental vulnerabilities places neural interconnections at an escalated risk of targeted erasure by glial actions, especially when faced with stressors in the latter stages of neural maturation. They contend that such synaptic diminishment hampers the functional efficacy of pyramidal neurons situated in the cortex, amplifying cognitive deficits and affective irregularities. Concurrently, it weakens inhibitory governance over mesostriatal conduits, engendering an excess of dopaminergic activity and the subsequent emergence of psychotic phenomena. This analytical framework not only demystifies the typical onset of schizophrenia during the transition from adolescence to early adulthood but also sheds light on its core causative elements and symptomatic characteristics. Furthermore, it suggests prospective routes for medical intervention aimed at synaptic entities, microglial populations, and immunological systems.

Two Experts Reviews address schizophrenia: Nakamura & Takata cover the molecular pathology of schizophrenia, providing an overview of existing knowledge and new directions for future research. McCutcheon et al. address cognitive impairment in schizophrenia, from etiology and pathophysiology to treatment [5, 6]. Then, two very timely systematic reviews address vital topics. Fond et al. provide a systematic review and meta-analysis of 37 studies from 25 high- and low-to-middle-income countries addressing self-stigma in schizophrenia [7]. Solmi and colleagues then estimate the meta-analytic prevalence of comorbid mental disorders in individuals at clinically high risk of psychosis, making the case for transdiagnostic assessment [8].

In an exciting Immediate Communication, Lin et al. address an old model with new insights, suggesting that endogenous retroviruses drive the evolvement toward ASD susceptibility and hijack transcription machinery during development [9].

Three more fundamental papers address potential underlying mechanisms: Bennison and associates demonstrate that the cytoplasmic localization of ADNP through 14-3-3 promotes sex-dependent neuronal morphogenesis, cortical connectivity, and calcium signaling [10]. Guixà-González et al. studied the impact of membrane lipid polyunsaturation on dopamine D2 receptor-ligand binding and signaling [11]. Akbarian and colleagues promoted the induction of dopaminergic neurons for neuronal subtype-specific modeling of psychiatric disease risk [11, 12].

Imaging studies address specific types of psychosis. Wang et al. show in a 7-Tesla MRS study longitudinal changes in brain metabolites in healthy controls and patients with first-episode psychosis [13]. Rogdaki et al. document with a [18 F]-DOPA PET study striatal dopaminergic alterations in individuals with copy number variants at the 22q11.2 genetic locus and their implications for psychosis risk [14, 15].

Further work on the 22q11.2 deletion was conducted by Lin et al., who showed that rare coding variants as risk modifiers of the 22q11.2 deletion implicate postnatal cortical development in syndromic schizophrenia [16].

Several other papers provide advances in multiple research topics within the broad areas of schizophrenia and psychosis. In a meta and mega-analysis, Merritt et al. show variability and magnitude of brain glutamate levels in schizophrenia [17]. Mayeli and colleagues report shared and distinct abnormalities in sleep-wake patterns and their relationship with the negative symptoms of schizophrenia spectrum disorder patients [18]. Lotan et al. used a prediction model based on iron and ferritin, and their data provided a pathophysiologic link between perturbed cortical iron biology and schizophrenia; they then suggested that the achievement of optimal cortical iron homeostasis could offer a new therapeutic target [19]. Lu showed that in mice, atypical antipsychotics antagonize GABAA receptors in the ventral tegmental area GABA neurons to relieve psychotic-like behaviors [20].

Two papers stand out in the area of genetics of schizophrenia and psychosis. Rammos et al. used family-based analysis to ascertain the contribution of rare and common genetic variants to school performance in schizophrenia [21]. Exciting work by van den Oord and associates shows that genes implicated by a methylome-wide schizophrenia study in neonatal blood show differential expression in adult brain samples [22]. Alameda and colleagues explored the mediation of DNA methylation across the epigenome between childhood adversity and First Episode of Psychosis-findings from the EU-GEI study. They delved into the interplay between Childhood Adversity (CA) and DNA-methylation (DNAm) in the context of psychotic disorders. Employing state-of-the-art epigenetic analyses on blood samples from individuals experiencing their first psychotic episode and healthy controls, the study scrutinized whether DNAm could serve as a biological bridge linking CA and psychosis. Though the research found a palpable association between CA and psychosis, the mediation effect of DNAm was not statistically robust. Intriguingly, some genes implicated in psychosis did show altered methylation levels under less stringent statistical criteria, pointing to possible nuanced roles. Furthermore, disparate genes appeared to be associated with different forms of childhood adversity, hinting at

diverse biological pathways. These preliminary insights, although tantalizing, necessitate further validation.

On the autism front, LaSalle examines in an Expert Review the epigenomic signatures that reveal mechanistic clues and predictive markers for autism spectrum disorder [23]. More et al. identified rare genetic variants in 21 highly multiplex autism families and examined the role of diagnosis and autistic traits [24].

Weigel and associates demonstrate that MYT1L haploinsufficiency in human neurons and mice causes autism-associated phenotypes that can be reversed by genetic and pharmacologic intervention [25]. Bruce et al. elegantly showed altered behavior, brain structure, and neurometabolites in a rat model of autism-specific maternal autoantibody exposure [26]. Their study explored how maternal autoantibodies (aAbs) related to immune dysregulation can affect offspring's brain structure and behavior, potentially leading to autism spectrum disorder (ASD). Using a rat model mimicking maternal autoantibody-related ASD (MAR-ASD), researchers observed disrupted social behavior and vocalizations in rat offspring, along with specific brain volume changes and altered brain metabolites. Their findings suggest that MAR-ASD aAbs can impact behavior and neuroanatomy, echoing clinical observations in ASD.

Pretzsch et al. examined cross-sectional and longitudinal neuroanatomical profiles of distinct clinical (adaptive) outcomes in autism [27]. Their study conducted a longitudinal analysis of 333 individuals, both autistic and neurotypical, to understand the neurobiological correlates of varying clinical outcomes in autism. By grouping autistic participants based on changes in adaptive behavior, the researchers found distinct neuroanatomical and genetic profiles corresponding to different clinical outcomes. These findings may pave the way for targeted interventions in autism treatment, enhancing the prospects of precision medicine.

This exciting special issue of *Molecular Psychiatry* ends with perceptive comments by Zengeler & Lukens on the study from Bruce et al. (also in this issue) that misguided antibodies change the course of brain development [28]. Significantly, Zengeler & Lukens also raise critical questions for future research on maternal autoantibodies (aAbs) and their potential role in ASD. Unlike existing models that emphasize the role of cytokines, this study suggests that neurodevelopmental changes might occur independently of cytokine levels. Questions loom about the different immune triggers that can yield similar ASD-related behaviors and the specific cellular targets adversely impacted by these aAbs. Moreover, the mechanisms by which these aAbs enter fetal cells and potentially disrupt brain maturation remain unexplored. The ultimate queries are why some mothers possess these antibodies and how they are transferred to embryos, as these could illuminate new pathways for therapeutic intervention.

In future issues, *Molecular Psychiatry* will continue to publish outstanding articles that advance research in ASD and psychosis.

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ADDITIONAL INFORMATION

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