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A redux of schizophrenia research in 2021

Another year of schizophrenia research has passed by despite the challenges of the COVID-19 pandemic. A redistributed healthcare system that is skewed towards the needs of managing the pandemic has come at the cost of severe mental illness (Ab et al., 2022). Additionally, the pandemic has led to worse outcomes in persons with psychosis (Fond et al., 2021; González-Blanco et al., 2020; Nemani et al., 2021). The pandemic has also amplified the already existing mental health care disparities across race and culture (Ferrarelli and Keshavan, 2020); Davis et al. (2022) have recently outlined the barriers and potential solutions for equitable care. Despite these challenges, schizophrenia research has evolved over the past year, and we look back at these advances in the field.

1. Prodrome, early intervention, biomarkers, and early psychosis

Advances continue to be made in understanding environmental and neurobiological determinants and mechanisms of transiting from prodromal to manifest psychotic states. Negative (Devoe et al., 2021) and cognitive symptom evaluation through validated instruments aim to supplement the existing ones that are skewed towards identifying positive psychotic symptoms in prodromal states (Strauss et al., 2020). Inflammatory (Kelsven et al., 2020; Perry et al., 2021), neurolinguistic (Bilgrami et al., 2022; Spencer et al., 2021), frontocentral P300 amplitudes, and biochemical assays (erythrocyte sphingomyelin and phosphatidylethanolamine) (Alqarni et al., 2020a, 2020b), have shown promise as biomarkers of transition (Park and Miller, 2020; Tang et al., 2020). A decreased global efficiency of the default mode resting activity (Cao et al., 2020), and altered reward processing mediated by the dysfunctional ventromedial prefrontal cortex (Millman et al., 2020) also predict this transition to psychosis.

Despite a growing acknowledgement of the heterogeneous phenotype of at-risk mental states (Malhi et al., 2021), early intervention research in psychosis has gained substantial ground (Woods et al., 2021a). Pharmacological strategies such as omega 3 fatty acids and their role in the prevention of psychosis continue to be elusive (Thompson et al., 2020). However, there are more encouraging reports of the real-world efficacy of psychological and psychosocial interventions (Formica et al., 2020; McGorry et al., 2021). Cognitive training, when applied in high-risk subjects, showed promising results; however, feasibility challenges still remain, indicating an urgent need to engage younger individuals with perhaps a different approach (Friedman-Yakoobian et al., 2020; Glenthøj et al., 2020).

In the coming years integrated biomarkers such as allostatic load combined with functionality assessment may guide transdiagnostic and personalized risk calculators (Puntis et al., 2021) to quantify individualized risks that may aid early intervention and secondary prevention (Oliver et al., 2021; Radua et al., 2021; Worthington et al., 2021).

2. Sleep and behavior

Sleep shares a complex relationship with schizophrenia and therefore it is unsurprising that the sleep deprivation model furthers our understanding of schizophrenia. Electrophysiological and cognitive studies have identified associations between sleep oscillation abnormalities and worsening clinical manifestations of schizophrenia (Castelnovo et al., 2020; Hennig et al., 2020; Kumari and Ettinger, 2020). A shorter duration of sleep is associated with more paranoia and poorer quality of sleep is associated with more hallucinatory experiences (Ferrarelli, 2020); these may also signal transition to psychosis (Clarke et al., 2021). Sleep deprivation produces changes in sensorimotor gating, attention, working memory, executive function, and social cognition. Concerns over the specificity of sleep biomarkers in psychosis do remain. Nevertheless, resetting healthy sleep oscillations (Manoach et al., 2020; Zhang et al., 2020) through cognitive-behavioral therapy (Waters et al., 2020) and neuromodulation (Fröhlich and Lustenberger, 2020) may improve overall treatment outcomes in schizophrenia.

There is a strong need to replicate these observations and derive a clear mechanistic understanding of the relationship between sleep and psychotic manifestations using high-definition electroencephalograms and functional neuroimaging techniques. This will provide a stronger theoretical framework for future treatment studies.

3. Newer agents and treatment optimization

The role of the glutamatergic system in schizophrenia has been receiving increased attention in the past decade and has gained traction in the past few years (Benesh et al., 2020; Egerton et al., 2020; Kelleher et al., 2020; Roberts et al., 2020; Zeppillo et al., 2020). Magnetic resonance spectroscopy studies have elaborated the dysfunction of glutamate and glutathione in psychosis (Sydnor and Roalf, 2020). Glutamatergic modulators including inhibitors of glycine transporter 1, D-amino acid oxidase, and phosphodiesterase, as well as α7 nicotinic acetylcholine receptor agonists are promising avenues based on preclinical and early clinical studies (Egerton et al., 2020; Oh and Fan, 2020). Interestingly, targeting glutamatergic agents during prodrome and early psychosis may have definitive advantages over dopaminergic blockage (Chaumette et al., 2020; Tiihonen et al., 2021). Newer agents such as lumateperone – a modulator of dopaminergic, serotonergic, and glutaminergic neurotransmission (Correll et al., 2021) offer hope; while

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addition of newer agents such as samidorphan to mitigate olanzapine induced weight gain will aid in improved tolerability (Kahn et al., 2021).

Prediction of antipsychotic response in schizophrenia is slowly moving from clinical and socio-demographic towards biological markers such as inflammation and resting state functional connectivity (Enache et al., 2021; Mehta et al., 2021; Mongan et al., 2020; Yang et al., 2021). This is a first step towards identifying disease-biology-based predictive biomarkers that can subsequently help in (a) the early identification and treatment of resistant schizophrenia, (b) treatment planning and resource allocation, and (c) delivering personalized treatments (Kraguljac et al., 2021).

Personalized precision medicine is increasingly relevant with clozapine use, with recent evidence hinting that Asians need roughly half the recommended dose of clozapine since they achieve higher serum clozapine values as compared to Caucasians (de Leon et al., 2020; Suhas et al., 2020).

Recent psychopharmacology research in schizophrenia may have not resulted in substantial increase in the number of effective interventions. However, it has paved a way for optimization strategies of several existing drugs to improve efficacy, tolerability, and safety.

4. In the near future

A consistent issue with schizophrenia research is the lack of uniform outcome and assessment measures. Additionally, a vast majority of randomized controlled trials in schizophrenia exclude patients who do not fit into eligibility criteria due to reasons such as suicidality, tardive dyskinesia, medical comorbidities, and treatment resistance (Taipale et al., 2022). Such patients who represent one in five real-world patients need to be represented in scientific studies for better ecological validity. Future science in schizophrenia should also focus on uniformity of assessment measures evaluating and reporting core outcomes (Campana et al., 2021; Woods et al., 2021b; Zipursky et al., 2020).

Neuroimaging research will stand to gain with larger sample sizes, facilitated by multinational collaborative efforts. The applications of novel imaging techniques such as synaptic vesicle glycoprotein ligands in positron emission tomography imaging to evaluate synaptic dysfunction, neuromelanin magnetic resonance imaging to examine dopamine and neurite orientation dispersion, and density imaging to examine gray matter will soon be put to test (Keshavan et al., 2020).

Artificial intelligence-based data acquisition and ecological momentary assessments provide real-world data that may provide valuable insights into psychosis (Durand et al., 2021; Parrish et al., 2020). Deep learning applications are likely to be increasingly relevant to unravel the neurobiology, understand the transition, prognosticate and practice personalized precision medicine in schizophrenia (Cortes-Briones et al., 2021). Such research is still in its infancy (Haining et al., 2021; Torous and Keshavan, 2021) and yet, is likely to evolve rapidly, signaling an exciting paradigm shift in schizophrenia research.

CRediT authorship contribution statement

SS reviewed the literature and prepared the first draft of the manuscript. UMM supervised SS, identified the themes, and edited the manuscript.

Declaration of competing interest

None of the authors have any conflicts of interest to declare.

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