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Emerging and evolving concepts in the pathobiology and treatment of psychosis.

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EDITORIAL

Emerging and Evolving Concepts in the Pathobiology and Treatment of Psychosis

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While psychotic illness endures as a major public health issue, investigations continue to slowly provide increasing insight into the disorder. These insights are now seen to be of two types: Those *evolving* increase our understanding incrementally along established lines with which we feel comfortable, for example genome-wide association studies of genetic risk, neuroimaging studies of brain structure and function and antipsychotic drug development,[1-5] as they relate to specific psychotic diagnoses, most typically schizophrenia. Those *emerging* are more radical and challenge these 'comfort zones', for example recent evidence that: psychotic ideation and associated psychopathology can be present in young persons across the general population;[6] early intervention for features associated with 'clinical high risk' and at the first psychotic episode may, respectively, ameliorate the emergence of diagnostic psychotic symptoms and improve long-term

outcome;[7-9] schizophrenia-related psychopathology, pathobiology and risk genes are disrespectful to conventional diagnostic boundaries.[1,3,10,11]

Three contemporary factors synergise in advancing our understanding of psychotic illness: the first is increasing sophistication of molecular genetic and structural and functional neuroimaging techniques; the second is a continually increasing number of studies that are generating results using these techniques; the third is capitalising on the breadth of this evidence base through the application of meta-analytic techniques that extract 'core' pathobiologies in psychotic illness. This third factor is facilitated by the increasing altruism of individual research groups world-wide to pool their findings into ever larger collaborative, trans-national datasets for analysis by global consortia.[2,12] In counterpoint is the withdrawal of many major pharmaceutical companies from what are perceived to be both insurmountable scientific and associated commercial challenges in the development of new drugs for the treatment of psychotic illness and indeed for other neuropsychiatric disorders.[5,8,13,14] This Special Issue addresses a number of these *evolving* and *emerging* challenges.

Studies on the pathobiology of psychotic illness in general, and of schizophrenia in particular, continue to provide increasing substance to long-standing models of (a) underlying genetic risk, environmental risk factors and the interactions between them, and (b) how they may synergise in promoting a developmental pathophysiology characterised by dysfunction in dopaminergic-glutamatergic systems of subcortical-cortical brain networks.[3,4,15-17] However, newer, potentially important processes are emerging. The review by Cao and Zhen[18] focuses on small noncoding RNAs, known as microRNAs (miRNAs), that are now recognized as essential post-transcriptional

regulators in gene expression. They are important in brain development and neuroplasticity and abnormal expression and dysfunction of miRNAs are known to be involved in the pathophysiology of many neuropsychiatric diseases, including schizophrenia. These authors summarize recent findings on schizophrenia-associated dysregulation of miRNAs, the functional roles of such dysregulation in the development and pathogenesis of schizophrenia, and the potential therapeutic implications of miRNA dysregulation in psychotic illness.

Further clues are emerging from more classical routes, namely substance-induced psychosis and less studied, but potentially equally important, instances of organic psychosis. Such psychopathology, perhaps better described as secondary psychosis, can develop for diverse reasons, including toxic/metabolic disorders, widespread neuropathology and focal brain lesions. Joyce[19] reviews post-stroke psychosis, a phenomenon that has contributed particularly to understanding the pathobiology of delusions. These are associated with lesions of the right lateral prefrontal cortex or locations with connectivity thereto, indicating a hub for delusions in a cortical-subcortical neural network that receives afferents from midbrain dopamine neurons. These analyses complement and elaborate findings in schizophrenia[4] and underpin the use of antipsychotic medication as the treatment of choice for both conditions.

In relation to treatment, it is sobering that, after six decades of involvement,[20] over recent years several pharmaceutical companies have announced withdrawal from the development of antipsychotics, leaving a reduced number still in the field that are complemented by a small number of biotech companies.[13,14] Despite several alternative mechanistic approaches, none has yet displaced attenuation of hyperactivity in

dopaminergic systems, which remains the only common denominator among all known antipsychotic drugs.[4,5,8,13-15] From this foundation, variant approaches are emerging that target alternative routes to influencing aspects of dopaminergic function related to antipsychotic activity and side effect liability. Among these, Suzuki and Kimura[21] review the recent history of inhibitors of phosphodiesterase10A (PDE10A), consider the heterogeneity of PDE10A inhibitors, and suggest that one particular profile of activity is critical to produce preclinical indicators of heightened efficacy, including amelioration of cognitive dysfunction, and superior safety profiles. They then go on to outline the pharmacological properties of the novel PDE10A selective inhibitor TAK-063 that appears to have this profile and summarize preliminary findings from initial clinical studies.

The 'holy grail' of psychosis research is prevention, which is predicated on a viable concept and a reliable marker of those young persons who will and will not go on to develop a psychotic illness. Such indices have not yet been identified. However, studies are investigating early interventions, both psychological and biological, for young persons identified as at 'clinical high risk' for psychotic illness using criteria that are emerging and undergoing continual refinement.[8,9] In preclinical studies, models of psychotic illness involving early interventions that are followed only later by the development of psychosis-related abnormalities[22] provide a platform for investigating any effects of early psychological and/or biological interventions to delay or even prevent the subsequent emergence of those abnormalities. Diana and colleagues[23] consider this field and then describe recent studies that investigate a nitric oxide (NO) donor in treating *vs* preventing distinct behaviors related to each of positive, negative and cognitive

symptoms in a developmental model of schizophrenia. In this model, early treatment with the NO donor prevented the emergence of such behavioral abnormalities in adult animals without inducing untoward effects and the authors discuss the implications of these and related findings.

Conventional nosology involves distinct diagnostic categories of diseases, with psychosis having been associated classically with schizophrenia in dissociation from affective disorder. However, emerging evidence suggests that psychotic illness is, in reality, disrespectful to such diagnostic categories and may be better conceptualized in terms of dimensions of psychopathology. This disrespect is apparent in terms of the overlapping psychopathology and pathobiology of schizophrenia and bipolar disorder,[1,3,10,11,15] but is most stark in relation to the juxtaposition of schizophrenia and major depressive disorder with psychotic features.[24,25]

In this context, Kingston and colleagues[26] compare the clinical characteristics and long-term psychopathological and functional outcome in schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder with psychotic features. They report that at 6-year follow-up these four psychotic diagnoses are characterized by quantitative rather than qualitative differences in psychopathology, functionality, quality of life and service engagement and suggest that these four diagnoses are arbitrary categories within what is, in reality, a milieu of psychosis. In a complementary manner, Meltzer and colleagues[27] start from an alternative perspective by describing a case that, over her lifetime, has evidenced discrete, non-overlapping periods of treatment-resistant bipolar disorder, major depressive disorder with psychotic features and schizophrenia, followed by sustained remission. They compare initial pharmacological non-response,

subsequent remission and associated longitudinal neuroimaging findings in this case with those of her multiple counterparts, all of whom participated in the same clinical trial of treatment-resistant schizophrenia.

Such co-occurrence of psychosis and major depressive disorder presents a specific psychopathological challenge, given that anhedonia is recognized both as a negative symptom of the cardinal psychotic illness, schizophrenia, and as a primary affective symptom of major depressive disorder. This trans-diagnostic challenge is reviewed by Lambert and colleagues,[28] who consider the extent to which anhedonia, a dysregulation of the reward circuit, is characterized by both psychopathological and pathobiological similarities and differences across these two diagnostic categories. Greater understanding of these similarities and differences may improve psychological and pharmacological interventions to ameliorate the adverse impact of anhedonia, however conceptualized, on long-term functioning and quality of life.

Given emerging recognition that the psychopathologies of psychotic illness and major depressive disorder are not mutually exclusive but, rather, can and often do co-occur in the same individual, it is timely to reconsider also the action of antidepressant drugs. Liu and colleagues[29] investigate the effects of Hcyb1, a novel inhibitor of phosphodiesterase2A (PDE2A), in two contexts: as a putative antidepressant agent and as a neuroprotective agent in terms of increasing cell viability/promoting neuronal proliferation. They report Hcyb1 to exert both antidepressant-like effects in behavioral models and neuroprotective effects in cell lines that are likely mediated by cAMP/cGMP-CREB-BDNF signalling, disruption of which has been implicated both in depression and psychosis and in antidepressant and antipsychotic drug action.[30,31]

In conclusion, we hope that this Special Issue illuminates (a) important aspects of *evolving* concepts of schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder with psychotic features, and (b) how these aspects are increasingly complemented by yet more heuristic *emerging* concepts of psychotic ideation, psychotic illness and pathobiology across conventional diagnostic boundaries within a melieu of psychosis. Such juxtaposition refreshes the field and increases the likelihood of progress.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

References

1. van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374:635-645.
2. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511:421-427.
3. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet*. 2016;388:86-97.

4. Howes OD, McCutcheon R, Owen MJ, Murray RM. The role of genes, stress, and dopamine in the development of schizophrenia. *Biol Psychiatry*. 2017;81:9-20.
5. Morrison PD, Murray RM. The antipsychotic landscape: dopamine and beyond. *Ther Adv Psychopharmacol*. 2018;8:127-135.
6. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry*. 2016;15:118-124.
7. Clarke M, McDonough CM, Doyle R, Waddington JL. Are we really impacting duration of untreated psychosis and does it matter? Longitudinal perspectives on early intervention from the Irish Public Health Services. *Psychiatr Clin North Am*. 2016;39:175-186.
8. Millan M, Andrieux A, Bartzokis G, et al. Altering the course of schizophrenia: progress and perspectives. *Nat Rev Drug Discov*. 2016; 15:485-515.
9. Carpenter WT. Clinical high risk controversies and challenges for the experts. *Schizophr Bull*. 2018;44:223-225.
10. Owen MJ. New approaches to psychiatric diagnostic classification. *Neuron*. 2014;84:564-571.
11. Pearlson GD, Clementz BA, Sweeney JA, Keshavan MS, Tamminga CA. Does biology transcend the symptom-based boundariesd of psychosis? *Psychiatr Clin North Am*. 2016;39:165-174.
12. Goodkind M, Eickhoff SB, Oathes DJ, et al. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*. 2015;72:305-315.
13. Hyman S. Time for new schizophrenia Rx. *Science*. 2014; 343:1177.

14. Forray C, Buller R. Challenges and opportunities for the development of new antipsychotic drugs. *Biochem Pharmacol*. 2017;143:10-24.
15. Waddington J, Hennessy R, O'Tuathaigh C, Owoeye O, Russell V. Schizophrenia and the lifetime trajectory of psychotic illness: developmental neuroscience and pathobiology, redux. In: Brown A, Patterson PH, eds. *The Origins of Schizophrenia*. New York, NY: Columbia University Press; 2012:3-21.
16. European Network of National Networks studying Gene-Environment interacstions in Schizophrenia (EU-GEI), van Os J, Rutten BP, et al. Identifying gene-environment interactions in schizophrenia: contemporary chellenges for integrated, large-scale innvestigations. *Schizophr Bull*. 2014;40:729-736.
17. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*. 2014;383:1677-1687.
18. Cao T, Zhen X. Dysregulation of miRNA and its potential therapeutic application in schizophrenia. *CNS Neurosci Ther*. 2018 (in press).
19. Joyce E. Organic psychosis: the pathobiology and treatment of delusions. *CNS Neurosci Ther*. 2018 (in press).
20. Leucht S, Leucht C, Huhn M, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry. 2017;174:927-942.
21. Suzuki K, Kimura H. TAK-063, a novel PDE10A inhibitor with balanced activation of direct and indirect pathways, provides a unique opportunity for the treatment of schizophrenia. *CNS Neurosci Ther*. 2018 (in press).

22. Pletnikov M, Waddington J. *Modeling the Psychopathological Dimensions of Schizophrenia: From Molecules to Behavior*. Amsterdam, The Netherlands: Elsevier; 2016.
23. Diana MC, Peres FF, Justi V, et al. Sodium nitroprusside is effective in preventing and/or reversing the development of schizophrenia-related behaviors in an animal model: the SHR strain. *CNS Neurosci Ther*. 2018 (in press).
24. Waddington JL, Buckley PF. Psychotic depression: an underappreciated window to explore the dimensionality and pathobiology of psychosis. *Schizophr Bull*. 2013;39:754-755.
25. Owoeye O, Kingston T, Scully PJ, et al. Epidemiological and clinical characterization following a first psychotic episode in major depressive disorder: comparisons with schizophrenia and bipolar I disorder in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Schizophr Bull*. 2013;39:756-765.
26. Kingston T, Scully PJ, Browne DJ, et al. Functional outcome and service engagement in major depressive disorder with psychotic features: comparisons with schizophrenia, schizoaffective disorder and bipolar disorder in a 6-year follow-up of the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *CNS Neurosci Ther*. 2018 (in press).
27. Meltzer HY, Sim M, Anderson A, et al. A within-subject consideration of the psychotic spectrum disorder concept in a patient in remission associated with cortical grey matter recovery. *CNS Neurosci Ther*. 2018 (in press).
28. Lambert C, Da Silva S, Ceniti A, et al. Anhedonia in depression and schizophrenia: a trans-diagnostic challenge. *CNS Neurosci Ther*. 2018 (in press).

29. Liu L, Zheng J, Huang X, et al. The neuroprotective and antidepressant-like effects of Hcyb1, a novel selective PDE2 inhibitor. *CNS Neurosci Ther*. 2018 (in press).

30. Yang B, Ren Q, Zhang JC, Chen QX, Hashimoto K. Altered expression of BDNF, BDNF pro-peptide and their precursor proBDNF in brain and liver tissues from psychiatric disorders: rethinking the brain-liver axis. *Transl Psychiatry*. 2017; 7: e1128.

31. Diniz CRAF, Casarotto PC, Resstel L, Samia RLJ. Beyond good and evil: a putative continuum-sorting hypothesis for the functional role of proBDNF/BDNF-propeptide/mBDNF in antidepressant treatment. *Neurosci Biobehav Rev*. 2018 (in press).