Characterising novel pathways to schizophrenia

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New approaches to schizophrenia research and policy can provide a substantive basis for early intervention and better care

For the past 20 years, much of the clinical and basic science research related to schizophrenia has been based on the belief that the disorder results largely from genetically determined abnormalities in brain development.[1,2] Although some perinatal factors (eg, intrauterine infection and hypoxia during labour) have been conceded, they are still considered within the constraints of the neurodevelopmental model. Against this background of "genetic developmentalism", preventive and early intervention strategies have often been discounted. Further, this nihilistic view has been reinforced by major gaps in clinical care,[3] partial response to pharmacological or psychosocial interventions,[4] and premature deaths from suicide, injury and vascular disease.[5]

Currently, simplistic genetic or developmental approaches are giving way to relevant polygenic models, or are approached based on more complex gene–environment interactions.[6,7] It is likely that multiple genetic factors that influence brain development, glial cell structure and function, and a wide range of other neurochemical, neurohormonal, circadian and neuroimmunological factors are all relevant. Importantly, many of these genetic risks appear to be shared with other major psychiatric disorders (notably bipolar disorder) and other disorders of early childhood brain development (eg, autism).

"How does an environmental factor … get inside the nervous system and alter its elements to generate the symptoms of a disordered mind?"[7] The traditional notion that there is little variance in the incidence of schizophrenia is not consistent with more recent epidemiological analyses.[8] The latter suggest the likelihood of a wide range of potential environmental risks. The challenge lies in using new neuroscience tools to help us understand which specific environmental factors, occurring at which points along the postnatal to postpubertal developmental course, have the capacity to result in such profound perturbations of central nervous system function.

Early neurodevelopmental models have exaggerated the importance of deviations before puberty. By contrast, the more dramatic deviations, reflected in subclinical and clinical stages of illness, occur during adolescence and early adulthood.

The critical role of postpubescent cannabis exposure has only been confirmed recently (see McGrath and Susser in this supplement, *page S7*).[9] Much attention is now being paid to the potential relevance of other drug exposures, notably use of amphetamine-type stimulants (Hermens and colleagues, *page S22*).[10] Here, the key question is not whether these substances simply precipitate psychotic symptoms but rather whether amphetamine-type stimulant-related psychoses are biologically equivalent to psychotic disorders that are not associated with these same exposures.

Infective and other inflammatory risk factors for psychotic disorders have been proposed previously. They are now being reconsidered in light of advances in our understanding of likely interactions with genetic variations in immune response and related glial cell biology (Hickie and colleagues, *page S17*).[11]

The differences between male and female patterns of illness onset strongly suggest a moderating effect of oestrogen exposure. This observation has underpinned the development of a very significant new direction in adjunctive pharmacotherapy with oestrogen-based treatments (Kulkarni, *page S37*).[12]

Early intervention and longitudinal studies now demonstrate that social and cognitive deterioration are not necessarily characteristic features of schizophrenia and other psychotic disorders (McGorry and colleagues, *page S33*).[13] The critical insight from recent neuroimaging studies has been that active brain changes (notably in frontal and temporal lobe structures) take place during the transition from subclinical to clinical stages of active psychosis (Wood and colleagues, *page S10*).[14] Contrary to the "early-insult" proposition, neurocognition is often relatively intact throughout the subclinical or prodromal stage.[15] Further, active interventions during this early phase appear to at least delay illness progression.[16-18] Some novel pharmacological approaches appear to prevent brain deterioration.[19] These findings have underpinned the search for other early neuroprotective strategies (eg, lithium, omega-3 fatty acids, and antidepressant or anticonvulsant therapies).[20,21]

The focus of much basic and developmental research may now shift to cellular-based approaches that track critical changes in neuronal and glial cell architecture during childhood and adolescence. The key finding has been the reduction in synaptic connections in frontal lobe structures in the postpubertal period. This active process may be accelerated in those at risk of psychotic disorders or may occur against the background of failure to achieve maximal synaptic connections in late childhood (Bennett, *page S14*).[22] This line of research has the potential to identify new cellular and molecular targets for modification of this at-risk pathway.

Consistent with this approach, the clinical staging model proposed by McGorry and colleagues is more radical than it may first appear.[23] It challenges the dogma perpetuated by specialists who deal largely with adult patients — that each of the major psychiatric disorders has its own unique pathophysiological pathway. By contrast, the clinical staging model suggests a "trunk-and-branch" analogy, with the early stages of major psychiatric disorders sharing common risk factors and phenotypic trajectories (the "trunk"). Only after the later phases of frontal lobe development (ie, typically in the early 20s) do individuals develop the more specific symptom features (the "branches") that we currently use to underpin *Diagnostic and statistical manual of mental disorders* or International classification of diseases diagnoses.

This model places greater emphasis on a search for common, rather than unique, risk factors. It requires the use of different sampling strategies, with active recruitment of age- and stage-appropriate patient and control participants. It places great empha-

sis on the need for biomarkers of earlier stages. We need to have some confidence that we can predict progression before we engage in more assertive interventions. This process has been aided in other neurological disorders by tracking reactive features such as microglial response to illness onset. Preliminary evidence suggests such an approach may be viable in patients with schizophrenia — particularly if such data are combined with other neurophysiological, neuropsychological or inflammatory markers (Banati and Hickie, *page S26*).[24]

Most importantly, the clinical staging model posits that many of the most undesirable outcomes of schizophrenia could be prevented by interventions delivered at more general biological mechanisms (eg, preservation of frontal cortical structures, regulation of central corticotrophin-releasing factor responses, maximisation of brain-derived neurotrophic factor function, normalisation of circadian rhythm disturbance). Traditional biological markers (eg, dopamine 2 receptor blockade) may be more relevant to the later stages of the illness. Development of a sophisticated clinical trials program to test the staging model is an international priority. To achieve this, we need to link with clinical platforms, nationally and internationally, that recruit subjects early in their illness course (as proposed under the *headspace* framework[25]).

Much of the social stigma and health services neglect that accompany the diagnosis of schizophrenia have been perpetuated by a "sterile" clinical, research and health policy agenda. We urgently need a national policy agenda that encourages collection of real data and dissemination of critical information to consumers and carers (Crosbie, *page S43*),[26] and a timely focus on reducing premature death through better attention to medical risk factors (Lambert and Newcomer, *page S39*).[27]

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