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Editorial

Psychosis prediction 2.0: why child and adolescent mental health services should be a key focus for schizophrenia and bipolar disorder prevention research

Ian Kelleher

Summary

Existing approaches to psychosis prediction capture only a small minority of future cases. Recent research shows that specialist child and adolescent mental health services (CAMHS) offer a (previously unrecognised) high-risk and high-capacity approach for psychosis early identification, prediction and, ultimately, prevention.

Keywords

Psychotic disorders; schizophrenia; epidemiology; out-patient treatment; in-patient treatment.

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Psychosis prediction has been a major focus of psychiatric research for a quarter of a century. The engine of growth for this research was the development of structured assessments of attenuated psychotic symptoms aimed at identifying individuals at risk of psychosis, which emerged in Melbourne, Australia, and quickly spread to other parts of the world. The idea behind this approach was to allow intervention even before the onset of frank psychosis, ideally to prevent the illness. This came to be known as the ultra-high risk or clinical high risk (CHR) approach and inspired a generation of clinicians and researchers to consider the possibility of prevention of severe mental illness. Thousands of papers have now been published using the CHR approach and many clinical guidelines internationally, including National Institute for Health and Care Excellence (NICE) guidelines, recommend CHR assessments to identify individuals at risk of psychosis.

Challenges

The CHR approach has hugely influenced modern psychiatry in its goal for the prediction and prevention of severe mental illness. In terms of psychosis prediction and prevention, however, recent studies have highlighted important limitations of the CHR approach. In particular, recent research has shown that this approach identifies only a small proportion of future psychosis cases, even in areas with readily accessible, high-profile CHR clinics. In the South London and Maudsley (SLaM) catchment area of London, UK, which has a long-established, free-to-access CHR clinic, researchers found that just 4% of psychosis cases were preceded by a CHR diagnosis.[1] In Melbourne, Australia, the home of the CHR paradigm, just 14% of psychosis cases were preceded by a CHR diagnosis, leading the researchers to conclude that 'other methods are needed to identify those at risk for a psychotic disorder'.[2]

A second limitation of the CHR approach is that a network meta-analysis of CHR studies found no clear evidence for the effectiveness of any specific intervention in preventing transition to psychosis in this population.[3] Furthermore, two systematic reviews have shown that rates of transition to psychosis do not differ between 'naturalistic' centres (i.e. centres that do not offer specific interventions but just follow patients over time) and centres that provide comprehensive interventions (including, for example, individual case management, family interventions and cognitive–behavioural therapy). Therefore, despite decades of research, we lack clear evidence to support any specific interventions to prevent psychosis in the CHR approach.

Developmental sensitivity

A rate-limiting step in the clinical utility of high-risk approaches is that they must identify individuals during the developmental window of sensitivity, when preventive interventions can be effective. A large majority of CHR studies to date have been conducted in predominantly adult samples. The pathophysiology underlying schizophrenia, however, appears to be a product of disordered maturational processes that occur in the context of adolescent brain development, including disruption to synaptic pruning, evolving functional connectivity and maturation of the dopaminergic system within the prefrontal cortex.

Research in animal models of schizophrenia suggests that adolescence is a critical developmental window during which interventions may prevent progression of pathophysiological changes found in psychosis. Researchers have shown, for example, that serious cognitive and network dysfunction that emerge in animal models of schizophrenia may be prevented by the administration of dopamine D_2 receptor antagonists or by environmental enrichment specifically in adolescence (but not in adulthood).

A neuroscience-informed approach would suggest that intervention before the end of adolescence may be necessary to prevent the pathophysiological changes underlying psychosis. The average person attending CHR services, on the other hand, is an adult in their 20s. A shift in focus towards identifying risk for

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psychosis specifically in childhood and adolescence may be needed if we are to advance psychosis prevention efforts.

Identifying risk for psychosis in adolescence: high-risk systems

An alternative to focusing on symptoms associated with elevated psychosis risk (as in the CHR approach, which assesses subclinical psychotic symptoms) is to focus on systems associated with psychosis risk. Epidemiologically informed risk systems are systems in which risk factors for the relevant outcome (in this case psychosis) are naturally concentrated, for example various healthcare, educational or social care systems. A neuroscience-informed approach to risk systems for psychosis would also focus specifically on systems in which risk factors are concentrated in childhood and adolescence, i.e. during a developmentally sensitive window of opportunity for intervention.

We recently showed that a specific healthcare system that captures elevated risk for psychosis in children and adolescents is the paediatric emergency department. Specifically, we showed that children and adolescents who presented to hospital emergency departments with self-harm had a similar level of psychosis risk as children and adolescents diagnosed as being at clinical high risk for psychosis.[4] At the same time, while this group had an elevated risk of psychosis, they made up only a small proportion of all future psychosis cases, meaning that additional (ideally, higher-capacity) approaches are also needed.

Another candidate risk system for identifying individuals at risk of psychosis in youth is specialist child and adolescent mental health services (CAMHS). Psychotic disorders are uncommon diagnoses in CAMHS and the reasons for attending CAMHS have typically been considered to differ significantly from the reasons for attending specialist adult mental health services (where the large majority of psychosis diagnoses occur). However, many risk factors for psychosis are heavily enriched in children and adolescents attending CAMHS – not only early-life problems with mental health but also problems with language acquisition, motor coordination, cognitive function, educational attainment, social communication and substance use.

Using longitudinal Finnish national healthcare register data for all individuals born in Finland in 1987, we recently showed that, although psychosis diagnoses are uncommon in CAMHS, individuals who had attended CAMHS at some point in childhood had a very elevated risk of psychosis when followed to age 28.[5] Absolute risk for psychosis or bipolar disorder by 28 years of age varied from 13% for individuals who had attended out-patient CAMHS (ages 11–17 years) to 37% for individuals who had been admitted to an in-patient adolescent CAMHS unit (ages 13–17 years). What is more, a full 50% of all psychosis diagnoses in the population occurred in individuals who had, at some point in childhood, attended CAMHS.

These findings highlight CAMHS as a high-capacity, high-risk system for future psychosis prediction (and, ultimately, prevention) research. What is more, crucially, individuals presenting to CAMHS are, by definition, within a developmental window of opportunity for preventive interventions – i.e. they are all children and adolescents – which means that adolescent brain maturational processes that are believed to underlie psychosis are still possible targets for intervention.

The high capacity for psychosis prediction within CAMHS also highlights new opportunities to advance aetiology research. Neuroimaging research, for example, has shown that the core structural brain abnormalities associated with psychotic disorders are already established by the time of diagnosis, meaning that the factors involved in the development of these abnormalities remain unclear. Adolescents attending CAMHS provide an important large group for future research to understand the (potentially multiple) pathways to psychosis, including the development over time of structural brain abnormalities prior to schizophrenia onset. Improved understanding of developmental pathways to psychosis will, in turn, identify new treatment targets for psychosis prevention.

Ethical considerations

An extensive literature has looked at ethical questions around screening for clinical high risk for psychosis in the general population. It is important to recognise, however, that 'attending CAMHS' is not a screening approach. The research described above has, rather, simply quantified the level of risk for psychosis that naturally occurs in CAMHS populations.

It is also important to note that exploration of neurodevelopmental factors contributing to a young person's presentation to CAMHS is already a key part of the work carried out in CAMHS. At present, however, the neurodevelopmental factors given clinical consideration tend to be within the domains of autism spectrum, attention deficit and impulsivity disorders, and specific learning difficulties. An appreciation of these neurodevelopmental factors is a key part of developing an individual formulation and treatment plan. Adding information on other domains of neurodevelopmental risk, including psychosis risk, can only strengthen this work. Furthermore, the interplay between psychosis risk and a young person's mental health should no more be overlooked in CAMHS than the interplay between other neurodevelopmental factors and their mental health.

Conclusions

The CHR paradigm has shifted the landscape of psychiatric research towards the bold idea of early intervention and prevention. It is important that we continue to build on this bold ambition, to increase the proportions of future cases of severe mental illness that we can identify early. Specialist CAMHS provide enormous, previously under-recognised potential for the prediction and, ultimately, prevention of schizophrenia spectrum and bipolar disorders. Future research on psychosis risk, therefore, should prioritise studies of young people attending CAMHS. This should include studies to further refine risk prediction within this risk-enriched group. New priorities should also include research on preventive interventions informed by developmental neuroscience. What is more, additional intervention opportunities will be identified through important aetiological research that this high-risk approach will make possible. An exciting future lies ahead for prediction and prevention research within CAMHS.

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Declaration of interest

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Psychiatry in history

The Fairy Tale King and his royal psychiatrist: the contribution to neuroscience of Dr Johann Bernhard Aloys von Gudden, psychiatrist to King Ludwig II

Madhusudan Dalvi

During a recent trip to Munich when I passed Starnberg Lake, my mind was transported back to June 1886, when a great tragedy struck a doctor and patient, both found drowned in mysterious circumstances. The patient was a king and the doctor was his psychiatrist. A small wooden signboard is the only reminder of this tragedy where the King of Bavaria Ludwig II and his psychiatrist Dr Johann Bernhard Aloys von Gudden lost their lives. This incident largely eclipses Gudden's immense contributions to cognitive neurosciences, which is tragic in itself.

In 1843 Gudden had entered the University of Bonn to study philosophy, subsequently changing to medicine and continuing in the Universities of Bonn, Halle and Berlin. He obtained his medical degree with distinction in 1848. For his doctoral dissertation, he studied torsional eye movement. He joined the Rhineland Mental Asylum in Siegburg as an assistant to eminent psychiatrist Carl Wigand Jacobi. From 1870, he was the co-editor of the journal *Archiv für Psychiatry und Nervenkrankheiten*, with Theodor Meynert, who discovered the nucleus basalis of Meynert, and Karl Westphal, famous for his contribution to the study of the accessory nucleus of the third cranial nerve. Gudden was appointed Director of the District Mental Hospital in Werneck in 1855 and in 1869 he was appointed Professor of Psychiatry at the University of Zurich. Wilhelm Griesinger, head of the Zurich Mental Asylum, had a big influence on him in treating patients with respect, dignity and without coercion when 'human rights' were non-existent. In 1872, Gudden took over as Director of the District Mental Institution in Munich, and subsequently became a full professor of psychiatry at the University of Munich, where Emil Kraepelin, Franz Nissl and Auguste-Henri Forel were his students. He developed the Gudden's microtome, for sectioning the human brain, and his work on neurodegeneration predates Arnold Pick and Alois Alzheimer. He was one of the joint discoverers of retrograde degeneration, also known as Wallerian degeneration, along with Bartolomeo Panizza and Augustus Volney Waller. He pioneered removal of sense organs and cranial nerves in young animals and found that this led to secondary atrophy. His other important findings include the fact that destruction of certain areas of the cerebral cortex causes atrophy of specific thalamic nuclei, which gives us an understanding today of how cortical and subcortical networks interact and an insight into how long-distance neural networks become dysfunctional. His observation that lesions in the cortex do not cause atrophy in the peripheral nervous system has been named Gudden's law. He discovered the inferior commissure, the connecting tract between the medial geniculate bodies. He described the tegmental nuclei known today as the dorsal and ventral tegmental nuclei of Gudden. Recognition of the role of these tegmental nuclei in cognitive function is gaining momentum as new research findings highlight the critical importance of several extra-hippocampal structures, including the tegmental nuclei of Gudden, in cognitive functions, which resonates with new research findings that the dorsal tegmental nucleus has head-direction cells. This is a big move away from the hippocampus-centric view of amnesia to a more distributed cognitive functional circuit model. It led him to suggest a new subject, *Nervenheilkunde* (neuropsychiatry).

Just before the tragedy at Starnberg Lake Dr Gudden had diagnosed King Ludwig II with an advanced state of paranoia. Interestingly, he also considered a diagnosis of 'Caesarean madness', made famous by Ludwig Quidde in a psychological study of the Roman emperor Caligula, who was presented as a megalomaniac, corrupted by the conditions of monarchist rule. Gudden's obituary, written for the *BMJ* by Dr Charles Workman, described him as a kindly man, much liked and respected by his patients.

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