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Transition to Adulthood: The Critical Period for Pre-emptive, Disease-modifying Care for Schizophrenia and Related Disorders

Patrick McGorry[*,1,2]

[1]Centre for Youth Mental Health, Department of Psychiatry, University of Melbourne, Australia; [2]Orygen Youth Health Research Centre, Melbourne, Australia

*To whom correspondence should be addressed; Orygen Youth Health, Locked Bag 10, Parkville, VIC 3052, Australia; tel: +61-3-9342-2850, fax: +61-3-9342-2948, e-mail: pmcgorry@unimelb.edu.au

There is an urgent need and a global opportunity to rethink not only the dominant research paradigms in etiological research but also to invest in less constrained strategies which cut across the existing diagnostic silos to seek out common risk factors, late as well as early neurodevelopmental processes, pathophysiologies, and novel treatment strategies. The high-quality research presented in this special issue of *Schizophrenia Bulletin* makes a compelling case for such a rethink. While there is still a genuine disconnect between our understanding of the complex and dramatic brain changes that occur during the transition to adulthood and the concurrent surge in incidence of mental ill-health, there is no doubt that a much more serious focus on the perionset stage of clinical disorders in young people with their rapidly evolving brains, social environments, and life trajectories could be extremely productive. Research access to these early stages of illness would be catalyzed by the widespread construction of engaging stigma-free portals and clinical scaffolding appropriate for young people in the 21st century. The latter are urgently required to supersede traditional models of care, which have served both patients and families so poorly, and equally have failed to unlock a deeper understanding of the origins and progression of potentially serious mental disorders.

Key words: youth mental health/early intervention/mental illness

Introduction

The transition to adulthood is the period during which nearly all the potentially serious mental disorders that disable or kill during the ensuing decades of adult life have their onset.[1,2] This was first highlighted for schizophrenia in the 19th century and reflected in familiar, now historical terms such as "adolescent insanity" and "dementia praecox."[3] Despite this major etiological clue, as Uhlhaas[4] points out in his introductory article to this issue, until recently, there has been a relative blind spot in our research paradigms, which have conceptualized schizophrenia as an early neurodevelopmental disorder with most of the risk and putative neurobiological insult seen as concentrated perinatally and early in life.[5–7] Despite the sustained surge in interest in early psychosis and first-episode research and elaborations of the 1980's neurodevelopmental theory into the 2- and 3-hit models (see Gogtay et al,[8] in this issue, and Insel[9]), there still seems to be a curious reluctance to give serious research attention to the period during which the clinical phenotypes of schizophrenia, and indeed most of the other major mental disorders of adult life, emerge.

There is no logical reason for this imbalance in research valence, which may represent the all-too-familiar resistance of older paradigms to yield to newer ones, even when they are revisions of the earlier version and wholly compatible. The combination of genetic vulnerability, early insult, and childhood risk indicators is certainly part of the story. It is clearly not the whole story and may well not be the main story. Uhlhaas[4] has summarized the support for the early developmental model. It seems biologically plausible that a combination of genetic risk and perinatal biological insults can establish vulnerability for later mental disorder, but the animal models and epidemiological data do not indicate that these factors are necessary or sufficient for disorder, nor whether they create the specificity for the future phenotype.

While birth cohort studies have revealed subtle and nonspecific emotional, cognitive behavioral risk indicators in a proportion of cases during the otherwise latent prepubertal childhood period, these are statistical deviations from ultimately healthy controls and are nonspecific with poor predictive power for not only for schizophrenia but also for caseness of any sort. The real indication of incipient disorder usually emerges

postpuberty in the majority of cases via clinical precursor or prodromal "stages", which are subthreshold for traditional diagnostic categories such as schizophrenia yet which confer substantial impairment and distress nonetheless. This is when better predictive power finally emerges, though the exit syndromes are still diverse. Despite this long latent period, the dominant view remains that some version of what has been termed developmental allostasis[10] occurs, in which an early lesion produces a vulnerability which is compensated for until this mechanism is overwhelmed during adolescence, when the early lesion is revealed and the clinical phenotype released. Uhlhaas (this issue)[4] is quite correct in suggesting that this notion places excessive weight on the modest evidence for early risk and specific childhood indicators.

The early neurodevelopmental hypothesis, in which patients are seen as "doomed from the womb", essentially yokes vulnerability and risk on the one hand to early clinical disorder on the other. A clinical staging approach (see below) seeks to separate out these processes so that independent risk factors and processes can operate as in other complex disorders. So while it is possible that changes occurring in the adolescent brain "reveal" or "release" an early deficit resulting in clinical disorder, it is equally possible that they can initiate or underpin emerging disorder de novo and in their own right via new varieties of pathophysiology, without the need for an early insult or lesion. So there are 2 potential and non-mutually exclusive pathways to "disease": one an inexorable or revealed deviation from normal neurodevelopment and another, e.g. psychosis initiated by cannabis use, which involves additional synergistic pathophysiological influences. The latter model distinguishes options for both preventive interventions targeted at vulnerability, as well as novel clinical interventions targeted at early-stage phenotypes, allowing more scope for the exploration of the latter.

How do the articles in this issue throw light on this crucial theoretical and clinical issue? The common theme that they share is a focus on the late maturation of brain circuits during adolescence and early adulthood. These major changes in brain development are reflected in robust animal research and putative disease models (Hoftman and Lewis;[11] O'Donnell[12]) and in biomarkers such as structural magnetic resonance imaging change (Gogtay et al[8]) and neural synchrony that demonstrate subtle and yet profound maturational changes. In humans, these occur in intense and dynamic interaction with the kaleidoscopic social environment with all of its risks and demands for the emerging adult, and from this crucible of gene-environment interaction emerges either successful maturation or alternatively the evolution of mental disorders. This is a uniquely fertile ground for research and it deserves much more serious attention. Hoftman and Lewis[11] allow for multiple sensitive periods of interaction between the environment and brain development. O'Donnell[12] appears to favor the developmental allostasis model in which the cortex becomes disinhibited as a result of a revealed interneuron defect which could have multiple causes. In contrast, Uhlhaas and Singer[13] express cautious sympathy for a more dominant role of adolescent brain changes in the specific denouement of psychotic disorders in their review of the development of neural synchrony and large-scale cortical networks. They make a compelling case for neural synchrony as a potentially useful biomarker or endophenotype to study alongside others and in relation to the emergence of clinical phenotypes of adolescent onset disorders. Similarly, imaging studies conducted across the transition from the ultrahigh risk stage to first-episode psychosis and other diagnostic outcomes are also consistent with an active process at that point (Gogtay et al[8], this issue). Other pathophysiological candidate mechanisms such as oxidative stress and inflammation[14] could become activated de novo and trigger the onset of symptoms. Yet, there is little evidence that any of these candidate processes have much specificity for current diagnostic boundaries, and we lack data from the onset stages.

What is striking about this collection of articles is the wide gap between the neuroscience of adolescent brain development and active study of key biomarkers of this process of maturation and its vicissitudes in the perionset stage of a broad range of major mental disorders in young people. We are certainly a long way off biomarker-assisted early diagnosis, but we have to begin to fill in the pieces of the puzzle focusing on the perionset period much more seriously. For all these reasons, this special issue of *Schizophrenia Bulletin* devoted to brain development and neurobiological processes during adolescence is most welcome and timely.

My commentary will endeavor to place this tantalizing scientific material on the neurobiology of adolescence in a developmental, epidemiological, and therapeutic context. Broader conceptual frameworks and diagnostic strategies with greater utility, analogous to those utilized in other major health domains are essential. If we are able to look more broadly across the landscape of mental and substance use disorders in young people, we may be able to see how to create much better ways to pre-empt their destructive personal and social impact and in the process reduce stigma. I will profile encouraging developments in responding to mental ill-health in adolescents and emerging adults, which reflect the need for a greatly expanded and strengthened stigma-free approach. Such reform and investment will complement and facilitate the research directions covered in this special issue.

Transition to Adulthood: Developmental and Epidemiological Synchrony

One of the failures of the mental health field so far is not to have appreciated that the timing and pattern of mental ill-health impacts so strongly on young people who, on

the threshold of adult life, have the most to lose. So has the society as a whole in reduced human capital or "mental wealth" and economic productivity.[15] Furthermore, a key paradox of the developed world is that while their material well-being and physical health have dramatically improved, the mental health of young people in transition from childhood to adulthood has been steadily declining over recent decades.[16,17] The incidence pattern for mental and substance use disorders is now almost the mirror image of that seen for physical disorders, with 75% emerging before the age of 25 years and emerging adults (16–24 years) showing the peak 12-month prevalence for any disorder across the lifespan.[2,18,19] Mental ill-health is the major source of burden of disease in otherwise healthy young people, being responsible for over 50% of this.[20,21] The consequences even for mild and transient disorders are significant; for more severe disorders, they can be enduring and catastrophic. A recent New Zealand study[22] estimated that up to 50% of young people in this transition age will experience at least 1 diagnosable episode of mental ill-health with a directly proportionate negative impact on earning potential, educational outcomes, and social integration at age 30 years. The scene for this erosion of life chances is often set in childhood, but more commonly, it takes the ever-changing climate of adolescence and emerging adulthood to release the variety of overlapping clinical phenotypes we recognize as clinicians, the incidence of which surges through adolescence and peaks between 18 and 25 years. Paus et al[23] posed the question "why do many psychiatric disorders emerge during adolescence" and provide an answer based on subtle aberrations of brain maturation and development caused by the interaction between genetic and environmental factors (Uhlhaas[4] and Feinberg[24]). Their thesis is highly compatible with the ideas contained within this special issue. However, it is vitally important for research conducted within this neuroscience paradigm to give sufficient weight to the power and malleability of the environmental influences shaping the risk and expression of mental ill-health and sustained disorder in young people.

From puberty, with all of its biological upheavals, young people face a whole series of stressful challenges. Without sufficient "scaffolding,"[25] it is very hard to make the transition to independent adulthood without experiencing periods of mental ill-health, which can so easily become recurrent and entrenched. The developmental challenges include forming a stable identity in a world which is changing at a very rapid rate, negotiating often harsh, and depleted educational environments where bullying is rife, forming secure peer relationships and gradually separating from the family of origin, managing the drive to risk-taking and avoiding harmful use of the array of licit and illicit substances available, and finding a vocational pathway with some sense of purpose. As if this were not enough to cope with, unexpected bursts of "outrageous fortune", such as the death of a parent, parental mental illness or substance abuse, violent assault, or a natural disaster, can derail or thwart the lives of young people at a time they are relatively ill-equipped to cope.

Many people make the mistake of assuming that because emotional distress, functional decline and damaging behaviors are common in young people, this is "normal" and largely transient, and to intervene would be unnecessary or even harmful. This confuses being common with being benign: a serious error with often fatal consequences. Malaria is common in many developing countries but hardly benign. Young people, with the highest incidence and prevalence of mental ill-health, receive the least help to overcome these threats to their survival, well-being, and contribution to others. Reinforcing this ambivalence about offering effective care is an excessively traditional biomedical mindset and a treatment context divided into a child-oriented system on the one hand and a limited adult system on the other, both of which are distinctly unappealing to young people.[26,27] So far we have made only desultory efforts to understand what is behind this rising tide of mental ill-health and to respond to it in a manner congruent with the sensitivity and sophistication of which advanced 21st century societies should be capable.

Clinical Staging: A Heuristic Strategy for Intervention and Understanding the Neurobiology of Mental Disorders

> "Currently, mental disorders are diagnosed by symptoms that emerge at a late stage, presumably years after brain systems veer from more typical development." Insel[28]

The critical point in diagnosis for all potentially serious disorders is when risk transforms into a clinical syndrome. Early diagnosis is vital wherever effective treatments exist. The accuracy of diagnosis in general medicine can be sharpened and validated by the use of biopsies or biomarkers of other types. For psychiatry, such "biosignatures"[29] remain aspirational. Our traditional diagnostic categories in psychiatry have major limitations in helping us to capture this critical point in early diagnosis. Anchored as they are to the later stages of the clinical phenotype, they have functioned as diagnostic silos of questionable validity, and may have actually obstructed the path to discovery of key etiological processes.[30] Modern genetic research has further questioned their validity[31] and their utility is also debatable as they struggle to fulfill the primary purpose of clinical diagnosis, namely the differential selection of treatment strategies. This is where the deceptively simple diagnostic refinement of clinical staging may be useful in reengineering our approach.[32,33] We have described this model in detail over several publications.[34–35]

Mental ill-health can be difficult to distinguish from transitory and normative changes in emotions and behavior, which are often regarded as part of normal

development and the human condition, especially in young people. The latter interpretation is often spuriously reinforced by the fact that many of these initial periods of distress and breakdown may resolve relatively quickly at least at first, even with minimal or no intervention.[36] However, it is important not to trivialize the significance of these bursts of mental distress because subthreshold symptoms strongly predict future disorder, and future chronicity will be seriously underestimated.[37,38] We lack a clear consensus and criteria for defining the threshold for initial caseness. How symptoms are acquired, intensify, and cohere into syndromes, how these ebb and flow, and how they compound into vocational failure, substance misuse, behavioral disturbance, and social exclusion have not been widely considered.[37,38] We also lack valid definitions for distinguishing between benign and self-limiting states and those, which represent the early stages of what will become persistent and disabling conditions.[39] We must learn to tolerate and even welcome what are currently dismissed as "false positives" and create a stigma-free fast track to enable them to be distinguished from phenotypically similar early stages of serious illness. We encourage women with newly identified breast lumps and men with the onset of central chest pain to urgently seek medical care, even though we know that a substantial percentage will have a benign explanation. This mindset can be translated to the psychiatric field if we can overcome 1 or 2 perceived barriers, namely the effects of stigma and the risk of overtreatment of earlier detected cases.

Clinical staging, a deceptively simple and practical tool found useful in other areas of medicine, may provide a way forward.[32–34] In a pre-emptive psychiatry based on the clinical staging paradigm, end-stage syndromes such as deficit schizophrenia may fade into the background as destinations to be avoided.[7,40] Clinical staging differs from conventional diagnostic practice; in that it not only defines the extent of progression of a disorder at a particular point in time but also where a person lies currently along the continuum of the course of an illness. The differentiation of early and milder clinical phenomena from those that accompany illness extension, progression, and chronicity, lies at the heart of the concept, which therefore makes it especially useful in adolescence and early adulthood, when most adult-type disorders emerge for the first time. A staging framework enables clinicians to select treatments relevant to earlier stages of an illness and generally assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course. Staging allows the timing of treatment and the constant need to balance risk and benefit to come into focus. It provides an antidote to the genuine issue of overtreatment if access to care is provided earlier.

A key feature of clinical staging is that it must cut across current diagnostic boundaries and not be exclusively or narrowly applied within the "tram tracks" of 1 putative category, such as schizophrenia for example. This is because we already know that the earliest clinical phenotypes associated with a need for care are nonspecific and involve a mix of mood, anxiety, and other partial syndromes frequently associated with substance use and personality dysfunction. Syndromes like schizophrenia, mania, recurrent, and severe unipolar depression generally emerge in a stable way some time later, and even then, in many cases, blends of these are the end result despite the best efforts of hierarchical diagnosis. The clinical staging model has been created by the same forces as the National Institute of Mental Health Research Domain Criteria framework[29] which tentatively extends the clinical boundaries for research beyond the current perimeters. However, by casting the net even wider and augmenting this with the notion of stage, which has temporal and progressive elements as a further key dimension in the matrix, clinical staging may not only sharpen intervention research but also unpick and crystallize biosignatures[29] in a more meaningful way.

Insel has also carefully elaborated the staging idea in relation to schizophrenia, apparently to illustrate the principle[7,40]; however, in my view, this sells the heuristic potential of the concept short. It will be more liberating and enlightening if applied *agnostically* rather diagnostically. In addition to its potential value in structuring clinical trials with multiple syndromal outcome targets, an agnostic staging model may point the way to a clinicopathological version in which the biomarkers and neurobiological processes described in this special issue, as well as many others (for examples, see ref. [41–43]), can be related as biosignatures not only to clinical phenotypes but also to stage of disorder. If we stick with current silo boundaries, many of these insights could remain hidden or opaque.

New Stigma-free Clinical Platforms for Young People

One of the catalysts and enablers of the growth in new knowledge, new treatments, and better cost-effective outcomes in early psychosis have been the development worldwide of novel clinical service platforms for young people in the early stages of psychotic illnesses.[44,45] Now operating in hundreds of locations worldwide; these potential clinical laboratories provide better access to low stigma therapeutic environments with an optimistic and holistic approach, which has enabled us to get much closer to the earliest clinical stages of psychotic disorders.[46] Not only is the duration of untreated psychosis much shorter in such settings but also people with moderate functional impairment and distress, yet subthreshold symptoms, are also seeking and receiving help. It is much more difficult and many would say undesirable to attempt these early intervention strategies in traditional psychiatric settings, which are dominated by much older patients with severe and enduring mental disorders. Early psychosis programs have reduced stigma, shortened treatment delays, reduced suicide risk, and

improved outcomes the cost-effectiveness of care.[44,46–50] They have also made possible unique studies examining biomarkers in relation to emerging psychotic illness.[42,51,52]

These experiences, positive as they have mostly been, have revealed a wider possibility for radically improving clinical care for young people who bear the brunt of mental disorders and their corrosive impact on life chances and trajectories. There is a missing stream of mental health care in our societies which needs to cover the period of need for greatest accessibility, agility, and strength; namely the years from puberty to the mid-20s, when so much change is occurring in brain development and the internal and social worlds of the emerging adult, and when the force of morbidity of mental ill-health is at its peak.[26,53] Despite this, young people have the worst access to mental health care across the lifespan and the cultures of care are totally unsuited to their needs, with the result that they fail to engage or secure tenure of care even if access is achieved.[17,54,55]

In Australia and Ireland, but also in Canada, the United Kingdom, and small parts of Asia and the United States, real progress is being made in designing and upscaling up of innovative platforms of care with a broad and flexible diagnostic focus for young people aged 12–25 years.[44,56–58] The first element is a form of youth-friendly enhanced primary care in which universal access is available to all young people at a venue located in the heart of the community, which has the ambience of a youth café or drop-in center, yet with the back-of-house multidisciplinary expertise (general practitioners, allied health professionals, drug and alcohol counselors, vocational experts, and sessional psychiatrists) offered within a genuine ''one-stop shop.'' Other key features involve community education, e-health portals, and youth and family participation. These programs are very popular with young people and families and have already provided care to more than 35 000 young Australians in 30 sites nationwide under the headspace banner (www.headspace.org.au). They provide a stigma-free portal to more specialized care for the subset of young people with potentially severe and complex disorders, including schizophrenia, which is provided within early psychosis and similar specialized youth mental health services.[44,59] These platforms are likely to receive increasing support in the coming years, especially in developed nations with universal access to health care, and create ideal conditions for the development of novel therapies and scientific exploration of the perionset stage of a range of mental and substance use disorders, including schizophrenia and other psychotic and mood disorders.

Future Directions

There is an urgent need to rethink not only to the dominant research paradigms in etiological research as stated by Insel[9,28] but also to go further and invest in alternative approaches which cut across existing diagnostic silos to seek out common risk factors, neurodevelopmental processes, pathophysiologies, and novel treatment strategies. A focus on the perionset stage of clinical disorders in young people with rapidly evolving brains and life trajectories could be extremely productive and would be greatly assisted by the construction of 21st century clinical scaffolding to replace the traditional models of care which have served both patients and families poorly and have not facilitated access to deeper understanding of the origins of potentially serious mental disorders.

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