Section 1 Conceptual and Strategic Issues

Chapter 1

Diagnosis without Borders

A Pluripotential Approach to Preventive Intervention in Emerging Mental Disorders

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Diagnosis in medicine has been seen as an essential process in choosing appropriate treatment and predicting the future course of the illness, and providing a sense of clarity and relief to patients that their illness is legitimate and understood. In many fields of medicine the diagnostic process has evolved in complexity over the past few decades from a predominantly clinical process based on a careful case history and physical examination to a blend which places a great deal of weight on investigations aimed at staging and stratifying or personalising treatment in a more precise manner. The term *precision medicine* (National Research Council, 2011) has been coined to reflect this aspiration and growing reality. New technology has boosted the power and precision of diagnosis, though it has reduced reliance on high-level clinical skill and expertise, which commands less respect (Moffitt, 2016).

By contrast, in psychiatry, attitudes to diagnosis remain ambivalent and polarised, and its value is continuously questioned both in professional circles and in the public arena (Greenberg, 2013; McGorry, 2013). Recent revisions to international diagnostic systems for psychiatry have reignited this deep ambivalence, which reflects Cartesian tensions between the extremes of 'mindless' and 'brainless' psychiatry (Dominguez et al., 2011). New life has been injected into an enduring culture war (Angell, 2011) in which victories are elusive or pyrrhic. As this storm subsides we risk entering a new period of stasis in which old ideas are recycled (Jablensky, 2016) and admittedly erudite yet ultimately frustrating metaphysical analyses are presented (Kendler, 2016). Other equally erudite reviews (Stephan et al., 2016a; 2016b) pose all the key questions but provide few answers. How can we move beyond such static, even defeatist, mindsets to the heuristic? Is there a more productive pathway? Several possibilities have been advanced (Borsboom, 2017; Cuthbert & Insel, 2010; Kotov et al., 2018; McGorry et al., 2006). But first let us consider what is the fundamental purpose of diagnosis.

The Nature and Purpose of Diagnosis

Robert Kendell (1975a) pointed out four decades ago that human beings possess three sets of characteristics. The first set of characteristics is more or less universal and is shared with all other human beings, such as having essential organs like the brain, possessing the ability to think and reflect, and being able to breathe. The second set is unique to that individual, such as their fingerprints, dental records, particular skin blemishes and personal life experiences. The third set of characteristics is those that are shared with some but not other human beings. Only the latter group is of use for the purposes of classification and therefore for diagnosis, which is a specific form of classification.

In purely medical diagnosis, there are now layers and subsets within this third domain. For example, some people with breast cancer share this characteristic with each other, but not with those who do not have breast cancer. However, they can be further subgrouped according to the stage of the illness in that they share certain features linked to stage (notably extension or spread of the disease) with some breast cancer sufferers and not with others. Further profiling, subcategorisation or *stratification* (Trusheim et al., 2007), as it is known, can be carried out using specific genotyping and use of other biomarkers. This increasing precision means that the treatment options can be personalised in quite a fine-grained manner (Collins & Varmus, 2015). However, we still do not approach the reductio ad absurdum that treatment may ultimately be uniquely different for every individual. There are still groupings, albeit much smaller than before, and the treatment sequence according to stage is also especially important.

In psychiatry, in the light of the mind–body split as created by Cartesian dualism, many are prepared to ask the question: does diagnosis really apply at all? Impressed by the great diversity of human experience and the uniqueness of the individual, which manifests at the level of the person and character, they argue that even stratification is insufficient and that *every* individual's mental health care must be unique and personalised. This is an argument that could apply most clearly to psychological forms of therapy, and it is true that the critique of the value of diagnosis in psychiatry is usually advanced by proponents of psychological therapies as the sole or dominant form of treatment. Psychoanalysis arguably represents the most extreme form of this perspective. However, taken to such an extreme, this implies that no knowledge or evidence derived from the care of other people could ever be used in the care of each new or distinct individual. This means starting anew with every new patient as a brand new learning experience. However, even in the domain of personality and character, there are subgroups and dimensions of commonality. Yet the fact is that we do all have some unique personal characteristics and experiences, we all feel a level of uniqueness as human beings as well as a sense of commonality and kindred spirit, and we would like to be related to, with this uniqueness understood and accepted. These unique aspects can be critical in personalising therapy and, for this reason, psychiatry is the field within medicine where personalised medicine is already achievable.

These considerations do not mean that psychiatric diagnosis is necessarily fundamentally different from medical diagnosis but that we need to pay more attention to not only stratifying the treatment as best we can by stage and subgroup, but also having an element in every patient of uniquely and individually tailored care. Indeed, while it is especially important in psychiatry, this may well be necessary in patients with physical diseases too if we can see beyond the mind–body split.

> The deeper we delve into the nature of mental illness, the clearer it becomes that cherished distinctions between diagnostic categories might be partly illusory.
>
> (Stephan et al., 2016a)

The other substantial difference between medical and psychiatric diagnosis is arguably maturational, in that the latter is still largely syndromal or, worse, still 'polythetic', made up of a collection of clinical features assembled by committees or based on historical sources. Traditional views (Jablensky, 2012; 2016) require there to be points of rarity between syndromes which are seen as being composed of sets of clinical features cohering in a limited number of patterns with 'points of rarity' typically seen between them. However, in real life this is the exception rather than the rule, especially as syndromes

emerge. In the formation of syndromes it is apparent that some symptoms create risk for others. The analogy with clouds was one used by Robert Kendell, and indeed symptoms ebb and flow, cohere and dissipate in just that manner. Boundaries between such phenotypic expressions are indistinct, overlapping and unclear. The concept of comorbidity is a natural extension or corollary of this scenario. In physical disease, there are genuinely comorbid pathophysiological processes such as diabetes and ischaemic heart disease which coexist, with one often acting as a risk factor for the other. In psychiatry, it is far from clear that when syndromal co-occurrence occurs that this indicates comorbidity of the same type. The underlying biology may be the same or different. We are not able to be at all clear about this. Stephan et al. (2016a) contend that the dysfunctional brain appears to be quite limited in the number of major syndromal patterns it can create.

The final issue is that while diagnosis in its applied sense as providing a guide to treatment selection and outcome may be useful across the board in mental health, it may struggle more for acceptance beyond the traditional core of mental disorders, notably psychoses and severe mood disorders (Kendell, 1975b). When applied to the border zones of common mental disorders, anxiety, depression, personality dysfunction and crisis responses, the personal uniqueness argument gives the impression at least of having more strength, at least as a major influence on the problems, the value of specific biological treatments is less clear, and the boundaries of normality and need for care from mental health professionals more contested by the public, governments and sections of the mental health field (Frances, 2013). While there are valid debates to be had here, the dichotomy between low and high prevalence or common mental disorders is false, and has been unhelpfully used to ration access to quality mental health care in a way that would be quite unacceptable in physical medicine; for example, deserving low prevalence or 'genuine' cases of serious mental illness versus the less deserving 'worried well', including subthreshold cases where much treatable chronic distress and disability resides. On the other hand, with the revolution in 'awareness' in high-income country settings, this scenario is changing, and it is the common mental disorders that are gaining better acceptance and access to care, while the more severe and persistent mental disorders are increasingly neglected (Demyttenaere et al., 2004; Wang et al., 2002). In order to step back from this familiar vortex, which confuses so many, and fascinates and oddly gratifies some, it is crucial to seek some practical solutions.

Diagnosis: Classification with Utility

Diagnosis is essentially *classification with utility* (Kendell & Jablensky, 2003). The aim is to characterise the clinical phenotype in a condensed or shorthand way that helps to distinguish those who are ill and in need of health care from those who are not, and genuinely enhance the selection of treatment and prediction of outcome. Medicine is a pragmatic field, utility in medicine is the ultimate test, and this utilitarian definition is necessary and sufficient to justify the central role of diagnosis in clinical practice. If an underlying pathophysiology or biosignature can be closely linked, then that is welcome added value. Yet much of current psychiatric diagnosis has low utility and such biosignatures remain elusive, or are transdiagnostic. This is part of the reason for its weak and ambivalent support for diagnosis among many mental health clinicians as well as the wider world. Nor do the current diagnostic systems appear to have optimally assisted the search for disorder-specific pathophysiological mechanisms and biological and cognitive markers;

indeed they may well have obscured such progress. Hence, many researchers are seeking other heuristic frameworks (Cuthbert & Insel, 2010; Kendler et al., 2011; Kotov et al., 2018; McGorry et al., 2010). The latter can be divergent from and fail to meet clinical needs.

Other problems that have been highlighted by critics include continuing poor reliability, despite the advent of operational criteria, potentially harmful effects of the more stigmatising diagnoses, the inevitably bureaucratic and political nature of the international classification industry, the retention of time-honoured diagnostic categories past their use-by date, while at the same time poorly validated new categories have mushroomed (i.e. from 182 disorders in DSM-II to 265 in DSM-III and 297 in DSM-4), and poor predictive value for consumption of health care resources (Rutledge & Osler, 1998). To this could be added a failure to clearly define the earliest clinical stages of emerging mental disorders as has been done in other medical illnesses. This has hampered preventive psychiatry and the capacity for early diagnosis. A consequent lack of confidence in, even suspicion of, early diagnosis, combined with stigma and a failure to invest in mental health care to scale, has helped to embed late diagnosis, inadequate quality of care and consequently poorer outcomes across the world, which seem inevitable through the lens of the 'clinician's illusion', and which further entrench stigma and therapeutic nihilism, and reinforce the dichotomy between the high-prevalence or common mental disorders (often derided as overlapping with the 'worried well'). With new versions of the DSM and ICD, we can expect little more than incremental and desultory change, increasingly buffeted by the forces of public opinion, politics and ideology (Ahuja & McGorry, 2012; Boseley, 2012; Carey, 2012; Frances, 2010). We are faced with some stark choices. These are: a resigned acceptance of the status quo and a retreat into another round of introspection (Jablensky, 2016; Kendler, 2016); a revival of earlier attempts to develop a system based on quantitative nosology (Kotov et al., 2018); and the design of innovative and heuristic new approaches (Cuthbert & Insel, 2010; McGorry et al., 2007). A creative leap is desperately required, but is it within reach or merely a mirage, or another false dawn?

Mental Ill-Health Starts Well before Traditional Diagnosis

Mental ill-health has to start somewhere. Eaton et al. (1995) described how what we call symptoms arise either from *intensification* of subjective experiences or behaviours that have been present for some time or from *acquisition* of new experiences or behaviours, or most commonly a combination of both. Daily human experience involves periodic and sometimes intense and mercurial changes in affect and salience in response to the social environment. When these become more prominent, they can be discerned as subclinical 'microphenotypes', which wax and wane, interact sequentially or become confluent, and may mature or stabilise towards pure or hybrid 'macrophenotypes' (van Os & Linscott, 2012). This process is undeniably fluid and dimensional, and several (but not endless) dimensions of psychopathology can be readily identified, such as aberrant salience and affective dysregulation. Categories could be arbitrarily imposed within such dimensions, but the notion of the syndrome, in which various elemental symptoms somewhat predictably cohere but also impact on each other over time (Kendler et al., 2011), is an important construct to retain. In real people, and these phenomena can be best observed in young people in transition to adulthood when the force of incidence of mental ill-health surges to a peak (McGorry et al., 2011; Paus et al., 2008), several dimensions of psychopathology emerge sequentially and concurrently in an interactive and dynamic way, ebbing and

flowing. Persistence and severity (perceived distress) are key dimensions setting the threshold for need for care (Dominguez et al., 2011), irrespective of the specific constellation of features. An initial or provisional diagnosis merely represents a categorical decision that there is a need for care on the basis of severity and persistence of distress with or without clear-cut impairment, though this has also involved a recognition of this need for care and help-seeking by the person or someone close to them. This is a minimalistic approach that does not overextend specific diagnosis, which is usually not necessary to offer initial and non-specific forms of intervention. We know it is challenging to rigidly define the boundary between 'normality' and mental disorder and need for care. But how critical or feasible is it to create such a precise definition? Could it even be self-defeating? And could we tolerate a 'grey area' or fuzziness, with soft and flexible entry (and exit) and personal choice as key features of a new primary care culture? One variable is the person's level of tolerance of suffering, which is highly variable in relation to both physical and mental symptoms. Unlike in physical medicine, where even asymptomatic 'normal' people have no problem accessing preventive health care of many kinds, financial forces, an exaggerated fear of stigma and labelling, and perhaps also of poor-quality care, tend to oppose this tolerance and flexibility in mental health.

The debate over whether a *clinical high risk, ultra-high risk* or *attenuated psychosis syndrome* (CHR, UHR or APS – a constellation of low-grade psychotic experiences in help-seeking and distressed individuals that research indicates represents a precursor syndrome of first-episode psychosis) should be included in the DSM-5 brought all of these issues to the fore (Carpenter & van Os, 2011; Fusar-Poli & Yung, 2012; Woods et al., 2010). It also showed that while this concept was a genuine advance, its key value may be prototypical; there is a bigger fish to fry, namely a broader transdiagnostic precursor stage (McGorry et al., 2018). The classical patterns of psychopathology that are represented in the major psychiatric disorders, such as schizophrenia, major depression, borderline personality disorder, anorexia nervosa and bipolar disorder, are late-stage concepts, largely derived from late nineteenth- and early twentieth-century tertiary care settings. Advances in psychiatric epidemiology have revealed widespread subdiagnostic and relatively non-specific expression of mental ill-health in the general population; some of this is transient or intermittent, some persistent, but most of it justifies a need for care, and there is substantial cumulative public health impact (Judd et al., 2002; Linscott & van Os, 2013). A key question is how these phenomena should link with and shape diagnostic classification. All major psychiatric disorders have early clinical stages or 'prodromes' during which sustained distress and disability embed and care is needed, yet this occurs well before traditional diagnostic 'clarity' is achieved (McGorry et al., 2006). Primary care physicians know this only too well and find the DSM and ICD relatively unhelpful. They are finding the greater flexibility of new transdiagnostic staging-based models liberating. Recent work suggests that persistence of psychotic experiences with associated distress in the general population begins to approach the level of risk for sustained psychotic disorder as seen in enriched clinical APS samples (Kaymaz et al., 2012; van Os & Linscott, 2012).

The UHR criteria for psychosis, developed by our group over 20 years ago (Yung & McGorry, 1996; Yung et al., 1998), do have a strong valence for psychosis as an outcome, yet even with this as the primary target, other targets were hit, and a substantial proportion of patients manifest other syndromal outcomes, mainly mood and anxiety, much but not all of which had been expressed prior to the emergence of psychotic symptoms. This indicated that introducing a single prodromal or early clinical phenotype (APS) within one of the

diagnostic silos in an otherwise relatively unchanged DSM-5, without reference to other diagnostic streams, would produce an asymmetry that could obscure the wider issue and undermine wider reform. The current UHR or APS criteria were clearly not the last word on the issue, and ultimately this is the reason that we support the decision (made for other reasons) to not include the definition in the main clinical section of the DSM-5. Most psychosis researchers believe the predictive power of these UHR criteria should be enhanced using additional clinical predictors and key biomarkers; however, this may be a very challenging task in isolation, given the syndromal nature of the exit syndrome of interest and the overlap and comorbidity that is inevitable. Alternatively, we can take a broader transdiagnostic view, as suggested originally by Cuijpers (2003), who stressed the value of including multiple outcome targets or exit syndromes, particularly when each of these individually is of relatively low incidence. This makes a virtue of necessity, and particularly when the emerging syndromes we are seeking to define are somewhat elusive, overlapping and unfold sequentially. Traditionally, this has been handled with hierarchical models with organic and psychotic syndromes 'trumping' more common syndromes regarded as less specific and lower in the hierarchy. Another response to this issue is the clinical staging model, which allows predictors and preventive treatment for multiple specific exit syndromes to be studied in parallel and allows the possibility that risk factors and treatment strategies alike may be common or cross-diagnostic (McGorry et al., 2007). This certainly reflects the behaviour of clinicians and may help to account for 'off label' broad-spectrum use of both drug and psychosocial treatments. This is generally seen as a vice, rather than a case of clinical reality exposing the fiction created by the wishful thinking of an excessively reductionist biological psychiatry, and cemented by the FDA and the pharmaceutical industry, that an array of poorly validated and differentiated syndromes can be equated with diseases.

Are Early Clinical Phenotypes Pluripotential?

This discussion and the logic of Cuijpers (2003) suggests the notion of pluripotentiality of the early clinical phenotypes of mental disorders and the value of expanding the UHR operational definition with subthreshold features and risk markers for several non-psychotic exit syndromes to define a broad-spectrum ultra-high-risk or pluripotential state. Such a definition might be expected to result in greater enrichment of the sample for progression to one or more of several forms of sustained, recurrent mental disorder of at least moderate severity. It might then be feasible to identify from within a less specific and undifferentiated cohort of distressed and help-seeking young people the enriched subset at greatly enhanced risk of serious mental illness, and would pave the way for sophisticated sequential treatment trials to be conducted in due course. The sequences of evolving syndromes may be linear, consistent with a hierarchical model, or much more variable, with homotypic, heterotypic and mixed patterns of evolution. Other approaches have sought to capture and design natural structures and pathways within a closed system of psychopathology (the Hierarchical Taxonomy of Psychopathology (HiTOP) and network analysis – see Chapters 3 and 4). HiTOP attempts to cross-sectionally provide a hierarchical dimensional approach to psychiatric classification (Kotov et al., 2018), whereas network theory conceptualises mental health as a system in which the interplay between symptoms underpins disorder onset (Borsboom, 2017). Alternatively, the 'p factor' approach proposes that a general psychopathology factor underlies a range of disorders, representing lesser to

greater severity of psychopathology (Caspi et al., 2014). Although these approaches may facilitate the mapping of mental disorders, their clinical utility remains unclear, particularly in guiding treatment planning.

Nonetheless, these raise a fundamental question of whether static quantitative nosology alone is capable of defining a system in which the natural structure of symptoms and syndromes can be utilised by clinicians to make treatment decisions. Furthermore, what is the relationship of the 'p factor' to subordinate components of the array of syndromes and symptoms? Is the 'p factor' a representation of pluripotentiality? Similarly, while network analysis allows longitudinal patterns to be captured, to what extent are symptom dynamics and influences the major determinants of emergence of fully fledged and stable syndromes and disorders?

Careful longitudinal studies from initial onset of symptoms and with broad entry criteria are needed to distinguish between a pluripotential model and one that is more hierarchical and deterministic. Concepts and tools such as the 'p factor', hierarchy staging and quantitative nosology are all of potential value and could be utilised in the creation of a more definitive model, which can only be validated through its utility. Using biomarkers or biosignatures to assess risk of progression or remission, to subtype within stages and further refine treatment would introduce 'profiling' and a more personalised or stratified approach. Ultimately, it may be that sophisticated sequential intervention studies stratified using biomarkers are needed to uncover early specificity behind a deceptively pluripotential screen. Alternatively, there may be some quasi-universal interventions which benefit all or most patients.

Clinical Staging May Be More Important than Prematurely Specific Syndromal Diagnosis

There is a natural tension between overtreatment and inhibiting the capacity for resilience and coping, and undertreatment, which is fuelled in psychiatry by poor awareness, stigma and limited access to care. To a large extent this is a false dichotomy, which along with stigma itself can be overcome by *normalising* approaches to early intervention, which include 'soft entry' to assessment and care in a welcoming and optimistic culture and setting. Crisis theory is one key framework that illustrates this point and allows normal responses to severe adverse life events to receive a safe and proportional therapeutic response event, even though the distress and impairment is understandable and mostly self-limited. Relief of distress and early and sustained care for the subgroup who turn out to not make a speedy recovery is fully justifiable. In the same way, early forms of therapeutic intervention in mental health care can generally have a light initial touch, with elements such as support, information, exercise and e-health as their mainstay. The clinical staging model in psychiatry (described in Chapter 2) adapted from general medicine ensures that interventions are proportional to both need and the risk of 'extension' of the clinical phenotype and its consequences (McGorry et al., 2006). It recognises that persistent and multiple 'microphenotypes' of disturbance can justify a need for care on their immediate merits *as well as risk* for progression to more familiar 'macrophenotypes'; however, it also recognises the need for blending dimensional and categorical models. Staging moves outside the current diagnostic boundaries to include the full spectrum of disorder, and while highly congruent with notions of an extended phenotype for individual disorders, which involves continuity with the healthy population, it places strong diagnostic emphasis

on where a person sits in the evolution of the clinical phenotype. A staging perspective explicitly recognises that this is a moving feast, and that there is homotypic and heterotypic continuity as well as discontinuity and remission. The goal of staging is to improve *diagnostic utility* in relation to treatment selection and evaluation. We regard this as preeminent in diagnosis and this contrasts so far with other new developments in diagnosis (Borsboom, 2017; Cuthbert & Insel, 2010; Kotov et al., 2018). Traditionally, the nexus between diagnosis and prognosis has been used as a criterion for judging utility. In our view, in psychiatry, this has been overemphasised and exaggerated, with frequent negative, even iatrogenic, consequences. Blending, and even embedding, prognosis within diagnosis led to the creation of the schizophrenia concept, which had the effect of extinguishing hope for recovery from generations of patients. Staging also has a longer-term heuristic goal of facilitating linkages between biological and cognitive markers and clinical phenotypes agnostically rather than diagnostically, though this may not be relevant to all mental health conditions.

Staging Aims to Enhance Treatment Selection, Safety and Success

So when would it make sense to move beyond a general diagnosis of 'mental ill-health' or the notion of a 'p factor'? This has to do with the specificity and safety of the range of psychosocial and biological treatments, and remains to be defined by further clinical research. It also has to do with the success or otherwise of simpler and more generic early-stage interventions. The principle could be that we should allow no more specificity in the diagnostic term or label than is necessary to guide treatment selection. We might start to see some of this specificity emerge with the advent of clearer, more stable and sustained, or severe syndromes or macrophenotypes such as psychosis, mania, depression, anxiety, addiction and the borderline syndrome, either alone or, more typically, in 'comorbid' blends. Network analysis, which maps the pathways of risk and flow of symptom patterns, might provide avenues for intervention targeting pivotal symptoms which increase risk for progression, such as insomnia or rumination. While the 'p factor' might conceal therapeutic targets, deploying a hierarchical lens beyond the top level (Reininghaus et al., 2013; 2016; 2018) similarly might guide therapeutic strategies. Alternatively, such treatment specificity might be determined by other variables. On the psychosocial side, it might be a question of matching different forms of psychotherapy to personal styles, temperaments and preferences, or practical needs. Biologically, there may be underlying endophenotypes or mechanisms which mean a response to a particular biotherapy will be positive and these mechanisms may very well manifest pleiotropy, meaning that the clinical phenotype varies for any single disturbed biomarker or mechanism. As concluded in this book (Chapter 14), it is obvious that new transdiagnostic clinical trials and other research designs are required to determine the value of staging and these related ideas.

Conclusion

Diagnosis that works for the patient, the family, the clinician and the researcher is definitely possible but it needs to be relatively simple, though multilayered. The current approach to revisions of the existing diagnostic manuals, rooted as they are in the psychiatry of traditional tertiary care, will not reinvent diagnosis. Nor will a stale and stalled introspection on the theme of diagnosis and its discontents, or a simple recycling of quantitative nosology from a static and purely psychopathological perspective. The field needs testable new models which are parsimonious enough to work in the clinic and yet

complex enough to support more personalised and sequential treatment selection. Clinical staging, a novel initiative that links the tertiary care perspective to the modern and more inclusive population-based and primary care context, may be best suited to take up the challenge of modernising the diagnosis of mental disorders from first principles. It could certainly be enhanced by quantitative nosology, network analysis and biomarkers as potent research and design tools. The most important benefit to be gained is better utility and a freer pathway to the holy grail of validity. This should moderate the ever-increasing generation (and occasional extinction) of diagnostic categories, by allowing the timing, and mode and extent of progression of illness, to anchor the diagnostic process, and forge a stronger link to treatment decisions sensitive to risk–benefit considerations and patient choice. Formal recognition of what is already tacitly accepted should follow: namely, that relative syndrome specificity is a later-stage marker of progression, severity and poorer outcome of illness, and that much is to be gained by acknowledging the need for proportional, and yet possibly pre-emptive, care in the earlier, relatively non-specific, stages of illness.

A crucial step in constructing such a novel diagnostic strategy is to operationally define the early clinical phenotypes, which require intervention in their own right, but also connote risk for later stages and more elaborated syndromes, which are likely to be multiply comorbid and more persistent, recurrent and disabling. The early clinical phenotypes may be initially truly pluripotential, or there may be early hints or warning signs, emerging symptom relationships and biosignatures suggesting particular sequences, patterns and outcomes. Treatments may also be characterised by cross-diagnostic effectiveness and preventive influence, and at the same time, have specificity for certain aspects as well. These considered conjectures require a more heuristic approach to the early course and treatment of mental disorders.

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