CLINICAL STAGING OF PSYCHIATRIC DISORDERS

How to Improve the Utility of Diagnosis for Patients, Clinicians and Researchers

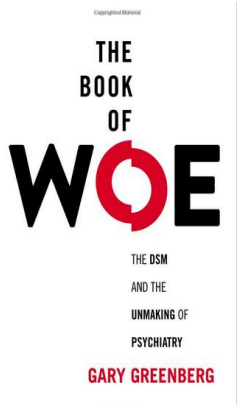
Patrick McGorry MD PhD University of Melbourne

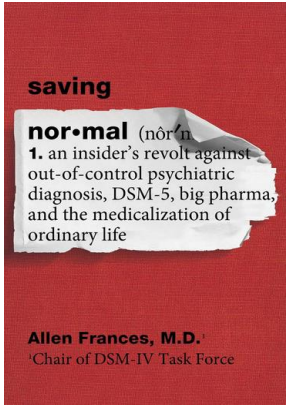
QUESTIONS

- How do mental disorders develop?
- How do we improve the prediction of onset and evolution of mental disorder?
- Do our diagnostic systems adequately capture the nature of psychopathology?
- What would a new diagnostic system with maximum clinical and research utility look like?
- Can the vast array of neurobiological research be brought through a more valid and useful diagnostic system into better focus and alignment with clinical and functional imperatives.
- Can we integrate current creative and technical approaches and what can we learn from each other?

CONTEXT

- Arguably held back by a nosological approach that is over a century old, these questions present an enormous enduring challenge for the mental health field of psychiatry.
- There has been conflict and disillusionment as a result, but…
- Recent years have witnessed a wave of new research strategies and theoretical concepts (e.g., clinical staging, HiTOP, RDoC, network theory, P factor, complex systems etc.) for modelling and predicting the onset and evolution of mental disorder.
- Nomothetic vs Ideographic and Formulation-based perspectives
- However, these approaches have largely remained separated from each other and working independently.





Redeeming diagnosis in psychiatry: timing versus specificity

Patrick McGorry, Jim van Os

In general medicine, diagnosis is a crucial step in the choice of appropriate treatment, prediction of the future course of an illness, education of patients and families, and helping patients to realise that they are not alone. By contrast, in psychiatry, attitudes to diagnosis remain mixed and polarised, and the value of diagnosis is continuously questioned. With revisions to the international diagnostic systems for psychiatry on the horizon, this deep ambivalence—derived from Cartesian tensions between "mindless" and "brainless" perspectives[1]—has surfaced once again, breathing new life into an enduring culture war.[2] How can this impasse be overcome? What is diagnosis actually about?

Essentially, diagnosis is classification with utility.[3] The aims are to characterise the clinical phenotype in a condensed or shorthand way that helps to distinguish people who are ill and in need of health care from those who are not, and to genuinely improve selection of treatment and prediction of outcomes. Utility in medicine is the ultimate test, and this utilitarian definition is necessary and sufficient to justify the diagnosis strategy in clinical practice. Value might be added to a diagnosis if

Little more than incremental and desultory change is expected in the forthcoming new versions of the DSM and International Classification of Diseases (ICD), which are increasingly buffeted by the forces of public opinion, politics, and ideology.[4–11] A transformation is needed, but is it feasible?

Mental ill health has to start somewhere. Eaton and colleagues[12] described how 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 frequently from a combination of both. Human experience involves periodic and sometimes intense and mercurial changes in affect and salience in response to the social environment. When these changes become more prominent, they can be discerned as so-called subclinical microphenotypes, which wax and wane, interact sequentially, or become confluent, and might mature or stabilise towards pure or hybrid macrophenotypes.[13] 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

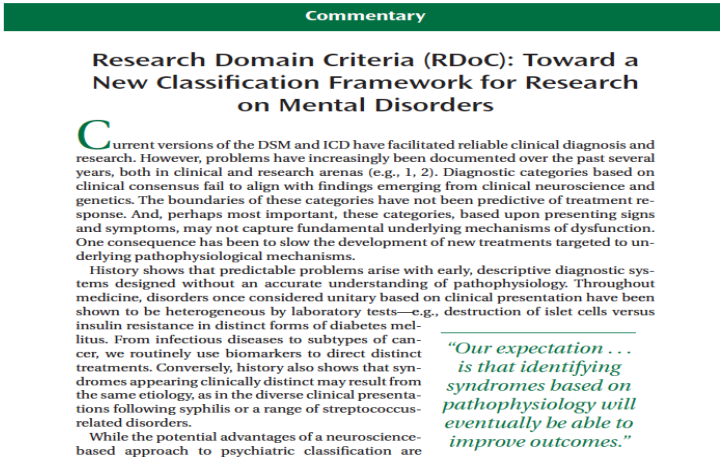
Lancet 2013; 381: 343–45

Orygen Youth Health Research Centre and Centre for Youth Mental Health, University of Melbourne, Melbourne, VIC, Australia (P McGorry MD); Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, European Graduate School of Neuroscience, Maastricht University, Maastricht, Netherlands (J van Os MD); and King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK (J van Os)

Correspondence to:
Dr Patrick McGorry, Orygen Youth Health Research Centre and Centre for Youth Mental Health, University of Melbourne, Parkville, VIC 3052, Australia
pmcgorry@unimelb.edu.au

Lancet Jan 26th 2013

RESEARCH DOMAIN CRITERIA (RDOC)



Commentary

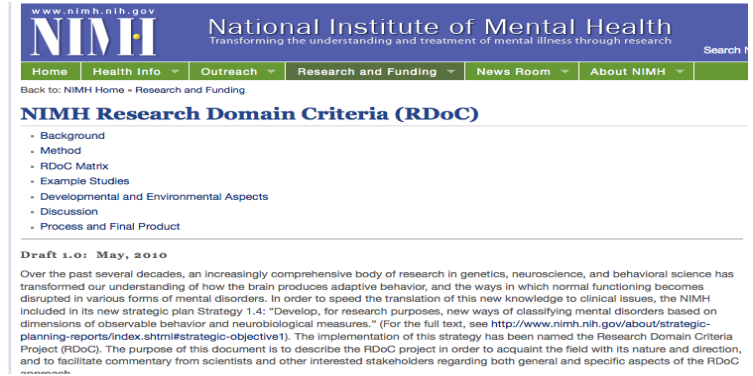
Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders

Current versions of the DSM and ICD have facilitated reliable clinical diagnosis and research. However, problems have increasingly been documented over the past several years, both in clinical and research arenas (e.g., 1, 2). Diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics. The boundaries of these categories have not been predictive of treatment response. And, perhaps most important, these categories, based upon presenting signs and symptoms, may not capture fundamental underlying mechanisms of dysfunction. One consequence has been to slow the development of new treatments targeted to underlying pathophysiological mechanisms.

History shows that predictable problems arise with early, descriptive diagnostic systems designed without an accurate understanding of pathophysiology. Throughout medicine, disorders once considered unitary based on clinical presentation have been shown to be heterogeneous by laboratory tests—e.g., destruction of islet cells versus insulin resistance in distinct forms of diabetes mellitus. From infectious diseases to subtypes of cancer, we routinely use biomarkers to direct distinct treatments. Conversely, history also shows that syndromes appearing clinically distinct may result from the same etiology, as in the diverse clinical presentations following syphilis or a range of streptococcus-related disorders.

"Our expectation . . . is that identifying syndromes based on pathophysiology will eventually be able to improve outcomes."

While the potential advantages of a neuroscience-based approach to psychiatric classification are



www.nimh.nih.gov

NIMH National Institute of Mental Health

Transforming the understanding and treatment of mental illness through research

Search N

Home | Health Info | Outreach | Research and Funding | News Room | About NIMH

Back to: NIMH Home » Research and Funding

NIMH Research Domain Criteria (RDoC)

- Background
- Method
- RDoC Matrix
- Example Studies
- Developmental and Environmental Aspects
- Discussion
- Process and Final Product

Draft 1.0: May, 2010

Over the past several decades, an increasingly comprehensive body of research in genetics, neuroscience, and behavioral science has transformed our understanding of how the brain produces adaptive behavior, and the ways in which normal functioning becomes disrupted in various forms of mental disorders. In order to speed the translation of this new knowledge to clinical issues, the NIMH included in its new strategic plan Strategy 1.4: "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures." (For the full text, see http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml#strategic-objective1). The implementation of this strategy has been named the Research Domain Criteria Project (RDoC). The purpose of this document is to describe the RDoC project in order to acquaint the field with its nature and direction, and to facilitate commentary from scientists and other interested stakeholders regarding both general and specific aspects of the RDoC

PERSPECTIVES

A paradigm shift in psychiatric classification: the Hierarchical Taxonomy Of Psychopathology (HiTOP)

Many have argued that a hierarchical dimensional approach to psychiatric classification would better align the nosology with data on the natural organization of psychopathology[1]. However, such proposals have often been resisted on the grounds that: a) consensus among dimensional models is lacking and b) categorical diagnoses are considered to be essential to clinical decision-making.

pect that it will. First, dimensional phenotypes have been found to have greater reliability and stronger associations with validators than categorical diagnoses[4], indicating that dimensional descriptions are more informative. Second, dimensions have been shown to be more useful in clinical research. HiTOP aligns much better than traditional diagnostic systems with the genetic architecture of mental disorders and with the

Published in final edited form as:
Clin Psychol Sci. 2014 March ; 2(2): 119–137. doi:10.1177/2167702613497473.

The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders?

Avshalom Caspi[1,2,3,4], **Renate M. Houts**[1], **Daniel W. Belsky**[5], **Sidra J. Goldman-Mellor**[6], **HonaLee Harrington**[1], **Salomon Israel**[1], **Madeline H. Meier**[1], **Sandhya Ramrakha**[7], **Idan Shalev**[1], **Richie Poulton**[7], and **Terrie E. Moffitt**[1,2,3,4]

[1]Department of Psychology and Neuroscience, Duke University

OPEN ACCESS Freely available online

PLOS | ONE

A Network Approach to Psychopathology: New Insights into Clinical Longitudinal Data

Laura F. Bringmann[1]*, Nathalie Vissers[1], Marieke Wichers[2], Nicole Geschwind[3], Peter Kuppens[1], Frenk Peeters[2], Denny Borsboom[4], Francis Tuerlinckx[1]

1 Department of Psychology, University of Leuven, Leuven, Belgium, **2** Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands, **3** Department of Clinical Psychological Science, Maastricht University, Maastricht, The Netherlands, **4** Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

Abstract

In the network approach to psychopathology, disorders are conceptualized as networks of mutually interacting symptoms (e.g., depressed mood) and transdiagnostic factors (e.g., rumination). This suggests that it is necessary to study how symptoms dynamically interact over time in a network architecture. In the present paper, we show how such an architecture can be constructed on the basis of time-series data obtained through Experience Sampling Methodology (ESM). The proposed methodology determines the parameters for the interaction between nodes in the network by estimating a multilevel vector autoregression (VAR) model on the data. The methodology allows combining between-subject and within-subject information in a multilevel framework. The resulting network architecture can subsequently be analyzed through network analysis techniques. In the present study, we apply the method to a set of items that assess mood-related factors. We show that the analysis generates a plausible and replicable network architecture, the structure of which is related to variables such as neuroticism; that is, for subjects who score high on neuroticism, worrying plays a more central role in the network. Implications and extensions of the methodology are discussed.

EDITORIAL

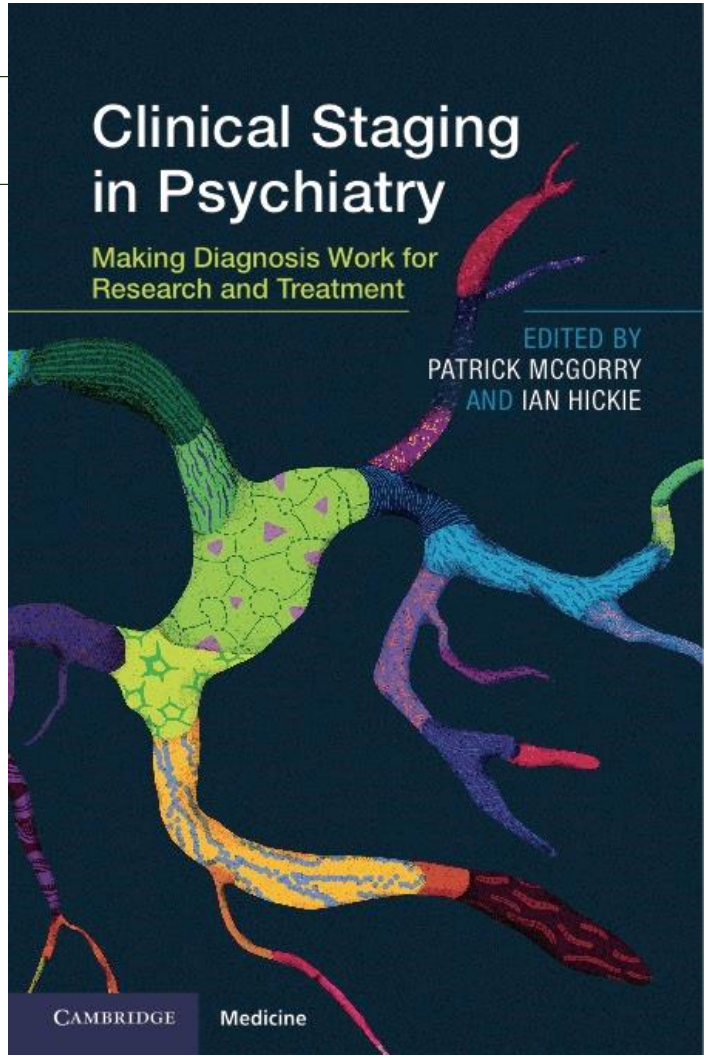
Why We Need a Transdiagnostic Staging Approach to Emerging Psychopathology, Early Diagnosis, and Treatment

Patrick McGorry, MD, PhD, FRCP, FRANZCP; Barnaby Nelson, PhD

One of the urgent challenges for psychiatry is to create a simpler, more useful approach to diagnosis.[1] Our traditional diagnostic systems are categorical and siloed, consisting of polythetic operational definitions of clinical phenotypes. The boundaries between syndromes and phenotypes are not clear and comorbidity is the rule rather than the exception. We know that dimensionality underlies most of these phenotypes and that distress, impairment, and need for care is not limited to the full threshold versions of these phenotypes. This means that a transdiagnostic approach is going to be necessary. The dynamics of early psychopathology are complex and emerging microphenotypes ebb, flow, and evolve in many patterns, which do not follow rigid train tracks to discrete macrophenotypes such as schizophrenia or bipolar disorder. The reification of these macrophenotypes has led to a spurious cer-

Related article page 211

There is a long tradition of conceptualization and study of brief or transient psychoses from the phenomenological tradition. In fact, much of this literature sought to distinguish these and similar phenotypes from the flawed but compelling concept of "process" schizophrenia. There are many interesting concepts from a range of cultures and traditions, and their common features included an abrupt onset, polymorphic and unstable features, a high level of disorganization, and very often an inference of psychogenic causation. For example, Brief Psychosis in the *DSM 3* was Brief Reactive Psychosis. These psychoses were, ironically in the present context, usually defined by the *lack* of a prodromal or dimensional precursor stage. In contrast, the concept of brief limited intermittent psychotic symptoms (BLIPS) as a warning sign for a first episode of sustained psychosis was part of an attempt to rise above the Kraepelinian framework and predict a first-episode psychosis (not merely nonaffective) of sufficient se-


Clinical Staging
in Psychiatry
Making Diagnosis Work for
Research and Treatment
EDITED BY
PATRICK MCGORRY
AND IAN HICKIE
CAMBRIDGE
Medicine

THE DEVELOPMENT OF IDEAS AND CONCEPTUAL FRAMEWORKS

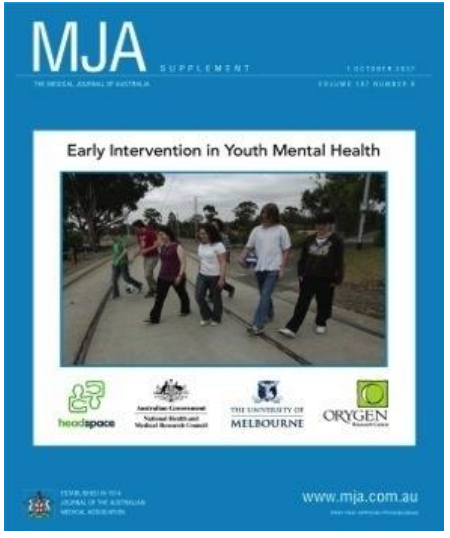
Editorial

As the American Psychiatric Association committees begin formal work on DSM-V, we welcome brief editorials on issues that should be considered in its formulation.

Issues for DSM-V: Clinical Staging: A Heuristic Pathway to Valid Nosology and Safer, More Effective Treatment in Psychiatry

Clinical staging is a proven strategy whose value is clear in the treatment of malignancies and many other medical conditions in which the quality of life and survival rely on the earliest possible delivery of effective interventions, yet it has not been explicitly endorsed in psychiatry (1–4). Clinical staging differs from conventional diagnostic practice in that it defines the progression of disease in time and where a person lies along this continuum of the course of illness. It enables the clinician to select treatments relevant to earlier stages because such in-

Viewpoint



Redeeming diagnosis in psychiatry: timing versus specificity

Patrick McGorry, Jim van Os

In general medicine, diagnosis is a crucial step in the choice of appropriate treatment, prediction of the future course of an illness, education of patients and families, and helping patients to realise that they are not alone. By contrast, in psychiatry, attitudes to diagnosis remain mixed and polarised, and the value of diagnosis is continuously questioned. With revisions to the international diagnostic systems for psychiatry on the horizon, this deep ambivalence—derived from Cartesian tensions between "mindless" and "brainless" perspectives[1]—has surfaced once again, breathing new life into an enduring culture war.[2] How can this impasse be overcome? What is diagnosis actually about?

Essentially, diagnosis is classification with utility.[3] The aims are to characterise the clinical phenotype in a condensed or shorthand way that helps to distinguish people who are ill and in need of health care from those who are not, and to genuinely improve selection of treatment and prediction of outcomes. Utility in medicine is the ultimate test, and this utilitarian definition is necessary and sufficient to justify the diagnosis strategy in clinical practice. Value might be added to a diagnosis if

Little more than incremental and desultory change is expected in the forthcoming new versions of the DSM and International Classification of Diseases (ICD), which are increasingly buffeted by the forces of public opinion, politics, and ideology.[4,5] A transformation is needed, but is it feasible?

Mental ill health has to start somewhere. Eaton and colleagues[6] described how 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 frequently from a combination of both. Human experience involves periodic and sometimes intense and mercurial changes in affect and salience in response to the social environment. When these changes become more prominent, they can be discerned as so-called subclinical microphenotypes, which wax and wane, interact sequentially, or become confluent, and might mature or stabilise towards pure or hybrid macrophenotypes.[7] 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

Lancet 2013; 381: 343–45

Orygen Youth Health Research Centre and Centre for Youth Mental Health, University of Melbourne, Melbourne, VIC, Australia (P McGorry MD); Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, European Graduate School of Neuroscience, Maastricht University, Maastricht, Netherlands (J van Os MD); and King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK (J van Os)

Correspondence to: Dr Patrick McGorry, Orygen Youth Health Research Centre and Centre for Youth Mental Health, University of Melbourne, Parkville, VIC 3052, Australia pmcgorry@unimelb.edu.au

COMMENTARY

Early Clinical Phenotypes, Clinical Staging, and Strategic Biomarker Research: Building Blocks for Personalized Psychiatry

Patrick D. McGorry

BJPsych | The British Journal of Psychiatry (2013) 202, 243–245. doi: 10.1192/bjp.bp.112.110858

Editorial

Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value

Jan Scott, Marion Leboyer, Ian Hickie, Michael Berk, Flavio Kapczinski, Ellen Frank, David Kupfer and Patrick McGorry

Summary

Staging models are used routinely in general medicine for potentially serious or chronic physical disorders such as diabetes, arthritis and cancers, describing the links between biomarkers, clinical phenotypes and disease extension, and promoting a personalised or stratified medicine approach to treatment planning. Clinical staging involves a detailed description of where an individual exists on a continuum of disorder progression from stage 0 (an at-risk or latency stage) through to stage IV (late or end-stage disease). The approach is popular owing to its clinical utility and is increasingly being applied in psychiatry. The concept offers an informed approach to research and the active promotion of indicated prevention and early intervention strategies. We suggest that for young persons with emerging bipolar disorder, such transdiagnostic staging models could provide a framework that better reflects the developmental psychopathology and matches the complex longitudinal inter-relationships between subsyndromal and syndromal mood, psychotic and other disorders.

Declaration of interest

None.

In Review

Clinical Staging: A Heuristic and Practical Strategy for New Research and Better Health and Social Outcomes for Psychotic and Related Mood Disorders

Patrick D McGorry, MD, PhD, FRCP, FRANZCP[1]; Barnaby Nelson, MPsych (Clin), PhD[2]; Sherilyn Goldstone, PhD[3]; Alison R Yung, MD, MPM, FRANZCP[4]

Most mental illnesses emerge during adolescence and early adulthood, with considerable associated distress and functional decline appearing during this critical developmental phase. Our current diagnostic system lacks therapeutic validity, particularly for the early stages of mental disorders when symptoms are still emerging and intensifying and have not yet stabilized sufficiently to fit the existing syndromal criteria. While this is, in part, due to the difficulty of distinguishing transient developmental or normative changes from the early symptoms of persistent and disabling mental illness, these factors have contributed to a growing movement for the reform of our current diagnostic system to more adequately inform the choice of therapeutic strategy, particularly in the early stages of a mental illness. The clinical staging model, which defines not only 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, is particularly useful as it differentiates early, milder clinical phenomena from those that accompany illness progression and chronicity. This will not only enable clinicians to select treatments relevant to earlier stages of an illness, where such interventions are likely to be more effective and less harmful than treatments delivered later in the course of illness, but also allow a more efficient integration of our rapidly expanding knowledge of the biological, social, and psychological vulnerability factors involved in the development of mental illness into a useful diagnostic framework.

Can J Psychiatry. 2010;55(8):486–497.

Molecular Psychiatry (2014), 1–9

www.nature.com/mp

EXPERT REVIEW

All the world's a (clinical) stage: rethinking bipolar disorder from a longitudinal perspective

E Frank, VL Nimgaonkar, ML Phillips and DJ Kupfer

Psychiatric disorders have traditionally been classified using a static, categorical approach. However, this approach falls short in facilitating understanding of the development, common comorbid diagnoses, prognosis and treatment of these disorders. We propose a 'staging' model of bipolar disorder that integrates genetic and neural information with mood and activity symptoms to describe how the disease progresses over time. From an early, asymptomatic, but 'at-risk' stage to severe, chronic illness, each stage is described with associated neuroimaging findings as well as strategies for mapping genetic risk factors. Integrating more biologic information relating to cardiovascular and endocrine systems, refining methodology for modeling dimensional approaches to disease and developing outcome measures will all be crucial in examining the validity of this model. Ultimately, this approach should aid in developing targeted interventions for each group that will reduce the significant morbidity and mortality associated with bipolar disorder.

Molecular Psychiatry advance online publication, 22 July 2014; doi:10.1038/mp.2014.71

Editorials

Clinical staging for mental disorders: a new development in diagnostic practice in mental health

Matching the timing and intensity of interventions to the specific needs of patients

Ian B Hickie
MB BS, MD, FRANZCP, Executive Director[1]

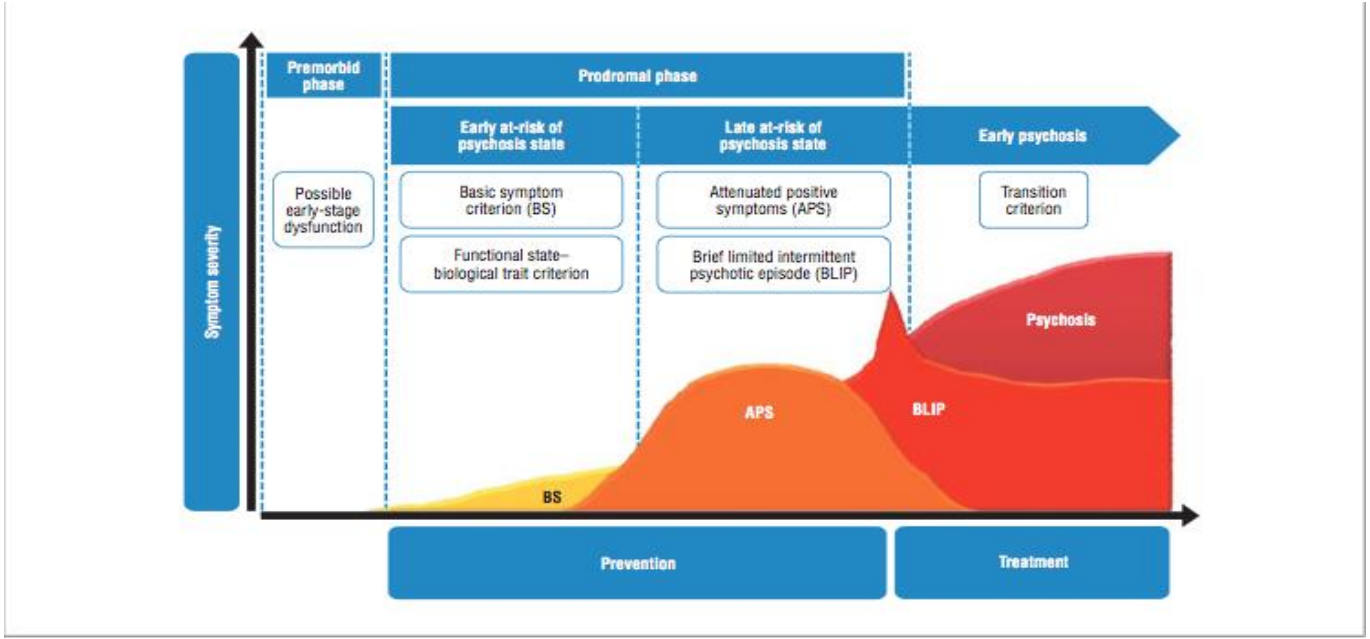
Jan Scott
MB BS, MD, FRCPsych, Professor of Psychological Medicine[2]

Patrick D McGorry
MD, PhD, FRANZCP, Executive Director,[3] and Head[4]

The release of the fifth edition of the *Diagnostic and statistical manual of mental disorders* (DSM-5)[1] classification system, scheduled for May 2013, will create controversy due to the expanded range of problems now classed as mental disorders. However, in our view, it is unlikely to improve clinical care. The ultimate test for any system of diagnosis is its clinical utility. That is, does it assist clinicians to improve their selection or sequencing of treatments and enable them to make more accurate major mental disorders begin between 15 and 25 years of age, a focus on enhanced care and novel clinical research during this critical developmental phase is a timely test of this framework.[5,8,9]

At its core, the clinical staging model recognises the full spectrum of illness experience. For example, for ischaemic heart disease, the staging model identifies individuals at risk (because of genetics, lifestyle or other risk factors), those with symptoms or related syndromes that suggest

UHR/CHR/PRODROME/STAGE 1B



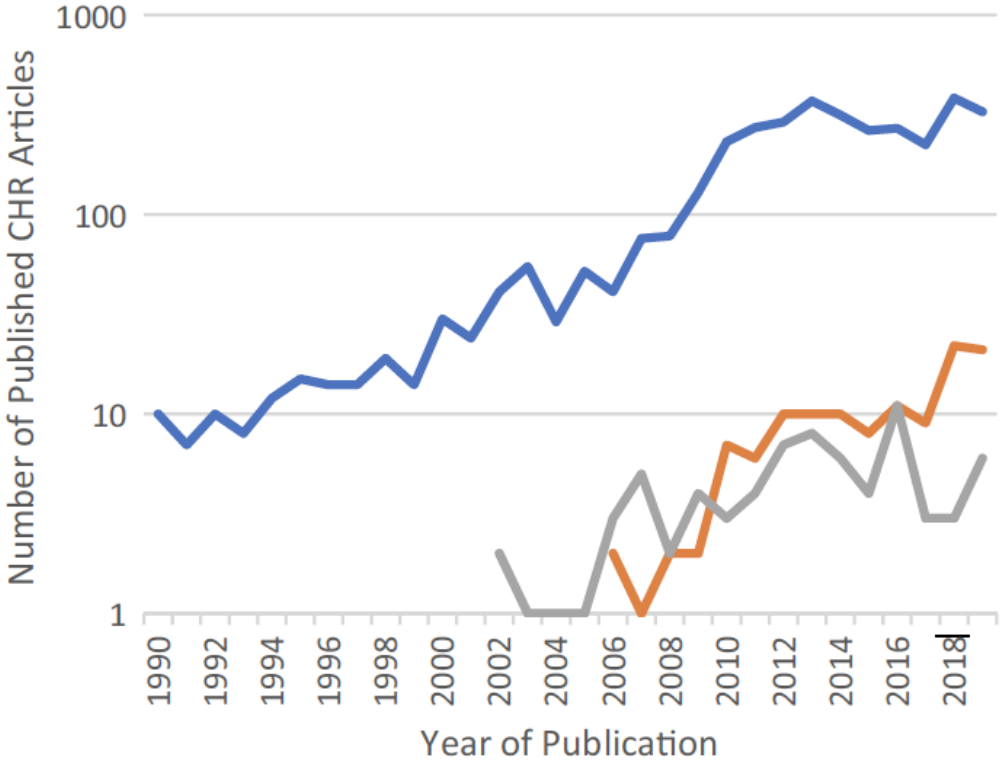


Fig. 1 Types of CHR Articles Stratified by Year. The blue line indicates any CHR article; the orange line indicates review papers; andthe grey line indicates CHR treatment studies.

META-ANALYSIS

Predicting Psychosis

Meta-analysis of Transition Outcomes in Individuals at High Clinical Risk

Paolo Fusar-Poli, MD, PhD; Ilaria Bonoldi, MD; Alison R. Yung, PhD; Stefan Borgwardt, PhD; Matthew J. Kempton, PhD; Lucia Valmaggia, PhD; Francesco Barale, PhD; Edgardo Caverzasi, PhD; Philip McGuire, PhD

Context: A substantial proportion of people at clinical high risk of psychosis will develop a psychotic disorder over time. However, the risk of transition to psychosis varies between centers, and some recent work suggests that the risk of transition may be declining.

Objective: To quantitatively examine the literature to date reporting the transition risk to psychosis in subjects at clinical high risk.

Data Sources: The electronic databases were searched until January 2011. All studies reporting transition risks in patients at clinical high risk were retrieved.

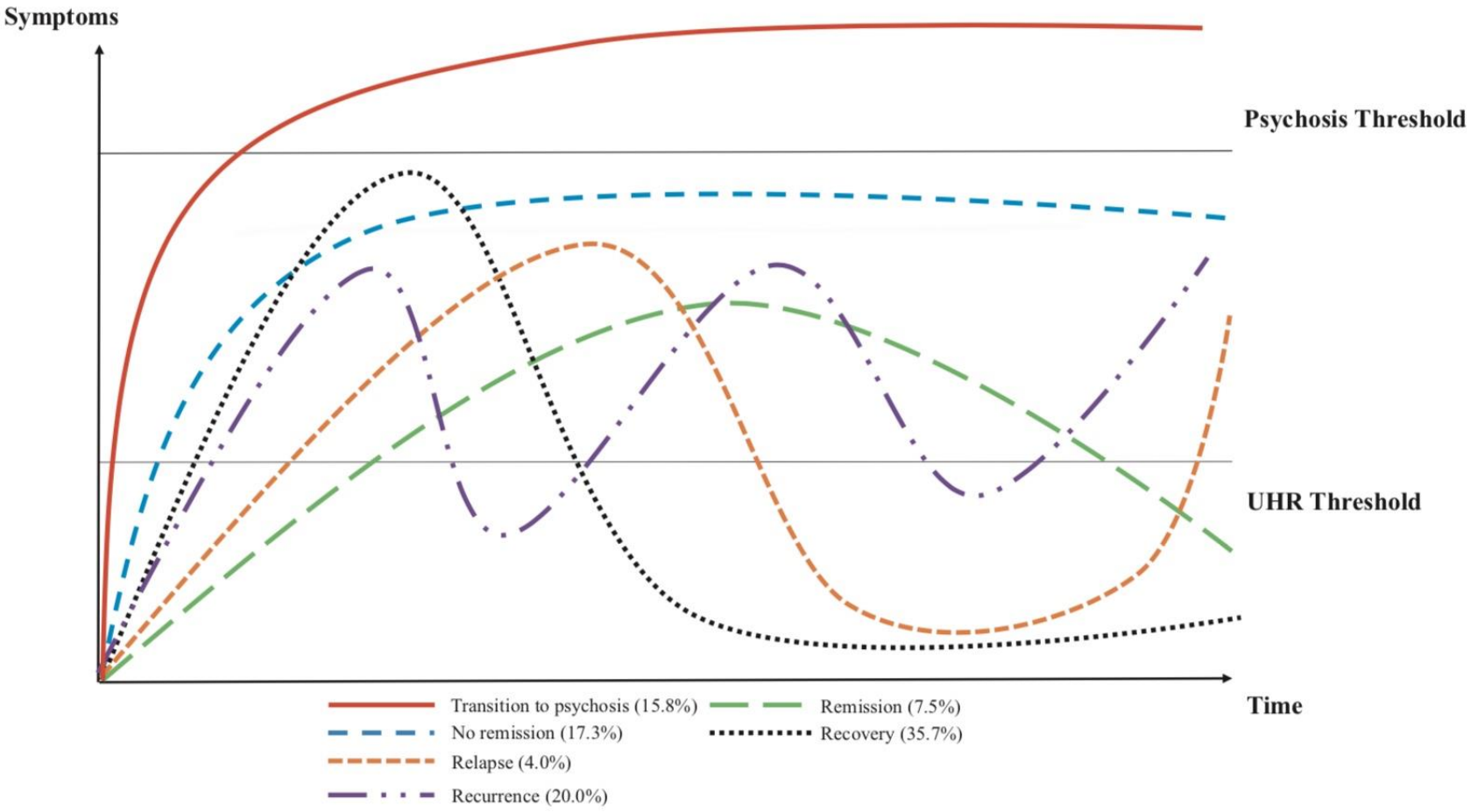
Study Selection: Twenty-seven studies met the inclusion criteria, comprising a total of 2502 patients.

Data Extraction: Transition risks, as well as demographic, clinical, and methodologic variables, were extracted from each publication or obtained directly from its authors.

Data Synth [illegible] transition risk, indepen[illegible] of the psychometric instru[illegible]ts used, of 18% af[illegible] 6 months of follow-up, 22% after [illegible]ear, 29% after 2 [illegible]rs, and 36% after 3 years. Signifi[illegible]t moderators acco[illegible]ing for heterogeneity acros[illegible]udies and influencing the [illegible] the age of participants, publication year, treatments received, and diagnostic criteria used. There was no publication bias, and a sensitivity analysis confirmed the robustness of the core findings.

Conclusions: The state of clinical high risk is associated with a very high risk of developing psychosis within the first 3 years of clinical presentation, and the risk progressively increases across this period. The transition risk varies with the age of the patient, the nature of the treatment provided, and the way the syndrome and transition to psychosis are defined.

Arch Gen Psychiatry. 2012;69(3):220-229


Symptoms
Psychosis Threshold
UHR Threshold
Time
Transition to psychosis (15.8%)
No remission (17.3%)
Relapse (4.0%)
Recurrence (20.0%)
Remission (7.5%)
Recovery (35.7%)

npj | Schizophrenia

www.nature.com/npjschz

REVIEW ARTICLE OPEN

Check for updates

Progression from being at-risk to psychosis: next steps

Jean Addington[1]✉, Megan Farris[1], Daniel Devoe[1] and Paul Metzak[1]

Over the past 20 years there has been a great deal of research into those considered to be at risk for developing psychosis. Much has been learned and studies have been encouraging. The aim of this paper is to offer an update of the current status of research on risk for psychosis, and what the next steps might be in examining the progression from CHR to psychosis. Advances have been made in accurate prediction, yet there are some methodological issues in ascertainment, diagnosis, the use of data-driven selection methods and lack of external validation. Although there have been several high-quality treatment trials the heterogeneity of this clinical high-risk population has to be addressed so that their treatment needs can be properly met. Recommendations for the future include more collaborative research programmes, and ensuring they are accessible and harmonized with respect to criteria and outcomes so that the field can continue to move forward with the development of large collaborative consortiums as well as increased funding for multisite projects.

npj Schizophrenia (2020)6:27 ; https://doi.org/10.1038/s41537-020-00117-0

DYNAMIC PREDICTION

INTERNATIONAL JOURNAL OF METHODS IN PSYCHIATRIC RESEARCH Open Access

ORIGINAL ARTICLE | Free Access

A new method for analysing transition to psychosis: Joint modelling of time-to-event outcome with time-dependent predictors

Hok Pan Yuen ✉, Andrew Mackinnon, Barnaby Nelson

First published: 24 September 2017 | https://doi.org/10.1002/mpr.1588 | Citations: 11

This work received support through an Australian Government Research Training Program Scholarship.

Development and Validation of a Dynamic Risk Prediction Model to Forecast Psychosis Onset in Patients at Clinical High Risk

Erich Studerus ✉, Katharina Beck, Paolo Fusar-Poli, Anita Riecher-Rössler

Schizophrenia Bulletin, Volume 46, Issue 2, March 2020, Pages 252–260, https://doi.org/10.1093/schbul/sbz059

Published: 29 July 2019

JAMA Psychiatry | Original Investigation

Multimodal Machine Learning Workflows for Prediction of Psychosis in Patients With Clinical High-Risk Syndromes and Recent-Onset Depression

Nikolaos Koutsouleris, MD; Dominic B. Dwyer, PhD; Franziska Degenhardt, MD; Carlo Maj, PhD; Maria Fernanda Urquijo-Castro, MSc; Rachele Sanfelici, MSc; David Popovic, MD; Oemer Oeztuerk, MD; Shalaila S. Haas, PhD; Johanna Weiske, MSc; Anne Ruef, MSc; Lana Kambeitz-Ilankovic, PhD; Linda A. Antonucci, PhD; Susanne Neufang, PhD; Christian Schmidt-Kraepelin, MD; Stephan Ruhrmann, MD; Nora Penzel, MSc; Joseph Kambeitz, MD; Theresa K. Haidl, MD; Marlene Rosen, PhD; Katharine Chisholm, PhD; Anita Riecher-Rössler, MD; Laura Egloff, PhD; André Schmidt, PhD; Christina Andreou, MD, PhD; Jarmo Hietala, MD, PhD; Timo Schirmer, PhD; Georg Romer, MD; Petra Walger, MD; Maurizia Franscini, MD; Nina Traber-Walker, PhD; Benno G. Schimmelmann, MD; Rahel Flückiger, PhD; Chantal Michel, PhD; Wulf Rössler, MD; Oleg Borisov, MD; Peter M. Krawitz, MD; Karsten Heekeren, MD; Roman Buechler, MD; Christos Pantelis, PhD, MD; Peter Falkai, MD; Raimo K. R. Salokangas, MD, PhD, MSc; Rebekka Lencer, MD; Alessandro Bertolino, MD, PhD; Stefan Borgwardt, MD; Markus Noethen, MD; Paolo Brambilla, MD; Stephen J. Wood, PhD; Rachel Upthegrove, MD, PhD; Frauke Schultze-Lutter, PhD; Anastasia Theodoridou, MD; Eva Meisenzahl, MD; Writing Group for the PRONIA Consortium

IMPORTANCE Diverse models have been developed to predict psychosis in patients with clinical high-risk (CHR) states. Whether prediction can be improved by efficiently combining clinical and biological models and by broadening the risk spectrum to young patients with depressive syndromes remains unclear.

OBJECTIVES To evaluate whether psychosis transition can be predicted in patients with CHR or recent-onset depression (ROD) using multimodal machine learning that optimally integrates clinical and neurocognitive data, structural magnetic resonance imaging (sMRI), and polygenic risk scores (PRS) for schizophrenia; to assess models' geographic generalizability; to test and integrate clinicians' predictions; and to maximize clinical utility by building a sequential prognostic system.

DESIGN, SETTING, AND PARTICIPANTS This multisite, longitudinal prognostic study performed in 7 academic early recognition services in 5 European countries followed up patients with CHR syndromes or ROD and healthy volunteers. The referred sample of 167 patients with CHR syndromes and 167 with ROD was recruited from February 1, 2014, to May 31, 2017, of whom 26 (23 with CHR syndromes and 3 with ROD) developed psychosis. Patients with 18-month follow-up (n = 246) were used for model training and leave-one-site-out cross-validation. The remaining 88 patients with nontransition served as the validation of model specificity. Three hundred thirty-four healthy volunteers provided a normative sample for prognostic signature evaluation. Three independent Swiss projects contributed a further 45 cases with psychosis transition and 600 with nontransition for the external validation of clinical-neurocognitive, sMRI-based, and combined models. Data were analyzed from January 1, 2019, to March 31, 2020.

MAIN OUTCOMES AND MEASURES Accuracy and generalizability of prognostic systems.

RESULTS A total of 668 individuals (334 patients and 334 controls) were included in the analysis (mean [SD] age, 25.1 [5.8] years; 354 [53.0%] female and 314 [47.0%] male). Clinicians attained a balanced accuracy of 73.2% by effectively ruling out (specificity, 84.9%) but ineffectively ruling in (sensitivity, 61.5%) psychosis transition. In contrast, algorithms showed high sensitivity (76.0%-88.0%) but low specificity (53.5%-66.8%). A cybernetic risk calculator combining all algorithmic and human components predicted psychosis with a balanced accuracy of 85.5% (sensitivity, 84.6%; specificity, 86.4%). In comparison, an optimal prognostic workflow produced a balanced accuracy of 85.9% (sensitivity, 84.6%; specificity, 87.3%) at a much lower diagnostic burden by sequentially integrating clinical-neurocognitive, expert-based, PRS-based, and sMRI-based risk estimates as needed for the given patient. Findings were supported by good external validation results.

CONCLUSIONS AND RELEVANCE These findings suggest that psychosis transition can be predicted in a broader risk spectrum by sequentially integrating algorithms' and clinicians' risk estimates. For clinical translation, the proposed workflow should undergo large-scale international validation.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2020.3604
Published online December 2, 2020.

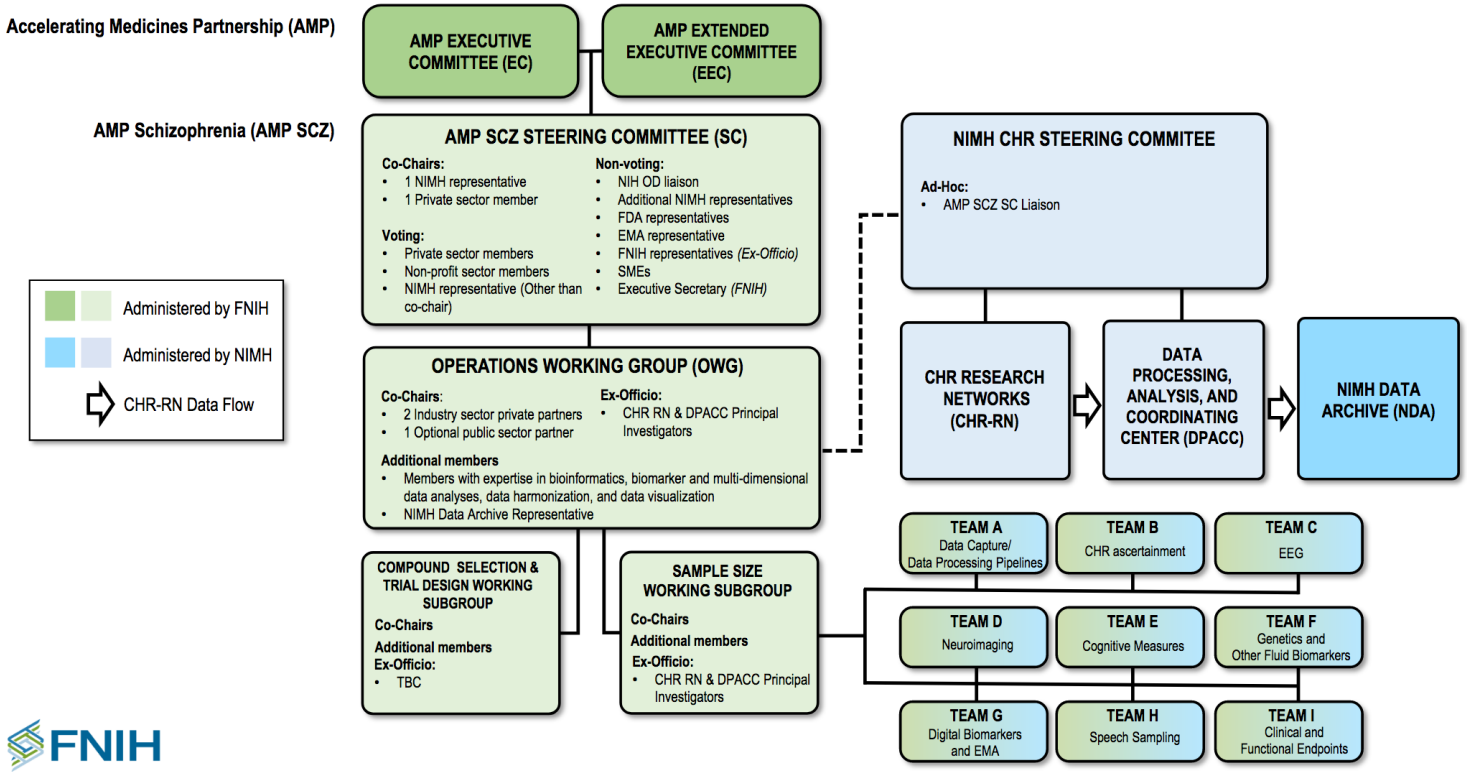
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of the PRONIA (Personalised Prognostic Tools for Early Psychosis Management) Consortium members appears at the end of article.

Corresponding Author: Nikolaos Koutsouleris, MD, Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Nussbaumstrasse 7, D-80336 Munich, Germany (nikolaos.koutsouleris@med.uni-muenchen.de).

AMP SCZ Organizational Structure



FNIH

Article

Outcomes of Nontransitioned Cases in a Sample at Ultra-High Risk for Psychosis

Ashleigh Lin, Ph.D.

Stephen J. Wood, Ph.D.

Barnaby Nelson, Ph.D.

Amanda Beavan, B.Sc.

Patrick McGorry, M.D., Ph.D., F.R.A.N.Z.C.P.

Alison R. Yung, M.D., F.R.A.N.Z.C.P.

Objective: Two-thirds of individuals identified as at ultra-high risk for psychosis do not develop psychotic disorder over the medium term. The authors examined outcomes in a group of such patients.

Method: Participants were help-seeking individuals identified as being at ultra-high risk for psychosis 2–14 years previously. The 226 participants (125 female, 101 male) completed a follow-up assessment and had not developed psychosis. Their mean age at follow-up was 25.5 years (SD=4.8).

Results: At follow-up, 28% of the participants reported attenuated psychotic symptoms. Over the follow-up period, 68% experienced nonpsychotic disorders: mood disorder in 49%, anxiety disorder in 35%, and substance use disorder in 29%. For the majority (90%), nonpsychotic disorder was present at baseline, and it persisted for 52% of them. During follow-up, 26% of the cohort had remission of a disorder, but 38% developed a new disorder. Only 7% did not experience any disorder at baseline or during follow up. The incidence of nonpsychotic disorder was associated with more negative symptoms at baseline. Female participants experienced higher rates of persistent or recurrent disorder. Meeting criteria for brief limited intermittent psychotic symptoms at intake was associated with lower risk for persistent or recurrent disorder.

Conclusions: Individuals at ultra-high risk for psychosis who do not transition to psychosis are at significant risk for continued attenuated psychotic symptoms, persistent or recurrent disorders, and incident disorders. Findings have implications for ongoing clinical care.

Am J Psychiatry Lin et al.; AiA:1–10

SPECIAL ARTICLE

Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry

Patrick D. McGorry, Jessica A. Hartmann, Rachael Spooner, Barnaby Nelson

Orygen, The National Centre of Excellence in Youth Mental Health, and Centre for Youth Mental Health, University of Melbourne, Parkville, Australia

The "at risk mental state" for psychosis approach has been a catalytic, highly productive research paradigm over the last 25 years. In this paper we review that paradigm and summarize its key lessons, which include the valence of this phenotype for future psychosis outcomes, but also for comorbid, persistent or incident non-psychotic disorders; and the evidence that onset of psychotic disorder can at least be delayed in ultra high risk (UHR) patients, and that some full-threshold psychotic disorder may emerge from risk states not captured by UHR criteria. The paradigm has also illuminated risk factors and mechanisms involved in psychosis onset. However, findings from this and related paradigms indicate the need to develop new identification and diagnostic strategies. These findings include the high prevalence and impact of mental disorders in young people, the limitations of current diagnostic systems and risk identification approaches, the diffuse and unstable symptom patterns in early stages, and their pluripotent, transdiagnostic trajectories. The approach we have recently adopted has been guided by the clinical staging model and adapts the original "at risk mental state" approach to encompass a broader range of inputs and output target syndromes. This approach is supported by a number of novel modelling and prediction strategies that acknowledge and reflect the dynamic nature of psychopathology, such as dynamical systems theory, network theory, and joint modelling. Importantly, a broader transdiagnostic approach and enhancing specific prediction (profiling or increasing precision) can be achieved concurrently. A holistic strategy can be developed that applies these new prediction approaches, as well as machine learning and iterative probabilistic multimodal models, to a blend of subjective psychological data, physical disturbances (e.g., EEG measures) and biomarkers (e.g., neuroinflammation, neural network abnormalities) acquired through fine-grained sequential or longitudinal assessments. This strategy could ultimately enhance our understanding and ability to predict the onset, early course and evolution of mental ill health, further opening pathways for preventive interventions.

Key words: At risk mental state, psychosis, ultra high risk, transition, transdiagnostic psychiatry, clinical staging, CHARMS, prediction strategies, network theory, dynamical systems theory, joint modelling

(World Psychiatry 2018;17:133–142)

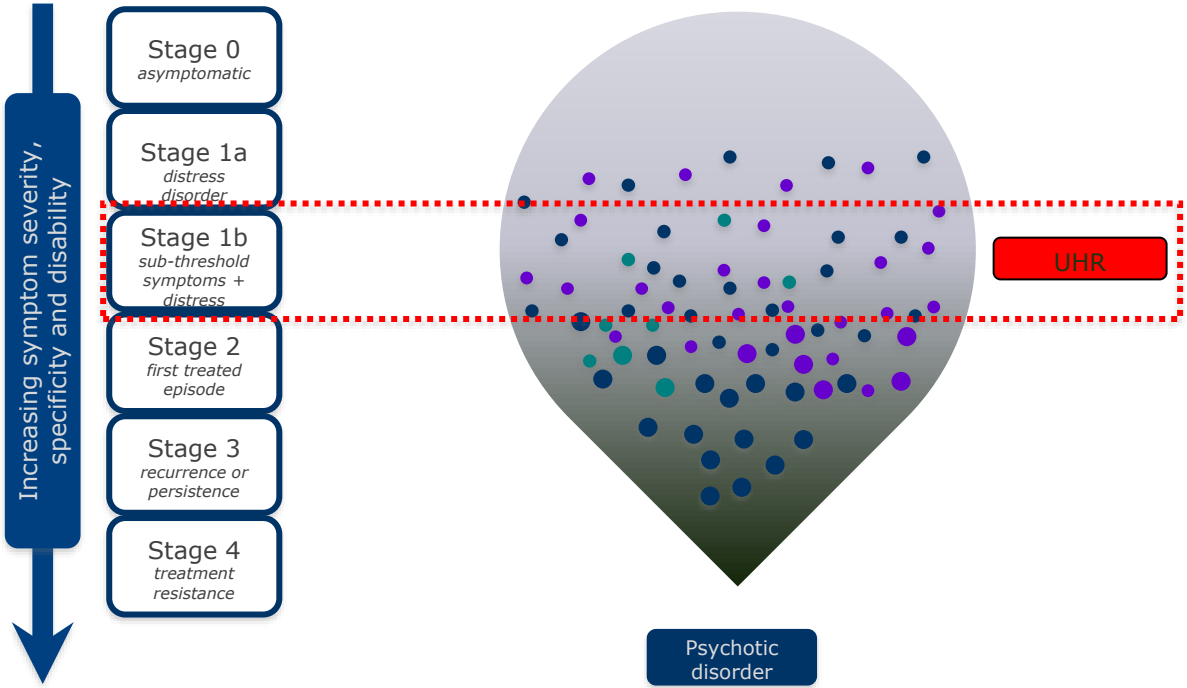


Figure 1A. Traditional UHR paradigm in the context of clinical staging

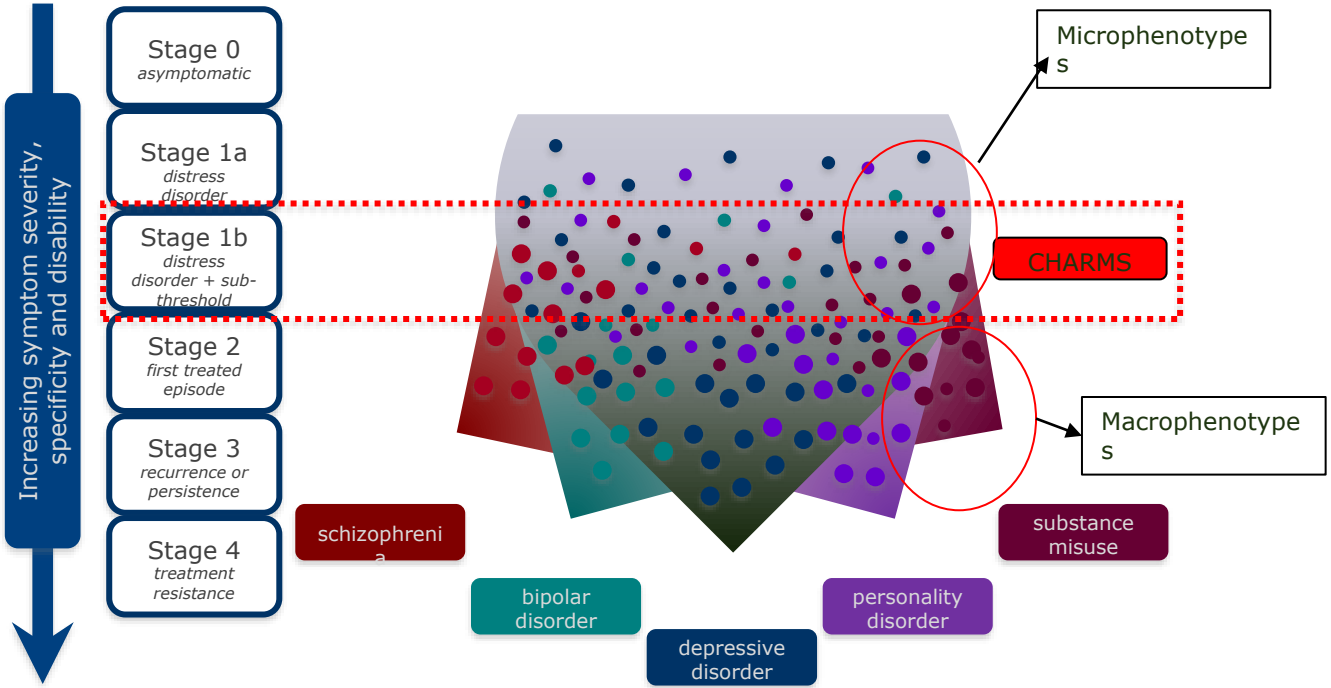


Figure 1B. New transdiagnostic CHARMS paradigm in the context of clinical staging

IORFINO ET AL 2019 TRANSDIAGNOSTIC STAGING IN PRACTICE

Research

JAMA Psychiatry | Original Investigation

Clinical Stage Transitions in Persons Aged 12 to 25 Years Presenting to Early Intervention Mental Health Services With Anxiety, Mood, and Psychotic Disorders

Frank Iorfino, PhD; Elizabeth M. Scott, MD, FRANZCP; Joanne S. Carpenter, PhD; Shane P. Cross, PhD; Daniel F. Hermens, PhD; Madhura Killedar, PhD; Alissa Nichles, PGDipAppPsy; Natalia Zmicerevska, MCouns; Django White, BLaS (Stats); Adam J. Guastella, PhD; Jan Scott, PhD, FRCPsych; Patrick D. McGorry, MD, PhD, FRCP, FRANZCP; Ian B. Hickie, MD, FRANZCP, FASSA, FAHMS

IMPORTANCE The large contribution of psychiatric disorders to premature death and persistent disability among young people means that earlier identification and enhanced long-term care for those who are most at risk of developing life-threatening or chronic disorders is critical. Clinical staging as an adjunct to diagnosis to address emerging psychiatric disorders has been proposed for young people presenting for care; however, the longer-term utility of this system has not been established.

OBJECTIVES To determine the rates of transition from earlier to later stages of anxiety, mood, psychotic, or comorbid disorders and to identify the demographic and clinical characteristics that are associated with the time course of these transitions.

DESIGN, SETTING, AND PARTICIPANTS A longitudinal, observational study of 2254 persons aged 12 to 25 years who obtained mental health care at 2 early intervention mental health services in Sydney, Australia, and were recruited to a research register between June 18, 2008, and July 24, 2018 (the Brain and Mind Centre Optymise Cohort).

MAIN OUTCOMES AND MEASURES The primary outcome of this study was transition from earlier to later clinical stages. A multistate Markov model was used to examine demographic (ie, age, sex, engagement in education, employment, or both) and clinical (ie, social and occupational function, clinical presentation, personal history of mental illness, physical health comorbidities, treatment use, self-harm, suicidal thoughts and behaviors) factors associated with these transitions.

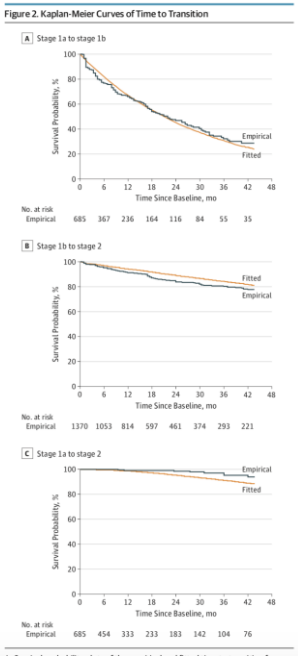
RESULTS Of the 2254 individuals included in the study, mean (SD) age at baseline was 18.18 (3.33) years and 1330 (59.0%) were female. Data on race/ethnicity were not available. Median (interquartile range) follow-up was 14 (5-33) months. Of 685 participants at stage 1a (nonspecific symptoms), 253 (36.9%) transitioned to stage 1b (attenuated syndromes). Transition was associated with lower social functioning (hazard ratio [HR], 0.77; 95% CI, 0.66-0.90), engagement with education, employment, or both (HR, 0.47; 95% CI, 0.25-0.91), manic-like experiences (HR, 2.12; 95% CI, 1.19-3.78), psychotic-like experiences (HR, 2.13; 95% CI, 1.38-3.28), self-harm (HR, 1.42; 95% CI, 1.01-1.99), and older age (HR, 1.27; 95% CI, 1.11-1.45). Of 1370 stage 1b participants, 176 (12.8%) transitioned to stage 2 (full-threshold) disorders. Transition was associated with psychotic-like experiences (HR, 2.31; 95% CI, 1.65-3.23), circadian disturbance (HR, 1.66; 95% CI, 1.17-2.35), psychiatric medication (HR, 1.43; 95% CI, 1.03-1.99), childhood psychiatric disorder (HR, 1.62; 95% CI, 1.03-2.54), and older age (HR, 1.24; 95% CI, 1.05-1.45).

CONCLUSIONS AND RELEVANCE Differential rates of progression from earlier to later stages of anxiety, mood, psychotic, or comorbid disorders were observed in young persons who presented for care at various stages. Understanding the rate and factors associated with transition assists planning of stage-specific clinical interventions and secondary prevention trials.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2019.2360
Published online August 28, 2019.

Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.
Corresponding Author: Frank Iorfino, PhD, Youth Mental Health Team, Brain and Mind Centre, University of Sydney, 94 Mallet St, Camperdown, Sydney, New South Wales, Australia 2050 (frank.iorfino@sydney.edu.au).



STAGING: DIAGNOSIS SANS FRONTIERES

- Some authors have attempted to mould the staging idea to the procrustean silos of existing late macrophenotypes. However, the essential feature of the model is that it is transdiagnostic.

- This does not mean that late macrophenotypes such as mania, psychosis and anorexia cannot be accommodated as they differentiate out and stabilize.

- The specificity of treatment approaches or otherwise can be examined and the spurious precision of the licensing of medications and other therapies replaced by a more flexible and accurate evidence-based approach as in mainstream health care.

The Dynamics of Subthreshold Psychopathology: Implications for Diagnosis and Treatment

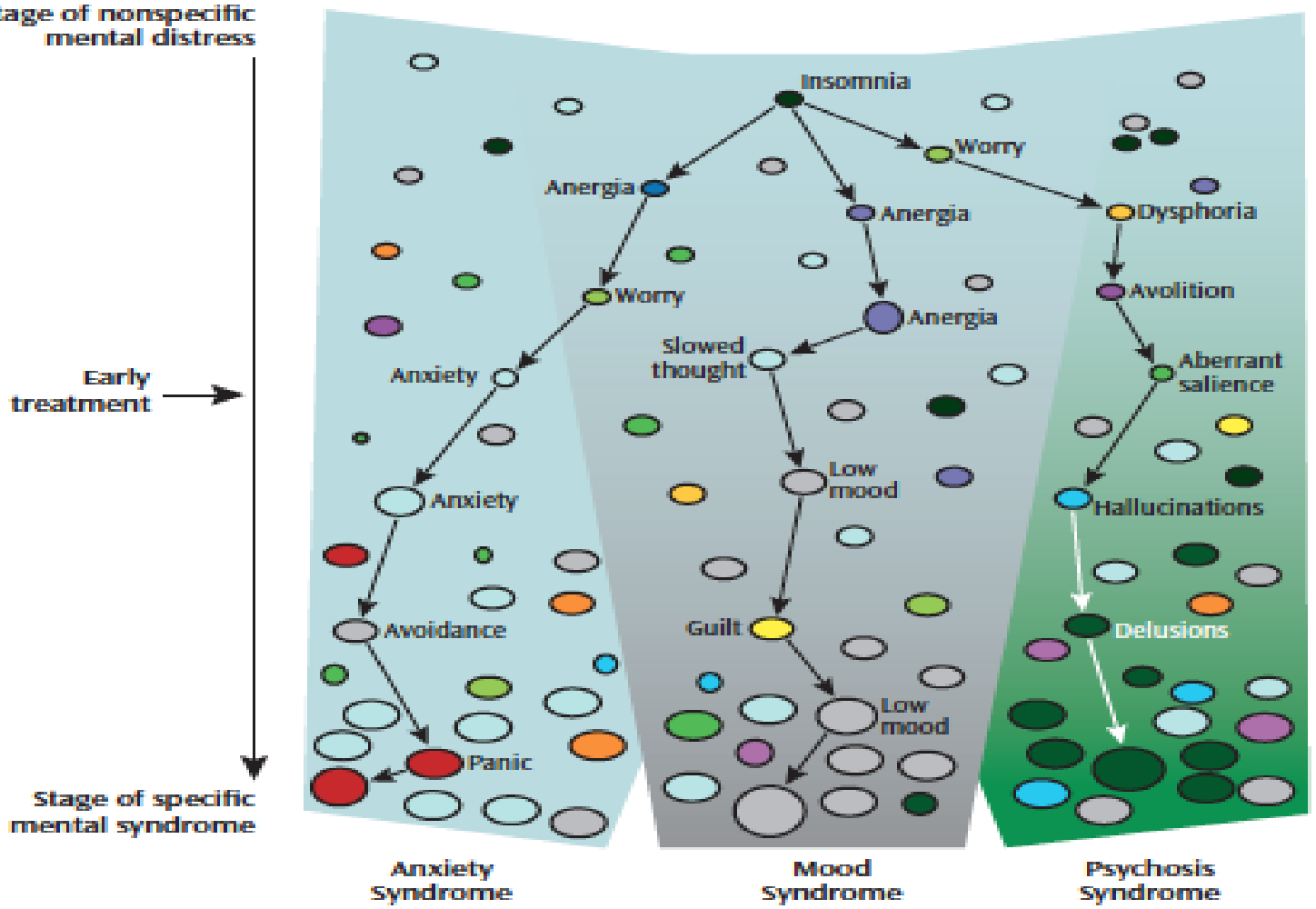
Subthreshold Extended Phenotypes

The article by Zammit et al. (1) in this issue of the *Journal* confirms that mental disorders appear to be continuous—phenomenologically and longitudinally—with subthreshold states, or extended phenotypes, of psychopathology. There is well-replicated evidence that major depression can be traced to subthreshold depressive states (2), common mental disorders to subthreshold neurotic symptoms (3), bipolar disorder to subthreshold mania (4), autism to subthreshold autistic traits (5), and psychotic disorders to subthreshold psychotic experiences (6). In addition, research indicates that normal variation and the extreme end of the distribution tend to share the same genetic and nongenetic causes (7–10), indicating at least a degree of etiological continuity in addition to psychometric and predictive continuity.

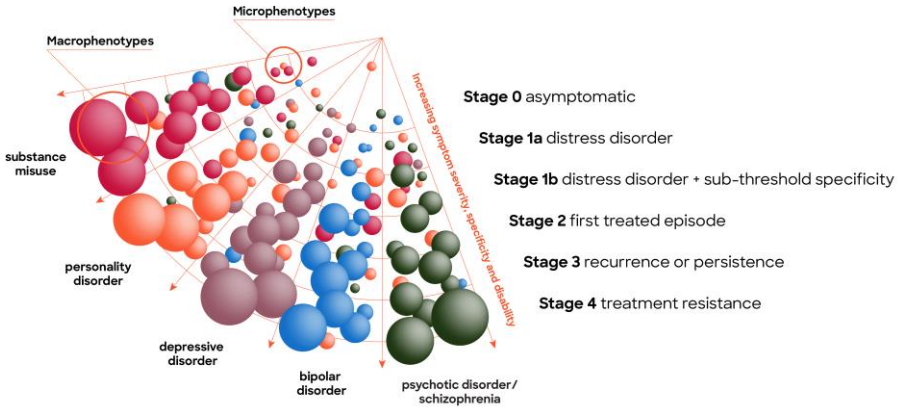
The earliest expressions of psychopathology are a nonspecific, mixed bag of affective dysregulation, aberrant salience, motivational alterations, anxiety states, and other early symptoms.

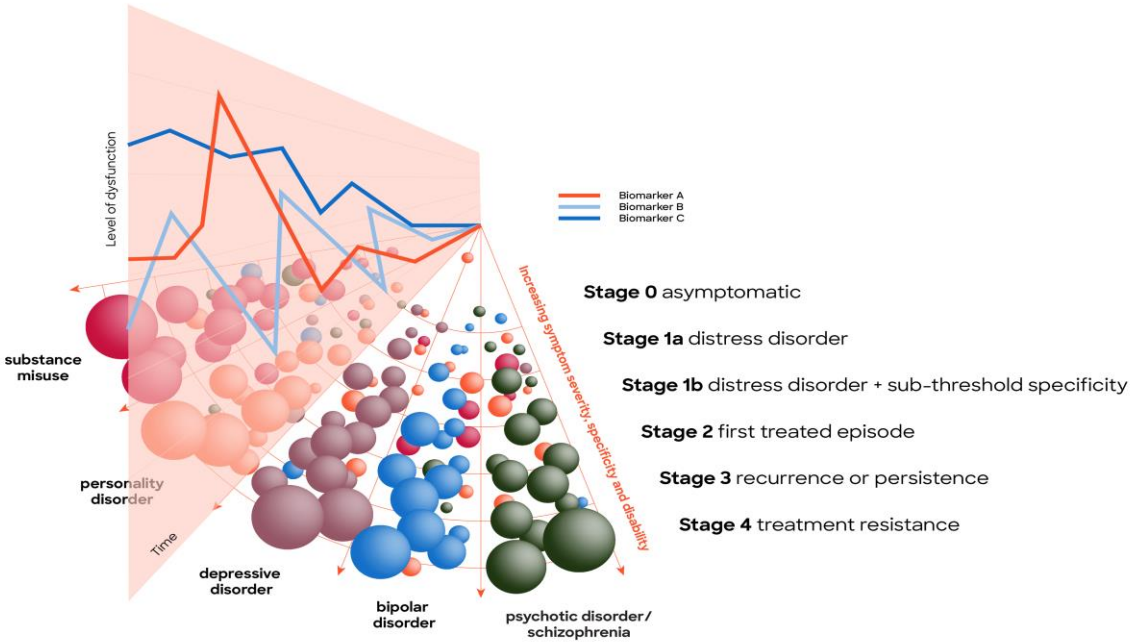
Subthreshold extended phenotypes in the general population are conceptually quite different from the "ultra-high risk" or "at-risk mental state" populations in the psychosis literature. In the area of psychosis, ultra-high risk or at-risk mental states refer

FIGURE 1. Staging Model of Causal Symptom Circuits[a]



STAGING IN 3D




Level of dysfunction
Biomarker A
Biomarker B
Biomarker C
Increasing symptom severity, specificity and disability
substance misuse
personality disorder
Time
depressive disorder
bipolar disorder
psychotic disorder/ schizophrenia
Stage 0 asymptomatic
Stage 1a distress disorder
Stage 1b distress disorder + sub-threshold specificity
Stage 2 first treated episode
Stage 3 recurrence or persistence
Stage 4 treatment resistance

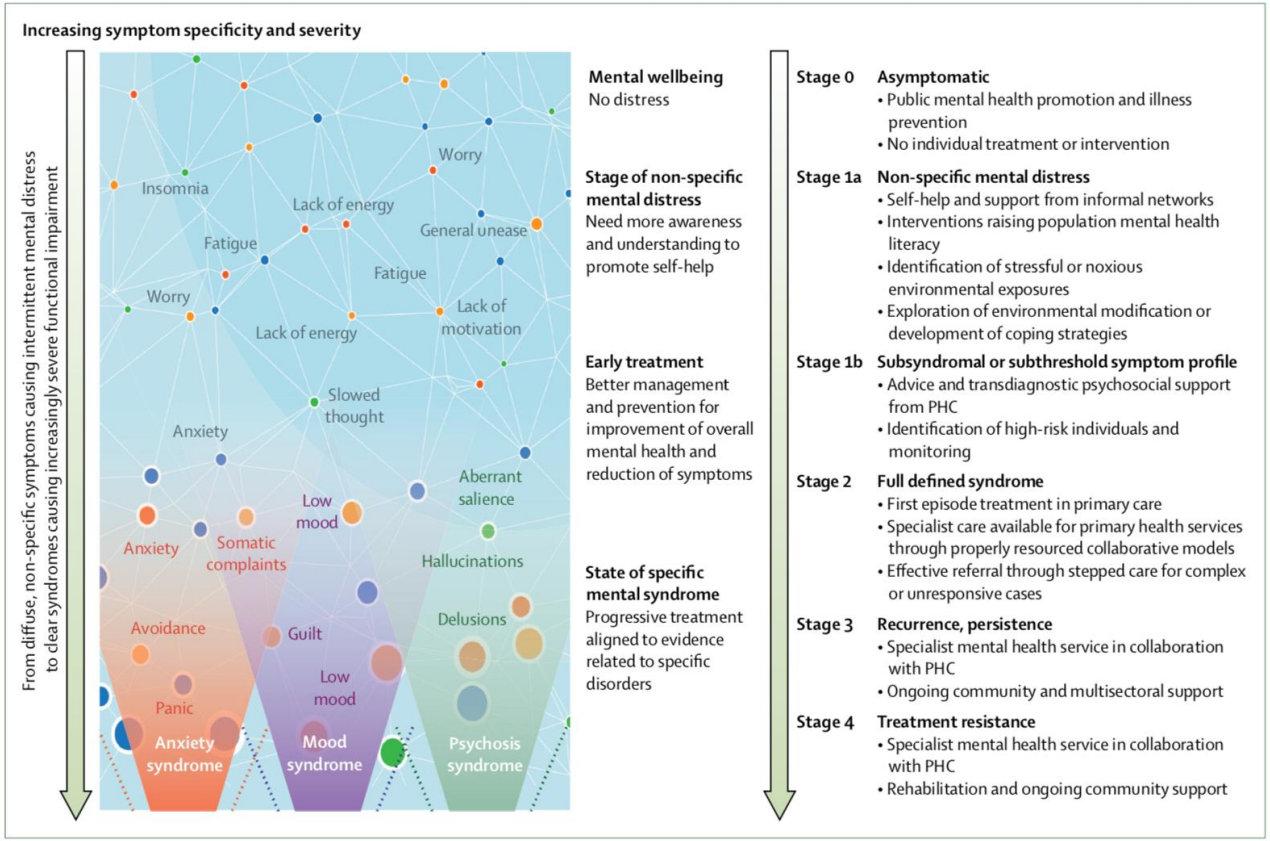
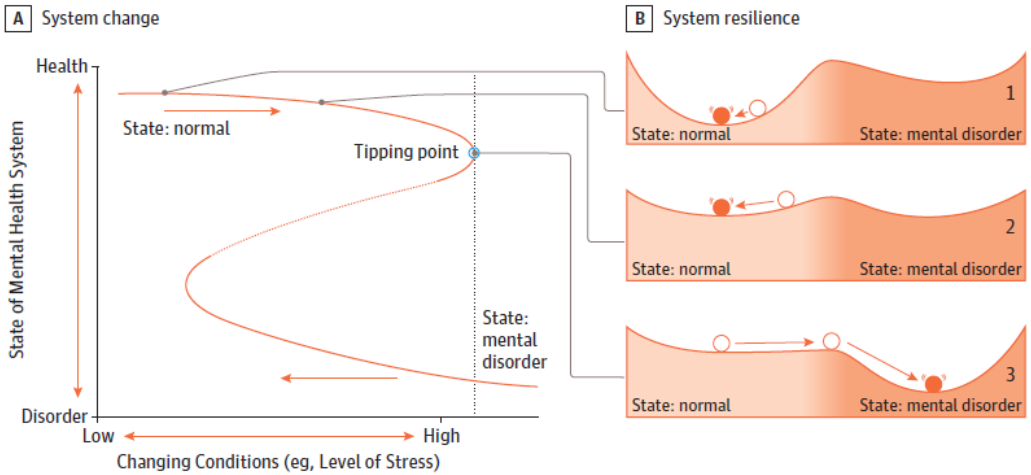


Figure 5: **A staging approach to the classification and treatment of mental disorders**
PHC=primary health care. Adapted from McGorry et al[73] and McGorry and van Os.[74]

PSYCHOPATHOLOGY AS COMPLEX DYNAMIC SYSTEM

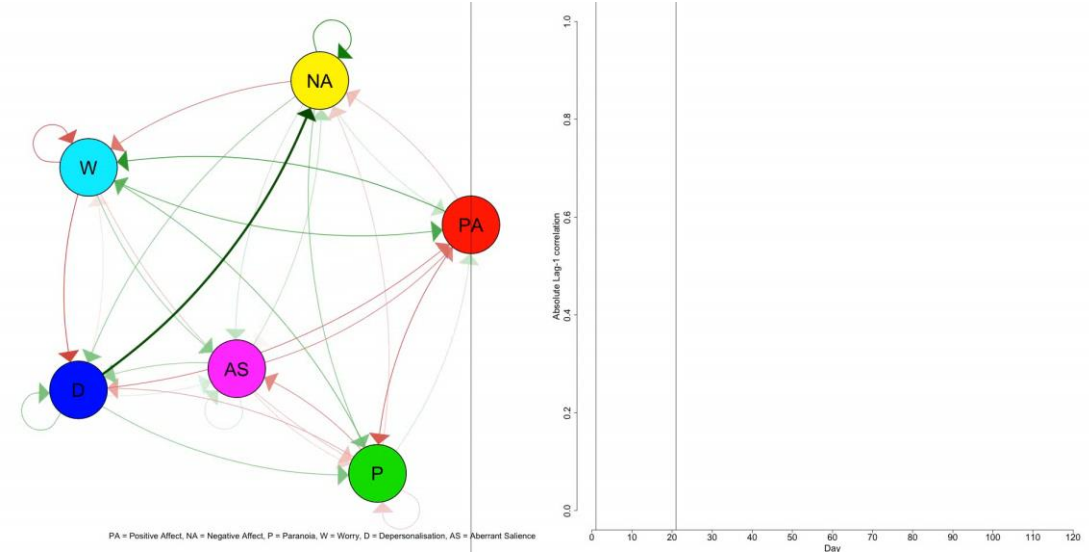
Alternative stable states



Nelson, McGorry, …,Hartmann *(2017). Moving from static to dynamic models of the onset of mental disorder. JAMA Psychiatry 74, 528-534*

PSYCHOPATHOLOGY AS DYNAMIC SYSTEM

Network theory: Dynamic networks in CHARMS (pilot)



Hartmann, McGorry, Nelson. Predicting critical transitions in the mental health of young people at risk of serious mental illness: A pilot study. In preparation.

JAMA Psychiatry | Review

Moving From Static to Dynamic Models of the Onset of Mental Disorder
A Review

Barnaby Nelson, PhD; Patrick D. McGorry, MD, PhD; Marieke Wichers, PhD; Johanna T. W. Wigman, PhD; Jessica A. Hartmann, PhD

IMPORTANCE In recent years, there has been increased focus on subthreshold stages of mental disorders, with attempts to model and predict which individuals will progress to full-threshold disorder. Given this research attention and the clinical significance of the issue, this article analyzes the assumptions of the theoretical models in the field.

OBSERVATIONS Psychiatric research into predicting the onset of mental disorder has shown an overreliance on one-off sampling of cross-sectional data (ie, a snapshot of clinical state and other risk markers) and may benefit from taking dynamic changes into account in predictive modeling. Cross-disciplinary approaches to complex system structures and changes, such as dynamical systems theory, network theory, instability mechanisms, chaos theory, and catastrophe theory, offer potent models that can be applied to the emergence (or decline) of psychopathology, including psychosis prediction, as well as to transdiagnostic emergence of symptoms.

CONCLUSIONS AND RELEVANCE Psychiatric research may benefit from approaching psychopathology as a system rather than as a category, identifying dynamics of system change (eg, abrupt vs gradual psychosis onset), and determining the factors to which these systems are most sensitive (eg, interpersonal dynamics and neurochemical change) and the individual variability in system architecture and change. These goals can be advanced by testing hypotheses that emerge from cross-disciplinary models of complex systems. Future studies require repeated longitudinal assessment of relevant variables through either (or a combination of) micro-level (momentary and day-to-day) and macro-level (month and year) assessments. Ecological momentary assessment is a data collection technique appropriate for micro-level assessment. Relevant statistical approaches are joint modeling and time series analysis, including metric-based and model-based methods that draw on the mathematical principles of dynamical systems. This next generation of prediction studies may more accurately model the dynamic nature of psychopathology and system change as well as have treatment implications, such as introducing a means of identifying critical periods of risk for mental state deterioration.

Author Affiliations: Orygen, The National Centre of Excellence in Youth Mental Health, The University of Melbourne, Melbourne, Australia (Nelson, McGorry, Hartmann);

Psychological Medicine

cambridge.org/psm

Invited Review

Cite this article: Wichers M, Schreuder MJ, Goekoop R, Groen RN (2018). Can we predict the direction of sudden shifts in symptoms? Transdiagnostic implications from a complex systems perspective on psychopathology. *Psychological Medicine* **49**, 380–387. https://doi.org/10.1017/S0033291718002064

Received: 20 March 2018
Revised: 27 June 2018
Accepted: 19 July 2018
First published online: 22 August 2018

Key words:
Complex systems; psychopathology; transdiagnostic approach

Author for correspondence:
Marieke Wichers, E-mail: m.c.wichers@umcg.nl

Can we predict the direction of sudden shifts in symptoms? Transdiagnostic implications from a complex systems perspective on psychopathology

Marieke Wichers[1], Marieke J. Schreuder[1], Rutger Goekoop[2] and Robin N. Groen[1]

[1]University of Groningen, University Medical Center Groningen, Department of Psychiatrie, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), Groningen, The Netherlands and [2]Department of Mood Disorders, Parnassia Group, PsyQ, The Hague, The Netherlands

Abstract

Recently, there has been renewed interest in the application of assumptions from complex systems theory in the field of psychopathology. One assumption, with high clinical relevance, is that sudden transitions in symptoms may be anticipated by rising instability in the system, which can be detected with early warning signals (EWS). Empirical studies support the idea that this principle also applies to the field of psychopathology. The current manuscript discusses whether assumptions from complex systems theory can additionally be informative with respect to the specific symptom dimension in which such a transition will occur (e.g. whether a transition towards anxious, depressive or manic symptoms is most likely). From a complex systems perspective, both EWS measured in single symptom dynamics and network symptom dynamics at large are hypothesized to provide clues regarding the direction of the transition. Challenging research designs are needed to provide empirical validation of these hypotheses. These designs should be able to follow sudden transitions 'live' using frequent observations of symptoms within individuals and apply a transdiagnostic approach to psychopathology. If the assumptions proposed are supported by empirical studies then this will signify a large improvement in the possibility for personalized estimations of the course of psychiatric symptoms. Such information can be extremely useful for early intervention strategies aimed at preventing specific psychiatric problems.

SPECIAL ARTICLE

Biomarkers and clinical staging in psychiatry

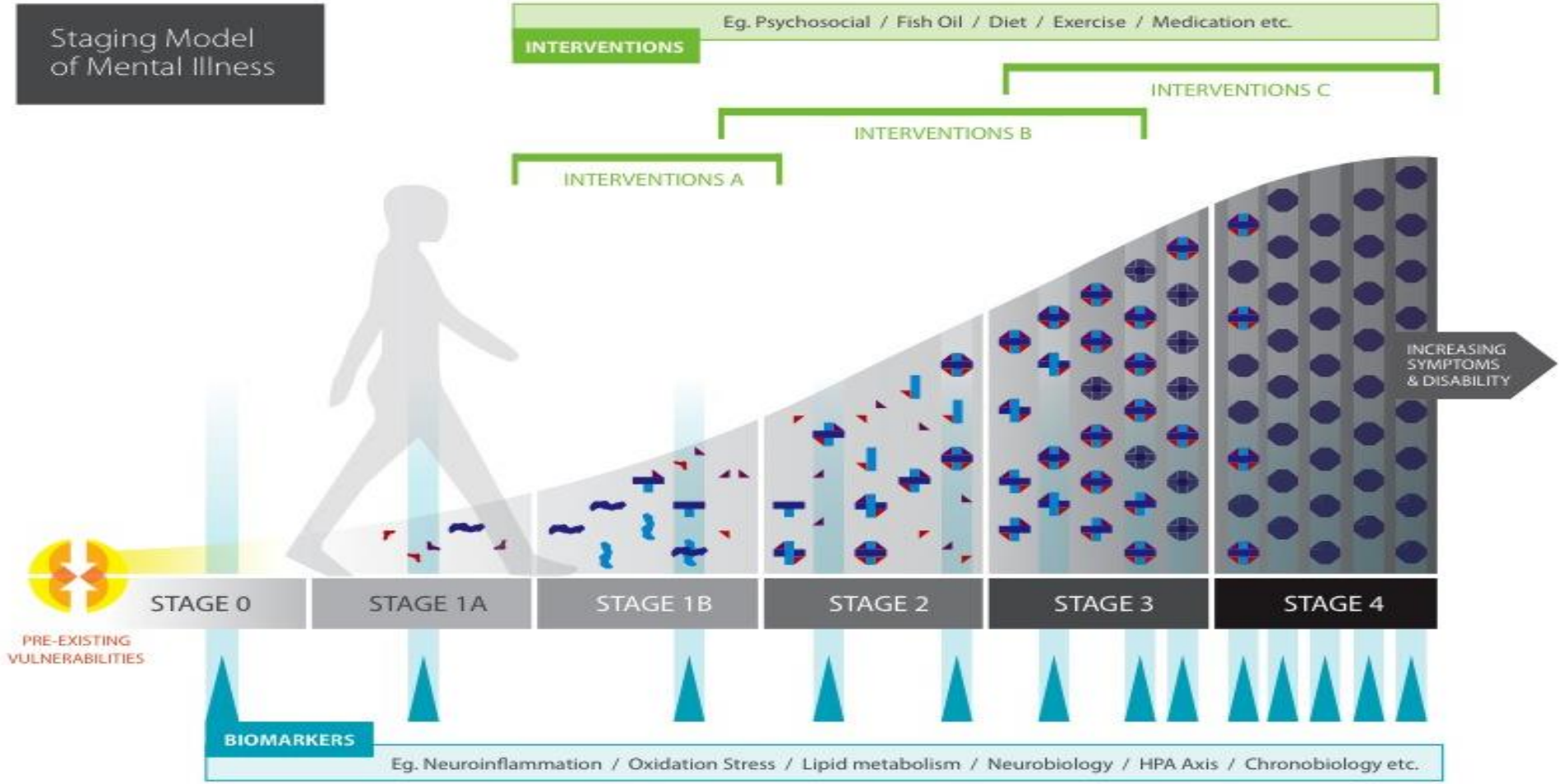
Patrick McGorry[1], Matcheri Keshavan[2], Sherilyn Goldstone[1], Paul Amminger[1], Kelly Allott[1], Michael Berk[1,3], Suzie Lavoie[1], Christos Pantelis[4], Alison Yung[5], Stephen Wood[6], Ian Hickie[7]

[1]Orygen Youth Health Research Centre, Centre for Youth Mental Health, Department of Psychiatry, University of Melbourne, Melbourne, Australia; [2]Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, MA, USA; [3]School of Medicine, Deakin University, Geelong, Australia; [4]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, Australia; [5]Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK; [6]School of Psychology, University of Birmingham, Birmingham, UK; [7]Brain and Mind Research Institute, University of Sydney, Sydney, Australia

Personalized medicine is rapidly becoming a reality in today's physical medicine. However, as yet this is largely an aspirational goal in psychiatry, despite significant advances in our understanding of the biochemical, genetic and neurobiological processes underlying major mental disorders. Preventive medicine relies on the availability of predictive tools; in psychiatry we still largely lack these. Furthermore, our current diagnostic systems, with their focus on well-established, largely chronic illness, do not support a pre-emptive, let alone a preventive, approach, since it is during the early stages of a disorder that interventions have the potential to offer the greatest benefit. Here, we present a clinical staging model for severe mental disorders and discuss examples of biological markers that have already undergone some systematic evaluation and that could be integrated into such a framework. The advantage of this model is that it explicitly considers the evolution of psychopathology during the development of a mental illness and emphasizes that progression of illness is by no means inevitable, but can be altered by providing appropriate interventions that target individual modifiable risk and protective factors. The specific goals of therapeutic intervention are therefore broadened to include the prevention of illness onset or progression, and to minimize the risk of harm associated with more complex treatment regimens. The staging model also facilitates the integration of new data on the biological, social and environmental factors that influence mental illness into our clinical and diagnostic infrastructure, which will provide a major step forward in the development of a truly pre-emptive psychiatry.

Key words: Biomarkers, clinical staging, diagnostic reform, early intervention, personalized medicine, pre-emptive psychiatry, youth mental health

(World Psychiatry 2014;13:211–223)


Staging Model of Mental Illness
INTERVENTIONS
Eg. Psychosocial / Fish Oil / Diet / Exercise / Medication etc.
INTERVENTIONS C
INTERVENTIONS B
INTERVENTIONS A
INCREASING SYMPTOMS & DISABILITY
STAGE 0
STAGE 1A
STAGE 1B
STAGE 2
STAGE 3
STAGE 4
PRE-EXISTING VULNERABILITIES
BIOMARKERS
Eg. Neuroinflammation / Oxidation Stress / Lipid metabolism / Neurobiology / HPA Axis / Chronobiology etc.

THE TASK

TO FORMULATE A GLOBAL COLLABORATIVE STRATEGY TO BUILD A DIAGNOSTIC MODEL WHICH:

1. HAS REAL UTILITY FOR CLINICIANS AND PATIENTS
2. IS UNDERSTOOD AND ACCEPTED BY PATIENTS AND SOCIETY
3. CULTURALLY UNIVERSAL AND ADAPTABLE
4. REMOVES BARRIERS TO DISCOVERY AND NOVEL THERAPIES AND TO IMPLEMENTATION OF FINDINGS

THE HOLY GRAIL

- Our aim is to forge a new way forward seeking to integrate the perspectives and methods of quantitative psychopathology, network analysis and EMA, and clinical staging congruent with ideographic and cultural perspectives.
- Our goal is to pave the way for a nosology that is fit for purpose and can guide treatment selection, and begin to orient and align the global neurobiological research endeavour much more to meaningful clinical goals.
- New research strategies and pathways could be formulated as stepping stones to this holy grail.

"So far so good. Let's hope we win."

REVOLUTION IN MIND

THANK YOU