Future in Psychopathology Research

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Psychopathology research has focused either on the analysis of the mental state in the here and now or on the synthesis of mental status abnormalities with biological markers and outcome data. These two schools of psychopathology, the analytic and the synthetic, make contrasting assumptions, take different approaches, and pursue divergent goals. Analytic psychopathology favors the individual person and unique biography, whereas synthetic psychopathology abstracts from the single case and generalizes to the population level. The dimension of time, especially the prediction of future outcomes, is viewed differently by these two schools. Here I outline how Carpenter’s proposal of strong inference and theory testing in psychopathology research can be used to test the value of analytic and synthetic psychopathology. The emerging field of personalized psychiatry can clarify the relevance of psychopathology for contemporary research in psychiatry.

The scientific foundation of psychiatry rests on clinical observation, and we must therefore guard against erosion of psychiatric phenomenology emerging from clinical casuistry, fragmented and pressured health care systems, and investigator bias and convenience.¹

Psychopathology is the scientific exploration of abnormal mental states.²⁻⁴ It is part of the core curriculum in the training of mental health professionals but has been marginalized in recent years by other pursuits in psychiatry, especially nosology and neuroscience research.⁵,⁶

In more general terms, psychopathology is also used to refer to unusual, strange, or alien mental states and behavior. As such, it can be found in everyday life and is a frequent topic of conversation.⁷ The value of psychopathology has been questioned because the normal/abnormal border of mental states is not clear and progress in understanding and explaining the structure of the human psyche has been slow.⁸

Is psychopathology still relevant for psychiatric research today? Or can we rely on other brands of psychiatric research to reveal the mechanism of mental illness? Here I propose that the dimension of time, including the ability to predict future outcomes, deserves greater attention in psychopathology research. It is necessary for our progress in psychiatric research.

Psychiatric Encounter

All psychopathology begins in the here and now of the psychiatric encounter. The encounter is usually between two people (clinician and patient/client/consumer) and may include relatives, caretakers, or law enforcement personnel. The encounter is shaped by the unique situation and includes observation, verbal communication, and, at times, a physical exam. The situation can vary considerably: crisis intervention in an emergency room, stabilization on an inpatient ward, or long-term treatment in an office. For researchers, it may be a nonclinical setting for the purpose of collecting epidemiological data in the community.

During the psychiatric encounter, the clinician is immersed in the detailed recording of behavior and mental states. This requires considerable training in psychiatric interviewing, which has always been and continues to be a major component in the training of mental health professionals.³,⁹

A crucial skill set is empathic engagement, necessary to uncover the person’s life story. This requires learning a list of mental faculties and behavioral domains that need to be explored in detail. How this list is constructed and how the clinician goes about the collection of information varies substantially between various traditions in psychopathology.

The focus can be on understanding what and how the person feels and thinks. The primary material is the first-person account, and the interviewer is trained in phenomenological analysis and empathic understanding. This may include the expectation that the examiner see the world like the person being interviewed.
In contrast, the gaze of clinical psychiatry is on the other, with a focus on the objective recording of signs and symptoms. It may include the translation of an individual into a list of signs and symptoms that can be quantified and measured. Both approaches can be linked to the study of the brain, the goal being an exploration of how the brain gives rise to an abnormal mind.

While the initial focus of any psychopathology is on the here and now, there is a long tradition in clinical psychiatry to look back into the life history and forward into the future, with the goal to predict course and outcome. This view allows the clinician to differentiate mental states that look similar at one point in time but different in the context of previous and future mental states. For example, depression may be diagnosed based on a single episode or as part of a recurring illness with additional episodes of depression, mania, and mixed states in between.

Schools of Psychopathology

Some psychopathology researchers have focused on the mental state in the here and now, while others have focused on the disease process over time. I will refer to these two schools of psychopathology as analytic and synthetic.

Analytic psychopathology dissects domains, modules, and functions of the human mind. (I use the adjective “analytic” here to refer to the analysis of mental states. It is not meant to refer to “psychoanalysis.”) The analytic approach has given rise to the large literature of descriptive psychopathology. It also includes a considerable effort, at the intersection of philosophy and psychiatry, to determine the basic structure of conscious and unconscious experience. Such efforts pursue the question: what is required for us to experience the world and how can this ability be perturbed in such a way that it leads to abnormal mental states?

Analytic psychopathology is often focused on one individual, not a group of individuals who might share similar experiences. This analysis may limit itself to the phenomenological exploration of psychopathology, including the abnormal experience of time.

However, it can easily be merged with an interest in the neural mechanisms of mental states. At times, the analytic stance leads to the claim that there are only signs and symptoms, but no syndromes and diseases, and that all progress in psychopathology research cannot go beyond the individual person.

In contrast, synthetic psychopathology merges data from the here and now with follow-up observations and biological markers to validate a proposed disease construct. This school embraces the idea that the longitudinal study of mental states and behavior is necessary for progress in psychiatry, as articulated by Karl Kahlbaum in 1878: “To avoid confusion, a new scientific terminology must be coined to name clinical groups differentiable in terms of the number and extension of psychological functions involved and in terms of course and outcome.” His paradigmatic diagnosis was catatonia, defined by distinct periods of decreased and increased psychomotor activity.

Kraepelin built on this reorientation—away from a cross-sectional and toward a longitudinal psychopathology—with his heuristic of the natural disease unit. Like Kahlbaum, he emphasized course and outcome, but he went further. He proposed that the clinical presentation, when recorded over the lifetime of a person, is due to a natural disease unit that can explain etiology and mechanism. If we find the natural disease unit, then we can explain the full clinical picture, define the pathology, track down the etiology, and ultimately cure and prevent. This hope of scientific discovery has fueled psychiatry research ever since Kraepelin proposed his brand of synthetic psychopathology.

Dimension of Time

If the here and now is all that is required to understand abnormal mental states, then history is irrelevant and the prediction of future events is ignored. If course and outcome are the focus, then the subjective experience matters less and mechanistic brain-mind models are less important. Over the last 100 years, the analytic and synthetic psychopathology schools have pursued their goals in parallel, at times in conflict with each other. Bostroem captured this tension well in 1923 when he contrasted Zustandsbild (mental state in the here and now) with Krankheit (the psychiatric disorder). This unresolved debate continues to vex investigators to this day.

Psychiatric nosology has avoided a clear position in this debate and has included the time dimension in several ways. For example, neurodevelopmental disorders are defined within a model of normal human and brain development and are diagnosed when crucial developmental milestones are missed. Posttraumatic stress disorder depends on the identification of a specific life event that triggers subsequent psychopathology. Dysthmic disorder is defined by a relapsing/recurring pattern of mood changes. In contrast, personality disorders are time invariant and can, by definition, be diagnosed in a cross-sectional setting.

A dual focus, on both current mental state and evolution of psychopathology over time, leads to misalignment and poor reliability of psychiatric diagnoses. Two such examples, ie, mixed states and schizoaffective disorder, are the by-product of the Kraepelinian dementia praecox/manic-depressive illness dichotomy.

Kraepelin considered manic stupor as the paradigmatic mixed state: a person presents with elevated/irritable mood, yet at the same time shows a slowed thought process and markedly decreased psychomotor activity. To diagnose a mixed state, the clinician needs to follow a patient over time, in order to assess how 3 domains of psychopathology (ie, abnormal mood, thought,
psychomotor behavior) relate to each other, compared with each respective baseline. Kraepelin used a graph of 3 sine waves to represent the 3 domains and proposed that there should be 8 mixed states. However, clinicians have never found several of the proposed mixed states. This is in large part due to the complex task of assessing several domains of behavior simultaneously and in comparison to a longitudinal baseline.

Schizoaffective disorder has been called a “nosological nuisance, but a clinical reality.” While there are alternatives to the categorical assessment of psychotic and mood symptoms, ICD-10 and DSM-5 treat schizoaffective disorder within the diagnostic class of schizophrenia spectrum disorders. On the one hand, criterion A for schizophrenia needs to be met, which translates into a minimum of 1 month of psychotic symptoms. On the other hand, mood symptoms need to be present for a “substantial portion,” which may be defined as anything above a minimum, such as 20%. Finally, the overlap of mood and psychotic symptoms may be limited to an active period of the illness or extend for long periods throughout the lifetime of the psychotic disorder. This uneven treatment of time makes the diagnosis schizoaffective disorder very unreliable.

We can make 3 conclusions: (1) Analytic psychopathology introduces the bias of the here and now and might miss important data for the discovery of disease mechanisms. (2) Synthetic psychopathology is accurate only in retrospect and has limited success in predicting the outcome of psychiatric illnesses, especially psychotic mood disorders. (3) Analytic and synthetic psychopathology are both constrained by the accuracy of autobiographic memory and access to collateral information.

**Model Testing**

Most psychiatry researchers embrace Kraepelin’s brand of synthetic psychopathology. This is not surprising because any justification of research has to embrace a heuristic that leads to the discovery of disease mechanisms and ultimately cure and prevention. However, most clinicians do not share this view. In fact, it is likely that a substantial number of psychiatrists are opposed to Kraepelin’s view because it does not focus on the person and the dyad in the psychiatric encounter. The divergent and at times opposing agendas have lead to a considerable segregation of various schools in psychiatry.

Carpenter and colleagues proposed that strong inference and theory falsification is not reserved to the natural sciences but can be implemented successfully in psychiatric research. The goal of psychopathology should be the demarcation of the abnormal from the normal mental state, in order to identify the need for treatment and early intervention. Toward this end, it is fruitful to contrast patient groups who are predicted to share some features of psychopathology but not others (eg, all show reality distortion, but only a subset suffers from negative symptoms). Testing such hypotheses has several advantages, including the matching for confounding factors such as duration of illness and treatment effects. Can we harness the current progress in research technologies (eg, neuroimaging tools, statistical genetics) and clinical care delivery (eg, electronic medical records) to make progress in psychopathology research? Personalized psychiatry has emerged as an area of translational research where this could happen. It allows us to test whether an individual patient, assessed at one point in time, will share clinical features and disease mechanisms with similar patients over time.

**Personalized Psychiatry**

Personalized psychiatry uses phenotypic and genotypic data to create prospective models for a person suffering from mental health problems. This may include predicting the response to treatment, the course of the illness, and the ultimate outcome. Can we use personalized psychiatry to improve the uneven treatment of time in the psychopathology and nosology of psychiatric disorders? Can we overcome the segregation of different schools and support more stringent theory testing at the intersection of research and clinical practice? Here I briefly review 3 emerging methods (the longitudinal study of brain structure/function, large-scale phenotyping, and the study of the temporal dynamic of the human genome) and conclude with an example of how they can be employed in psychopathology research.

Longitudinal studies of brain structure and function are demanding, mainly due to difficulties in recruiting probands for studies that are not considered diagnostic and due to attrition over the course of the study (which typically run for at least 2 years). However, the increasing availability of noninvasive brain imaging modalities makes it possible now to marry the cross-sectional study design of clinical neuroscience with the longitudinal study design of epidemiology and health outcomes research. Several compelling studies using longitudinal designs have now been published, and this field of psychiatric research is poised to make significant discoveries, especially if the design includes a test of treatment effects.

Large databases of phenotypic data are now available to discover new genetic mechanisms. They are referred to as phenome-wide association studies, as a counterpart to the more well-known genome-wide association studies. Sophisticated electronic medical records now provide the opportunity to discover genetic mechanisms without defining a priori the diagnostic group or crucial clinical features. In addition, experience sampling methods allow for a rich data collection in nonclinical settings and will contribute to a more personalized assessment of psychopathology.

The human genome is not static over the course of a person’s life but has a remarkable temporal dynamic. We
have been aware of the temporal profile of mRNA expression and its impact on psychopathology for some time now. More recently, we have also learned that studying the complex pattern of DNA methylation is crucial for our understanding of psychiatric disorders. And even at the level of allelic variation, which we had accepted as a fixed blueprint for the human body, somatic mutations in brain cells might be a crucial genetic determinant of psychopathology.

Let us take the example of auditory verbal hallucinations to assess the contributions of analytic and synthetic psychopathology. We have learned much from first-person accounts of voice hearers, and we have developed detailed questionnaires and rating scales. More recently, we have been able to record the frequency and quality of auditory hallucinations in real life. Neuroimaging researchers have been able to capture characteristic images of brain activation that are closely related to the experience of hearing voices. These are compelling contributions of the analytic approach.

Initial longitudinal and treatment studies have now shown that specific brain activation patterns predict the response to transcranial magnetic stimulation in patients who experience auditory hallucinations. In addition, structural changes in a network subserving auditory processing and language are found consistently in patients who frequently experience hearing voices. These are compelling examples of the synthetic approach.

What is now needed is the testing of several strong hypotheses: (1) Do functional and structural brain abnormalities differentiate between a psychotic patient with and without auditory verbal hallucinations? If so, can we employ imaging to diagnose auditory hallucinations? And can we predict and then follow treatment response with neuroimaging methods? (2) Can we differentiate the form, severity, duration, and functional impact of auditory verbal hallucinations in each person at the level of the brain? (3) What are the environmental and genetic risk factors leading to auditory verbal hallucinations? Does the experience of hearing voices change the molecular and cellular architecture of the brain?

In conclusion, the dimension of time deserves greater attention in psychopathology research. Personalized psychiatry allows us to study each person in detail, follow them over time, and extrapolate from single cases to shared mechanisms of psychopathology in large samples.

**References**


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