Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis

Klaas E Stephan, Dominik R Bach, Paul C Fletcher, Jonathan Flint, Michael J Frank, Karl J Friston, Andreas Heinz, Quentin J M Huys, Michael J Owen, Elisabeth B Binder, Peter Dayan, Eve C Johnstone, Andreas Meyer-Lindenberg, P Read Montague, Ulrich Schnyder, Xiao-Jing Wang, Michael Breakspear

Contemporary psychiatry faces major challenges. Its syndrome-based disease classification is not based on mechanisms and does not guide treatment, which largely depends on trial and error. The development of therapies is hindered by ignorance of potential beneficiary patient subgroups. Neuroscientific and genetics research have yet to affect disease definitions or contribute to clinical decision making. In this challenging setting, what should psychiatric research focus on? In two companion papers, we present a list of problems nominated by clinicians and researchers from different disciplines as candidates for future scientific investigation of mental disorders. These problems are loosely grouped into challenges concerning nosology and diagnosis (this Personal View) and problems related to pathogenesis and aetiology (in the companion Personal View). Motivated by successful examples in other disciplines, particularly the list of Hilbert's problems in mathematics, this subjective and eclectic list of priority problems is intended for psychiatric researchers, helping to re-focus existing research and providing perspectives for future psychiatric science.

Introduction

Psychiatry, more than any other medical discipline, faces major conceptual and practical challenges. Despite enormous efforts, diagnostic classifications are still based solely on symptoms and signs, with causes and mechanisms varying across patients within existing diagnostic categories.[1–5] Without tests to predict efficacy and guide individual treatment,[6] psychiatrists undertake a prolonged process of trial and error to find an effective therapy,[7] and the pace of drug development has been disappointing.[8]

This unsatisfactory state of affairs is not because of a scarcity of research efforts. The study of mental disorders has attracted many researchers from various specialties, and neuroscience has hardly lacked seminal findings. Nevertheless, few, if any, breakthroughs in basic scientific research have led to substantive improvements in psychiatric clinical practice. This lack of improvement motivates a refocusing of existing psychiatric research agendas, identifying priority questions that are crucial for making fundamental progress.

Rather than adopting a single overarching framework, this Personal View provides a list of problems and challenges that we—an international group of clinicians and scientists from diverse specialties—believe should play a central part in future scientific investigation of mental disorders. Inspired by previous examples from other disciplines—eg, the famous list of Hilbert's problems in mathematics[9]—our list of priority problems is eclectic and subjective and does not claim to provide systematic or exhaustive coverage of all important problems in psychiatric research. As in Hilbert's list, our problems differ in scope and nature: some are formulated as questions with a simple answer, others call for more complex solutions, and yet others are formulated as proposals.

Although we deliberately decided not to constrain the list by using a particular theory or framework, its components have a common root, originating from discussions at a scientific symposium,[10] during which every participant was challenged to state what they perceived as "the single most important problem or hypothesis that needs to be addressed to endow psychiatry with a mechanistic, neuroscientifically informed basis". We continue this theme here, collating priority problems for psychiatry suggested by contributors from different specialties and with different perspectives. The problems are loosely grouped into two sets: the problems in this Personal View concern classification and diagnosis, whereas the companion paper[11] presents challenges relating to pathogenesis and aetiology. We hope that this collection of challenges will provide guidance and inspiration for future psychiatric research.

In this Personal View, the problems concern several fundamental (and not wholly unrelated) themes. One problem is whether symptoms, syndromes, or signs are the most appropriate starting point to relate the pathology of psychiatric disease to its mechanisms. A second major problem is how best to reconceptualise the classification of disease. Several problems relate to the heterogeneous nature of psychiatric diseases and suggest different approaches for dissecting the diagnostic spectra. One major theme is whether a categorical or dimensional perspective is more appropriate when considering pathophysiology and nosology. In this context, it is worth emphasising that we do not assume a single concept of disease across the problems discussed, because different degrees of discreteness probably exist across disorders.[12,13] Finally, several of the approaches discussed in this Personal View (and the companion report) call on computational perspectives, which, as pointed out in the first of the challenges discussed next, depend on the conceptual and fundamental assumption that the mapping between mental and neuronal states is computable.

(Prof E B Binder); **Department of Psychiatry, University of Edinburgh, Edinburgh, UK** (Prof E C Johnstone MD); **Central Institute of Mental Health, University of Mannheim, Mannheim, Germany** Prof A Meyer-Lindenberg MD); **Computational Psychiatry Unit, Virginia Tech Carilion Research Institute, Roanoke, VA, USA** (Prof P R Montague); **Department of Psychiatry and Psychotherapy, University Hospital Zurich, University of Zurich, Zurich, Switzerland** (Prof U Schnyder MD); **Center for Neural Science, New York University, New York, NY, USA** (Prof X-J Wang PhD); **Institute of Brain and Cognitive Science, NYU Shanghai, Shanghai, China** (Prof X-J Wang); **and Queensland Medical Research Institute, Brisbane, QLD, Australia** (Prof M Breakspear PhD)

Correspondence to:
Prof K E Stephan, Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich & ETH Zurich, Zurich, Switzerland
stephan@biomed.ee.ethz.ch

Problem 1: Is mapping between mental states and brain states computable?

One of the goals of neuroscience research is to establish a class of mappings between the measurable states of the brain and some rendering of what is called a mental state (including cognitive, affective, and motivational states). Mental states are modelled as computations, so a key question is whether mental states and brain states can be mapped onto one another by computable functions. Simply speaking, a function $f(x)$ is computable if a procedure with a finite number of steps can convert x into $f(x)$,[14] comparable with Hilbert's tenth problem, which concerns the existence of a general procedure to determine, in a finite number of steps, whether any given diophantine equation is solvable in rational integers.

If the mapping between the mental and brain states is computable, modern brain and behavioural science becomes a matter of engineering—albeit a subtle and complex one. However, if the mapping between mental and brain states is not computable (for reasons not yet known), this will have profound and adverse consequences for computational psychiatry, which aims to formalise understanding and diagnosis of mental disease.[15–21] This endeavour is bound to fail in ways difficult to anticipate if pertinent connections between brain and mental states are not computable. Problem 1 thus must be resolved for the promise of formal or computational approaches to be realised.

Two further qualifications apply. First, the problem does not change its basic character if the requirement for classically computable mapping is replaced with quantum computable mapping. Second, the answer to this problem might depend on whether content externalism[22] is true of the mental states being examined.

Problem 2: What should be the status and role of symptoms in psychiatry?

Diagnostic schemes based purely on symptoms are not reliable in clinical settings,[23] are temporally unstable and unspecific[24,25] (with high rates of comorbidity[26] strongly related to severity),[27,28] and offer scarce, divergent, and sometimes even misleading guidance on treatment. Yet symptoms are what bring patients to clinicians and, crucially, clinicians have no alternatives to rely on, despite an enormous research effort yielding a large number of cognitive, neurobiological, and other correlates for each diagnosis.

Priority problem 2 is the status and role of symptoms in psychiatry, which comes with two questions. First, should symptoms have a similar status and role as in other branches of medicine, in which they are crucial to narrowing down the possible underlying diseases? If that is the case, what is the minimum combination of symptoms (or syndrome) that maximises information about differences in the efficacy of available treatment options? Does this set of symptoms reliably differentiate between those who do and do not need treatment—ie, does the set of symptoms define a disease?

Second, again with reference to other branches of medicine, do symptoms define a series of diseases that can be disentangled with the help of neurobehavioural measures? If so, what is the relation between them—eg, are neurobehavioural measures informative only within groups of symptoms or are they useful across and independent of symptoms?

Problem 3: Integrating a dimensional perspective on general psychopathology with categorical definitions of disease entities

The deeper we delve into the nature of mental illness, the clearer it becomes that cherished distinctions between diagnostic categories might be partly illusory. The long-held dichotomy between affective disorders and schizophrenia has already been seriously questioned, and further results have led to questions about the even more fundamental distinction between neurosis and psychosis. Specifically, longitudinal studies[28,29] suggest that a single common factor underlies vulnerability to an array of mental symptoms, from depression through anxiety to psychosis. This factor—called by some the p (psychopathology) factor[28]—has been suggested to be similar to the g (general intelligence) factor that can be used to measure performance across a wide range of seemingly disparate cognitive tasks.[30] The p factor is suggested to provide a unitary measure with remarkable power to explain and elucidate the trajectory of mental illness, irrespective of diagnosis. Just as different cognitive tasks affect the value of g, so might different psychopathological domains affect the value of p indicating different severities of disease.[29]

Moving forward, psychiatric research cannot ignore the fact that large longitudinal datasets seem to be telling us that diagnostic categories provide only an approximation of much deeper patterns. This does not abnegate the importance of diagnosis in psychiatry; indeed, we should be wary of eschewing syndrome-based approaches and trying to conquer psychiatric uncertainty one symptom at a time. Such a piecemeal approach might offer isolated victories but would surely fail to grasp how patients experience their illness in its entirety. A big question for psychiatry is how to encompass this deeper blurring of psychiatric boundaries without throwing away the careful observations of more than a century, which suggest that recognisable and reliable psychiatric sub-syndromes do exist. We should bear in mind that psychiatry's attempts to come to terms with the complexities of mental illness are beset by the same problems the brain faces when making sense of a world of ambiguous, noisy, and incomplete datasets. The brain's solution to this problem is to use its expectations, borne of previous experience, to generate hypotheses about deeper regularities that give rise to its sense data. However, when data violate

predictions, expectations might have to be changed. Failure to achieve a balance could be at the root of psychosis. Psychiatry should use its structures and priorities but should be sufficiently flexible to update them. The key challenge here, therefore, is to integrate emerging dimensional perspectives on mental illness with category-based approaches.

Problem 4: Show that the brain manifests disease in limited ways (possibly only three or four)

Although physicians have long recognised that every organ of the body can be affected by multiple diseases, the complexity of the brain does not seem to be reflected in the number of diseases recognised by psychiatrists. One reason could be that the classification of psychiatric disease groups together heterogeneous disorders; major depression is a good example, because debate over the divisibility of depression has already lasted more than a century,[31] with discussion continuing about its homogeneity as a clinical entity.[32] An alternative view is that the existing classification is cut too generously, with diseases long recognised as separate potentially being manifestations of the same underlying pathological changes—eg, the distinction between bipolar disorder and schizophrenia is the subject of a long-standing dispute (compare this with problem 13 in the companion Personal View).[33,34] The results of genetic studies in patients with psychiatric disease suggest that genetic factors are shared between disorders long thought to be distinct, including, for example, autism and schizophrenia.[35] The extent of genetic correlation between bipolar disorder and schizophrenia is remarkably high at 68%.[35] If we accept genetics as a way to define psychiatric disease, there could be more similarity between disorders than is currently accepted. The result of this dispute has implications for interpreting attempts to relate disturbances in known neurobiological processes with disease (see, for example, the Research Domain Criteria project[4]). More fundamentally, it raises the question of whether the brain has a limited number of ways of responding to acquired or inherited dysfunction.

Problem 5: Bridging the comparative gap: can preclinical models help to establish diagnostic criteria based on observable signs?

Concepts of disease in psychiatry largely rely on reported symptoms rather than observable signs. This is unsurprising, because many symptoms have no easy analogue in signs. Yet, much of our knowledge about the molecular, cellular, and circuitry mechanisms of psychiatric disorders is based on preclinical models in non-human animals, but, of course, we never know the symptoms that these animals experience subjectively. How can we bridge this gap and claim with confidence that a behavioural, genetic, or lesional model shows a psychiatric disorder?

Several attempts have been made to establish informative preclinical models, but many of the identified links to psychiatric disorders are circumstantial. For example, in rodents, anxiolytic drugs reduce some types of anxiety-like behaviour in approach-avoidance conflict tests such as the elevated plus maze or the open field.[36] However, this does not prove that these frameworks model generalised anxiety disorder. Additionally, it is clear from models of schizophrenia and depression that preclinical animal tests reflect only some behaviours reminiscent of the respective psychiatric disorder, not the disorder itself.[37]

This comparative and translational gap is a challenge that we need to overcome; however, it also offers an opportunity to redefine clinical research. Even in a healthy state, the emergence of subjective experience from processes in the mind or nervous system is not well understood, and is certainly less well understood than the process underlying implementation of observable behaviours. This means that subjectively perceived symptoms are problematic as a basis for further development of psychiatric diagnoses. Instead, convincing preclinical non-human models could provide objective tests based on observable behaviour. For example, if we believe that learned helplessness is a good preclinical model of depression[38] in terms of its antecedents and the ensuing observable signs, why would we not believe that these signs might enable diagnosis, prediction of the efficacy of treatment, or definition of subgroups—perhaps better than current diagnostic schemes and symptom assessments?

The psychiatric literature abounds with preclinical models that show observable aspects of psychiatric disorders. Systematic assessment of whether the defining signs of those models are also defining signs of clinical states might allow psychiatrists to refocus on a battery of signs not symptoms. This could bring diagnosis and prediction of the best treatment closer to the underlying causes of disease—be it a defined biological cause or a process better described at an abstract (psychological or computational) level. However, the increase in diagnostic accuracy might result in an unintended consequence: a divergence in the approaches used by clinicians and by patients (who are compelled to see a doctor because of symptoms; compare this with problem 2), as is already evident for other branches of medicine.

Problem 6: What is the higher order structure of fundamental mechanisms relevant for diagnostics?

The central goals of computational psychiatry[15,17–19,39–41] are to develop mechanistic models based on principles that formalise functional objectives in areas such as perception, motivated action, and cognition and to explore how aberrations in such mechanisms lead to mental illness. Beyond a few individual mechanisms that lead to isolated symptoms, a much more comprehensive approach is needed to radically transform psychiatric diagnostics.[39,41] Indeed, one underlying aberration can

lead to different symptom profiles (depending on other biological and cultural factors) and, conversely, different mechanisms can lead to the same symptoms.[42,43]

For example, mechanisms of reinforcement learning in corticostriatal circuitry might explain changes in motivated behaviour across mental illnesses.[17] An imbalance in learning from positive and negative decision outcomes, induced by altered corticostriatal dopaminergic function, can cause a form of impulsivity exemplified by pathological gambling. However, the same imbalance with other background factors could fuel tenacity in the face of frequent setbacks—in other words, it becomes a feature rather than a problem unless taken to a pathological extreme (but with very different symptoms than in a pathological gambler). Conversely, impulsive behaviours can arise from aberrations of distinct mechanisms (eg, fronto-subthalamic communication impeding the ability to pause and reconsider when faced with an impulsive urge).[44,45]

Although refined methods can disentangle these individual mechanisms, patients often have clusters of symptoms and mechanisms rather than just one symptom or mechanism. One goal is therefore to develop diagnostic strategies that identify clusters of mechanisms that are amenable to treatment, using multidimensional functional profiles that combine neural and behavioural indices to assess distinct identifiable mechanisms.[39,41,46] Herein lies the crux of the problem: not only do we not know many of the relevant mechanisms themselves, we also do not know the best methods for describing their higher order structure for different individuals, which is essential for revamping diagnostics.

The challenge outlined here thus is computational. We need to learn more about mechanisms, but it is important to discover how they cluster together. In essence, we need to study the natural structure of mechanisms of fundamental relevance for mental disease. Common classification schemes are supervised or unsupervised (ie, with or without prior knowledge of the categories), but psychiatry needs to discover the optimal combination. When there is evidence that some mechanisms are relevant for mental illnesses, supervised methods can emphasise those factors and de-emphasise others that are less likely to induce mental illness (or to interact with those that do). We also need unsupervised methods for the many cases in which we do not have the luxury of a validated mechanistic model. What is the proper combination of supervised and unsupervised clustering methods, including the transition from unsupervised to supervised as knowledge accumulates? Moreover, the clustering scheme needs to be stable to be used as a legitimate diagnostic—ie, adding a new measure should not lead to radical shifts in assignment to clusters. We therefore also need a formal criterion to determine whether clustering of relevant mechanisms has stabilised sufficiently to be used pragmatically.

Problem 7: New approaches to patient stratification are needed for neuroscience research

Before we can endow diagnostics in clinical psychiatry with a mechanistic, neuroscientifically informed basis, we need to reconsider how we classify psychiatric disorders for research. Greater neuroscientific and mechanistic understanding is hoped and expected to come to underpin diagnosis. However, the key question is how to measure and define psychopathology in the meantime to give the best chance of identifying underlying disturbances in brain function. It is increasingly clear that diagnostic categorical approaches, as enshrined in DSM and ICD and used in the clinic, are both too broad and too narrow for this purpose[2]—ie, they delineate complex, multifaceted, and heterogeneous syndromes that are not clearly demarcated from each other or from wellness. Studies that attempt to relate measures of brain function to specific categorical diagnoses, as defined by DSM and ICD, have repeatedly not found adequate specificity and sensitivity. Measures of symptoms and signs, or groups of these, that better index shared underlying mechanistic disturbance are needed. This approach will probably need to include both dimensional and categorical measures, use markers of underlying mechanisms such as measures of cognition, brain structure, and neurophysiology, and adopt a longitudinal and developmental perspective. Such studies will necessarily be agnostic to diagnostic status. Measures of stable trait abnormalities, which may be progressive, will need to be distinguished from measures of state abnormalities relating to present psychopathology. An emerging consensus on appropriate measures and a greater focus on more detailed phenotyping in studies of clinical samples will be needed and measures that can readily be translated to model systems will be useful.

Problem 8: Develop computational assays for symptom-guided reassembly of psychiatric nosology

Generative models provide a probabilistic mapping from unobservable system states to measurements, and inverting this mapping allows inferences about hidden states to be made from data. This notion from probability theory has inspired an influential neuroscientific concept: computational theories view the brain as representing a generative model that predicts the sensory inputs caused by states of the world (and chosen actions) and that is constantly updated according to experience.[47–49] Model inversion enables the brain to infer, from its sensory inputs, environmental and bodily states,[47,50] volatility in the physical and social world,[51,52] and capacity for control.[53]

This perspective has powerful implications for identifying disease-relevant building blocks of computation and physiology. For example, under generic approximations,[54–56] updates to models depend on two quantities: prediction errors and precision (inverse uncertainty). Different prediction errors might be

encoded by phasic dopamine, acetylcholine, and glutamate signals in different circuits and might induce the synaptic plasticity needed to update models, whereas precision weighting might be implemented by slower changes in release of dopamine or acetylcholine .[55,57–60]

The priority challenge here is to develop so-called computational assays[20]—ie, generative models for characterising (anomalies of) computational and physiological components of the generative models implemented by individual brains. Inferring patient-specific disease mechanisms by applying such assays to neuroimaging and behavioural data could allow a heterogeneous spectrum of diseases to be divided into subgroups that are computationally or physiologically distinct. Early prototypes of computational assays[52,61] and attempts to dissect heterogeneous patient groups exist[40] but are far from being useful in the clinic, and treat computation and physiology separately. Development of unified models with enhanced inferential capacity might enable us to reassemble classifications by differentiating, symptom by symptom, alternative computational and pathophysiological explanations.

For example, in delusions, can we distinguish different roles of glutamatergic, cholinergic, and (autocrine) dopaminergic midbrain inputs for dysregulation of dopamine neuron activity?[62] For hallucinations, can we distinguish (cholinergic) hyperprecision of predictions in higher auditory areas[63] from hypoprecision of (gluta-matergic) prediction error signals from lower auditory areas?[64] With respect to fatigue, can we identify distinct patient subgroups in whom the brain's model of interoceptive inputs signals constant surprise because of persistent violation of fixed beliefs (homoeostatic setpoints) regarding metabolic states or bodily integrity and in whom this enduring dyshomoeostasis induces high-order beliefs about lack of control and low self-efficacy?[65] Finally, can we generally detect patients without any primary physiological impairment who display (approximate) Bayes optimal inference but under unusual or conflicting beliefs, and can these beliefs be pinpointed through model selection?

Problem 9: Computational assessment of learning dysfunctions for a dimensional perspective on psychiatric disorders

Do the more than 300 disorders in psychiatry constitute separate disease entities with distinct neurobiological correlates? Probably not. In clinical practice, anti-depressants are given to improve negative mood in patients with disorders from different classifications—eg, depression, alcohol dependence, and schizophrenia. Conversely, neuroleptic medications improve not only psychotic symptoms but also symptoms of acute delirium tremens or mania. We and others have therefore suggested that neurotransmitter systems targeted by these drugs are disturbed in multiple mental disorders and that their respective dysfunctions contribute to basic dimensions of people's behaviour.[66–68]

Dysfunction of monoaminergic neurotransmission has long been assumed to contribute to specific changes in mood and motivation—eg, dopamine dysfunction can cause anhedonia by impairing reward processing.[69] Furthermore, dopamine and serotonin differentially support learning from reward and punishment[57,70] with clinically relevant results. Specifically, in psychosis, stress-dependent changes in release of dopamine can attribute salience to otherwise irrelevant stimuli;[66] similarly, release of dopamine elicited by some misused drugs and drug-associated cues attributes incentive salience to irrelevant stimuli and promotes drug seeking and relapse.[71,72] By contrast, serotonin dysfunction might specifically interact with processing of aversive stimuli and learning from aversive events.[73,74]

A computational approach to behavioural analysis allows the association of trial-wise learning quantities with brain imaging signals.[75] This model-based approach might help to define neurobiologically relevant processes in the spectrum of psychiatric disorders. Specifically, it can distinguish between the use of alternative behavioural strategies and physiological changes—eg, functional deactivation of a patient's ventral striatum in response to informative errors can be interpreted as neuronal dysfunction only if the patient applies the same behavioural strategy as a reference group. Comparison of statistical models can be useful to rule out that a specific participant is just inattentive or uses a strategy that is not guided by informative errors.[76]

Computational approaches hold great promise for characterising key dimensions of neural dysfunction across classification boundaries. For example, impaired prediction of reward is associated with negative mood in schizophrenia, alcohol dependence, and major depression and might thus constitute an important pathophysiological dimension of mental disorders.[77] However, a comprehensive account of similarities and differences in learning from reward and punishment in different mental disorders is missing. The challenge here is to use computational modelling to disentangle shared and specific changes of learning mechanisms and their neurobiological correlates across mental disorders and to establish a basis for a dimensional perspective across the boundaries of classification.

Conclusion

This compilation of priority problems was deliberately left unconstrained. Nevertheless, several overarching themes emerge from the ensuing candidate statements. Perhaps most notable is the question of whether psychiatric classification should adopt a categorical or dimensional view.[12] Some of the problems (eg, problems 6 and 8) have leaned towards a categorical approach, reviewing ways to dissect the diagnostic spectra into discrete subgroups, whereas others (eg, problems 3, 4, and 9) have discussed dimensions (possibly very few or even singular) that predispose to mental disease. In

some sense, when considering mental diseases as arising from disturbances of fundamental physiological or computational processes, a dimensional view might seem natural (and perhaps unavoidable), since these processes are governed by variables that are typically continuous in nature (eg, the strength of specific synaptic connections or extracellular concentrations of particular neurotransmitters). However, from the perspective of a dynamic system, categorical and dimensional perspectives coexist and can be reconciled.[40] For example, continuous changes of synaptic variables within neuronal circuits can introduce bifurcations (ie, abrupt qualitative shifts in system behaviour) and might hence induce categorically distinct mental states and behaviour.[78] As discussed in problems 3 and 7, a future classification will probably embrace both categorical and dimensional perspectives of mental disease.

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