Charting the Landscape of Priority Problems in Psychiatry – Part I: Nosology and Diagnosis.

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Summary

Contemporary psychiatry faces major challenges. Its phenomenological nosology continues to lack mechanistic interpretability and predictive guidance; treatment largely depends on trial and error; drug development is impeded through ignorance of potential beneficiary subgroups; neuroscientific and genetics research has yet to impact disease definitions or to contribute to clinical decision-making. In this parlous setting, what should psychiatric research focus on?

In two companion papers, we present a list of concrete 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 article) and those addressing pathogenesis and aetiology (in the companion article). Motivated by successful examples in other disciplines (particularly the famous list of “Hilbert’s problems” in mathematics), this subjective and eclectic list of priority problems is intended to provide inspiration for the field, helping to refocus existing research and providing perspectives for future psychiatric science.

Introduction

More than any other medical discipline, psychiatry faces major conceptual and practical challenges. Despite enormous efforts, present diagnostic classifications continue to be confined to the level of symptoms and signs, leaving causes and mechanisms inherently inhomogeneous over diagnostic categories.¹⁻⁵ As predictive tests guiding individual treatment do not exist⁶, therapy struggles with prolonged trial and error processes⁷, and the pace of drug development has been disappointing⁸.

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

Rather than adopting a single over-arching framework, this article provides a list of concrete problems and challenges that we – an international group of clinicians and scientists from diverse fields – believe should play a central role in future scientific investigations of mental disorders. Inspired by previous examples from other disciplines (*cf.* the famous list of “Hilbert’s problems” in mathematics⁹) this list of priority problems is eclectic and subjective and does not claim to provide a systematic nor exhaustive coverage of all important problems in psychiatric research. As in Hilbert’s list, its constituents differ in scope and nature; some are formulated as questions with a simple answer, others call for a more complex resolution, and yet others are formulated as proposals.

Although we deliberately decided not to constrain the list by a particular theory or framework, its constituents have a common root. That is, this list originates from discussions at a recent scientific symposium¹⁰ where each participant was challenged to state what she or he perceived as “the single most important problem or hypothesis that needs to be addressed to endow psychiatry with a mechanistic, neuroscientifically informed basis”. Here, we continue this theme, collating priority problems for psychiatry from different fields and perspectives. These problems are loosely grouped into two sets: while the problems in this paper concern nosology and diagnosis, the companion paper presents challenges in relation to pathogenesis and aetiology. We hope that, collectively, these challenges provide guidance and inspiration for future psychiatric research.

In this first paper, the problems revolve around several fundamental (and not completely orthogonal) themes. One question is whether symptoms, syndromes or signs are the most appropriate starting points for relating psychopathology to mechanisms. A second major question is how to best reconceptualise current disease classifications. Several of the problems presented concern the heterogeneous nature of current disease entities and consider different approaches for dissecting the diagnostic spectra. In particular, a major theme is whether a categorical or dimensional perspective is more appropriate for pathophysiological and nosological considerations. In this context, it is worth emphasising that we do not assume a unitary disease concept across the problems discussed; different degrees of discreteness likely exist across disorders.^{11,12} Finally, several of the approaches considered in this (and the companion) paper call on computational perspectives. As pointed out by the first of the challenges below, this rests on a conceptual and fundamental assumption: that the mapping between mental and neuronal states is a computable function.

Problem 1: Is the mapping between mental states and brain states computable? (P.R. Montague)

Among its various goals, research in neuroscience seeks 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 now modelled as computations and so the question asks 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 exists which converts x into $f(x)$ in a finite number of steps;¹³ cf. Hilbert's 10th problem).

If the mapping between mental and brain states is computable, then the completion of modern brain and behavioural sciences is in a strong sense an engineering problem, albeit an extremely subtle and complex one. If this is not true (for reasons not now known) then there are profound and adverse consequences for the formal understanding and treatment of mental disease, a budding field called computational psychiatry.¹⁴⁻²⁰ To be specific, such an endeavour is bound to fail in ways difficult to anticipate if pertinent connections between brain and mental states are not computable. In this sense, Problem 1 is essential to resolve, if we are to realise the promise of formal or computational approaches.

Two further qualifications apply. First, the problem does not change its basic character if the requirement for classically computable mappings is replaced with quantum computable mappings. Second, it is possible that the answer to this problem may depend on whether content externalism²¹ is true or not of the mental states being examined.

Problem 2: What should the status and role of symptoms in psychiatry be? (Q.J.M. Huys)

Diagnostic schemes based purely on symptoms suffer from a lack of reliability in clinical settings,²² are temporally unstable and unspecific^{23,24} with high rates of comorbidity²⁵ strongly related to severity^{26,27} and offer little, divergent, and sometimes even misleading, guidance to treatment. Yet, symptoms are what brings patients to clinicians. Critically, clinicians have as yet no alternatives to rely on, despite an enormous research effort yielding a profligate number of cognitive, neurobiological and other correlates for each of the diagnoses.

The priority problem proposed here is: what should the status and role of symptoms in psychiatry be? More specifically, this question comes in two forms.

First, one can ask: Should it be similar to other branches of medicine, where symptoms critically narrow down the possible underlying diseases? In that case, what is the minimal set of symptom combinations (syndromes) that maximises information about the differential efficacy of currently available treatment options? And does this symptom set reliably differentiate those who do and do not require treatment (i.e. does it actually define a disease)?

Second, again with reference to other branches of medicine: do symptoms circumscribe a series of diseases which can be disentangled with neurobehavioural measures? If so, what is their relationship: are the neurobehavioural measures informative only within symptom complexes, or across and independently of them?

Problem 3: Integrating a dimensional perspective on general psychopathology with categorical definitions of disease entities (P.C. Fletcher)

The more we delve into the nature of mental illness the clearer it becomes that cherished distinctions, upon which our diagnostic categories rest, may be partly illusory. The long-held

dichotomy between affective disorders and schizophrenia has already been seriously questioned and, recent results question an even more fundamental distinction – between neurosis and psychosis. Specifically, longitudinal studies^{27,28} suggest a single common factor underlying vulnerability to an array of mental symptoms from depression to anxiety to psychosis. This factor – called by some the “p” (psychopathology) factor²⁷ – has been considered comparable to the “g” (general intelligence) factor that may determine performance across a wide range of seemingly disparate cognitive tasks.²⁹ The p-factor, it is suggested, provides just such a unitary dimension and has remarkable explanatory power in elucidating the trajectory of mental illness, irrespective of diagnosis. Just as different cognitive tasks place differential load on “g”, so different psychopathological domains may reflect the range of severity of “p”.²⁸

In moving forward, psychiatric research cannot ignore the fact that large longitudinal datasets seem to be telling us that current 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 simply eschewing syndrome-based approaches and trying to conquer psychiatric uncertainty one symptom at a time. Such a piecemeal approach may offer isolated victories but would surely fail to grasp how patients experience their illness in its entirety. But a big question for psychiatry is how to encompass this deeper blurring of psychiatric boundaries without throwing away over a century’s careful observational work suggesting that there are indeed recognisable and reliable psychiatric sub-syndromes. One thing that we should, perhaps, bear in mind is that psychiatry’s attempts to come to terms with the complexities of mental illness are beset by the same problems faced by the brain in making sense of a world of ambiguous, noisy and incomplete data. The brain’s solution to this problem is to use its expectations, borne of prior experience, to generate hypotheses about the deeper regularities that give rise to its sense-data. But where the data violate predictions, the expectations may have to be changed. A failure to achieve a balance may be at the root of psychosis. Psychiatry also must use its structures and its priors, but it must be sufficiently flexible to update them. This is the key challenge I propose: to integrate emerging dimensional perspectives on mental illness with the current category-based approaches.

Problem 4: Show that the brain manifests disease in limited ways [possibly only three or four] (J. Flint)

While physicians have for long recognized multiple diseases associated with each of the internal organs, one might argue that the much higher complexity of the brain does not appear to be reflected in the number of diseases that psychiatrists recognize. One reason could be that the current classification of psychiatric disease groups together heterogeneous conditions, a good example being major depression: debate over the divisibility of depression has already lasted more than a century³⁰ with continuing discussion about its homogeneity as a clinical entity.³¹ An alternative view is that existing nosology is cut too generously, and that diseases long recognized as separable may be manifestations of the same underlying pathology: there is a long standing dispute about the distinction between bipolar disorder and schizophrenia (*cf.* Problem 13 in the companion paper).^{32,33} Most recently, the advent of genetic studies of psychiatric disease has indicated that genetic factors are shared between disorders long thought to be distinct, including for example autism and schizophrenia.³⁴ The degree of genetic correlation between bipolar disorder and schizophrenia is remarkably high: 68%.³⁴ If we accept genetics as a way to define psychiatric disease, then it seems there may be more similarity between disorders than currently accepted. Just how this dispute will turn out has implications for interpreting attempts to relate disturbance in known neurobiological processes to disease (for example see the Research Domain Criteria (RDoC) project⁴). More

fundamentally, it raises the question as to whether the brain has a limited number of ways of responding to acquired or inherited dysfunction.

Problem 5: Bridging the comparative gap: can pre-clinical models help to establish diagnostic criteria based on observable signs? (D.R. Bach)

Disease concepts in psychiatry largely rest on reported symptoms, rather than observable signs. This is unsurprising as many symptoms have no easy analogue in signs. Yet, much of our knowledge on the molecular, cellular, and circuit mechanisms of psychiatric disorders is based on pre-clinical models in non-human animals. Of course we never know the symptoms that these animals may experience subjectively. How can we bridge this gap and claim with confidence that a behavioural, genetic, or lesion model reflects a psychiatric disorder?

Numerous attempts to establish informative pre-clinical models have been made, 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 in the elevated plus maze or the open field.³⁵ Yet, this does not prove that these paradigms model generalised anxiety disorder. Also, in schizophrenia and depression models, it has become clear that pre-clinical animal tests can only be taken to reflect certain behaviours reminiscent of the respective psychiatric condition, not the condition *per se*.³⁶

This comparative and translational gap has remained a continuing challenge that we need to overcome. However, it offers at the same time an opportunity to redefine clinical research. Even in a healthy state, the emergence of subjective experience from processes in the mind or in the nervous system is not understood – certainly less well than the implementation of observable behaviours. This renders subjectively perceived symptoms a problematic basis for further development of psychiatric diagnosis. Instead, convincing pre-clinical non-human models may be able to furnish objective tests based on observable behaviour. For example, if we believe that learned helplessness is a good pre-clinical model of depression,³⁷ in terms of its antecedents and the ensuing observable signs, then why would we not believe that these signs might enable diagnosis, treatment prediction, or subgroup definition – and perhaps a better one than current diagnostic schemes and symptom assessments?

The psychiatric literature abounds with pre-clinical models which reflect observable aspects of psychiatric disorders. Systematically assessing whether the defining signs of those models are defining signs of clinical states may allow refocusing psychiatry on a battery of signs, not symptoms. This could bring diagnosis and treatment prediction closer to the underlying aetiology of disease, be it a defined biological cause or a process better described on an abstract (psychological or computational) level. This increase in diagnostic accuracy, however, may incur an unintended consequence: a divergence of the concepts used by clinicians and by patients (who are compelled to see a doctor because of symptoms; cf. Problem 2), respectively, as already evident in other branches of medicine.

Problem 6: What is the higher order structure of fundamental mechanisms relevant for diagnostics? (M.J. Frank)

A central goal of computational psychiatry^{14,16-18,38-40} is to develop principled mechanistic models that formalize functional objectives in areas such as perception, motivated action and cognition, and to explore how aberrations in such mechanisms lead to mental illness. But beyond a few individual mechanisms of isolated symptoms, a much more comprehensive approach is needed for radical transformation of psychiatric diagnostics.^{38,40} Indeed, the same underlying aberration can lead to divergent symptom profiles (depending on other biological

and cultural factors), and conversely, the same apparent symptoms can emerge from different mechanisms.^{41,42}

For example, reinforcement learning mechanisms in corticostriatal circuitry may explain alterations in motivated behaviour across mental illnesses.¹⁶ An imbalance in learning from positive vs. negative decision outcomes, induced by altered corticostriatal dopaminergic function, can cause a form of impulsivity exemplified by pathological gambling. But depending on other background factors, the very same imbalance could fuel tenacity in the face of frequent set-backs – i.e., “a feature, not a bug”, unless taken to a pathological extreme (but then with very different symptoms than a gambler). Conversely, impulsive behaviours can arise from aberrations of distinct mechanisms (e.g., fronto-subthalamic communication, impeding the ability to pause and reconsider when faced with an impulsive urge^{43,44}).

While refined methods can disentangle these individual mechanisms, patients often show clusters of symptoms and mechanisms, not just a single one. One goal is to develop diagnostic strategies that identify clusters of mechanisms that are amenable to treatments, using “multidimensional functional profiles” that combine neural and behavioural indices each assessing distinct identifiable mechanisms.^{38,40,45} But herein lies the crux: 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 across individuals, which is essential for revamping diagnostics.

The challenge outlined here thus amounts to a computational one. We need to learn more about mechanisms, but it is vital to discover how they cluster together. In essence, we need to study the natural structure among mechanisms of fundamental relevance for mental disease. Common classification schemes are either supervised or unsupervised, but psychiatry needs to discover the optimal combination. When there is prior evidence that some mechanisms are relevant for mental illnesses, supervised methods can emphasise those factors and collapse across others that are less likely to induce mental illness (or interact with those that do). But 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 with knowledge accumulation? Moreover, to be used as a legitimate diagnostic, the clustering scheme needs to be stable: adding a new measure should not lead to radical shifts in cluster assignments. Thus we also need a formal criterion for determining whether clusterings of relevant mechanisms have stabilized sufficiently to be used pragmatically.

Problem 7: New approaches to patient stratification needed for neuroscience research (M. Owen)

Before we can endow diagnostics in clinical psychiatry with a mechanistic, neuroscientifically informed basis we need to re-consider how we currently classify psychiatric disorders for research. It is to be hoped and expected that greater neuroscientific and mechanistic understanding will ultimately come to underpin diagnosis. However, the key question is how we should measure and define psychopathology in the meantime in order to give us the best chance of identifying underlying disturbances in brain function. It is increasingly clear that current 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 that is, they delineate complex, multifaceted and heterogeneous syndromes that are not clearly demarcated from each other or from wellness. Studies attempting to relate measures of brain function to specific categorical diagnoses as defined by DSM and ICD have repeatedly failed to demonstrate findings with adequate specificity and sensitivity. What we need are measures of symptoms and signs, or

groups of these, that better index shared underlying mechanistic disturbance. It seems likely that this approach will need to (i) involve both dimensional and categorical measures, (ii) utilize markers of underlying mechanisms such as measures of cognition, brain structure and neurophysiology, and (iii) adopt a longitudinal and developmental perspective. Such studies will necessarily be agnostic to current diagnostic status. There will be a need to distinguish measures of relatively stable “trait” abnormalities, which may be progressive, from those indexing “state” abnormalities relating to current psychopathology. This will require an emerging consensus on appropriate measures and a greater focus on more detailed phenotyping in studies of clinical samples. It will also help to use measures that can readily be translated to model systems.

Problem 8: Develop computational assays for symptom-guided reassembly of psychiatric nosology (K.E. Stephan)

Generative models represent a probabilistic mapping from unobservable system states to measurements; inverting this mapping allows for inference on hidden states from data. This notion from probability theory has inspired an influential neuroscientific concept: computational theories view the brain as instantiating a generative model which predicts the sensory inputs caused by states of the world (and chosen actions) and is constantly updated against experience.⁴⁶⁻⁴⁸ Model inversion allows the brain to infer, from its sensory inputs, environmental and bodily states,^{46,49} volatility in the physical and social world,^{50,51} and capacity for control.⁵²

This perspective has powerful implications for identifying disease-relevant building blocks of computation and physiology. For example, under generic approximations,⁵³⁻⁵⁵ model updates depend on two quantities – prediction errors (PEs) and precision (inverse uncertainty). Different PEs may be encoded by phasic dopamine (DA), acetylcholine (ACh), and glutamate signals in different circuits and induce synaptic plasticity required for model updating, while precision-weighting may be implemented by slower changes in DA or ACh release.^{54,56-59}

The priority challenge proposed here is to develop “computational assays”;¹⁹ i.e., 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 for dissecting heterogeneous spectrum diseases into subgroups that are computationally and/or physiologically distinct. Early prototypes of computational assays^{51,60} and attempts of dissecting heterogeneous patient groups exist³⁹; however, these are far from reaching clinical utility and treat computation and physiology separately. Development of unified models with enhanced inferential capacity may enable us to reassemble nosology by differentiating, symptom by symptom, alternative computational and pathophysiological explanations.

For example, in delusions, can we disambiguate differential roles of glutamatergic, cholinergic and (autocrine) dopaminergic midbrain inputs for dysregulation of DA neuron activity?⁶¹ For hallucinations, can we distinguish (cholinergic) hyper-precision of predictions in higher auditory areas⁶² from hypo-precision of (glutamatergic) PE signals from lower auditory areas?⁶³ Concerning fatigue, can we identify distinct patient subgroups where the brain’s model of interoceptive inputs signals constant surprise due to persistent violation of fixed beliefs (homeostatic setpoints) regarding metabolic states or bodily integrity, and in whom this enduring dyshomeostasis induces high-order beliefs about lack of control and low self-efficacy⁶⁴? Finally, can we generally detect patients without any primary physiological impairment who display (approximately) Bayes-optimal inference but under unusual and/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 (A. Heinz)

Do the more than 300 disorders in psychiatry constitute separate disease entities with distinct neurobiological correlates? Probably not. In clinical practice, antidepressants are given across nosological boundaries to improve negative mood; e.g., in depression, alcohol dependence, or schizophrenia. Conversely, neuroleptic medication can not only improve psychotic symptoms but also symptoms of acute delirium tremens or mania. Therefore, we and others have suggested that neurotransmitter systems targeted by these drugs are disturbed in multiple mental disorders and that their respective dysfunctions contribute to basic dimensions of human behaviour.⁶⁵⁻⁶⁷

It has long been assumed that dysfunction of monoaminergic neurotransmission contributes to specific alterations in mood and motivation; for example, dopamine dysfunction may cause anhedonia by impairing reward processing.⁶⁸ Furthermore, dopamine and serotonin differentially support learning from reward and punishment^{56,69} with clinically relevant consequences. Specifically, in psychosis, stress-dependent dopamine release alterations can attribute salience to otherwise irrelevant stimuli;⁶⁵ similarly, dopamine release elicited by drugs of abuse and drug-associated cues attributes incentive salience to irrelevant stimuli and promotes drug seeking and relapse.^{70,71} By contrast, serotonin dysfunction may specifically interact with processing of aversive stimuli and learning from aversive events.^{72,73}

A computational approach to behavioural analysis allows the association of trial-wise learning quantities with brain imaging signals.⁷⁴ This model-based approach may help to define neurobiologically relevant processes in the spectrum of psychiatric disorders. Specifically, it can distinguish the use of alternative behavioural strategies from physiological alterations: For example, a patient's functional deactivation of the ventral striatum in response to informative errors can only be interpreted as neuronal dysfunction if she or he applies the same behavioural strategy as a reference group. Statistical model comparison can rule out that a given participant is just inattentive or uses a strategy that is not guided by informative errors.⁷⁵

Computational approaches bear great promise for characterising key dimensions of neural dysfunction across nosological boundaries. For example, impaired reward prediction is associated with negative mood in schizophrenia, alcohol dependence and major depression and may thus constitute an important pathophysiological dimension of mental disorders⁷⁶; however, to date, a comprehensive account of similarities and differences in learning from reward and punishment in different mental disorders is missing. The challenge proposed here is to use computational modelling for this purpose, disentangling shared and specific alterations of learning mechanisms and their neurobiological correlates across mental disorders and establish a fundament for a dimensional perspective across nosological boundaries.

Concluding remark

As explained in the Introduction, 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 nosology should adopt a categorical or dimensional view (see ref. 11 for a more fine-grained differentiation). Some of the problems (e.g., 6 and 8) have leaned towards the former, considering approaches to dissecting the current diagnostic spectra into discrete subgroups, while others (e.g., 3, 4, 9)

have reflected on 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 may seem natural (and perhaps unavoidable) since these processes are governed by parameters that are typically continuous in nature (e.g., the strength of certain synaptic connections, or extracellular levels of particular neurotransmitters). However, from a dynamic system perspective, categorical and dimensional perspectives co-exist and can be reconciled.³⁹ For example, continuous variations of synaptic parameters within neuronal circuits can introduce bifurcations (i.e., abrupt qualitative shifts in system behaviour) and may hence induce categorically distinct mental states and behaviour.⁷⁷ In brief, as noted by Problem 7 above, a future nosology will likely embrace both categorical and dimensional perspectives on mental disease.

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All authors contributed to the discussions on which this paper is based and/or contributed an individual problem statement. KES took primary responsibility for compiling and editing the paper; MB and KJF undertook additional editing. The text was subsequently revised and approved by all authors.

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