



Charting the landscape of priority problems in psychiatry, part 2: pathogenesis and aetiology

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This is the second of two companion papers proposing priority problems for research on mental disorders. Whereas the first paper focuses on questions of nosology and diagnosis, this Personal View concerns pathogenesis and aetiology of psychiatric diseases. We hope that this (non-exhaustive and subjective) list of problems, nominated by scientists and clinicians from different fields and institutions, provides guidance and perspectives for choosing future directions in psychiatric science.

Introduction

This Personal View is the second of two companion papers offering a list of priority problems for research on mental disorders. The collation of this list originated from a meeting,¹ at which key challenges for contemporary psychiatry were discussed: nosological schemes that are not informed by pathophysiology or aetiology, diagnostic categories that amalgamate diseases with presumably different disease mechanisms, lack of clinical tests for predicting individual outcome or treatment response, and frustratingly slow progress in translating advances in the understanding of epigenetics or neural circuit function into diagnostic procedures or therapeutic approaches.

As detailed in our first paper²—and in accordance with problem lists in other subjects (such as Hilbert's problems in mathematics³)—this list does not strive for a single and intrinsically consistent framework but represents an eclectic collection of challenges. It reflects the subjective opinions of scientists from various institutions and fields, collected in an unconstrained, bottom-up manner, and illustrating the breadth and diversity of problems that need to be addressed to advance psychiatry. Our hope is that, collectively, both papers will help chart a landscape of priority challenges in psychiatry, providing guidance and orientation for future research.

The companion article presented challenges in relation to nosology and diagnostics, opening with a problem that bears structural resemblance to Hilbert's tenth problem. In this Personal View, we continue and conclude our list, focusing on questions concerning pathophysiology and aetiology. We begin with the role of gene–environment interactions for the aetiology of mental diseases and which of these might mediate resilience to disease. We then move to pathophysiological accounts at the circuit level, considering mechanistic markers differentiating psychotic diseases as a specific example and, more generally, the fundamental importance of a formal mathematical understanding of neuronal circuit function and brain dynamics for pathophysiological theories in psychiatry. To conclude, we switch to a computational perspective, discussing the

key role of Bayesian concepts for understanding aberrant inference and decision making.

The final point shows the growing influence of mathematical concepts on psychiatric research (eg, the emerging specialty of computational psychiatry^{4–10}). It is therefore perhaps not entirely surprising that, on the way, we encounter Hilbert's sixth problem and end on the very same note as Hilbert: with a problem related to variational calculus (his 23rd and last).

Problem 10: Derive a tractable account of the systems-level effect on the human brain of epidemiologically validated high-risk causal factors

Given the high prevalence, severity, and chronicity of mental illness, the ideal response must be prevention. Although prevention is difficult (but getting easier) for genetic risk factors, environmental risks might be modifiable, which could have a significant effect—eg, addressing the risk associated with urban birth could lead to 30% fewer cases of schizophrenia, an illness on which the European Union spends more than €100 billion a year.¹¹

Studies of validated environmental risk factors such as urban birth,¹² migration,¹³ and early neglect or abuse might converge on a neuronal core system including the perigenual cingulate cortex, subcortical structures (such as the amygdala, ventral striatum, and hippocampus) regulated by it, and prefrontal regions, which in turn regulate the perigenual cingulate cortex.¹⁴ These data show an effect on brain function and even structure. If these early studies are replicated and if understanding of this neuronal system increases, a tractable account of how the environment (adversely and positively) affects the brain could inform prevention in at least three ways. First, deriving a measurable intermediate phenotype of environmental risk should show the mechanisms through which environmental risk factors act and thus suggest psychosocial means for intervention (eg, if involved circuits are critical for emotional regulation). Second, such circuits might be directly targetable by biological treatments (eg, prosocial neuropeptides seem to act on circuits related to the perigenual cingulate

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cortex). Third, providing a quantitative measure of risk, even in people who are clinically well, will enable a neuroepidemiological approach towards environmental factors. Such an approach might enable the identification of components for which prevention can be contemplated—eg, by identifying specific aspects of the urban environment (such as green space) that can be modified.

Beyond prevention of environmental risk, similar circuits seem to be affected by genetic risk factors of genome-wide significance, both common (such as some polymorphisms of *CACNA1C*¹⁵) and rare (such as schizophrenia-associated copy number variants¹⁶); such insights might begin defining a system in which nature and nurture converge. If so, then solving this problem will also help to define systems-level mechanisms of gene–environment interactions, which in turn will be useful to stratify people’s responses to risk exposure. Finally, to the degree that these circuits explain important facets of the risk architecture of mental illness, they could be useful to derive and (biologically) validate cross-diagnostic dimensions for psychiatric diagnoses (ie, neurophysiologically characterised disease mechanisms which are not confined to any of the conventional, symptom-based diagnostic entities).¹⁷

Problem 11: What are the mechanisms of gene–environment interplay in psychiatry?

An increasing number of epidemiological, twin, and molecular genetic studies suggest that both genes and the environment are important and interacting factors in risk for and resilience to psychiatric disorders.^{18,19} Some specific gene–environment interactions have been reported for psychiatric disorders, but these could be affected by confounding and insufficient power.^{20,21} To overcome problems of purely statistical interactions, a better understanding of the molecular, cellular, and systemic mechanisms of this interplay is needed. Gaining such an understanding is challenging because both the genetic and environmental contributions are complex, with polygenic risk factors combining both common and rare variants, and environmental factors affecting individuals in utero or earlier.

Both genetic and environmental factors, via epigenetic changes, can cause lasting changes in transcription and thus cell and circuit function.²² However, it is unclear how polygenic risk factors, affecting hundreds of genes or more, interact with complex environmental factors, both positive and negative, throughout development, and lead to cell-type and circuit-specific changes that alter discrete behaviours. Thus, it is of interest to know whether genetic variants can alter sensitivity to environmental change per se, as suggested by some studies,^{23,24} and depending on timing, type, and duration, if they can lead to the opposite outcomes given the same genetic background. If so, what would be the molecular triggers of such differentiation? This knowledge could guide new

treatments. Finally, diagnostic categories share many genetic and environmental risk factors. How these factors interact to shape more specific symptom presentations has not yet been elucidated.

To achieve a better understanding of this interplay, several methodological developments are needed. These include longitudinal human studies with objective measures of the environment, plus innovative cellular and animal experimental systems to model polygenic risk factors during different developmental stages and environmental events. Finally, molecular and imaging tools should be developed to map functional changes in single cells and circuits as well as mathematical and statistical models for tracking changes over time.

A map of the sequence of events by which a given polygenic risk or resilience background leads to longlasting molecular, cellular, circuit level, and systemic changes in complex environments will be relevant to early risk detection, disease prevention, and new treatments. It will also help to identify shared and distinct pathways of disease risk in psychiatry and possibly means of diagnosis based on biology.

Problem 12: Understanding mechanisms of resilience

In the index of Diagnostic and Statistical Manual of Mental Disorders 5, the term resilience does not occur.²⁵ This is a remarkable omission: if psychiatric diagnostics and treatments are to be based on mechanistic neuroscientific concepts of mental illness, the psychobiological underpinnings of human beings’ great potential of resilience to stress and trauma need to be understood.^{26–28}

Resilience can be broadly defined as an individual’s ability to cope adaptively with stressful life events. Stress has long been recognised as a risk factor for the development and maintenance of most mental disorders. However, most people remain healthy after exposure to stressful or traumatic events, and some even seem to have positive psychological changes.²⁹

Resilience is complex and multidimensional, and it has been linked to many biological, psychological, and social factors.³⁰ Genetics, epigenetics, and gene–environment interactions play a role—eg, polymorphisms of the serotonin transporter gene.³¹ Intact function of the neuroendocrine system (eg, neuroactive steroids), reward circuitry (dopamine), and extinction processes also seem important.³² From a psychological perspective, positive emotions (optimism, humour, gratitude, altruism) and cognitive flexibility have been identified as resilience-mediating factors.²⁶ Social support in the aftermath of trauma is the strongest protective factor, across all types of trauma, against the development of post-traumatic stress disorder.³³ A person’s capacity to maintain values and purpose in life despite adverse life stressors and support through religion and spirituality are additional factors supporting resilience. Various activities—such as regular aerobic exercise, mindfulness-based training,

yoga, and meditation—also seem to enhance resilience to stress.^{34,35} And finally, there may be cultural aspects of resilience, such as the concept of individualism versus collectivism, which are only starting to be recognised.

The human species has achieved dominance in the world thanks (partly) to its development of eusociality,³² integrating selfishness and altruism, and its unparalleled resilience to all sorts of biological, psychological, and social stressors. The findings described here illustrate that, in one sense, we already know much about resilience. However, the available empirical data only outline factors associated with individual resilience, and do not describe mechanisms that might define specific patient subgroups and inform targeted treatments. These mechanisms should be elucidated in detail and how they contribute to the development, maintenance, and recovery from stress-induced mental illness needs to be understood. One promising goal in this regard is to decipher mechanisms for balancing positive and negative valence—eg, dopaminergic mechanisms of reward processing under stress.

Problem 13: Can a mechanistic marker be found for diagnosis of schizophrenia and bipolar illness? What are the pitfalls?

The value of diagnostic classification is rarely questioned in medicine because diagnosis determines treatment choice and prognosis. In psychiatry, diagnoses are less reliable because biological markers are rare and treatment responses are not specific. When syndromal diagnoses were introduced,³⁶ disorders throughout medicine were defined purely clinically, much as most psychiatric disorders are still. The subsequent development of pathology, microbiology, and other disciplines provided biological markers of pathophysiology, rendering diagnoses more specific and more reliable. Sometimes this led to effective treatments. But such developments have not occurred in psychiatry with a few exceptions such as neurosyphilis and pellagra.

The differentiation between schizophrenia and bipolar illness concerned psychotic disorders of young people in whom no organic (ie, anatomical or physiological) basis could be demonstrated.³⁷ The nature of this difference, and how best to harness it for differential diagnosis, is still a major challenge for psychiatry.³⁸ Imaging research has shown group differences between schizophrenia,³⁹ bipolar illness,⁴⁰ and healthy controls. These findings are not yet suitable for use as a diagnostic marker, but refinements are being made, and computational methods of image analysis offer tantalising possibilities.⁴¹

However, there could be pitfalls. About 6% of first episodes of schizophrenia have an organic basis, not initially apparent⁴² (eg, syphilis, sarcoidosis, or an endocrine disorder). How some of these disorders would affect neuroimaging measures is unknown. Other cases are associated with substance misuse. Again, in the acute situation, the effect of this on neuroimaging measures is

unknown and it might affect prognosis. Some patients with schizophrenia associated with substance misuse might have a lasting recovery (unusual in schizophrenia) if they remain abstinent. Both the neuroimaging pictures and the prognosis of the schizophreniform states associated with so-called legal highs are unclear. Furthermore, not all organic conditions are known. For example, anti-NMDA receptor encephalitis was not defined until 2008.⁴³ The prognosis of death or ongoing impairment in 25% of such patients can be much improved by immunosuppressive treatment.⁴⁴

Finally, it might be difficult to distinguish between predisposition and clinical state. The established neuroimaging differences between patients with schizophrenia or bipolar illness and healthy controls are attenuated when clinically unaffected relatives of patients are used as controls.^{45,46} Mechanistic markers for psychiatric diagnoses would have clinical value and would provide leads for the ultimate goal of pathophysiological understanding. They would however augment, rather than replace, clinical diagnosis.

Problem 14: What are the principles of cognitive-type microcircuits in a large-scale brain system, and how do their impairments explain mental disorders?

The mammalian neocortex is thought to contain a canonical microcircuit. However, even though different cortical areas share the same architecture, they might differ quantitatively in many ways, such as the strength of local recurrent connections, or the distribution of diverse subtypes of inhibitory neurons. In such nonlinear networks, quantitative differences could give rise to qualitatively different dynamics and computations, leading to the emergence of novel functions.

Cognitive deficits that characterise psychiatric disorders primarily affect association areas in cortex and the related subcortical systems. This raises the question: what are the microcircuit properties that enable a cortical area, such as the prefrontal or posterior parietal cortex, to subserve cognitive functions by contrast with early sensory processing or motor responses?

Biophysically realistic neural circuit modelling has identified a cognitive-type microcircuit capable of both decision making and working memory.^{47,48} In this model, slow excitatory reverberation generates persistent activity underlying working memory, and gradual temporal accumulation of information about alternative options in decision making. Strong recurrent excitation is balanced with negative feedback mediated by several kinds of inhibitory neurons, which are crucial for the tuning of activity patterns, synchronous rhythms, the system's ability to filter out irrelevant distractors for robust working memory maintenance, and winner-take-all competition leading to a choice in decision processes. Moreover, such a circuit endowed with reward signalling and plasticity can account for learning in adaptive choice behaviour. This

model offers a platform to interrogate how abnormalities at the cellular and synaptic levels might explain cognitive deficits in patients with mental illness.^{8,49}

This finding raises a hypothesis: that canonical microcircuits exist for core cognitive functions such as working memory, selective attention, response inhibition, decision making, or rule-based task switching. If so, understanding each of these cognitive building blocks would provide insights into the underlying biological and computational deficits associated with mental disorders. This perspective breaks boundaries of traditionally defined disease categories, consistent with frameworks such as those provided by the Research Domain Criteria⁵⁰ in the USA or the Medical Research Council Mental Health Review Group in the UK.⁵¹ A further priority is to elucidate how various cognitive building blocks are assembled and deployed in a large brain system to produce flexible behaviour and complex cognition.

Problem 15: A Fokker-Planck equation for the brain

Unifying mathematical theories have had enormous success in science, essentially solving the problems of electromagnetism, gravity, thermodynamics, and particle physics. While each solution takes a particular form, they are linked by deeper principles—such as conservation (eg, of mass, energy) and minimisation (eg, of entropy, free energy). Understanding these deep links was the goal of Hilbert's sixth problem: "To treat in the same manner, by means of axioms, those physical sciences in which already today mathematics plays an important part; in the first rank are the theory of probabilities and mechanics". Likewise, the processes that prescribe the dynamics of the brain's physical states should be governed by a closed set of equations that could be discovered and written down. What might the equations for the brain look like, how will they be obtained, and will they be relevant to psychiatry?

The Hodgkin-Huxley equations, which explain the firing of a single neuron, exemplify the application of mathematics to neurobiology. Do these equations solve neuroscience? The difficulty is that perception, cognition, and action do not generally reflect the activity of individual neurons, but rather the mass action of many thousands of neurons.⁵² Just as the equations of motion for a particle did not solve the problem of diffusion (two centuries separated Newton and Einstein), knowledge of how neurons spike is not sufficient to understand brain function. So the equations for the brain should describe the temporal dynamics of the statistics (mean, variance, kurtosis) of large neuronal ensembles.⁵³ This type of equation is known as the Fokker-Planck equation; it prescribes how stochastic fluctuations and deterministic processes (probabilities and mechanics) interact to yield population-level activity.

Obtaining the Fokker-Planck equation is not as foreboding as one might think. First, the deterministic component can be obtained from physiology: temporal filtering of synaptic activity by dendrites,⁵² waves of

pulses spreading through cortical tissue,⁵⁴ thalamic loops,⁵⁵ and interactions via the connectome⁵⁶ prescribe spatial and temporal terms. Second, the deeper form of the equation—nonlinearities within and between deterministic and stochastic terms—can be inferred by measuring the temporal⁵⁷ and spatial⁵⁸ statistics of cortical activity.⁵⁹ These measurements show that the dynamics reflect periods of weak linear stability interspersed by sudden, unstable transitions,^{60,61} with strongly nonlinear effects amplifying microscopic fluctuations.⁶² Third, increasingly sophisticated inversion methods enable the disambiguation of competing models.⁶³ Despite tremendous progress,^{64–66} deep mathematical challenges remain. It might be sufficient for the community to agree upon a small family of Fokker-Planck equations, until a single generating Fokker equation can be derived.

This mathematical approach has already yielded some clinical success, explaining seizures,^{67–69} cortical hypoxia,⁷⁰ and anaesthesia.⁷¹ However, these successes are largely owed to the gross disturbances in dynamics—visible to the naked eye—that characterise such conditions. In psychiatry, the explananda are probably more subtle. A more definitive translation requires one further logical step: equating the statistics of population-wide neuronal activity with representations of properties of objects in the external world; namely, that the mean states reflect expected value, whereas variance and kurtosis describe the precision of that representation.^{62,72} This step would, in our opinion, link a Fokker-Planck treatment of the brain to the powerful emerging machinery of computational psychiatry.⁹

We thus propose that a priority problem for psychiatry is to base knowledge of cortical function and dysfunction on axioms of brain dynamics: to treat the field of psychiatry in the same manner as other branches of natural science, drawing from the theories of probability and dynamics to discover a Fokker-Planck equation for the brain.

Problem 16: The problems of priors

Any useful understanding of dysfunctional decision making must be grounded in an understanding of functional decision making. The most powerful normative account—Bayesian decision theory—specifies that people should choose actions that optimise their expected future utility, averaging over all their uncertainties.^{73–75} While healthy individuals do an impressively approximate job in matching Bayesian decision theory, in disease it breaks down in three characteristic ways: (1) patients can succeed at solving an incorrectly conceived problem; (2) patients can fail to solve the correct problem; or (3) patients can correctly solve a problem that is an accurate reflection of past experience, but fallaciously characterises the present and future.⁷⁶

The power behind Bayesian decision theory comprises two structurally different sorts of prior. One involves hard-wired (often called Pavlovian) policies,^{77–79} which

circumvent the need for learning what to do in response to demands that can be external (eg, threats to the self or homeostasis) or internal, in the very inferences necessary to make Bayesian decision theory work (eg, the deployment and control of attention, working memory, and planning).⁸⁰ Problems with these policies lead to many instances of type 2 breakdowns. The second is a set of evolving prior distributions or expectations about the self and the world. These also fill in when data are lacking, but in terms of inference rather than action, and thereby affect every aspect of behaviour, including generalisation and exploration, leading to breakdowns of type 1 and 3.

Both sorts of prior, and indeed their rich and complex interactions, merit substantial sustained scrutiny. Prior policies are realised in the most diverse aspects of the neural architecture of cognition—eg, serotonergic neuromodulation, asymmetries between direct and indirect pathways through the striatum, and the organisation of defence in the periaqueductal grey. However, gross and subtle effects abound, and they are only beginning to be understood. A much richer understanding of the nature and use of these priors is essential.

Prior distributions, with their probably intricate hierarchy, are more mysterious still, especially how they are represented in the brain and updated by experience. The effects they have on all the components of Bayesian decision theory need to be understood; particularly, their propensity to admit permanent miscalibration—ie, the processes that maintain the maladaptive expectations about the world that they impose despite the possibility of collecting data that would correct the misconceptions. The most pressing problem is our ignorance of the true prior distribution over environments. This should lie at the heart of all understanding; it is time to collect some statistics.

Problem 17: Understanding psychiatric pathophysiology in terms of the computational processes that underlie inference

Hilbert said that “The organic unity of mathematics is inherent in the nature of this science, for mathematics is the foundation of all exact knowledge of natural phenomena”. There is an argument that one does not need to look beyond Hilbert’s list to find outstanding challenges for psychiatric research: the final item (23: Further development of the methods of the calculus of variations) remains prescient. Variational methods underlie most formal approaches to research in neuroscience—from modelling complex brain imaging data, to understanding neuronal computations. In psychiatry, formal (mathematical) approaches have been promoted as part of computational psychiatry. So why are computational (variational) approaches so important?

To understand psychopathology one has to understand how the brain works. Computational neuroscience offers a compelling answer; namely, that the brain works by inferring the causes of its sensations. Psychopathology

therefore represents false inference (eg, hallucinations are false inferences about the sensorium, delusions are based on false inference about agency, dysmorphophobia can be cast as false inference about the body). The challenge then is to understand psychiatric pathophysiology in terms of the computational processes that underlie inference. This is where the calculus of variations becomes useful; specifically, in approximate Bayesian inference or variational Bayes.⁸¹

A neurobiologically plausible implementation of approximate Bayesian inference (a form of bounded rationality) is predictive coding—a process theory that assigns specific roles to neuronal populations, canonical microcircuits, and hierarchical (extrinsic) connections.^{82,83} So how could this process theory explain false inference? One promising candidate is the neuronal encoding of confidence in the beliefs produced by inference. Psychologically, this corresponds to the salience or precision afforded to sensory evidence,⁸⁴ whereas physiologically it is thought to be encoded by the gain or excitability of neuronal populations.⁸⁵ This accords with concepts like aberrant salience,⁸⁶ while explicitly implicating modulatory neurotransmission in pathophysiology.⁸⁶

Although an example, this line of thinking poses important questions—eg, how do neuromodulators (such as dopamine) conspire with NMDA receptors and inhibitory interneurons to change postsynaptic gain? And how is this compromised in schizophrenia?^{87–89} Is the common (functional) pathway a failure to optimise the balance between excitation and inhibition (ie, gain control)? And can it be measured in terms of fast synchronous neuronal activity?⁹⁰ Crucially, what does the implicit dysconnection mean in terms of false inference? And can it be ameliorated?

Synopsis

Collectively, the problems show the multitude of levels—genetic, synaptic, neuronal, circuit, computational, cognitive, environmental, and social—that require scientific scrutiny for developing comprehensive models of disease. In particular, the bridging principles by which levels interact need to be understood in far greater detail.

In brief, the fundamental twin challenge arising from the problem statements in our list is to develop mechanistic models of mental disease that, first, embody a multilevel representation of disease mechanisms (eg, the effects of specific constellations of genetic and environmental factors on neuronal circuit formation and plasticity, and the ensuing consequences for the computational capacity and behavioural repertoire), and, second, transform these models into diagnostic tools, which enable clinical predictions for individual patients and support a redefinition of contemporary nosology. Clearly, these are formidable problems, which will require a concerted community effort and close interdisciplinary collaborations. We hope that our list will provide helpful guidance and inspiration for this endeavour.

Contributors

All authors contributed to the discussions on which this paper is based or contributed an individual problem statement. AM-L wrote problem 10. EBB wrote problem 11. US wrote problem 12. ECJ wrote problem 13. X-JW wrote problem 14. MB wrote problem 15. PD wrote problem 16. KJF wrote problem 17. KES compiled and mainly edited the paper; MB and KJF did additional editing. The text was subsequently revised and approved by all authors.

Declaration of interests

We declare no competing interests.

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