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Commentary

The Future: Moving from Phenotypically Defined Diseases Toward Pathophysiological Systems

Mark R. Keezer[1,2], Prisca R. Bauer[3] and Josemir W. Sander[2,4,5]

[1]Centre de recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec, H2X 0A9, Canada, [2]Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103SW, The Netherlands, [3]Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Freiburg, University of Freiburg, 79104, Germany, [4]UCL Queen Square Institute of Neurology, London WC1N 3BG, & Chalfont Centre for Epilepsy, Chalfont St Peter, SL9 0RJ, UK and [5]Neurology Department, West of China Hospital, Sichuan University, Chengdu 61004, China

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The traditional approach in medicine is to define diseases phenotypically based on clinically demonstrable signs and symptoms. When our understanding of the nervous system was embryonic, neurological and psychiatric conditions were considered to have the same origin as they commonly co-occur, leading to the historical association of these specialities.[1] As our appreciation for differences in conditions affecting the central nervous system (CNS) increased, the study of "organic diseases" of the nervous system became strictly separated from mental illness. Advances in genetics and neurobiology have shed new light on almost all conditions that affect the CNS. They have provided the basis for attempts at biological treatments, leading to these specialities edging closer to each other. Whether neurology and psychiatry should re-merge is a matter of debate. Notably, newly identified disease markers could lead to novel definitions of neurological and psychiatric conditions based on their pathophysiological underpinnings rather than phenotype and symptomatology.

Despite this increased understanding of pathophysiological processes, we continue to divide diseases into phenotypic categories: mood disorders, movement disorders, epilepsy and cerebrovascular disease, amongst others. This approach has been largely successful due to the fortuitously close association between phenotype and pathophysiology. It is most often pathophysiology that determines, for instance, whether a treatment is efficacious or not. Recognising a migraine headache as distinct from an epileptic seizure allows neurologists to consider prescribing a triptan rather than an antiseizure medication. This symptomatic approach, unfortunately, is fallible. The symptoms are similar but treating a migrainous visual aura will not be like treating an epileptic visual hallucination.

The future of neurology and psychiatry will be different. Our growing understanding of complex disease mechanisms allows diseases to be defined by their multi-factorial pathophysiological underpinnings rather than phenotype and symptomatology. There are recent attempts, for example, to reorient the scientific community to a biological definition of Alzheimer's disease based on biomarkers of neuropathological changes attacking the individual rather than on the clinical manifestations they may (or may not) manifest.[2] The new classification of epilepsy is founded on the concept of potentially overlapping aetiologies which only together produce the final epilepsy syndrome.[3] We propose that the neuroscience community continue this move beyond pure symptomatic classification schemes towards pathophysiological classifications for all CNS disorders, including psychiatric conditions.

We propose that neurological and psychiatric diseases can be divided into seven interacting pathophysiological spectra: degenerative, functional, structural-connective, infectious, metabolic, toxic/nutritional deficiency and immune/inflammatory (Table 1 and Figure 1a). We have chosen to use the term spectra to emphasise that these categories exist in gradations between individuals. In addition, they are not mutually exclusive, and a single disease or process may belong to several ranges. Cerebral trauma, for example, is an interaction between structural (from the cerebral contusion) and inflammatory processes.[4] This potential to interact is critical, as one spectrum's presence and gradation likely influences others at play in an individual. Such complex system interactions are increasingly emerging as central to all areas of biology and medicine.

Understanding the pathophysiological spectra involved in neurological or psychiatric disease, however, is insufficient to entirely understand why the same condition results in different clinical manifestations in other individuals. Such an understanding requires moving beyond a disease-oriented focus toward a systems approach. The CNS responds to injury or disease activators differently depending on their interactions with other factors. Complex system interactions emphasise a move away from the individual organism, organ, molecule, gene or disease. They instead focus on how different entities interact with each other and their environment to result in the final system function (or dysfunction).[5] Systems approaches emphasise that various factors can mutually influence each other in feedback loops instead of simplistic

Corresponding author: Ley Sander, Box 29, UCL Queen Square Institute of Neurology, London WC1N 3BG, UK. Email: l.sander@ucl.ac.uk

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Table 1: Definitions of pathophysiological spectra

Interacting pathophysiological spectra	Definition
Degenerative	Related to a progressive deterioration in the function of the nervous system, often in association with the accumulation of an abnormal molecule within neurons, usually proteins (e.g., alpha-synuclein or tau).
Functional	Related to a disruption of normal neurophysiological function, often paroxysmal (e.g., migraine or epilepsy).
Structural	Related to a physical lesion that impairs the normal function of the nervous system (e.g., neoplasm or trauma).
Infectious	Related to an infectious and self-replicating agent (e.g., viral encephalitis or bacterial meningitis).
Metabolic	Related to the individual's synthesis, storage or energy consumption, often involving enzymatic processes (e.g., mitochondrial diseases or porphyria).
Toxic/nutritional deficiency	Related to the accumulation of an exogenous and substance harmful to the nervous system (e.g., animal venom or heavy metals) or the lack of an essential nutrient (e.g., vitamin B12 or zinc deficiency)
Immune/inflammatory	Related to the immune system activation (e.g., limbic encephalitis or multiple sclerosis).
Modifiers	
Genome and methylation status	Epigenetic changes allow for the external environment to influence the phenotypical expression of the genome.
Stage of CNS development	Also incorporates neuronal plasticity (which is intimately related to mental health and frailty)
Internal environment	Proteomics, metabolomics and other ~omics, general physical and mental health.
External environment	These include social factors such as education, income, family support, biological factors such as air/water pollution, and medical and surgical interventions that a person may be exposed to. This can in turn influence the three modifiers described above in a circular manner.

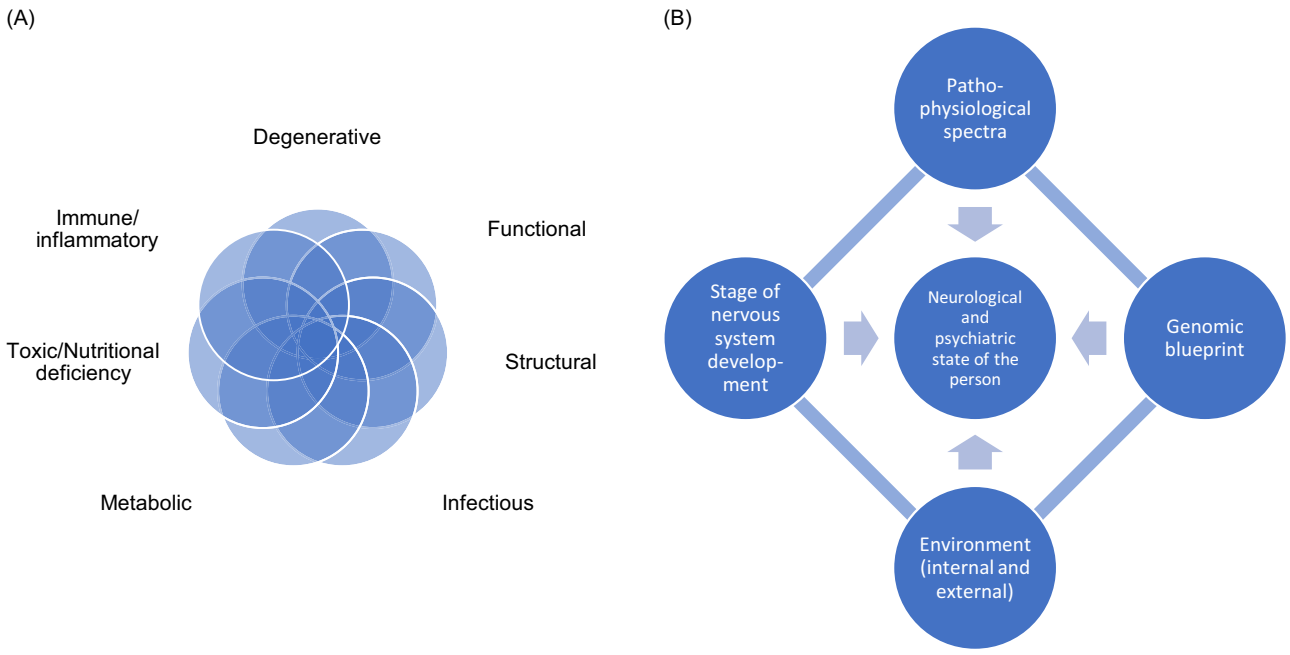

Figure 1: (A) The pathophysiological spectra for neurological diseases. (B) The modification systems that affect the neurological state of an individual.

mono-linear cause–effect relationships. To understand complex diseases, successful collaborations with multiple disciplines in systems biology, using informatics and mathematical models informed by philosophy, will allow us to understand molecular pathways and circular feedback loops and the clinical presentation in a person and the population. This would align with other contemporary attempts, notably in psychiatry, to develop further the Biopsychosocial model introduced in the 1970s, to account for complex feedback loops, learning and plasticity.[5,6]

We propose that these factors working outside of the interacting spectra be referred to as modifiers (Figure 1b). These are the mechanisms determining the clinical presentation in an individual and "system", given the potential for myriad and complex interactions between these systems and the pathophysiological spectra. We

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propose that these modifiers be divided into the individual's genome and methylation status, the stage of nervous system development, the internal environment (proteomics, metabolomics and other ~omics, but also psychological factors) and the external environment (including social and biological factors such as pollution and global warming).

The interplay between spectra and modifiers will determine the disorder's characteristics in an individual. Hippocampal malrotation, for example, is a congenital malformation generally asymptomatic; however, it increases the risk of febrile status epilepticus in some young individuals.[7] It has been suggested to increase the subsequent risk of hippocampal sclerosis and mesial temporal lobe epilepsy. Epigenetic changes modify gene expression through DNA methylation, histone modifications and microRNA regulation.[8] Epigenetic changes are a clear means for the external environment to influence the phenotypical expression of the genome. They can explain symptomatic differences between individuals in response to their environment and changes in phenotype in the same individual with increasing age. Multiple sclerosis starts as an inflammatory disease, but there is evidence of genetic risk factors, in particular variants within the human leukocyte antigen complex and that these interact with environmental stimuli such as Epstein Barr virus exposure, smoking and adolescent obesity.[9]

Advances in understanding the human CNS allow for increasingly pathophysiology-based organisations and classifications of neurological and psychiatric diseases. Going beyond this, we propose that systems relevant approaches will deepen this understanding. We present a view where the complex interactions between pathophysiological spectra and modifiers (including general physical and mental health and the environment) are needed to understand the disease state of an individual. An emphasis on the biological-systemic underpinnings of illness will allow for more refined hypotheses regarding targeted interventions. Other areas of medicine are moving toward personalised approaches, tailoring treatment and interventions to the individual, thus improving care and increasing the chances for cure. We are hopeful that a biological-systemic approach will also encourage personalised care in neurology and psychiatry.

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