Edited by
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Systems Biology in Psychiatric Research

From High-Throughput Data to Mathematical Modeling

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Foreword

Our mental activities are obviously results of very complex and dynamic systems. Systems biology has been mostly concerned with understanding cellular systems as well as disease states of human beings. Insufficient attention has been paid to linking our understanding of molecular systems and psychology. This book embarks on challenges of paving the ground for systems biology of psychiatry. While effects of molecular level perturbations on neuronal activities are actively investigated, mostly in the context of molecular neuroscience, framing such research in the context of psychiatry is a novel enterprise. At the cellular level, challenges of systems biology are not only on computing, but also on obtaining well coordinated and quantitative data so that precision of the model can be improved and verified. Quantitatively describing and measuring psychiatric observations in a proper manner is a true challenge. At the same time, introduction of systems biology into psychiatry may require a new level of understanding, as modeling efforts may force psychiatrists to describe the subject more quantitatively and with broader coverage. Dynamic models have to be calibrated using data supposed to exist. Systems biology of psychiatry entails a whole new set of problems that are even more difficult to solve. This book marks the beginning of a long journey.

Bon voyage
Tokyo, February 2010

Hiroaki Kitano

Contents

Preface

Mentally ill individuals frequently report abnormal experiences such as hearing voices of absent persons. Although this is taken as a subjective report on a dysfunctional mental state, modern psychiatry increasingly conceives mental disorders as brain disorders. This view is strengthened by the increasing influence of the biological sciences on psychiatry. However, the reduction of mental states to brain states has not been successful until now. Therefore, from a clinical perspective, it is important to keep these two points of view apart. This issue of philosophy of mind is covered in the introductory section of this book.

Nevertheless, biological psychiatry has provided so much new information about brain processes related to mental illnesses that explanatory concepts have to be developed to put these pieces of data together into a conceptual framework of brain function and dysfunction. These attempts to construct systemic relations between biological processes in brain areas or between molecular processes within neurons usually end up in graphical diagrams with boxes and arrows that might be called qualitative models.

In the wake of cybernetics and systems theory, analogies between brain and electrical circuits have already been drawn and very early on in the 1950s, computer-based models were constructed to insert neurobiological data into the framework of artificial neuronal networks. To achieve these tasks, a great deal of mathematics had to be applied – a field disliked by many physicians and biologists. Those network models were elaborated on the basis of electrical signals, spikes from single neurons, and global brain currents, which are recorded by the electroencephalogram. Despite great progress made in the development of mathematical tools of signal analysis, the main question remained focused on the detection of local distribution patterns of synchronization or desynchronization of various frequencies in brain currents.

The beginning of the twenty-first century marked the advent of a new strategy in molecular biology and genetics termed “systems biology”. Systems biology tries to tie together experimentation and building of theoretical models in a dialectic mode. This new approach fits very well with the present focus of biological psychiatry – the analysis of the genome and proteome. There is also an urgent demand in

pharmaceutical companies to better understand mental disorders on the molecular biological level for the development of new and more efficient substances for psychiatric treatment. Many drugs used in clinical practice do not fulfill modern standards of specificity and low unwanted side-effects. It seems to be timely to join the rather new field of "molecular psychiatry" with systems biology. There are presently not many conferences, publications, student courses, or other academic activities that try to connect molecular psychiatry and neurobiology with systems biology. To this end, we have organized several interdisciplinary workshops devoted to the advancement of "computational neuropsychiatry" and "systems neuropsychiatry."

In this book, we try to put together some recent developments in specialized fields of systems biology in psychiatry. We hope that one or more of the chapters will raise the reader's interest and curiosity to read further in other publications. We also would like to direct the reader's attention to some basic concepts and findings of psychiatry, and to methodological approaches from computational sciences that permit us to build computational models of disorders of brain functions. This may lead to the design of new types of experiments that explicitly take into account hypotheses on a systems level.

Munich, Mannheim, and Düsseldorf
February 2010

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Part One
Introduction

Part I presents an introduction to the basic issues of psychiatry. Chapter 1 on philosophical aspects by Felix Tretter delineates some aspects of the historical development of science and philosophy. Focus is on philosophy of mind, philosophy of science, and "neurophilosophy" – special fields of fundamental importance for reflection of psychiatry, its concepts, its methods, and its theories. This chapter also describes the rise of philosophy in biology and systems biology.

The second basic chapter, Chapter 2 by Felix Tretter and Peter Gebicke-Haerter, gives an overview on general psychiatry, beginning with an introduction into the methods, diagnostics, and therapy of mental disorders. The main part is an introduction to the neurobiological basis of modern psychiatry. Brain anatomy, cellular physiology, and molecular mechanisms are briefly outlined, and examples are given by referring to findings in schizophrenic patients. Finally, first attempts at computational modeling are presented, mainly with respect to working memory functions in schizophrenia.

Subsequently, in Chapter 3, Marvin Schulz and Edda Klipp provide a brief but comprehensive outline of systems biology from a biochemical point of view. The reader will find methods used in the "wet" laboratory of biochemists and also methods from the "dry" laboratory of computational scientists.

Chapter 4 provides an overview by one of the pioneers of systems biology, Denis Noble. From his seminal work on the heart, he extends the view to systems biology of the brain. He also includes a brief outlook on the philosophical dimension of his research project.

1
Philosophical Aspects of Neuropsychiatry

Felix Tretter

> Mental disorders are brain disorders.
>
> [after Griesinger, 1882, 1845]

Psychiatry as the science of mental disorders must integrate biological, psychological-clinical and social data and aspects. This implies several philosophical problems that are usually overlooked. First, biological psychiatry aims to relate mental phenomena to brain phenomena. This is a fruitful effort, but it might end up in a vision of total reduction and substitution of mental phenomena to brain mechanisms. Regarding this tendency in research, several philosophical restrictions have to be considered:

- *Philosophy of mind* presents several limitations of identifying the mind with the brain that might relate to clinical psychiatry. One basic limitation is related to the reductionistic aim to substitute the subjective experience by categories of brain research. It is also not sufficient to reduce consciousness to the physicochemical properties of neurons (the "emergence problem").
- *Philosophy of science* presents results of the analysis of the history of concepts and methods of physics that should also be considered. In that respect it is to be determined if brain correlates "explain" mental disorders. In a philosophical sense, "explanation" means the application of general laws to specific cases. This is more than description by observational data because explanatory propositions imply logical operations. In addition, the part–whole problem tackles the consistent understanding of the brain by detailed knowledge of the behavior of molecules. This is important if one considers that systems biology aims to create a computer-based model of the cell. For this project mathematics plays a crucial role. Taking into account that psychiatry depends on the methods and results of numerous academic disciplines it seems to be interesting to establish the new field of "neurophilosophy." Such a platform seems to be very important when studying the effects of molecules on mental states.

1.1
Development of Research Paradigms and Strategies in Psychiatry

At the early times of scientific psychiatry, about 100 years ago, clinical practice dominated the knowledge of psychiatry. Psychiatrists could only observe human behavior disorders and describe them verbally. Case studies were used to characterize the different disorders. At that time the explanations of the causes of mental disorders were very speculative. One approach was to explain mental disorders as a consequence of sins. Only a few therapeutic tools were available, and it is well known that therapeutic chairs with restraints of body movements and shock treatments were very usual from that time up until the 1970s. In the 1950s psychoanalysis also became influential and therefore psychological mechanisms were claimed to be the causes of mental disorders.

Little by little, psychiatry was established within medicine as a natural science of mental disorders. This took quite a lot of time (see Chapter 5 by Kawohl and Hoff). Emil Kraepelin was maybe the first to establish psychiatry as a science concerned with the quantification of psychic functions and states (Kraepelin, 1902). He was interested in measuring the cognitive performance of psychiatric patients compared to normal subjects, as was proposed by Wilhelm Wundt when starting experimental psychology (Wundt, 1896). In this situation, Kraepelin was also trying to distinguish the different forms of madness by objective criteria. As a consequence, Kraepelin identified different disease entities such as "dementia praecox" and "depression" (Kraepelin, 1902). Dementia praecox was subsequently named "schizophrenia" by Eugen Bleuler (Bleuler, 1911). Later, diseases such as Alzheimer's disease, anxiety disorders and addictions came into the catalogue of psychiatric disorders (Sadock and Sadock, 2007). Details of the history of psychiatry are presented in Chapter 5 by Kawohl and Hoff.

Increasingly, the tools of natural sciences as they were established in medicine were also applied in psychiatry from the 1930s. As a consequence, neuropathology and genetics were already developed before World War II. After the war, the diagnostic tools were improved, and rating scales and operational definitions were established. The severity of a disease could be "measured" by objective and/or subjective rating scales. In the 1960s, animal models for mental disorders were additionally developed, and more data were obtained by using neurobiological experiments (e.g., from the brains of socially deprived animals modeling depression).

After several decades of psychological psychiatry from the 1960s to the 1990s, mental disorders were related more and more to their biological roots. The main reasons were several observations:

- The induction of psychosis by brain disorders such as infections and by drug consumption.
- The clustering of mental disorders in some families that indicated heredity.
- The treatment effects of some pharmaceuticals.

At present, the dominating research paradigm in psychiatry is the research strategy of neuropsychiatry and biological psychiatry (Andreasen, 2004).

The aim of neuropsychiatry or biological psychiatry is to relate mental phenomena to brain phenomena. This approach was already initiated by Wilhelm Griesinger

(Griesinger, 1882, 1845) who stated that "insanity is merely a symptom complex of various anomalous states of the brain." He also coined the phrase "Mental disorders are brain disorders" used as the opening quotation in this chapter. Methodologically, experimental and clinical brain research focused on imaging, electrophysiology, histology and molecular biology studies. Today, from brain downstream, over neuronal circuits and local networks, the neurons and their molecular structures are studied in order to identify pathologies. By the development of electrophysiological methods such as electroencephalography (EEG) and various imaging methods, brain correlates of mental disorders were identified that suggested that the brain is the organ that can "cause" or "produce" mental disorders. For instance, progress in molecular biological methods has helped to identify genes that could be candidates for the causation of schizophrenia. However, this approach has not succeeded in "explaining" schizophrenia. It also has to be assumed that only the symptoms, not the time-course, of schizophrenia can be "explained" by molecular biology. Additionally, rather than molecules alone, both cells and cellular networks must be identified to explain the symptoms. Presumably, only processes at circuits of local cell assemblies can be the basis of understanding symptoms of mental disorders.

We are now in the situation where the classification of mental disorders established by international classification systems such as the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (WHO, 1992) or the *Diagnostic and Statistical Manual of Mental Disorders*, text revision, 4th edn (American Psychiatric Association, 2000) are being criticized again – some authors suggest that the symptoms, the signs, or the so-called "endophenotypes" that are related to neuroscience should be the focus of reference (Hyman, 2007). The new classification system, the 11th revision of the *International Statistical Classification of Diseases and Related Health Problems*, will have to integrate several new radical points of view that are partially based on biological data that were obtained by the study of mental illness (see Chapter 5 by Kawohl and Hoff).

Additionally, some neuroscientists suggest that phenomenological terms should be avoided in the scientific context and should be substituted by neurobiological terms (Crick, 1994). In this view, psychiatric examination can be described as the "behavioral examination of the brain" (Taylor and Vaidya, 2009, p. 56). However, it is not proven that contents of experience such as hallucinations can be completely represented by behavioral observations (Kim, 1998). Regarding this philosophical issue, this behavioristic position is related to the origin of reductionistic "neurophilosophy" – a term that has been used by Patricia and Paul Churchland, for instance, since the 1980s (Churchland, 1986, 2007).

1.2
The Mind–Body Problem – Philosophy of Mind

Everyday experience provides evidence that we are awake and consciously living organisms, subjects, persons that can initiate and inhibit motor behavior by thoughts. This (self-)experience suggests that the so-called "mind" can control the body. Most

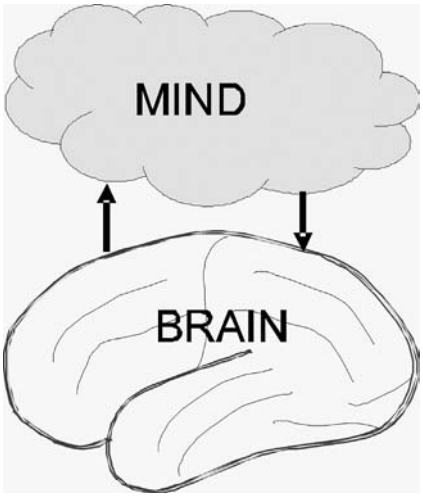

Figure 1.1 The basic problem of brain and mind – who controls whom?

individuals have also experienced that alcohol can change the mind. Therefore, it is evident that a drug that is in the body can influence the mind. Here, "mind" means mental states and processes such as conscious experience, thinking, feeling, planning, imagination, desires, and so on. These experiences have been known since the ancient Greek philosophers, and therefore the "mind–body problem" has a very long tradition in the history of our philosophical and psychological concepts (Figure 1.1). It was resolved in a dualistic conception in the sense of Rene Descartes until recent years, when neurobiology showed much progress in studying mental processes. These findings started a wave of monistic conceptions that claim that the mind is just a function and a state of the brain, and that there is no special entity that can be called the "mind," "soul," and so on (Place 1956; Block 1980; Churchland 1984; Chalmers 1995).

This discussion is important for neuropsychiatry and therefore some basic aspects are mentioned here. Recommended interesting textbooks on the philosophy of mind are Heil (2004), and on neurophilosophy are Bennett and Hacker (2003) and Northoff (2000, 2004).

In principle, only a few main positions can be distinguished in the brain–mind debate (Figure 1.2):

i) The brain controls/produces the mind (*materialism*, *physicalism*, *epiphenomenalism*, *supervenience*; e.g., Churchland, 1981, 1984; Kim, 2002). This concept has growing influence at present and it is preferred by most neuroscientists.
ii) The mind controls/influences the brain (*mentalism*, *idealism*). This most traditional position is supported by the everyday experience that I can move my hand if I intend to do it. Traditional philosophical idealists think that the world and also the brain are the result of the action of a distinct mental entity. This position is hard to combine with views of natural science.

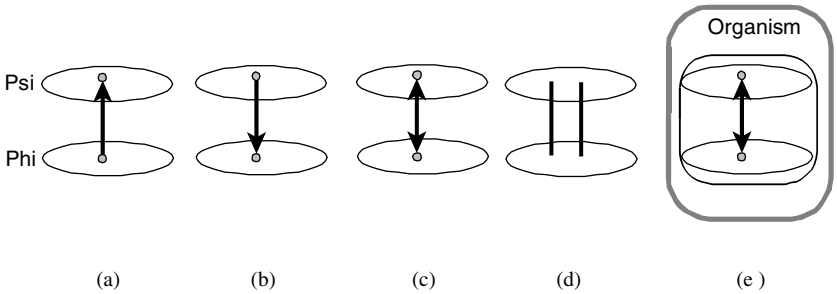

Figure 1.2 Five main concepts of mind brain relations. (a) The brain produces and/or controls the mind. (b) The mind controls the brain. (c) There are interactions between the brain and mind. (d) The mind is identical with the brain. (e) The brain/mind is an organ/function of the person/organism.

iii) The mind and the brain interact and influence each other (*dualism*; e.g., Popper and Eccles, 1977; Libet, 2005). This position is quite common, with difficulties of explanation of downward causation (Walter and Heckmann, 2003). In scientific psychology and psychiatry, interactive dualism has reached a wide acceptance; at present only aspect dualism or property dualism are proposed based on the difference of methods of studying the brain.

iv) The mind is the brain and the brain is the mind (*identity concept, materialism, monism*; Churchland, 1981; Davidson, 1970). Owing to reasons of logic, this concept was preferred in the professional debate since the activities of the Vienna Circle (Stadler, 2001). The psychological terms should be eliminated and substituted by neurological terms (Carnap, 1928, 1932). However, this position also has logical difficulties.

v) The brain is the organ of the person, of the subject (*phenomenology*; McGinn, 1989). In the traditional concept of phenomenology, the experiencing subject is the frame of reference so that the brain is only an organ of the whole.

The most interesting question in the brain–mind debate is (Chalmers, 1995; Jackson, 1982): what is the mind? The presently preferred answer is: it is a (dispositional) property of the brain. However, what is the brain? This question is not trivial, in such a way that the question of the nature of matter is interesting: if matter is mass then matter is, according to Einstein's famous equation, the ratio of energy divided through the squared speed of light. In this view, a trivial understanding of matter is not sufficient (Levine, 1983).

At present, many neuroscientists claim that the mind is only an epiphenomenon of the body (respectively, of the brain). In this view, the mind is similar to the piping of the steam locomotive – it is the product of the brain, but it cannot influence the producer (Crick, 1994; Edelman and Tononi, 2000)! Additionally, many experts in the field of the mind–body debate claim that there is no ego and no self (Bennett and Hacker, 2003; Metzinger, 2009). Also, consciousness is supposed to be a "mirror" that can only "represent" some actions of the brain. But what is the mirror?

1.2.1 Monism and Dualism

The mind, in a preliminary definition, is approximately equivalent to subjective "experience," and is a phenomenon that can be expressed directly only by living organisms and that – with regard to consciousness – can be ascribed to "subjects" (Davidson, 1970; Jackson, 1982). From a scientific point of view, mental functions and activities must be expressed in functional terms that are characterized usually by "if–then" relations and that represent the typical input–output relation or black box perspective (Block, 1980; Putnam, 1965). This is obviously not completely possible if a system exerts "spontaneous" (i.e., intrinsically conditioned) behavior.

In his historical paper "What is it like to be a bat," Thomas Nagel has shown that it is nearly impossible to identify or substitute observations that are made by a subject by observations that are made by a brain researcher (Nagel, 1974). This is known as the basic problem of the complete substitution of the "subjective" first-person perspective by the ("objective") third-person perspective of science (Levine, 1983; Shoemaker, 1996).

In contrast, the monistic position is closely related to identity theory (Section 1.2.3) and denies the functional relevance of mental events. This position says that there is only a brain that is relevant for mental processes that are epiphenomena. Some authors state that mental states are illusions of the subject or of the brain (Crick, 1994; Dennett, 2006). Only a few famous neuroscientists such as Benjamin Libet are at least methodological dualists (Libet, 2005).

The experimental bases for monistic positions are seen in the experiments testing the "free will" that were conducted by Benjamin Libet (Libet *et al.*, 1983). By recording EEG signals, these experiments gave evidence that decisions made by a subject occur about 300 ms prior to their conscious intentions to act. However, the subjects have to be trained to participate in these experiments so that they only execute a trained reaction to a special experimental situation and do not exert a free will that is related to a personal important event such as a marriage, buying a car, and so on. For this reason, from a methodological point of view, it is not conclusive to propose that the mind cannot influence motor actions and to substitute the terms for mental phenomena by terms for brain phenomena.

This controversy between monists and dualists is very complicated as not only the concept "mind" cannot be defined easily and directly, but also the concept "brain" is not as clear as it seems. This is important, because a precise definition must be presented in order to enable a precise discussion. It must also be kept in mind that the brain is necessary for mental states and processes but it is not a sufficient condition for them. The mind cannot be expressed in kilograms or cubic centimeters as properties of the brain, and also localizations of functions are very limited – we have about 40 areas for visual functions and many areas such as the striatum have many functions. Also, the cerebellum is not involved in conscious processes, so the "brain" is a different category too global. Mental states, on the other hand, are cognitions, emotions, memories, drives, and so on. These states and processes differ quite markedly. Finally, there is no strong correlation between intelligence and brain size or brain weight.