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.

Systems Biology in Psychiatric Research.
Edited by F. Tretter, P.J. Gebicke-Haerter, E.R. Mendoza, and G. Winterer

ISBN: 978-3-527-32503-0

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.

Systems Biology in Psychiatric Research.
Edited by F. Tretter, P.J. Gebicke-Haerter, E.R. Mendoza, and G. Winterer

ISBN: 978-3-527-32503-0

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

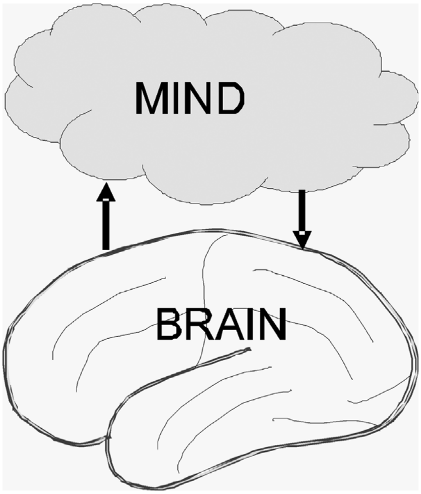

Figure 1.1 The basic problem of brain and mind – who controls whom?

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.

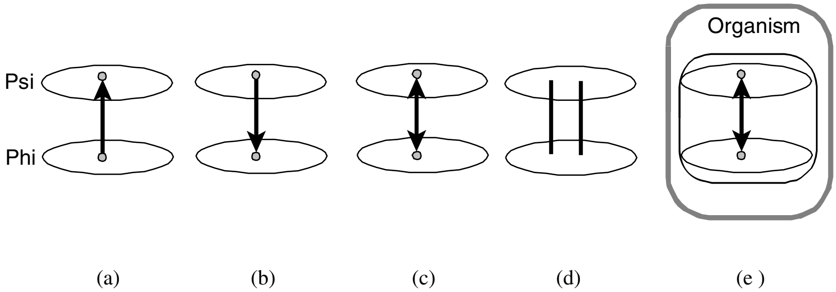

Figure 1.2 Five main concepts of mind brain relations. (a) The brain produces and/or controls the mind. (b) The mind controls the brain. (c) There are interactions between the brain and mind. (d) The mind is identical with the brain. (e) The brain/mind is an organ/function of the person/organism.

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.

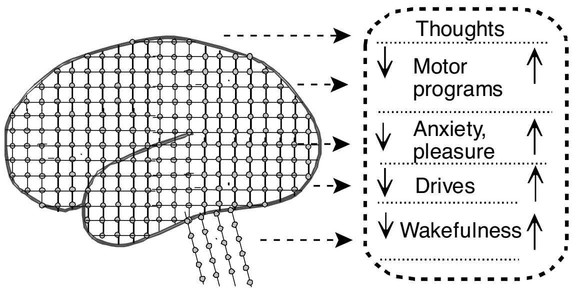

Figure 1.3 The brain as a network of neurons and some inter-related mental functions.

Therefore, a simple brain–mind relation obviously cannot hold. For the reasons mentioned above, regarding complexity and connectedness, the perspective that conceives the brain as a network and the mental to be a system seems to be more appropriate (Figure 1.3). These aspects have not yet been discussed sufficiently and, therefore, we do not have a "solution" of the brain–mind problem at present.

1.2.2 Correlation

Psychological measures and physiological measures, in a first step, can only be correlated. However, the identification of "experiences" with electrical brain signals is problematic. For instance, many brain signals are analog signals, whereas mental events such as a thought, a perception, a recognition, a memory, or a decision are sudden mental events that can be interpreted as digital signals (Figure 1.4). This can be seen in the discussion of the experiments of Libet mentioned above that were performed to determine the temporal structure of volitional processes (Libet *et al.*, 1983). The punctual decision was experienced later than the deviation of the averaged EEG signal from the reference line. In this way, discrete phenomena of single units (action potentials of neurons) can induce qualitative new properties if they are seen as phenomena of a collective of units (field potentials) and as population phenomena: the degree of coherence or coincidence of discharge of single units can determine the coding properties of the activity of these neuronal elements (Freeman, 2000, also see Chapter 6 by Freeman).

1.2.3 Identity Theory and its Problems

One of the leading concepts in the brain–mind debate is the concept of the identity of the brain and mind (Lewis, 1966). From the point of view of some philosophers, the "same" properties of the mind and the brain justify the assumption of an identity. However, a light sensation is not the same as an electrical brain event, just as not every electrical brain event is related to a light sensation. Obviously, this position has its limitations. However, there is a striking advantage – by considering identity theory,

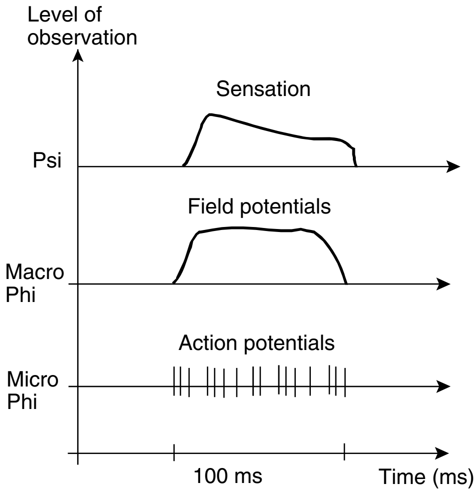

Figure 1.4 Relations of psychophysical observations – sensations as continuous processes (analog signals) are related to discrete events of neurons. Even if the time–activity curve is similar, how are these signals correlated and is there an "identity?" This problem is already given when micro events (action potentials) are related to macro states of a neuronal network (field potentials).

the question regarding the ontological quality of brain and mind and the nature of the relation between brain and mind can be resolved in principle. See Figure 1.5.

However, regarding the identity concept, it becomes clear that not only the mind is loosely defined, but also the term "brain": Northoff (2000) shows that it is important to distinguish between the structural brain, the functional brain, and the mental brain. The structural brain, for example, also refers to the cerebellum that usually is not seen as an important structure for conscious processes as it seems to be concerned mainly with motor coordination. Therefore, it should be declared what kind of function the cerebellum has. The functional brain is that part of the brain that has well-defined functions such as automatic habitual behavior, which is organized in subcortical structures or conscious experience that requires highly interconnected neuronal networks. The mental brain is that subsystem of the total brain that is related to mental functions.

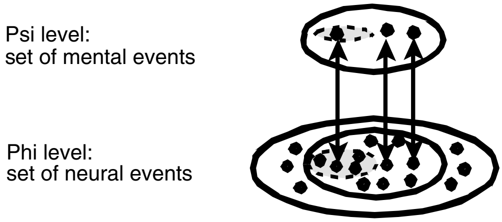

Figure 1.5 The problem of identity relations between mental events (Psi level) and neural events (Phi level).

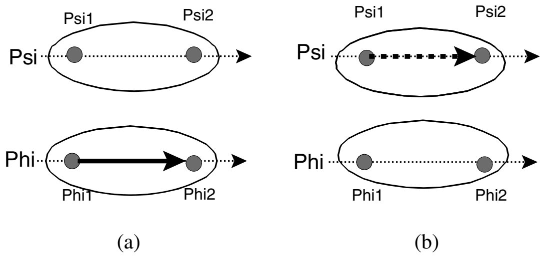

Figure 1.6 Parallel causality in the physical level (Phi) and in the mental level (Psi) and in between.

1.2.4 Causation

The everyday experience that I can move my limb if I want raises the concept of a mental power that can control the physical. An extreme position in philosophy of mind assumes that the mind controls the brain that controls the body. However, in this concept the mind is understood as an immaterial entity. This implies the problem that it cannot be explained how an immaterial system can cause processes in a physical system. As a result of this difficulty, most neuroscientists reject mentalism and prefer a monism that identifies the mind and the brain. However, it is not possible to eliminate the methodological difference between subjective experience (first-person perspective) and objective scientific observations (third-person perspective), so that total reductions of mind onto brain are not conclusive. See Figure 1.6.

1.2.5 Supervenience

The supervenience concept is a very sophisticated concept of duality that says that the mind "supervenes" the brain, meaning that there is a special entity that is influenced by brain processes, but that has no influence on brain processes (Kim, 1998). It says that several brain processes can influence a mental event, but no two mental events can be caused by the same neural event. Supervenience is not saying that "the mental is the physical," but it assumes that the mental is caused or produced by the physical brain (Kim, 2002). Noting that different physical conditions can cause identical mental events ("multiple realization"), several critical arguments against the identity thesis are answered (Figure 1.7).

1.3 The Conditions of Scientific Knowledge – Philosophy of Science

Some philosophers have tried to analyze the structure of science. This specialized approach is usually called the "philosophy of science" or "metascience" (Bunge, 1998) and first attempts at a philosophy of science of psychiatry have already been made

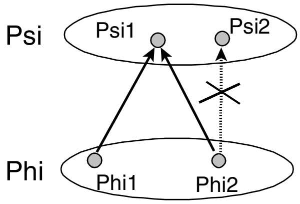

Figure 1.7 Scheme of the "supervenience" concept – multiple possibility of the physical causation of psychological events. A psychological event Psi1 can be generated by two or several physical events Phi1, Phi2, and so on; however, a Phi event (e.g., Phi2) cannot generate two Psi events; or a Psi event can be generated by different Phi events, but a Phi event can only generate a specific Psi event.

(Cooper, 2007). The main subject of these studies was physics. Mainly in the 1920s, theoretical physicists such as Albert Einstein, Niels Bohr, Werner Heisenberg, Erwin Schrödinger, and others, generated a discussion that was devoted to metaproblems of theoretical physics: Is light matter or a wave? What does measurement mean? Is measurement independent of the observer? Is quantum physics the basis that the universe is developing in an undetermined way? Is the world a set of stochastic events?

One controversy was between researchers that focused on experimental research (empiricists) and others that focused on theoretical research: experimentalists, for instance, claim that we need more data in order to understand the functions and dysfunctions of the subjects that are studied. Theoreticians, on the other hand, criticize that we do not see the wood because of looking at the trees: observation without theory seems not to be possible.

One main center of this metascientific discussion was the Vienna Circle of the 1920s with Rudolf Carnap, Karl Popper, and others (Stadler, 2001). For instance, this group discussed the difference of observations and theory. This discussion is still ongoing as observations imply a theory of observation and as theories need empirical terms in order to be tested. In the meanwhile, many meta-analyses were performed regarding these problems. Some of the philosophical results can be used as guidelines for a metatheory of biology and also of biological psychiatry. In recent years, biology and philosophy have cooperated increasingly (Sober, 2000; Boogerd *et al.*, 2007). This will be presented briefly later.

1.4
Experimental Research – From Observation to Theory

For experimentalists, the field of theories is disliked. In discussions it is very often said that we do not have enough data to build theories and, in some cases, theory is called "speculation." Such a position, from a view point of the philosophy of science, is not appropriate, because how do we know at which time we do "know enough?" Who knows why and when we should start to build theories? Is observation possible without theory? Furthermore, what do "understanding" and "explaining" a phenomenon like mental disorders actually mean?

Many experimentalists think that (experimental) research means to put questions to "nature" and obtain answers. Often, answers raise more questions that require more data to understand the functions of the system under study (e.g., the brain). Usually experimentalists understand their work as data collecting and hypothesis testing – they have observations, then they formulate a hypothesis, and then they set up a new experiment in order to test the hypothesis. A hypothesis is a proposition that states that an observation is not a random deviation from a reference value, but is a systematic variation (difference hypothesis). Another type of hypothesis should clarify if the observable is the result of the action of another conditional variable or not (causal hypothesis). The hypotheses are tested by experimental set-ups and by statistical analysis of the observed values of the measured variables. By variation of conditions the results of experimentation allow us to make the hypothesis more precise. In early stages of research only qualitative measurements and hypotheses are possible, whereas in stages of more sophisticated experimental research large quantitative databases are obtained. In principle, the cycle of empirical research (i.e., observation, hypothesis, experiment, observation, new hypothesis, etc.) seems to iterate in an endless cycle, suggesting that there is no need for theory (Figure 1.8). However, any observation implies theory, for instance regarding criteria whether the observation is "true" or an artifact (e.g., theory of measurement and theory of errors). Experimentalists often state also that they do not need "theory." In this context, it should be kept in mind that, for instance, even simple hypotheses are based on theoretical assumptions that are very often implicitly integrated into the hypothesis: any observation is based on a theory of measurement. When measuring some

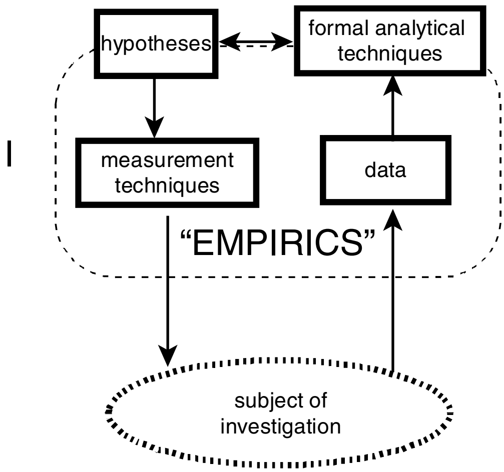

Figure 1.8 Cycle of empirical research (I, "empirics"; Tretter, 2005; Kell and Knowles, 2006). Observations and databases induce the formation of hypotheses that can be tested by specific experimental set-ups and measurement techniques.

phenomenon, it is assumed that the respective measure is an indicator for the respective phenomenon, such as a clinical symptom.

This antitheoretical position is similar to that of the logic empiricism as it was designed, for instance, by Rudolf Carnap (1928, 1932). In Carnap's view, psychology should be reduced to physics. At present, we have to state that this program has not succeeded.

1.4.1 Hypotheses and Theory

In this context it has to be mentioned that hypotheses are propositions that relate different observations to each other. Therefore, a set of hypotheses can be classified as a theory, especially if "explanatory" hypotheses are included. Explanatory hypotheses can be recognized if they are constituted by the word "because." In this case it is referred to a general law (Hempel and Oppenheim, 1948; Hempel, 1965). Also, the distinction between empirical propositions and theoretical propositions is not clear-cut. Therefore, even hypotheses are theoretical propositions that can be tested empirically. Theories can also be understood as (complex) hypotheses. In this view, several connected hypotheses can be understood as a "theoretical framework" (Bunge, 1998). See Figure 1.9.

Science is not only based on experimental (or at least observational) data, but also has a field that can be called "theoretical research." Theoretical research is not "speculation," but it has its own methodology of reasoning and theory building, as will be demonstrated later.

Regarding these aspects, we can note the gestalt psychologist Kurt Lewin: "There is nothing more practical than a good theory" (Lewin, 1952, p. 169).

1.4.2 The "Epistemic Cycle"

There is a reciprocal inter-relation between theory and experimentation. A theoretical proposition must be tested empirically again by experiments. Then, additional propositions can be made that could be integrated into the theoretical framework of the respective research field. For this reason experimental work does not only encompass observing and measuring alone, but also implies thinking and theory

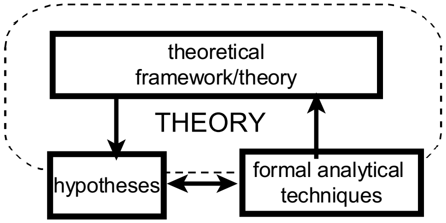

Figure 1.9 Theory, analytical tools and theory-derived hypotheses.

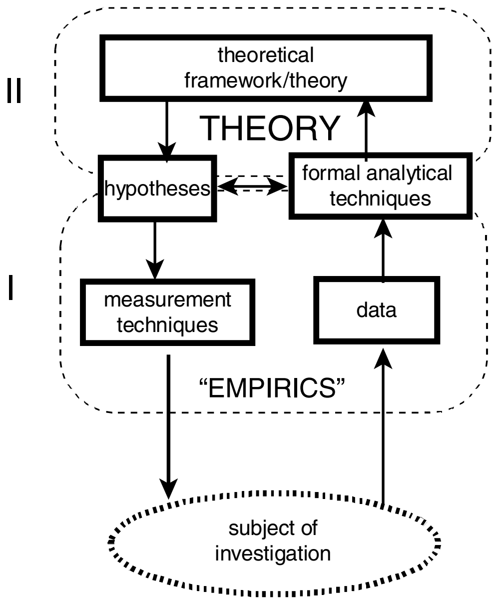

Figure 1.10 The cycle of scientific knowledge with two subcycles between empirical research (I, "empirics") and theoretical research (II, "theory"; Bunge, 1998; Tretter, 2005; Kell and Knowles, 2006). Empirical data have to be related to a theoretical framework (model, theory) by complex data analysis that can be tested by computer experiments and that again can induce gathering of new data.

formation. This interplay between experimental research and theoretical research can be demonstrated by examples in the history of physics (Newton, 2007).

Several terms have been coined for this process, like the "epistemic cycle of research" or "research cycle" or "knowledge cycle" (Bunge, 1998; Tretter, 2005; Kell and Knowles, 2006). See Figure 1.10.

In the context of this view it also has to be mentioned that stages of qualitative research are followed by stages of quantitative research, both in empirical research as well as in theoretical research. In early stages of research, only qualitative observations are available. Later, when more sophisticated measurement technologies are developed, quantitative data are retrievable. In parallel, initially only qualitative hypotheses and theories can be set-up; however, when quantitative data can be used, quantitative theoretical models and hypotheses can also be constructed.

1.4.3 Top-Down Analysis – Reductionism?

Empirical science aims to isolate a single factor that generates the phenomenon that should be explained – light is composed of photons that could be isolated theoretically and by experiments, and the constitution of water could be reduced to one atom of oxygen and two atoms of hydrogen. In biology and medicine, the "reductionistic

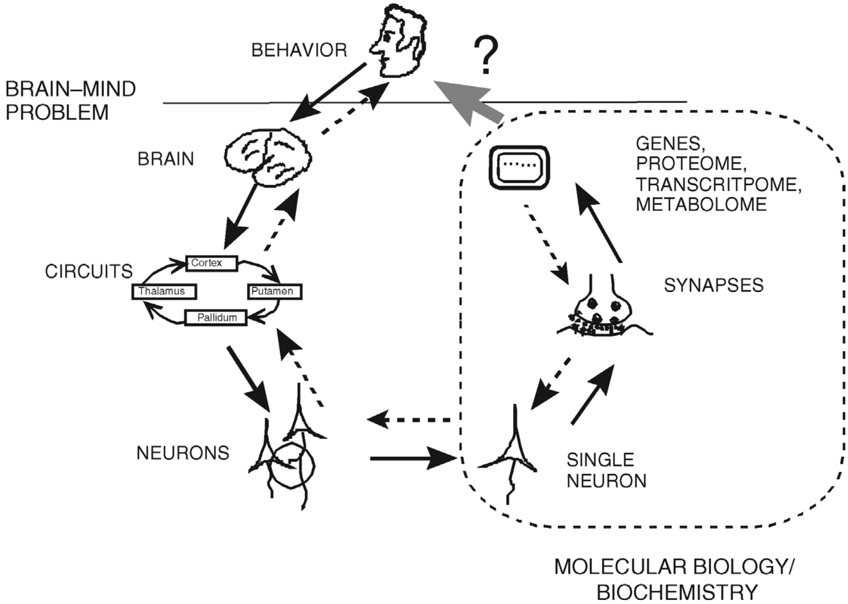

Figure 1.11 The reductionistic research strategy in neuropsychiatry and the field of molecular biological investigation. This implies the micro–macro problem as one aspect of the brain–mind problem – how can behavior be "explained" by genes?

paradigm" is also driven by the aim and hope to find the "master molecule" or the "master gene." It is questionable whether or not it can be expected that the molecular basis of mental disorders can be identified by this reductionistic research strategy (Figure 1.11).

This reductionistic research strategy is generally a successful way to understand the structure of nature. However, detailed information on structure does not necessarily allow us to understand the global function of the system – knowledge of the parts of a clock does not imply the understanding of the mechanics of the whole clock. At present, the methodology of systems thinking might be helpful in the interplay with new multiple-unit measurement techniques in experimental molecular biology.

1.4.4
Bottom-Up Explanations – Holism?

From a philosophical point of view this top-down approach entails the problem of bottom-up explanation of the behavioral and clinical macro-phenomena by micro-phenomena such as molecular peculiarities. There are explanatory gaps that cannot be explained by physical and chemical categories, but that need bridge concepts that explain new emergent phenomena (Bedau and Humphreys, 2007) such as self-organized synchronization of activity of neurons and so on (Singer, 1999). For example, the interactions of molecules of a system evoke the temperature of the respective system; however, temperature is not a property of single molecules. In this way, the explanation of spike activity of a neuron is based on the fact that activation of several ion channels allows the rapid exchange of ions between the intracellular and extracellular space, as demonstrated by Hodgkin and Huxley (1952). Edelman and Tononi tried to "explain" consciousness as one property of re-entrant activity of highly connected neuronal circuits only by neurophysiological terms (Edelman and Tononi, 2000). Regarding psychiatry, there is the need for a neurobiological explanation of phenomena such as "craving" in addiction, "hallucinations" in schizophrenia, or "suicidality" in depression.

One research strategy that opens new perspectives for understanding complex biosystems is called "systems biology" (Kitano, 2002a, 2002b; Klipp *et al.*, 2005, 2009; Palsson, 2006). In principle, systems biology develops strategies to design experimental research in a systemic view, and to use computer-based modeling and experimental simulations in order to understand the network processes in cells, tissues, organs, and the whole organism (Noble, 2006, 2008). Promising approaches of systems biology start at the level of genomics, transcriptomics, proteomics, metabolomics, and other fields of "-omics" (Palsson, 2006). Methodologically, it is based on mathematics, informatics, and experimental molecular biology.

In the context of this new way of thinking in biology, the term "scientific knowledge" needs to be clarified.

1.5 Theoretical (Neuro)psychiatry

Regarding the "epistemic cycle" (Section 1.4.2), it has to be seen that there is no explicit field that can be called "theoretical psychiatry." Instead, nearly all progress in psychiatry is thought to be based on experimental biological research. Only a few attempts can be seen that aim to construct a theoretical perspective.

Therefore, theoretical psychiatry could be defined as the field of hypotheses, models, and theories that describe and explain the mechanisms of mental disorders. In the case of neuropsychiatry, this description and explanation is provided by neurobiology. Biological research in the context of psychiatric issues has produced a rapidly expanding amount of data on the functions and dysfunctions of the brain. At present, neuropsychiatry is making much progress by using new molecular biological technologies such as microarrays. By this method, the molecular biological analysis of the genome, the transcriptome, the proteome, and the metabolome, in relation to psychiatric diseases, is proceeding very rapidly (Gebicke-Haerter, 2008). The data that are collected by high-throughput technologies demand more sophisticated instruments for data analysis in order to detect the coincidence of activation or inhibition of thousands of genes (Bhave *et al.*, 2007; Gebicke-Haerter, 2008; also see Chapter 13).

Basically, for theoretical neuropsychiatry, several methodological problems of theoretical brain research have to noted (*cf.* Tretter, Müller, and Carlsson, 2006; Tretter and Albus, 2007; Tretter, Gallinat, and Müller, 2008):

- The *complexity of neurobiological data* has to be reduced and the technically caused heterogeneity of data has to be controlled, In order to explain mental processes and their disorders, data that are obtained by different procedures such as imaging methods, electrophysiology, histology, biochemistry, pharmacology, molecular biology, and other techniques need integrative theoretical constructs that can bridge these gaps. Integrating distinct time or spatial domains is one of these challenges – electrophysiology has a good time resolution, but a bad spatial resolution as it is hard to measure the spatial meso-level (local networks) even with multiple electrode arrays. On the contrary, imaging methods have good spatial resolution, but need some seconds to generate the signals. Therefore, there always seems a methodological gap between the measurements.
- The *reconstruction of the whole brain* (or of functionally significant modules) on the basis of experimental and clinical data has to bridge some explanatory gaps regarding the difficulty in explaining single phenomena such as gestalt perception or emotions. This analytical challenge also includes the problem of integrating various timescales ranging from nanoseconds to weeks, months, or years. These aspects of the brain–mind problem is tackling neuropsychiatry and neuropsychology(Dennett, 2006; Searle, 1997, 2005; Tretter, 2007). Therefore, it is not sufficient to substitute psychological terms by neurobiological terms.
- The *structural and functional complexity* of the brain cannot be understood completely. For the brain, there are estimated to be about 10^{11} neurons each with 10^3 connections. This implies that in a neuronal pathway a signal or information "re-enters" the pathway after about four neurons (or synapses). Therefore, feedback loops are essential for the functional structure of the brain. If 10^2 spikes per second can occur, for 10^{14} synapses 10^{16} impulses have to be recorded and computed for modeling. This is beyond computability ("transcomputability"; von Foerster, 2002) and implies a challenge for modeling. In this view, the brain has to be conceptualized as a complex dynamic network (Edelman and Tononi, 2000; Tretter, 2005;Tretter, Gallinat, and Müller, 2008). As a consequence, systems science seems to be the appropriate approach in order to build theoretical models of the brain and its disorders, and to understand mental disorders.

The enormous complexity of data implies that mathematical tools such as multivariate statistics or graph theory have to be used for data analysis (see also Marin-Sangiuno and Mendoza, 2008). In a next step, for theory building in psychiatry, the integration of different and complex sets of data is necessary in order to represent this information in the respective model. For this reason, the model complexity exceeds the options of imagination alone. Therefore, computer-based data analysis and modeling becomes an increasingly important tool to study the operations of the various molecular networks. In a next important step, the results of these *in silico* experiments are transferred to the "wet" laboratory of biochemical and molecular biological experimentation. This procedure of integrating experimental research and theoretical research is cultivated in the context of systems biology (Savageau, 1976). Therefore, it seems to be promising to integrate systems biology into the field of psychiatry (Tretter and Albus, 2008; Tretter, Gallinat, and Müller, 2008). As the term "systems" is very general, it seems to be useful to characterize one possible academic reference discipline that is concerned with systems thinking, namely "systems science."

1.6
Systems Thinking

Systems thinking as a science could be a new direction and way of understanding organisms (Tretter, 1989; Ahn *et al.*, 2006a, 2006b). It is routed in the work of Norbert Wiener (1948) and Ludwig von Bertalanffy (1968) and it aims to understand systems on the basis of their signaling networks. Dynamics and complexity are central issues (Watts and Strogatz, 1998; Strogatz, 2001; Periwal *et al.*, 2006; Quarteroni, Formaggia, and Veneziani, 2006; Stelling *et al.*, 2006). The academic development of the systemic methodology is sometimes named "systems science," although it is hard to find university courses that teach these skills.

Systems thinking understands a system as being composed of elements and their relations. It also assumes that we are only able to understand the reality by constructing maps and models. In this view, modeling is a procedure that starts with qualitative concepts and ends up in mathematical models that can be tested by computer experiments (*in silico* experiments). Additionally, these models should help to explore the real systems (e.g., neurons) in experimental set-ups. With new data, the models are modified again and new computer simulations can be performed. Thus, a "viable" concept of the functional structure of the respective system is generated by iterative development of the models (Figure 1.12). Models are collected in order to provide a freeware set for other researchers (Finney *et al.*, 2006).

Some theories, such as catastrophe theory, chaos theory, or complexity theory, provide concepts that can be used to characterize the observed type of dynamics of the system under study. It should be mentioned here that cybernetics and systems science was substituted by informatics using the concept of "artificial neuronal networks" (Arbib and Grethe, 2001; Arbib, 2002) and now "computational (neuro) science" is the dominating field of modeling complex dynamical neuronal systems (Dayan and Abbott, 2005; Shiflet and Shiflet, 2006; Fishwick, 2007). "Complexity science" is also now booming (Boccara, 2004; Erdi, 2008).

We think that systems biology, together with ecology, will be the fields where the most fruitful developments in the theory of biosystems are going to be developed.

1.7
Perspectives – Towards a "Neurophilosophy"

The incredible amount of data that is generated by neurobiology was not noticed in the philosophy of mind up until the end of the 1970s. At that time, Karl Popper and Sir John Eccles tried to established a new philosophy of the brain and mind (Popper and Eccles, 1977). They proposed a dualistic concept of mind and brain, and even a third dimension that they called the world of cultural objects. In the 1980s, Patricia and Paul Churchland criticized the classical brain–mind debate and proposed a "neurophilosophy" based not only on neurobiology, but also on neuroinformatics, neurocybernetics, and artificial intelligence (Churchland, 1984, 1986). Several other authors followed this new approach (e.g., Northoff, 2000). See Figure 1.13.

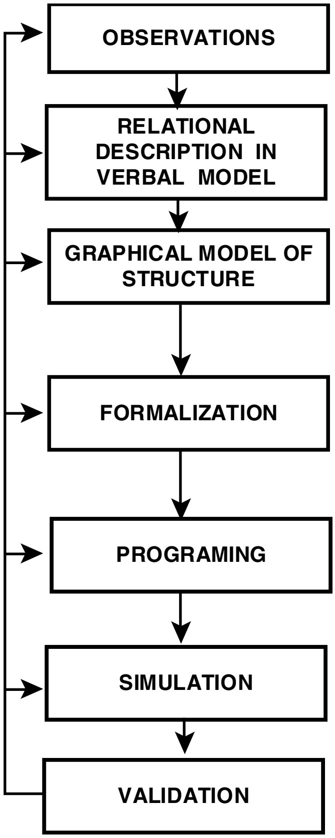

Figure 1.12 Steps of systemic modeling (Tretter, 2005): critical steps are the formalization and computerization of the model.

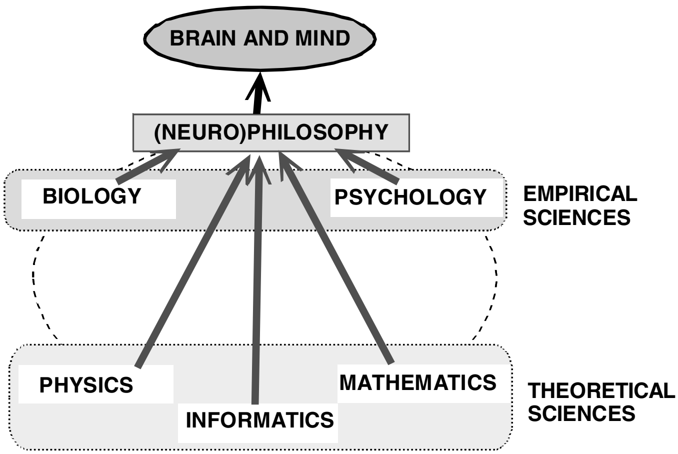

Figure 1.13 The structure of a multidisciplinary-based "neurophilosophy."

Table 1.1 Problem survey to the current brain–mind discourse as a questionnaire with examples (Tretter and Gruenhut, 2010).

1. Questions to the essence of brain and mind
   1.1 Materialism versus idealism
   If there are two different qualities, is there a mind as a special entity? If there is only one entity, which "entity" explains the other one?
   1.2 Dualism versus monism
   Does duality exist in a quality dualism?
   Is a methodological dualism justifiable?
   Can a monism be established now conclusively?
2. Questions focusing on the relationship between brain and mind
   2.1 Correlation and causality
   Methodologically considered: are only "correlations" between biological and psychological variables possible ?
   Are statements regarding causality relations more than (pure) hypotheses?
   2.2 Stochastics and determinism
   Is there already a deterministic theory of brain functions or is the statement about the determination of brain processes a hypothesis?
3. Questions regarding the methodology of analysis of brain and mind
   3.1 The internal viewpoint versus external viewpoint (first-person perspective/third-person perspective)
   Is a complete substitution of the internal subjective viewpoint by the external objective viewpoint possible (external is internal)?
   Is the subjective viewpoint the precondition for the brain–mind debate and also the problem?
   Is a priority of the external scientific viewpoint only possible in the case of elimination of the subjective perspective and does it lead to monistic materialism?
   3.2 Plurality of neurobiological methods and generalizations
   How can the different pictures of the brain be integrated that arise through neurophysiology, histology, radiology, and so forth?
   How can single discoveries be used for explicit generalizations?
   3.3 Relation of structure and function: "neuropsychological uncertainty relation"
   Can the following relation be formulated? "The more precisely the neurobiological area is determined in the brain, the less the psychological function becomes accurately definable" (multifunctionality of brain areas, unspecificity of ion channels) and "The more precisely the function is determined, the more inaccurate becomes the identification of the brain area of this function" (multilocality of functions).
   The multifunctionality can be derived reasonably from brain areas: there is an unspecificity of ion channels; the striatum is an area related to compulsive behavior, schizophrenia, addiction, and so on.
   The multilocality can be demonstrated easily: about 40 areas in the cortex are related to vision.
   3.4 Micro–macro problem
   Can conscious functions be explained by activity of a circumscribed number of neurons?
4. Problems of the participating disciplines
   4.1 Representation of the professional competence in the discussion
   Empirics, theory, and metatheory.
   Psychology as the science of experience and behavior is rarely integrated in the discussion: it is not very convincing if, for example, philosophers themselves develop theories without psychology.
   Brain research still has hardly any systematized theories and represents only research in an ensemble of theorems (theory elements).

(*Continued*)

Table 1.1 (*Continued*)

There exists a lack of cooperation of theory-competent disciplines such as physics, mathematics, and, above all, systems theory.
4.2 Interdisciplinary language problems
For interdisciplinary communication elaborated ordinary language is better than expert languages: is there an essential loss of precision?
Propositions very often show little systematization and therefore also logic consistency is poor
Dichotomic nominal category pairs ("determinism/indeterminism") should be avoided by "scaling" in "strong," "middle," and "weak".
4.3 Deficits of a theory of the brain
There are only few comprehensive theories for brain functions.
Concepts of brain theories lack systemic formulation that seems to be appropriate to the network character of the brain.

Here, we finally propose a concept of neurophilosophy that is based by multidisciplinarity. In this concept, philosophy should play a crucial role, and should integrate the various positions and arguments. It seems to be crucial for the mind–brain discussion that not only philosophers or only neurobiologists, but also other disciplines should discuss the empirical evidence and the theoretical and metatheoeretical aspects of the brain–mind relation. Some of these aspects are summarized in Table 1.1.

Although there is a wide debate in this field, there is still not enough institutionalization of such an interdisciplinary discourse that should be constituted by the integration of philosophy, psychology, neurobiology, and theoretical disciplines, such as informatics, systems research, and physics.

Acknowledgment

I am very grateful to Peter Gebicke-Haerter for valuable criticism, corrections, and discussions of the manuscript.

References

Ahn, A.C., Tewari, M., Poon, C.S., and Phillips, R.S. (2006a) The limits of reductionism in medicine: could systems biology offer an alternative? *PLoS Medicine*, **3**, e208.

Ahn, A.C., Tewari, M., Poon, C.S., and Phillips, R.S. (2006b) The clinical applications of a systems approach. *PLoS Medicine*, **3**, e209.

Andreasen, N. (2004) *Brave New Brain – Conquering Mental Illness in the Era of The Genome*, Oxford University Press, New York.

American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders, text revision*, 4th edn, American Psychiatric Association, Washington, DC.

Arbib, M.A. (ed.) (2002) *The Handbook of Brain Theory and Neural Networks*, 2nd edn, MIT Press, Cambridge, MA.

Arbib, M.A. and Grethe, J.S. (2001) *Computing the Brain: A Guide to Neuroinformatics*, Academic Press, San Diego, CA.

Bedau, M.A. and Humphreys, P. (eds.) (2007) *Emergence – Contemporary Readings in*

Philosophy and Science, MIT Press, Cambridge, MA.

Bennett, M.R. and Hacker, P.M.S. (2003) *Philosophical Foundations of Neuroscience*, Blackwell, Malden, MA.

Bhave, S.H., Hornbaker, C., Phang, T.L., Saba, L., Lapadat, R., Kechris, K., Gaydos, J., McGoldrick, D., Dolbey, A., Leach, S., Sariano, B., Ellington, E., Jones, K., Mangion, J., Belknap, J.K., Williams, R.W., Hunter, L.E., Hoffmann, P.L., and Tabakoff, B. (2007) The PhenoGen Informatics website: tools for analyses of complex traits. *BMC Genet.*, **8**, 59.

Bleuler, E. (1911) *Dementia Präcox oder die Gruppe der Schizophrenien*, Deuticke, Leipzig.

Block, N. (1980) What is functionalism, in *Readings in Philosophy of Psychology VI* (ed. N. Block), Harvard University Press, Cambridge, MA, pp. 174–181.

Boccara, N. (2004) *Modeling Complex Systems*, Springer, Berlin.

Boogerd, F.C., Bruggeman, F.J., Hofmeyr, J.-H.S., and Westerhoff, H.V. (2007) *Systems Biology – Philosophical Foundations*, Elsevier, Amsterdam.

Bunge, M. (1998) *Philosophy of Science*, vol. 2, Transaction Publishers, London.

Carnap, R. (1928) *Der Logische Aufbau der Welt*, Meiner, Hamburg.

Carnap, R. (1932) Psychologie in physikalischer Sprache. *Erkenntnis*, **3**, 107–142.

Chalmers, D. (1995) Facing up to the problem of consciousness. *Journal of Consciousness Studies*, **2**, 200–219.

Churchland, P.M. (1981) Eliminative materialism and the propositional attitudes. *Journal of Philosophy*, **78**, 67–90.

Churchland, P.M. (1984) *Matter and Consciousness*, MIT Press, Cambridge, MA.

Churchland, P.S. (1986) *Neurophilosophy: Toward a Unified Science of the Mind–Brain*, MIT Press, Cambridge, MA.

Churchland, P.M. (2007) *Neurophilosophy at Work*, Cambridge University Press, New York.

Cooper, R. (2007) *Psychiatry and Philosophy of Science*, McGill-Queen's University Press, Montreal.

Crick, F.H.C. (1994) *The Astonishing Hypothesis*, Simon & Schuster, London.

Davidson, D. (1970) Mental events, in *Experience and Theory* (eds. L. Foster and J.W. Swanson), University of Massachusetts Press, Amherst, MA, pp. 79–101.

Dayan, P. and Abbott, L. (2005) *Theoretical Neuroscience. Computational and Mathematical Modeling of Neural Systems*, MIT Press, Cambridge, MA.

Dennett, D.C. (2006) *Sweet Dreams. Philosophical Obstacles to a Science of Consciousness*, MIT Press, Cambridge, MA.

Edelman, G.M. and Tononi, G. (2000) *A Universe of Consciousness How Matter Becomes Imagination*, Basic Books, New York.

Erdi, P. (2008) *Complexity Explained*, Springer, Berlin.

Finney, A., Hucka, M., Borstewin, J., Keating, S.M., Shapiro, B.E., Matthews, J., Kovitz, B.L., Schilstra, M.J., Funahashi, A., Doyle, J., and Kitano, H. (2006) Software infrastructure for effective communication and reuse of computational models, in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts* (eds. Z. Szallasi, V. Periwal, and J. Stelling), MIT Press, Cambridge MA, pp. 355–378.

Fishwick, P. A. (ed.) (2007) *Handbook of Dynamic System Modeling*, Chapman & Hall/ CRC Press, Boca Raton, FL.

von Foerster, H. (2002) *Understanding Understanding: Essays on Cybernetics and Cognition*, Springer, Berlin.

Freeman, W.J. (2000) *Neurodynamics: An Exploration in Mesoscopic Brain Dynamics*, Springer, Berlin.

Gebicke-Haerter, P. (2008) Systems biology in molecular psychiatry. *Pharmacopsychiatry*, **41** (Suppl. 1), S19–S27.

Griesinger, W. (1882) *Mental Pathology and Therapeutics*, William Wood & Co., New York.

Griesinger, W. (1845) *Die Pathologie und Therapie der psychischen Krankheiten*, Krabbe, Stuttgart.

Heil, J. (2004) *Philosophy of Mind*, Oxford University Press, Oxford.

Hempel, C.G. and Oppenheim, P. (1948) Studies in the logic of explanation. *Philosophy of Science*, **15**, 135–175.

Hempel, C.G. (1965) *Aspects of Scientific Explanation*, Free Press, New York.

Hodgkin, A.L. and Huxley, A.F. (1952) Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *Journal of Physiology*, **117**, 500–544.

Hyman, St.E. (2007) Can neuroscience be integrated into the DSM-V? *Nature Reviews Neuroscience*, **8**, 725–732.

Jackson, F. (1982) Epiphenomenal qualia. *Philosophical Quarterly*, **32**, 127–136.

Kell, D.B. and Knowles, J.D. (2006) The role of modeling in systems biology, in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts* (eds. Z. Szallasi, J. Stelling, and V. Periwal), MIT Press, Cambridge, MA, pp. 3–18.

Kim, J. (1998) *Philosophy of Mind*, Westview Press, Boulder, CO.

Kim, J. (ed.) (2002) *Supervenience*, Cambridge University Press, Cambridge.

Kitano, H. (2002a) Systems biology: a brief overview. *Science*, **295**, 1662–1664.

Kitano, H. (2002b) Computational systems biology. *Nature*, **420**, 206–210.

Klipp, E., Herwig, R., Kowald, A., Wielring, C., and Lehrach, H. (2005) *Systems Biology in Practice*, Wiley-VCH Verlag GmbH, Weinheim.

Klipp, E., Liebermeister, W., Herwig, R., Wierling, C., Kowald, A., Lehrach, H., and Herwig, R. (2009) *Systems Biology: A Textbook*, Wiley-VCH Verlag GmbH, Weinheim.

Kraepelin, E. (1902) *Clinical Psychiatry*, Macmillan, New York.

Levine, J. (1983) Materialism and qualia: the explanatory gap. *Pacific Philosophy Quarterly*, **64**, 354–361.

Lewin, K. (1952) *Field Theory in Social Science: Selected Theoretical Papers*, Tavistock, London.

Lewis, D. (1966) An argument for the identity theory. *Journal of Philosophy*, **63**, 17–25.

Libet, B. (2005) *Mind Time*, Suhrkamp, Frankfurt.

Libet, B., Gleason, C.A., Wright, E., and Pearl, D. K. (1983) Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. *Brain*, **106**, 623–642.

Marin-Sangiuno, A. and Mendoza, E.R. (2008) Hybrid modeling in computational neuropsychiatry. *Pharmacopsychiatry*, **41** (Suppl. 1), S85–S88.

Metzinger, T. (2009) *The Ego Tunnel: The Science of the Mind and the Myth of the Self*, Basic Books, New York.

McGinn, C. (1989) Can we solve the mind–body problem? *Mind*, **98**, 349–366.

Nagel, T. (1974) What is it like to be a bat? *Philosophical Review*, **83**, 435–450.

Newton, R.G. (2007) *From Clockwork to Crapshoot: A History of Physics*, Pelknap Press of Harvard University Press, Cambridge, MA.

Noble, D. (2006) Multilevel modeling in Systems biology: from cells to whole organs, in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts* (eds. Z. Szallasi, V. Periwal, and J. Stelling), MIT Press, Cambridge, MA, pp. 297–312.

Noble, D. (2008) *Music of Life. Biology Beyond Genes*, Oxford University Press, New York.

Northoff, G. (2000) *Das Gehirn – Eine neurophilophische Bestandsaufname*, Mentis, Paderborn.

Northoff, G. (2004) *Philosophy of the Brain. The Brain Problem*, Benjamins, New York.

Palsson, B.O. (2006) *Systems Biology*, Cambridge University Press, Cambridge.

Periwal, V., Szallasi, Z., and Stelling, J. (2006) System modeling – why and how?, in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts* (eds. Z. Szallasi, V. Periwal, and J. Stelling), MIT Press, Cambridge, MA, pp. vii–viv.

Place, U.D. (1956) Is consciousness a brain process? *British Journal of Psychology*, **47**, 44–50.

Popper, K.R. and Eccles, J.C. (1977) *The Self and the Brain*, Springer, London.

Putnam, H. (1965) Brain and behavior, in *Analytical Philosophy* (ed. R.J. Butler), Blackwell, Oxford, pp. 1–19.

Quarteroni, A., Formaggia, L., and Veneziani, A. (eds.) (2006) *Complex Systems in Biomedicine*, Springer, Berlin.

Sadock, B.J., and Sadock, V.A. (2007) *Kaplan's and Sadock's Synopsis of Psychiatry*, 10th edn, Lippincott Williams & Wilkins, New York.

Savageau, M. (1976) *Biochemical Systems Analysis: A Study of Function and Design in Molecular Biology*, Addison-Wesley, Reading, MA.

Searle, J.R. (1997) *The Mystery of Consciousness*, Granta, London.

Searle, J.R. (2005) *Mind: A Brief Introduction*. Oxford University Press, New York.

Shiflet, A.B. and Shiflet, G.W. (2006) Introduction to computational science.

Modeling and Simulation for the Sciences. Princeton Univ. Press, Princeton, New Yersey.

Shoemaker, S. (1996) *The First-Person Perspective, and Other Essays*, Cambridge University Press, New York.

Singer, W. (1999) Neuronal synchrony: a versatile code for the definition of relations? *Neuron*, **24**, 49–65.

Sober, E. (2000) *Philosophy of Biology*, Westview Press, Boulder, CO.

Stadler, F. (2001) *The Vienna Circle*, Springer, Berlin.

Stelling, U.J., Doyle, F., and Doyle, J. (2006). Complexity and robustness of cellular systems. In: Szallasi, Z., Stelling, U.J., and Periwal, V. (eds.) System modeling in cellular biology. MIT Press, Cambridge, Mass. 19–39.

Stich, P. (1978) Autonomous psychology and the believe/desire thesis. *The Monist*, **61**, 573–591.

Strogatz, S.H. (2001): Nonlinear Dynamics and Chaos. With Applications to Physics, Biology, Chemistry and Engineering. The Perseus Books Group, New York.

Taylor, M.A. and Vaidya, N.A. (2009) *Descriptive Psychopathology*, Cambridge University Press, New York.

Tretter, F. (1989) Systemwissenschaft in der Medizin. *Deutsches Ärzteblatt*, **43**, 3198–3209.

Tretter, F. (2005) *Systemtheorie im klinischen Kontext*, Pabst, Lengerich.

Tretter, F. (2007) Die gehirn–geist-debatte. Wissenschaftstheoretische probleme in hinblick auf die psychiatrie [The brain–mind debate problems in the philosophy of science with regard to psychiatry]. *Der Nervenarzt*, **78**, 498, 501–504.

Tretter, F. and Albus, M. (2007) Computational neuropsychiatry of working memory disorders in schizophrenia: the network connectivity in prefrontal cortex – data and models. *Pharmacopsychiatry*, **40** (Suppl. 1), S2–S16.

Tretter, F. and Albus, M. (2008) Systems biology and psychiatry – modeling molecular and cellular networks of mental disorders. *Pharmacopsychiatry*, **41** (Suppl. 1), S2–S18.

Tretter, F. and Gruenhut, Ch. (2010) *Das Gehirn ist der Geist? Einführung in die Neurophilosphie*, Hogrefe, Göttingen.

Tretter, F., Müller, W. and Carlsson, A. (eds.) (2006) Systems science, computational science and neurobiology of schizophrenia. *Pharmacopsychiatry*, **39** (Suppl. 1).

Tretter, F., Gallinat, J. and Müller, W. (eds.) (2008) Systems biology and psychiatry. *Pharmacopsychiatry*, **41** (Suppl. 1).

von Bertalanffy, L. (1968) *General System Theory*, Braziller, New York.

Walter, S. and Heckmann, H.D. (2003) *Physicalism and Mental Causation*, Imprint Academic, Charlottesville, VA.

Watts, D.J. and Strogatz, S.H. (1998) Collective dynamics of 'Small World' networks. *Nature*, **393**, 440–442.

Wiener, N. (1948) *Cybernetics*, MIT Press, Cambridge, MA.

WHO (1992) *ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision*. WHO, Geneva.

Wundt, W. (1896) *Grundriss der Psychologie*, Engelmann, Leipzig.