Innovations in Cognitive Neuroscience
Series Editor: Vinoth Jagaroo

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Neurophenotypes

Advancing Psychiatry and Neuropsychology in the "OMICS" Era

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Preface

In recent decades, biology and medicine have seen developments that differ uniquely from the research contexts of the past. If there is a single term that captures these developments and the new landscape that they shape, it is 'omics.' It represents an approach to describing a biological entity or system using detailed, multi-scaled, multi-dimensional data and equally complex analyses of the data, both made possible by bioinformatics. 'Omics' is synonymous with systems biology, which deals with the relational understanding of complex, collective systems of organisms. So widespread and intense have been the proliferation of omics disciplines that it has prompted the expression in jest, 'Who needs another omics discipline?'

To the brain-behavioral sciences, omics is a welcome and much needed approach. Unraveling the complexity of the brain and the intricacies of interactions between the genome, the brain, and the environment demands an approach commensurate in its sophistication. Powerfully emerging omics approaches applied to the brain are moving brain science into a new era. Numerous genetic loci are showing statistically significant associations with schizophrenia in genomic studies involving tens of thousands of cases. Brain circuits are being linked to gene modules via transcriptomic studies of brain tissue. Genome-to-phenome mapping has inspired the discipline of cognitive phenomics. Connectomics signals the prospect of dense and detailed mapping of neurons. And the US National Institutes of Mental Health has set in motion Research Domain Criteria (RDoC), an initiative toward a brain-based nosology of mental disorders where neural circuits and related phenotypic markers form the units of analysis.

These developments translate into various breakthrough achievements. Though remaining far from fully understood, it has long been recognized that a multitude of variables are orchestrated in brain development and in brain-behavioral relationships. Even a 'simpler' question such as the adaptation of a neural circuit to a new stimulus requires the study of numerous elements and variables. With the omics scale of data volume, data specification, data quantification, and complex mappings between multi-level data sets, the functionality and methods are provided to investigate complex questions such as follows: What might be the

polygenic nature of a mental disorder and how might this be expressed at subcellular and synaptic levels or at the levels of neural circuits? How do the permutations of multiple brain systems result in specific patterns in cognitive functional domains? and How can the spectral nature of many cognitive and psychiatric disorders be understood in terms of the differential expression of neural systems? Such questions, as this volume illustrates, are no longer lofty and solely theoretical. And they are beginning to compel major course changes in the clinical neurosciences. The development of RDoC is evidence enough of the near certainty that description and diagnosis of cognitive and psychiatric disorders will shift from categorical approaches to dimensional approaches—where discrete, separable cognitive, and neural features along various continua converge to form a diagnostic profile.

There are many ways by which psychiatry and neuropsychology can engage with this new research environment. This volume is about one all-important step. To both serve and benefit from a meaningful integration with the omics approach to the brain, cognitive and neural features need to be described in a standardized, scientific format. For the cognitive and neural phenome to be systematically linked to the genome and to other shaping or modulatory factors, and for this to be carried out in an omics/informatics environment, the units of analysis are critically important. They need to be precise and they need to have relational utility so that they can be tied to all their shaping mechanisms and developmental precedents. The term 'neurophenotype' is used in this volume as a general term to describe this kind of neural or cognitive feature. The neurophenotype approach to brain-behavioral associations and clinical diagnoses relies on precise cognitive and neural markers. It differs from approaches that are phenomenological-descriptive and detached from brain science (psychiatric diagnostic manuals), or approaches that compound many cognitive processes into a poorly operationalized amalgam (a subtest in a neuropsychological battery) and which, at best, can only be tied to the brain at a gross anatomical level. The neurophenotype approach facilitates the understanding of a profile of cognitive and neural features of an individual, the coexpression or variable expression of a common set of features across different diagnostic groups, and the biological mechanisms that may mediate the features.

The neurophenotype approach is, however, in its infancy. Neurophenotypes are currently not specified in a uniform or organized manner. Some of this has to with the difficulty of circumscribing processes or neural systems that may constitute neurophenotypes. If neuronal, circuit, or neuroanatomic phenotypes are viewed primarily in terms of genetic precedents, the possible impact of non-genetic factors can obviously be raised. If circuit neurophenotypes are viewed as central mediators of cognitive processes, then a host of intrinsic and extrinsic circuit modulatory variables complicate the picture, and the question of just what is the circuit, arises. There are many putative neurophenotypes. Many neural systems and cognitive processes have been cast into working definitions as neurophenotypes. All of these can be debated. Neurophenotypes and all their formalisms are evolving, but as a force. The current stage of this development and its associated topics, especially as applied to the clinical neurosciences, are discussed in this volume.

The volume was motivated by the authors' interests in cognitive neuroscience and neuroinformatics (Jagaroo) and cognitive and psychiatric genetics and bioinformatics (Santangelo). The vibrant intersections of neuroscience and genomics contextualized within a genome-to-phenome landscape can be felt throughout the research literature. It is hoped that capturing these developments and organizing the themes using the format of a composed volume will help better engage the clinical neurosciences in the discourse.

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Part I
Research and Conceptual Developments

Chapter 1
Introduction and Structure of the Volume

Vinoth Jagaroo and Susan L. Santangelo

Biomedical research has over the past few decades been dominated by the revolution of molecular biology and genetics. Featuring prominently during this time has been the notion of "biomarkers." The very ubiquity of the term signifies the utility and promise of a strategy that identifies genetic, molecular, neurophysiologic, neuroanatomic, and neurocognitive features as indices of disease. The interest in biomarkers has been a part and parcel of the rise of molecular biology—certainly the mapping of the human genome which was driven in part by the goal of mapping genes to diseases (International Human Genome Sequencing Consortium 2001) was a major catalyst event. Biomarkers have been cast as objectively measured characteristics that signal a pathogenic condition or aid in predicting treatment efficacy and prognosis (Biomarkers Definitions Working Group 2001).[1] They may indicate disease presence, type, stage, etc., but may also aid in the subtyping of the

[1]The Biomarkers Definition Working Group was convened by the National Institutes of Health.

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normal phenotypes, and a biomarker may have stand-alone predictive power or may be useful when seen in specific combination with other markers.

Advances in molecular biology have been intertwined with technological advances enabling large, complex data sets to be captured, analyzed, and deciphered using automated procedures at high speed and relatively low cost. Biomarker developments have been closely tied with the "omics" revolution. "Omics" in terms such as *genomics*, *transcriptomics*, *proteomics*, and *phenomics* marks two notable features: (a) A massive scale of data sets or analytical variables processed via automated, "high-throughput" procedures; and (b) that which enables the former—computerized tools, databases, knowledge discovery/datamining algorithms, etc., encompassed by the field of *bioinformatics*. Over the last two-and-a-half decades, biomedical sciences have been marked by the "omics revolution." In the omics era, biomarker discovery has made great strides, which has sweeping implications for all biomedical disciplines.

Over the past decade and half, there has also been extensive discussion of markers in the context of the behavioral neurosciences. This surge of interest has been tied in part to major advances in genetic analysis, especially genome-wide association studies (GWAS)—high-throughput scans of the common variation in the entire genome that identify single-nucleotide polymorphisms (SNPs) associated with diseases. Such developments have given significant impetus to the idea of neurocognitive markers in the context of neuropsychology and neuropsychiatry. In these domains, specific cognitive and neural phenotypes or features have come to be viewed as constituent or putative markers—markers framed around the constructs of cognitive and neural systems. Discussion of neurocognitive markers went through a phase when it was heavily anchored around the very influential construct of the endophenotype (reviewed in other chapters). However, in the short span of the last ten years, the concept of neurocognitive markers has found itself in a new theoretical landscape, one marked by a confluence of a few major and inter-related developments. Altogether, these developments have been making for a greater push toward refined neurobehavioral descriptors. These developments are described below.

Genome-to-Phenome Mapping and Phenomics: The proliferation of the omics disciplines can also be viewed as the result of the greater force of "systems biology," the approach in biology that seeks to quantify genes, their molecular and protein products and regulatory functions, as well as the complex interactions between these elements. The mapping of an entire biological system involves the mapping of genes (the genome) to their products and functions—phenotypes or the "phenome." In between the genome and the most visible phenotype level, lies a myriad of phenotypic strata (proteins, cells, tissues, etc.). Many complex interactions occur between these "intermediate" phenotypes. The mappings between the genome and the phenome, intricate as they may be, are now rendered tractable with the advances in systems biology and information technology. However, while there have been considerable gains in profiling the genomic end of the genome-phenome spectrum, the phenomics end, especially in terms of neurobehavioral features, has not seen a commensurate level of analysis. For genomic data to have

greater utility and meaning, it needs to interface with similarly specified phenomic data. This calls for a finer specification of the phenome—"high-dimensional" phenomic data, described along a format that enables meaningful mappings with lower level phenomic data, and ultimately with the genome level. *Phenomics* is the discipline that seeks to specify and quantify the phenotype in such a manner as to enable the systematic understanding of the phenotype in the context of genomics, that is, to bring a systems-level analysis to the phenotype. With reference to neural systems and neurocognitive disorders, the phenomics approach can be framed around questions such as: How can the brain and brain-mediated illness be informed by the context of molecular biology, genetics, and the neurobiological systems that they shape? How can neuropsychiatry and neuropsychology reap the benefits of systems biology and integrative neuroscience?

Connectomics: Large-scale initiatives aimed at creating a detailed map of the structural connections of the brain have gotten under way in recent years. Known as "connectomics," these initiatives seek to understand neuronal and glial connectivity patterns in the entire brain. The envisaged map, "the connectome," can be described at many scales. They range from the cellular/microscale end to the white matter projection systems/macroscopic end. Microscale connectomics relies mainly on the tools of automated electron microscopy combined with artificial (computer) vision algorithms—images of tissue slices are integrated into 3D volumetric representations of a sample of brain tissue, showing cell structure, synaptic and subcellular detail. Macroscale connectomics relies mainly on fMRI (especially resting-state fMRI)—white matter fiber systems can be traced, and distributed functional brain networks can be mapped dynamically. The trajectory of connectomics has not been tied per se to the general initiative of phenomics; it has had a separate course. It just so happens to be a well-specified example of an initiative that meets the call of phenomics since it amounts to a rendering of the neural phenome. A number of issues have arisen around connectomics—questions such as the optimal scale (level of detail) at which the connectome should be specified, the utility of detailed maps. By any account though, connectomics is on the fast lane, and with the prospect of detailed neural mapping comes an array of challenges to behavioral neuroscience. If neural circuitry can be finely mapped, how are functional data to be overlaid on well-specified circuits of all scales? Transposing the problem to neuropsychology and psychiatry implies, again, that cognitive and behavioral constructs need be specified in a form that can be rendered compatible with emerging neural detail at the physical level. The development, described below, is even more explicit on this point.

Research Domain Criteria (RDoC): In 2008, the US National Institute of Mental Health laid out an initiative to describe and define mental disorders based on neural features that can be tied to the biology of the brain, that is, an initiative toward a nosology for mental disorders that is aligned with neuroscience. Diagnostic categories of mental disorders based on symptom clusters have faced some classic shortcomings, among them being the lack of representation of heterogeneity within diagnostic groups, ill-suitability to understanding comorbidity across diagnostic groups, and having a profound incompatibility with the current

era of biological and brain sciences. If what is termed a syndrome in a conventional classification system is comprised of a combination of discrete neural features, and if each feature can be mapped to specific genetic abnormalities, then it is theoretically possible to plot the genome-phenome matrix for each feature. With this type of mapping, the polygenic nature of mental disorders can be better elucidated as can the spectral nature of disorders and the complex permutations of a shared neural matrix that mediates the disorders. To enable such possibilities, RDoC adopts a dimensional view of a trait—viewing it along a continuum. It also postulates that dysregulation of "neural circuits" (variation in circuit phenotypes) accounts for disorders. In the genome-phenome matrix, RDoC is pitched at the level of the "neural circuit." While RDoC has been heavily debated since its inception, and remains at early stages of development, it marks a turning point in the study and classification of neurocognitive and neuropsychiatric disorders. It attempts to lay the groundwork for a neuroscience-based description of normal and disordered perception, cognition, and emotion as well as a neuroscience-centered nosology of mental disorders. This fundamentally changes the language and methods of classification.

Bioinformatics and Knowledge Discovery through Data Mining: Well established over the course of more than three decades, the discipline of bioinformatics needs little introduction. It is widely recognized for its highly specialized application of computer science, information science, and mathematics to the research context defined by the biomedical sciences. Specifically, it is geared to challenges around data cataloging, data visualization, and data mining—for patterns and comparisons among intricate and/or large data sets, and the drawing of conceptual frameworks for complex biological systems. Bioinformatics has developed in parallel with molecular biology and has gained prominence in the process. The application of bioinformatics in the neurosciences is often referred as *neuroinformatics*—exemplified by the Human Brain Project—that involved a host of neuroimaging tools, and a range of organism-specific databases on neural structure. In neuropsychology, there has been a slow but steadily growing call for a reformatting of the discipline to make it informatics-compatible.

Biomarker discovery is inseparable from bioinformatics. Analytic variables and data on a massive scale, as often seen in the omics disciplines, require automated data handling, extraction and databasing. High-dimensional data sets are manageable only with compatible forms of databases. And most significantly, pattern extraction across the data is algorithm-driven. The discernment of meaningful patterns in the data via data mining algorithms alone has come to be termed *knowledge discovery through databases* (KDD). It has emerged as a new ("fourth dimension") dimension of research and has come to be termed *discovery science*. That is, with the inordinate amount of research data available, discoveries can be made "in silica" (through bioinformatics and data mining methods)—discoveries made possible only with large or complex, and often pooled data sets, and which lie well outside the scope of single experiments or the capabilities of individual scientists. In contrast to traditional hypothesis-driven research, discovery science is generally hypothesis-generating.

In the omics environment, the achievement of bioinformatics-driven discovery hinges on a central operating principle: The data are coded and classified using a common format, thus enabling comparison between or across multiple strata in the genome-phenome matrix. Common ontological formats have been established to the point where one researcher's data set can be compared to another's using common descriptors fed into a computer. However, the glaring exception to this critical adaptation happens to be in the realm of neurobehavioral descriptors—neurocognitive- and neuropsychiatric-related processes, concepts, etc. And this problem is crucially tied in with the mission call of RDoC and phenomics. Further, integration across the G-P matrix is entirely dependent on informatics platforms. And if the processes of perception, cognition, and emotion, lying at one end of the G-P matrix are to be meaningfully integrated with other levels of analysis, these processes have to be spelled out in a language that is both compatible with a systems-level format and an informatics-driven integrative platform. Psychiatry and neuropsychology, hence, will need to face radical adjustments or realignments. The biomarker approach, fitting in with systems-level, informatics-geared analyses, is a logical strategy in aiding this transition.

The collective force of these developments has made for an environment where the biomarker approach to neurocognitive processes, in view of its sweeping significance must be engaged with. It is a strategy that is compelled by current technical advancements that show promise in the linkage of biology and behavior. In essence, the biomarker approach to brain and behavior is driven by developments around fundamental imperatives—the mapping of the biological matrix of the brain, from genes through to the neural circuits they shape; how behavior is an emergent property mediated by neural systems; and the parsing out of neural and cognitive features which will in turn aid in the understanding of their normal and abnormal variations and permutations. It is about the specification of neural systems and dynamic neural processes, and a descriptive framework for cognition and emotion that is commensurate with the emerging neural delineations. Clinical imperatives are in turn served by the biomarker approach. These markers may offer accurate predictive and diagnostic features, may serve to monitor disease state and progression, define clinical end points, and gauge clinical efficacy. The cataloging of brain-related biomarkers and their analyses through novel computational techniques and big data sets is fundamentally changing the way the brain and brain-related disorders are being approached.

The discourse on the biomarker approach in clinical neuroscience has been generally affirmative. Certainly arguments for the utility in defining intermediate phenotypes, the calls for phenomics, and the calls for an RDoC-based model for psychiatry have been passionate and explicit. However, the marker-phenotype approach has also met with critical examination: Exactly what defines neural and cognitive markers? What is the optimal level of definition when dealing with neural systems and the brain—the gene-, cell-, circuit-, or some other level? What kinds of markers, intermediate or otherwise, have relevance to neuropsychology and psychiatry? When dealing with cognition and emotion, mediated by multiple neural systems, how are discrete features to be parcellated? What

about environmental variables and the epigenome—how do they factor into a G-P matrix? Can the complexities of behavior and its mediating neural systems be neatly refracted using the G-P model? And is the nature of behavior and clinical practice such that a certain amount of (multifactorial/multivariate) fuzziness will always remain? These are just some examples of the many issues that can be raised in critique of the biomarker (neurocognitive marker) approach.

Yet, by any account of the current trends in systems biology, especially systems neuroscience, genomics, and phenomics, by any account of the overall discussion of RDoC (let alone the very compelling fact that the initiative has already been established), and by any account of the new informatics-driven research environment defined by "big data" and discovery science, it is abundantly clear that the biomarker and systems neuroscience approach in psychiatry and neuropsychology is not a passing trend. It is here to stay and will sooner than later change the entire playing field.

Within this context, this volume explores the domain of neural and cognitive markers in neuropsychiatry and neuropsychology. It outlines the factors that compel the biomarker approach. It relates some of the many processes seen as constituting markers in the neurobehavioral domains. It also highlights the theoretical complications arising when trying to define cognitive and neural systems as markers in the realm of cognition and emotion. The volume clearly takes the perspective that neurocognitive markers make for a fitting approach by which the clinical and cognitive neurosciences can strive toward greater connection with systems biology and genome-to-phenome integrative models. The motivation behind the volume was to organize and present this very significant topic to a greater professional audience—to take it beyond the relatively small and specialized research/academic clusters where different facets of the topic have been comfortably lodged. The topic of the volume is pertinent to both the clinical and research domains in neuropsychology, psychiatry, neurology, cognitive neuroscience, and allied disciplines. Current, cutting-edge developments in the brain sciences and systems biology call for the structure and processes of perception, cognition, emotion, motivation, mood, personality, etc., to be delineated in a new fashion. This structure is far more sophisticated than conventional psychometric quantification and phenomenological, syndromal-based clinical descriptions. This volume serves to outline this new operating environment. It serves to embrace the initiative of reformatting the clinical neurosciences so that they can better serve research and clinical imperatives. And, quite importantly, the volume also serves to highlight a multitude of issues that arise as psychiatry and neuropsychology find themselves in a new and arguably unprecedented, "disrupting," technological-scientific environment. But the volume neither attempts nor presumes to constitute an exhaustive rendering of the subject—which in this age of rapid research and informational shifts would be unrealistic. The volume simply offers a synopsis to serve as a basis for discourse in the clinical neurosciences, as prompted by compelling scientific shifts.

1.1 Coming to Terms: "Neurophenotype"

The concept of a neurocognitive marker does not fit a static or neatly circumscribed definition. Specification of the concept has been generally poor, hinging heavily on the endophenotype concept. And markers in the domains of neuroscience and cognition are inevitably shadowed by biomarker concepts that have a strong clinical orientation—the Biomarkers Definitions Working Group (2001) placed emphasis on biomarker utility in clinical applications—disease diagnosis, staging, etc. Certainly, the lack of consensus around the term "behavioral phenotype" has long been acknowledged (see Skuse 2000), while an attempted consensus-based working definition refers broadly to features and characteristics of cognitive and motor patterns that may have genetic associations (see Society for the Study of Behavioural Phenotypes, www.ssbp.co.uk). Definitions and conceptions of neurocognitive markers are likely to evolve dynamically, directed by new research gains and new analytic approaches. Yet, an operating definition of neural and cognitive markers at this early point in the volume is called for, as is a simple and expedient umbrella term to cover the expanse of potential neural and cognitive processes and patterns. We adopt the term "neurophenotype" for its conciseness and its embrace of neural systems and the sensory, cognitive, and emotional processes that they mediate.[2] Depending on the specificity of the application, parts of the volume may apply the terms "neural" or "cognitive" phenotypes. Our usage of the term "neurophenotype" (NP) rests on the following operating definition:

a. Neurophenotypes may be inclusive of all sensory, motor, cognitive, and emotive processes, and their neural correlates, ranging from subcellular processes, to all scales of circuitry, to neuroanatomic features, and including dynamic neural activation patterns (electrophysiological, functional imaging, etc.). However, it should be representative of the complexity or functional mechanism of the particular level/s in the phenotypic matrix in which it is situated.
b. A neurophenotype need not be associated exclusively with a disease state but must constitute, either singularly or in combination with other NPs, a reliable marker—differentially expressing in subgroups of the normal population, as well as in disease populations when compared to a normal population. However, what defines a "reliable" or even a "useful" marker is not a question we presume to resolve—but certainly entertain through the discourse of the volume. Notions of reliability and usefulness will in part be dictated by evolving research data.
c. A neurophenotype should ideally have an integrated fit, or have the potential to fit, within a larger associative, developmental, or physiological network. Examples of these are gene-regulatory networks (perhaps the best known

[2]The term was used by Sörös and Stanton (2012) in a discussion on a revised approach to studying auditory brain function, factoring in genomics and neuroimaging. The term has also been embraced by Craddock et al. (2013) in the context of neuroimaging-related phenotypes.

> Bakare et al. (2012) example), epigenetic-neurodevelopmental interactive networks; neurohormonal modulatory networks; and bio-electrically driven, gap-junction (synaptic)-mediated regulatory networks. In such associative networks, the NP may be part of a gene-linked causal chain, and may in some instances mark causality, but this is not a criterion. Certainly in this definition, the principle that a marker be tied via phenome-to-genome dissection to a genotype is not a requirement, and the rationale for this is summarized below and elaborated in Chap. 15.

Neural systems and hence the processes they mediate may be causally linked to deeper levels of the phenomic strata (e.g., proteins, cells), but their physical or functional patterns may also be significantly determined by (a) external, environmental, and epigenetic factors, (b) by intrinsic circuit dynamics that involve factors such as resting potentials, bioelelectric voltage gradients, and long-term potentiation, and (c) chemically based gradients and modulatory networks. The intrinsic dynamics of complex physiological networks can manifest patterns strong enough to instruct neural or cognitive phenotypes such that in these instances, the phenotypes are independent of gene-regulatory networks. This is a factor that is substantiated in Chap. 3 and shapes our working definition of NPs. All levels of neural and cognitive phenomic space are accommodated. And while these complex systems can in turn be conceived as interacting with the total phenomic makeup of the organism, such consideration is well beyond the scope of our focus. Wide accommodation of features runs the risk that any random feature, trait, or test result can be cast as a NP. We mitigate this seeming pitfall by applying the framework of an associated or linkage network within which a NP should ideally be contextualized. However, we also emphasize that regulatory networks that causally and scientifically frame NPs are not limited to gene networks. Further, in the context of phenomics and data-driven neuroscience, NPs may also be derived through informatics-driven discovery and may take novel forms; examples of this will be covered in later chapters.

1.2 Structure

The volume is structured in three parts. The first part of the volume (Chaps. 1–3) is introductory—presenting various research and conceptual developments in the neurosciences and biomedical arena that are directing changes in neuropsychology and psychiatry. It affirms the new omics environment while also highlighting the complications around NPs in the genome-to-phenome framework. In Chap. 2, we, Susan Santangelo and Vinoth Jagaroo, elaborate on some of the developments outlined in this introduction, developments that propel the NP approach. The focus on phenomics, connectomics, and RDoC details the landscape that compels the NP approach, especially NPs that are described at the level of "neural circuit." Chapter 3, by Vinoth Jagaroo, William Bosl, and Susan Santangelo, delves into the notion

of neural circuits. It appraises "circuit-centered" NPs by raising a number of factors that complicate circuit phenotypes, and also by addressing the value of circuit-centered NPs.

Part 2 of the volume (Chaps. 4–6) provides a review of the endophenotype (EP) concept. The currency it wields in the very subject of this volume necessitates some revisiting of the concept—the imperative in raising it has to do with the discourse on the broader concept of NPs. While NPs have evolved in ways far divergent from the EP concept, this concept has been a major influence in the NP/marker approach in neuropsychology and psychiatry. (A theme that is raised in the volume is that as much as the EP concept has facilitated a marker-based approach in the behavioral neurosciences; its inertia has also hindered a broader exploration of neural markers in all their complexity.)

In Chap. 4, a systematic review of the EP concept is given by Carrie Bearden, Anderson Winkler, Katherine Karlsgodt, and Robert Bilder. How EPs are differentiated from other markers and the criteria by which they are defined are laid out. Chapter 5, by Ellen Quillen, David Glahn, and Laura Almasy, further probes the strategy and utility of the EP approach but with special attention to the genetic and etiological heterogeneity of psychiatric diseases. As will be apparent to the reader, complications tied to the EP concept as seen through Chaps. 4 and 5, to varying degrees extend to NPs. Chapter 6, by Amy Vashlishan-Murray, provides a critique of the EP concept in the form expressed within an idealized notion of a genome-to-phenome framework. It examines assumptions made about heritability in GWAS studies, heritability of complex traits, and what they imply about the reliability and validity of genome-phenome situated EPs.

The third part of the volume (Chaps. 7–14) samples various neural and cognitive processes that have been or may be explored as NPs or cognitive EPs. Each chapter in this section describes a neural system or cognitive process and then explicitly examines how it may constitute an EP or NP. Because the extensive literature on cognitive EPs provided a common reference point for most of these chapters, they refer more frequently to the EP concept. The question of whether the cognitive or neural operation under discussion constitutes an EP or NP is also carried implicitly. It is to be judged by the reader against the backdrop of themes covered in the preceding parts of the volume.

Cognitive and neural phenotypes are still emerging concepts. It is infeasible that any single volume at this point can capture an optimally representative set of NPs. Nor can there presently be a finite set of questions and issues around NPs. The selection of putative or suggested NPs described in this second part of the volume was made through informal consultations with colleagues doing work on the subject and guided by surveys of the literature at the time the volume was conceived. It was also influenced by very practical constraints, namely aiming for a concise volume (fitting in with the Springer series of which this is part), and the availability of those invited to submit chapters. Completely different sets of topics in this second part of the volume could just as well serve the purpose of the section. The selection was configured so as to reflect a wide-ranging set of questions around the concept of the NP, not a wide-ranging assortment of possible NPs. (We

fully acknowledge that many kinds of NPs, including some that are prominent in the research literature, may not be represented in Part 3. The group of NPs constituted by functional magnetic imagining profiles is a case in point—a topic so extensive that it is better suited to a dedicated volume.)

Part 3 is arranged as follows: Chap. 7, by Kei Mochizuki and Shintaro Funahashi, deals with *response inhibition* and its related prefrontal circuitry. The authors then consider response inhibition as an EP with reference to attention deficit hyperactivity disorder. In Chap. 8, Bronwyn Graham and Mohammed Milad tackle *fear conditioning,* including neurobiological models of fear conditioning and extinction. Discussion of fear conditioning as an EP is also discussed in the context of anxiety disorders. *Error Processing* is the topic of Chap. 9 where Dara Manoach and Yigal Agam cover its behavioral hallmarks and its neural mechanisms. This is followed by a discussion of error processing as an EP through its manifestation in schizophrenia, obsessive compulsive disorder, and autism spectrum disorder. In Chap. 10, Marlene Oscar Berman and Kenneth Blum detail the neural network for *reward reinforcement*, with emphasis on the dopamine D2 receptor system. This is contextualized by a discussion of the evolutionary genetics of dopamine, followed by a discussion of reward dependence and deficiency as EPs, and how this plays out in addiction, impulsivity, and compulsivity.

Face Perception as an EP, the topic of Chap. 11, is discussed by Jennifer Richler and Isabel Gauthier. Concisely covered are the neurocognitve mechanisms of face perception, which is then examined as an EP in consideration of distinct functions of the Fusiform Face Area, and also against the complexity of face perception as cognitive–perceptual specialization. Chapter 12, on *Language Phenoptypes*, varies the general thematic structure of chapters in Part 3 in that it samples not a single EP specific to a functional domain or neural system but numerous EPs within a functional domain. Here, Mabel Rice and Helen Tager-Flusberg give attention to language EPs that have emerged in the realm of developmental language disorders and which can be examined in relation to typical language acquisition. Chapters 13 and 14 take us into the realm of elecrophysiological markers. In Chap. 13, Mei-Hua Hall discusses *event-related potentials* (ERPs) as EPs. Six ERPs are selectively profiled to demonstrate their utility in neuropsychiatric diagnosis and brain-behavior investigations. Chapter 14 by William Bosl relates to *encephalographic (EEG) data,* but the chapter offers a novel perspective on EEG data that is quite unlike the conventional interpretation of the data. Viewing the brain through the frame of dynamical systems theory ("chaos theory" in the mathematical and physical sciences), the chapter describes how subtle yet highly dynamic data are reflected in EEG, and how such data can be exploited in detecting brain disorders and in monitoring the brain over the life span. The chapter also brings forth the utility of and power of NPs in a data-driven context—describing how machine learning algorithms combined with portable EEG systems and big data platforms can be leveraged in the context of global mental health initiatives.

In Chap. 15, the concluding chapter, Susan Santangelo and Vinoth Jagaroo consider various implications for neuropsychology and psychiatry brought on by the

need for NP specification in the context of the omics operating environment. The chapter raises a few conceptual and programmatic adjustments from which these disciplines could benefit. They include as follows: Some constraints on the default (inertial) application of the EP concept in order that emerging concepts that better fit contemporary network models in neuroscience and genetics can be appreciated; refinement of cognitive and behavioral constructs in the form of NPs that are compatible with genome-phenome or other scientifically based causal-associative matrices; and the use of NPs as the currency by which these disciplines can partake in a data-driven knowledge environment via the tools of bioinformatics.

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Chapter 2
Brain and Cognition in the "Omics" Era

Susan L. Santangelo and Vinoth Jagaroo

The strategy of neural and cognitive markers as outlined in the introduction to the volume has been reinforced by some major research and theoretical developments. This chapter gives further consideration to these developments and includes some critical review. While the topics are greatly intertwined, they are described under specific subheadings below for ease of organization and explanation.

2.1 Genome-to-Phenome Mapping and Phenomics

Since the discovery of the structure of DNA, cell biology has been fundamentally organized around the now universal principal of DNA to RNA to proteins. How genes code for proteins, which in turn build cellular elements/cells, which form tissue types that then form organ systems, etc., has long been a central structural

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systems model in biology. Understandably then, the mapping of pathways by which genes exert their influence to build and modulate successive biological layers—genome-to-phenome ("gene-phene" or G-P) mapping—has been among the major goals of genomics (Bork et al. 1998; Korbel et al. 2005). With advances in molecular biology and with the advent of bioinformatics, the complex mappings between the genome and the phenome become tractable and feasible. G-P frameworks represent levels of analysis that describe and link the multi-level parameters in a complex biological matrix. And the mapping of these relationships hence becomes an all-important yet difficult challenge for genomics. The G-P framework is also an organizing model for systems biology " … that endeavors to quantify all of the molecular elements of a biological system to assess their interactions and to integrate that information into graphical network models … that serve as predictive hypotheses to explain emergent behaviors" (Hood et al. 2004).

In the complex equation of the G-P matrix, a thorough rendering of the picture at the phenotype level is a logical complement: If the expression of genes is to be traced to molecules, cells, tissue, organ systems, and behavior, then these characteristics, observable in different forms, are called to be systematically profiled. That is, characterization of the phenotype is a necessary complement to the progress in gene identification. Serving this agenda is the relatively new and flourishing discipline of *phenomics*. Schork (1997) made an early call for the discipline of phenomics (or "phenometrics" as he then suggested) which would seek to "unravel biochemical and physiological hierarchies leading from genes to clinical endpoints," a strategy that could be particularly useful in unraveling disease complexity.

> One could call the delineation of connections among various genes, gene products, intermediate phenotypes, and clinical endpoints "phenomics or "phenometrics" to match "genomics" and "biometrics" associated with aspects of pure genetic research. Such a science could proceed quite naturally by mapping genes involved in very low-level phenotypes and activities such as gene product variation and hormone amounts … and then attempt to link the phenotypes studied with higher-level phenotypes. (Schork, S107)

Figure 2.1 is an adaptation of Schork's schematic diagram representing a simplified "linear" relationship between a gene and its phenotypic product, via an expressed pathway. Many variations of such G-P schematics have since been rendered (e.g., Hunter and Borg 2003; Linden 2012), but Fig. 2.1 which is derived from the succinct version rendered by the Consortium for Neuropsychiatric Phenomics at UCLA (http://www.phenomics.ucla.edu/) has come to symbolize the phenomics strategy. Figure 2.2 is a more elaborate version and attempts to convey some of the hidden complexity in the model.

2.1.1 Phenomics as a Strategy and an Imperative

The case for phenomics, the systematic mapping of the entire phenome, has been cogently put forth in a series of articles by the UCLA group that has been leading

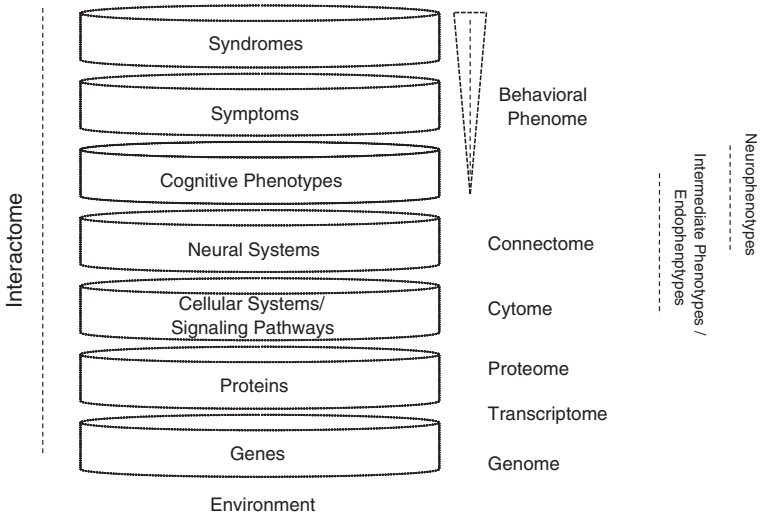

Fig. 2.1 Genome-to-phenome (G-P) framework. G-P frameworks may vary in the level of complexity spelled out and in the mappings described or hypothesized between the levels. The molecular levels typically described are genes (genome), elements, and processes of gene transcription (the transcriptome), and the resulting proteins (the proteome). Cellular levels characterize intracellular organelles, a host of intracellular processes, and cell types, altogether making a cellular phenotype (the cytome). Brain-related cellular organizational patterns and networks (the connectome) define phenotypes at a circuit level or in terms of morphologic or neuroanatomic features. Neurocognitive processes mediated by these brain systems may cluster into larger behavioral features or symptoms, and specific permutations of these may define a syndrome. Altogether, the behavioral elements comprise the behavioral phenome. Intermediate phenotypes or endophenoptypes are conceived as hidden (non-outward) phenotypes and more tractable to the genome. Neurophenotypes embrace a diversity of neural and cognitive systems and may overlap with cognitive endophenotypes. Interactions within a stratum or across the G-P strata can also be mapped (the interactome)

many initiatives in cognitive and neuropsychiatric phenomics (Bilder 2008; Bilder et al. 2009a, b; Freimer and Sabatti 2003). A central point made is that the explosion of genomics has given rise to a scenario where the large amounts of high-dimensional genomic data are unmatched by current phenomic dimensions. Finer levels of granularity and precision need to be brought to codifying the phenome so that a meaningful relational interface with the genome is facilitated. Phenotype descriptions that are incompatible with the linkage served by a G-P framework and genomics can hold back genotyping explorations (Freimer and Sabatti 2003) and has aptly been referred to as a "rate-limiting" step in terms of reaping the gains of genomic discovery (Bilder et al. 2009b). In making the case for the systematic cataloging of phenotypes, Freimer and Sabatti have called for a "Human Phenome Project," which would necessarily involve centrally coordinated and funded large-scale efforts toward objectively defined, refined, and standardized phenotypes. They also stipulated that such a strategy for phenotype discovery has to be enabled