Chapter 2
Brain and Cognition in the "Omics" Era

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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

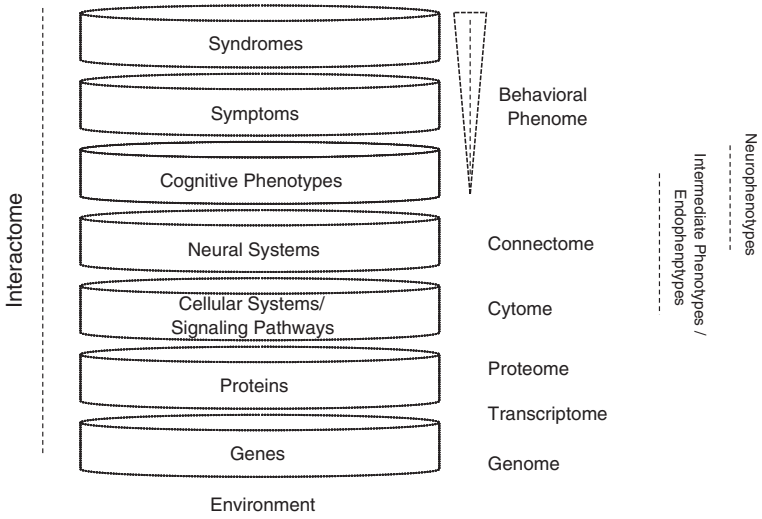

Fig. 2.1 Genome-to-phenome (G-P) framework. G-P frameworks may vary in the level of complexity spelled out and in the mappings described or hypothesized between the levels. The molecular levels typically described are genes (genome), elements, and processes of gene transcription (the transcriptome), 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

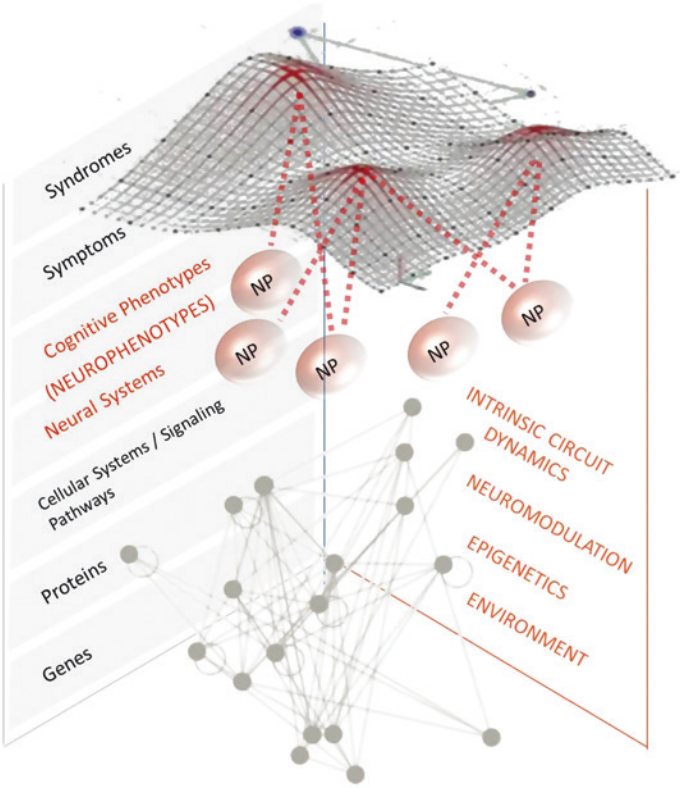

Fig. 2.2 Three-dimensional schematic of G-P space with highlights on the relational position of neurophenotypes. Multiple genes can have convergent effects on one or more NPs via intervening molecular and cellular systems (not detailed). One or more NPs may converge to produce a behavioral phenomic feature (symptom) of a disorder, and multiple features may define the disorder. The differential expression and permutations of phenomic features (manifesting as variations of a disorder) are represented in the figure by a multivariate Gaussian distribution. The *left wall* in the figure represents the G-P strata. The *right wall* represents environment, epigenetic, neuromodulatory, and other variables that are not driven by the genome but that may shape NPs (detailed in Chap. 3)

by novel methods of discovery with high-throughput analysis, which in turn will require a sophisticated informatics platform. And therein is a key aspect of phenomics—that the delineation of the phenome on scales compatible with a systems biology interface is necessarily informatics-driven. The strategy of phenomics as "the systematic study of phenotypes on a genome-wide scale" (Bilder 2008) "aims to capitalize on novel high-throughput computation and informatics technologies to derive genome-wide molecular networks of genotype-phenotype associations, or "phenomic associations" …" (Lussier and Liu 2007). Large-scale, coordinated efforts to this effect have already begun. While many phenomics consortia

centered on plants, mice, fish, and other non-human species have emerged, the leading consortium centered on (human) brain-related phenomics is the Center for Cognitive and Neuropsychiatric Phenomics (CNP) at UCLA (http://www.phenomics.ucla.edu/). This initiative is now well known for its investigations of working memory and response inhibition, from molecular to cognitive levels, using the case examples of schizophrenia and bipolar disorder.

2.1.2 Phenomics, Candidate Gene Studies, and GWAS

In the context of neuropsychiatry, the impetus for phenomics—serving the G-P associative framework—has been strengthened by the lack of meaningful findings both from candidate gene studies and, to a lesser extent, from GWAS: It has long been realized in psychiatric genetics that the candidate gene approach applied in the effort to seek genetic risk factors in psychiatric illness has not been particularly useful, in part because it involves a certain gamble that the investigator has chosen the correct genes to investigate, which is difficult, given the lack of empirical data on the underlying biology of psychiatric illness (McCarroll et al. 2014). For this and other reasons, including inadequate sample size and low statistical power, most positive associations between specific SNPs and diseases from candidate gene studies in psychiatry have not been replicated (Farrell et al. 2015; O'Donovan and Owen 1999; Sher 2002). The heterogeneity of psychiatric phenotypes, that is, their neural and behavioral permutations and overlaps, and conditions under which they present, may be best explained through combinatorial models that involve many genetic variants, epistasis, differential pathway expression, and a whole range of environmental variables that are seldom measured or modeled in genetic investigations. Hence, with such heterogeneity across the phenotypes, the effects of individual gene variants in the shaping of a particular phenotype are blurred (Congdon et al. 2010). (Section 2.3.2 references some of the often cited candidate genes in the context of neuropsychiatry.)

Until very recently, GWAS has not fared much better. While genome-wide association studies have had wide success in identifying SNPs tied to various types of medical conditions such as Crohn's disease, and Type I and Type II diabetes (Billings and Florez 2010; Franke et al. 2010; Liu and Anderson 2014), attempts at finding genes associated with neuropsychiatric conditions have lagged behind. It has long been argued that this has been due in large part to insufficient sample sizes and insufficient power of individual psychiatric GWAS to date (see Bloss et al. 2010; Congdon et al. 2010). In fact, recent meta-analyses of psychiatric GWAS data carried out by the Psychiatric Genomics Consortium (PGC) have lent support to this argument by demonstrating a clear correlation between the number of patient genomes interrogated and the number of significant associations found (in analyses of studies carried out between 2009 and 2014). Perhaps the most exciting demonstration of this was published in 2014 by the Schizophrenia Working Group of the PGC, which identified 108 statistically significant loci

associated with schizophrenia with a combined sample of nearly 37,000 cases and over 113,000 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Although 83 of the 108 loci identified in the PGC schizophrenia GWAS meta-analysis were novel, the most strongly associated locus in this and some previous GWAS was the major histocompatibility complex locus (MHC). The MHC contains genes involved in immune response, and the significant association with schizophrenia which was first identified in 1979 (McGuffin) was for a long time thought to be an artifact until a recent study, published in January 2016: Sekar et al. confirmed that not only is the association real, but that a common variant of a gene in the MHC locus—C4—produces proteins—C4-A and C4-B—that influence the rate of synaptic pruning. By analyzing the genomes of over 64,000 people, and then confirming this in studies of knockout mice, this study showed that an overabundance of C4-A leads to over pruning of synapses in the prefrontal cortex during critical periods of development. This paper, which followed up on a significant GWAS finding, was the first to demonstrate a clear biological mechanism for the development of schizophrenia. So one might plausibly argue that as sample sizes increase to be comparable to those used successfully in other chronic diseases such as Crohn's disease and diabetes, GWAS will be just as successful in identifying common variants (whose effect sizes are necessarily quite small) for psychiatric illness as it has been in these other disorders.

Nonetheless, the initially posited reasons for the difficulty in linking genes to neuropsychiatric conditions via GWAS (see Bloss et al. 2010; Freimer and Sabatti 2003) still have some relevance. They have to with (a) the heterogeneity of neurophenotypes; (b) the "dispersion" or scaling down of genetic effects across a phenome due to gene–gene and gene–environment interactions, and (c) the ambiguous, imprecise manner by which neural and cognitive functional systems have traditionally been described. Neuropsychiatric and neurocognitive illnesses are most often complex in terms of their symptom and neural systems profiles (phenotypic complexity), and the genetic components may be just as multifaceted (genetic complexity). A systematic dissection of brain-mediated illnesses requires a systematic rendering of physiological systems and mental operations to which genes and gene expression pathways can be tied.

2.1.3 Aligning Gene Networks with Phenotypic Elements

That the architecture between the genome and phenome is complex, making for enormous etiological complexity of neurocognitive and neuropsychiatric conditions, is generally not underestimated. However, giving significant boost to the G-P/phenomics agenda is the increasing evidence that this complexity can be unraveled with new, sophisticated research models and methods applied to the problem. Consider the following illustrative examples: The modular view of genes posits that genes work together or co-express within discrete biological modules (Oti and Brunner 2007; Wu et al. 2009): Drawing a modular organization among

genes and phenotypic features helps recognize G-P associations by reducing the complexity in G-P maps. This perspective is ultimately concerned with aligning gene networks with phenotype clusters. It highlights that a module (phenotype), for example, a cell type of an organelle or a protein complex, which then presents as a disease phenotype, can be tapped for a more tractable linkage down into the gene level. Further, the differential clustering of a common set of modules may help to map the relationships between a set of genes and their expression in syndromes with overlapping features. Diseases that share common phenotypic modules may share common gene modules. As Wu et al. (2009) have described, the disease phenome can be depicted as overlapping networks of disease features. "Similarly, the interactome is a network of genes linked by physical interactions between their protein products. The two networks are further linked by gene-phenotype associations … the proximity between disease genes in the gene network could explain the phenotypic overlap of diseases … [suggesting] a global concordance of topology between the phenotype network and the gene network" (p. 98). Franke et al. (2006) have well extolled the prospect of gene networks mapped to phenotype networks—where the functional relationships between gene modules can be mapped differentially to the overlying symptom clusters that present as disease. And a proof of concept that phenotypic overlap signals genotypic overlap has been systematically demonstrated (Wu et al. 2009).

Oldham et al. (2008) examined gene transcriptional patterns (the transcriptome) in cells taken from the cerebral cortex, the caudate nucleus, and the cerebellum of the human brain. Their analysis of gene co-expression in these cells revealed modules of co-expressed genes, each corresponding to unique cellular makeup of the brain regions analyzed. What was also remarkable about the study, aside from providing the first views into an organization of the transcriptome of the brain, was that the transcriptome modules were filtered out through the application of a bioinformatics/systems biology-based method of network analysis and correlation patterns[1] (ft. WGCNA). In this study, conducted "in silico," the results were gained "without making any a priori assumptions regarding the cellular constitution of the tissue analyzed …" (Oldham et al. p. 1279).

The study of the modular organization of genes—how they co-express in gene modules and how such modules and genetic programs govern the development of larger-scale neuroanatomic circuits—is at the cutting edge of developmental neurobiology and neurogenetics (see Geschwind and Rakic 2013; Oldham et al. 2008; Parikshak et al. 2015). "[C]omparative genomics provides a powerful platform for identifying the genes and adaptive regulatory changes involved in cerebral cortex expansion, arealization, and other human-specific cellular or connectivity phenotypes." (Geschwind and Rakic 2013, p. 637). For there to be a more meaningful analysis of a surface-topological phenotype landscape, one where symptom clusters (phenotype networks) can be tied to gene networks (see Fig. 2.1),

[1]Weighted Gene Co-expression Network Analysis (WGCNA) is a software package used to map gene correlation and cluster patterns from microarray drawn samples.

the necessity of a uniform and structured definition of phenotypes, is once again emphasized (Oti and Brunner 2007).

Daunting as genome-to-phenome integration may seem, and as impractical as the goal of mapping NPs to all the lower levels in the G-P space may appear, novel solutions are matched to the complexity of the task. The studies of modules of co-expressed genes and transcriptome modules cited above were made possible through the application of network science (a branch of mathematics and bioinformatics)—using network methods to parcellate genes and their transcripts within a broader molecular matrix: "Gene network methods are now being applied to integrate genetics with transcriptomics, epigenomics, and proteomics to identify causal molecular drivers of cellular, circuit-level, and brain-wide pathology in disease" (Parikshak et al. 2015). Such integration has been generating novel insights into autism spectrum disorder (Geschwind 2011; Pinto et al. 2014; Sanders et al. 2015) and brain degenerative diseases (Chen et al. 2015; Miller et al. 2013), as well as the evolution of the brain as relates to cognition (Geschwind and Rakic 2013; Konopka and Geschwind 2010). That very systems-level understanding that phenomics strives for in the interest of a fine-tuned, neuroscience-compatible understanding of neuropsychiatric conditions has certainly begun.

2.2 Connectomics

The "connectome" refers to an envisaged, detailed map of the structural connections of the brain on all scales, from the microscale cellular level to the macroscale of white matter fiber systems. Hence, *connectomics* is the omics-driven initiative toward mapping the connectome. It is concerned specifically with the structural arrangements and connectivity patterns of neurons and glial cells in the matrix of the brain, while recognizing the emergence of functional circuits via organized connections (Behrens and Sporns 2012; Sporns 2011, 2012; Sporns et al. 2005). Connectomics is, by definition, informatics-heavy. In view of the complexity of neural architecture and the scale of data volume generated by its mapping, connectomics relies on numerous novel tools for high-throughput image acquisition of micro- and macrocircuitry, and visualization of circuitry on a meta-scale through image integration (see Helmstaedter 2013; Marcus et al. 2011; Shibata et al. 2015).

Connectomics as an initiative has had a separable trajectory in relation to the general calls for phenomics. However, the connectomics and phenomics initiatives happen to coincide. The connectomics agenda neatly fits in with the mission of phenomics, and both of these developments are occurring at the same point in time. For all practical purposes, connectomics can be seen as a major avenue in brain science that happens to serve the phenomics agenda well. Many of the questions and issues seen within the connectomics initiative apply equally fittingly to phenomics at large. The issues provide a remarkable window into the challenges of phenomics as it relates to neural circuitry (and this is discussed later in this chapter).

Lying at opposite ends in terms of an anatomic-physiological scale are the two major branches of connectomics: (a) connectome mapping through fMRI (hence in vivo) methods, also known as MR connectomics, and (b) connectome mapping via predominantly in vitro methods, e.g., tissue slices viewed with microscopy and assembled with 3D visualization.[2] A review of either of these branches falls far beyond the scope and purpose of this chapter. Instead, we provide a few key points below, as they relate to the discussion of phenomics. (Various images in Fig. 2.3 (from Leergaard et al. 2012) correspond to the themes of this subsection.)

2.2.1 Connectomics on the Macroscale

MR connectomics has been extensively discussed in recent years (see, e.g., Behrens and Sporns 2012; Craddock et al. 2013; Kelly et al. 2012; Snyder and Raichle 2012; Van Essen et al. 2012; Zuo et al. 2010). MR connectomics explores white matter fiber systems and tracts by employing diffusion tractography (diffusion MRI) and, increasingly, with the resting-state fMRI (R-fMRI) paradigm. (In diffusion tractography, the paths of white matter bundles are inferred on a millimeter scale—based on the selective pattern and speed by which water molecules diffuse along and within myelinated axons. In R-fMRI, intrinsic brain connectivity is inferred based on co-activation of two or more cortical areas: Fluctuating activation patterns across spatially separated brain regions are correlated in terms of spontaneous co-activation patterns. The robustness and consistency of these statistical correlations are considered indicative of a structural network that functionally links the regions. Such functional connectivity is used to map out a "functional connectome.")

R-fMRI, also known as intrinsic functional connectivity (iFC), has grown explosively over the short span of the past ten years. Central to the R-fMRI approach is the value placed on endogenous activity across a neural network seen when the brain is "at rest," meaning, not engaged in evoked activity. This is in contrast to conventional task-dependent fMRI where only those response patterns phase-synchronous with the experimental task are of interest. In R-fMRI, the interest is in functional interactions between loci in circuitry while "at rest"—referred to as resting-state functional connectivity (RSFC). However, since networks identified through R-fMRI can also be identified with task-dependent activity, some have suggested that the term "task-free MRI" (TF-MRI) be used instead (Jones et al. 2012). Nonetheless, the method sheds light on intrinsic networks and modules of the brain, the spatial organization and temporal interaction

[2]The term "connectome" has come to stand for all scales of neural mapping, from microscopic (cell/synaptic) arrangements to macroscopic (white matter) projection systems, though it has been suggested that "connectome" better references microscale connections, and that the term "projectome" better represents macroscale connections (see Kasthuri and Lichtman 2007).

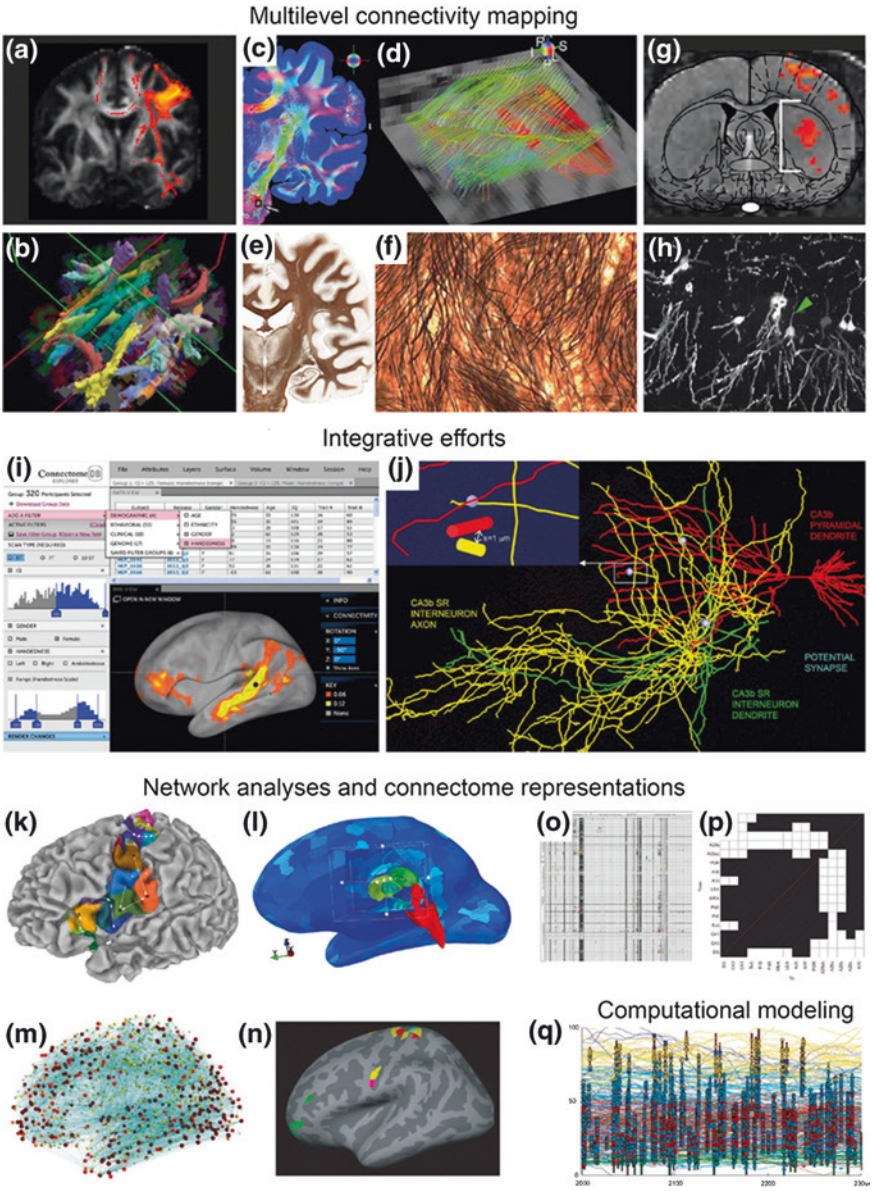

Fig. 2.3 Adapted and reproduced from the open source journal, Frontiers in Neuroinformatics (2012) 6:14. Leergaard TB, Hilgetag CC and Sporns O. *Mapping the connectome: multi-level analysis of brain connectivity*. Figure 1 in its original source served as a summary illustration of various forms of connectivity data/various types of connectomes (human and non-human): MRI tractography and related mapping (**a**–**f**); combined optogenetic and fMRI mapping (**g**); histological imaging (**h**); informatics tools for the aggregation and integration of connectivity data (**i** and **j**); brain network analysis—connectivity-based cortical parcellations and network motifs (**k**–**n**); connectome matrix representations from large-scale data mining efforts (**o**–**q**). Figure 1 serves equally well to represent multiple scales of circuitry and multiple forms of neurophenotypes—drawn from functional imaging parcellations or connectivity networks; histological and in vivo mapping data; and informatics-driven computational platforms

of these networks in the normal brain, and how they may be disrupted in neurocognitive and neuropsychiatric conditions, which is of key interest in R-fMRI.

Employing both diffusion fMRI and R-fMRI, the Human Connectome Project (HCP)[3] seeks to create a detailed, macroscale map of the "typical" connectivity in the normal adult human brain" (Barch et al. 2013; Smith et al. 2013).

2.2.2 MR Connectomics and Neurophenotypes

Nodal, regional, or dynamic permutative disruptions to functional or topological organization of large-scale brain networks, identified via MR connectomics, may constitute phenotypes at the regional or macrocircuit level (see Fornito and Bullmore 2012). R-fMRI is surpassing task-dependent MRI in terms of its utility in identifying NPs (Castellanos et al. 2013). Interpretation and modeling of the functional connectome rests on the critical tools of graph theory, graph statistics, and network science (branches of mathematics and statistics) that describe the principles of by which the nodes of complex systems interact.[4] They may reveal network organization—modular/nodal architecture, centrality in a network, nodal changes, and functional efficiency of the network. A picture of network dynamics is generated and may include, for example, specific patterns of temporal dependencies across nodes that are otherwise hidden in the network architecture. Brain networks derived from MR data are cast as annotated graphs. (The nodes drawn from fMRI studies are interpreted to represent distinct cortical, subcortical, or cerebellar nodes, though an "optimal" parcellation scheme is debatable.) Graph theory is then applied to understand the dynamics of brain network topology—a very new and emergent subspecialty in MR connectomics—that seeks to apply computational modeling to connectomics data in order to understand brain network dynamics as they manifest in neuropsychiatric disorders (see Cabral et al. 2014; Deco and Kringelbach 2014; Fornito et al. 2015; Xia et al. 2016, for excellent renderings of this topic). This area of computational connectomics is particularly focused on the following questions: What are the mechanisms by which aberrant network dynamics manifest in brain disorders? What is the network topological permutation (signature pattern) for each of various brain-related disorders? How can the functional dynamics of networks garnered through connectomics describe

[3]The HCP, run by the US National Institutes of Health, went into effect in 2010—funding research projects using noninvasive (fMRI) methods to begin the ambitious agenda of mapping out the connectome. See http://www.neuroscienceblueprint.nih.gov/connectome/.
The HCP has also been the subject of vigorous debate, facing questions about feasibility, viability, and utility. See Nature Neuroscience Editorial (2010) for a synopsis of the debate. Some of the issues are also touched upon in this chapter.

[4]"Graph" or "graph layout" in mathematical graph theory generally refers to the connectivity pattern in a network.

and predict maladaptive or pathological brain states? MR connectomics hence presents novel forms of NPs based on pathoconnectomic patterns or spatiotemporal dynamics across brain regions.

Potential NPs derived from MR connectomics, and centered on brain network connectivity patterns or functional dynamics, have been described across the spectrum of neuropsychiatric and neurocognitive disorders (for reviews, see Deco and Kringelbach 2014; Di Martino et al. 2014; Xia and He 2011). Further, such studies have also demonstrated that different brain disorders with overlapping symptomatology can be explained in terms of permutative profiles of large-scale canonical brain networks (Crossley et al. 2014; Fornito et al. 2015). Even though many refinements are still needed in the functional connectome initiative, it is a central player in image-based neurophenotypes and is especially compelling in the context of RDoC and the big data/knowledge discovery environment (Castellanos et al. 2013).

2.2.3 Connectomics on a Microscale

The second major branch of connectomics explores neural microcircuitry at the cellular and synaptic level—cellular-resolution connectomics. It seeks to catalog the brain in terms of neuronal and synaptic arrangement.

The resolution at which single cells, neurites, or synaptic structure are described is in the nanometer range. Microscale connectomics is integrally tied with high-throughput electron microscopy—which, by virtue of its power and its limitations, fundamentally shapes the initiative. A common data collection/analysis method used is the automated microtome that produces serial slices of neural tissue, each then passed on a conveyor belt to an automated electron microscope that generates a serial image set. A block of sequenced images is then analyzed manually and/or with the aid of computational vision (analysis) technology in order to align contiguous tissue elements and hence trace the neural structures (see Helmstaedter 2013; Shibata et al. 2015). The assembled 3D image block renders a cubic section of tissue volume (shown in Fig. 3.1d in Chap. 3). A saturated (comprehensive) connectomic reconstruction of a tiny sample (1500 μm^3) of mouse neocortical tissue analyzed with the above-described procedure was found to contain about 1407 axons and 1700 synaptic connections and immense synaptic redundancies (Kasthuri et al. 2015). With the currently estimated 86 billion neurons in the human brain (Azevedo et al. 2009), the prospect of high-density mapping of the entire brain is daunting even with automated microscopy.

Nonetheless, the connectomics initiative at the cellular level has particular instructive and informative value for the agenda of neural phenomics and RDoC: Aside from being aimed at the very goal of mapping phenomic structure at the neural level (and hence mapping circuits), the exploration of connectomics at this level leads to a host of questions and issues. These happen to impact the putative notions of circuits in RDoC and in circuit-centered neurophenotypes.

A vigorous debate about the need, utility, and practicality of creating a detailed map of the brain has ensued over the past decade (see: A critical look at connectomics 2010; Markram 2012; Marx 2013; Morgan and Lichtman 2013). There remains no consensus about the primary goals of connectomics, nor is there agreement about a set of standardized mapping techniques (Lichtman et al. 2014). Expressed definitions of potential scope varies from representational-probabilistic maps to detailed structural and connection mapping at the cellular scale (i.e., every neuron and synapse) to a wiring diagram that could also shed light on molecular and synaptic variations (see Lichtman et al. 2008; Morgan and Lichtman 2013).

Mapping the brain at such extremely fine levels of detail inevitably gives rise to the following questions: Is there an optimal level of resolution that best serves the understanding of the brain? and How will a mapped connectome account for dynamic changes (e.g., dendritic arborization and synaptic variables) that change with experience, maturation, and intrinsic modulatory factors? Some of those leading the efforts in microscale connectomics are careful to acknowledge that issues such as density scale and circuit stability may never be met with commonly agreed upon formula, but nonetheless have argued that a comprehensive, high-quality map of the brain is necessary if brain functions are to be understood (Kasthuri and Lichtman 2007; Lichtman and Sanes 2008; Morgan and Lichtman 2013): Having a detailed structural correlate against which biological and behavioral functions can be understood is better than a coarsely described correlate. Certain fundamental or canonical characteristics of brain networks may only be understood by mapping the connectivity patterns. Again, it is the challenges of microscale connectomics as thus far rendered through the actual initiative that translates into cautionary lessons and complications for neural phenomics and RDoC. This is laid out in Chap. 3 in a larger appraisal of neural circuits as neurophenotypes.

2.3 Research Domain Criteria (RDoC) and Related Developments

The old and difficult question of how to conceptualize and classify mental disorders took a very new turn in 2008. The US National Institute of Mental Health implemented a strategic five-year plan aimed at transforming the understanding and treatment of mental illnesses via a systematic application of scientific research. It laid down the following as the first objective among four in the strategic plan: "… in order for research on mental disorders to more fully harness the scientific power of brain-behavior science, sound efforts must be made to redefine mental disorders into dimensions or components of observable behaviors that are more closely aligned with the biology of the brain. Such an effort will result in a research-based description of key elements of mental disorders, providing even greater traction on the potential mechanisms that can cause mental suffering and

targets for more effective preemption and treatment" (National Institute of Mental Health 2008; www.nimh.hih.gov/about/strategic-planning-reports/index.shtml).

This initiative, called *Research Domain Criteria* (RDoC), has since been extensively discussed.

2.3.1 RDoC Structure and Rationale

The impetus for RDoC, and its structure and rationale, are given summary focus here—drawn from the NIMH Strategic Plan (2008), Berenbaum (2013), Cuthbert and Insel (2010a–c), Insel and Cuthbert (2009), Morris and Cuthbert (2012), Morris et al. (2014), Sanislow et al. (2010), Simmons and Quinn (2014).

RDoC prioritizes the identification and integration of biomarkers as they aggregate and constellate in mental disorders. The emphasis on a brain-based or evidence-based nosology is in contrast to conventional diagnostic systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or the *International Classification of Diseases* (ICD). These well-known classification systems rely on qualitative interpretations of behavior which are then matched to some degree to symptom clusters; they are phenomenologically based. Such cluster-based aggregations of signs and symptoms exclude other valuable phenotypic information and do not necessarily reflect scientific constructs of psychopathology.

A great deal of heterogeneity exists within and across clinical populations described by conventional diagnostic categories. This heterogeneity and comorbidity across psychopathologic categories can be described in large part as complex functional permutations of a broad yet common set of neural systems and genes. Mental disorders are polygenic. Yet conventional diagnostic systems are ill suited to profiling differential patterns of expression arising from common genes and neural systems. Discrete categories are forced and have artificial and "fuzzy" boundaries. Symptom cluster-based diagnostic systems do not lend themselves to a scientific bridging with the biological systems that mediate the behavioral symptoms. They offer no interface for biologically based research initiatives—where mental disorders can be deconstructed along domains of perceptual, cognitive, and emotional processes, mediated by complex neural systems. The overlapping symptoms in the clusters given by conventional classification may share common neural systems driven by common gene modules. And while such insights are progressing in neuroscience and genetics, the current diagnostic systems are not complementary to the scientific or evidence-based models. In contrast to neural systems and gene networks, the diagnostic systems are not informed by nor do they serve the understanding of phenotypic heterogeneity and clustering.

In response to these shortcomings, RDoC is geared to a formulation of a new system by which psychopathology is described. It proposes a system that is a based on a biologically informed conceptual model of the brain and brain-mediated disorders that is supported by empirical data (Fig. 2.4).

	Units of Analysis							
	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Negative Valence Systems								
Active Threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrativenon-reward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working Memory								
Declarative Memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation and Attachment								
Social Communication								
Perception and understanding of self								
Perception and understanding of others								
Arousal/Regulatory Systems								
Default mode network								
Sleep/Wakefulness								
Biological Systems								
Arousal								

Fig. 2.4 Summary of RDoC's matrix-based research framework. The *rows* in the matrix describe constructs or dimensions that represent the basic units of analysis. Related constructs are grouped as functional domains of behavior (*bold headings*). The *columns* represent the multiple perspectives or analytic variables (genome–phenome) that can be applied in describing a construct

The RDoC strategy also firmly embraces a brain-based marker approach. This compelling initiative has re-energized and reframed the utility of the NP approach in the behavioral and clinical neurosciences. The NIMH plan set forth various strategic objectives, among them (paraphrased from pp. 6–8, www.nimh.hih.gov/about/strategic-planning-reports/index.shtml):

- Development of an integrative understanding of basic brain–behavior processes that provide the foundation for understanding mental disorders;
- Identification and integration of biological markers and behavioral indicators associated with mental disorders; and
- Development, for research purposes, of new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological mechanisms.

To this effect, the RDoC framework is based on discrete dimensions of behavior and on neurobiological systems that can be measured. As a starting point, the guiding model for the RDoC classification framework specifies "constructs" or dimensions of behavior, such as *Approach Motivation* and *Working Memory*. Each

construct may have numerous subconstructs. Constructs fall under larger behavioral domains. RDoC incorporates the theme of multiple levels of analysis—a construct might be analyzed at the levels of genes, molecules, cells, circuits, physiological systems, behavior, etc. However, the RDoC system centers itself around the "neural circuit" level of analysis (detailed further below).

RDoC constitutes an initial instantiation of a model that details how scientific constructs in the biological sciences and behavioral neurosciences can be integrated to promote the discovery of a scientifically based description of behavior. RDoC applies a matrix-based research framework: The rows in the matrix correspond to the constructs or dimensions representing basic units of analysis, and these are subject to refinements with emerging research. Related constructs group together to form functional domains of behavior. An example of a domain is *Negative Valence Systems*, and it includes the constructs of *fear* and *potential threat*. A construct can be described from multiple perspectives, that is, various units of analysis (the variables). These analytic variables—genes, molecules, cells, circuits, physiological systems, behavior, and self-reports—are each represented by the columns of the matrix. The neural circuit level of analysis is the reference point around which the other levels of analysis are organized. RDoC describes cognitive and neural features along a continuum—normal traits with variations in "dimension." Neurophenotypes (stable markers) of these traits would therefore hold much more utility.

In theory, this leads to the possibility of a diverse set of NPs with numerous permutations, where combinatorial associations of neurophenotypes make for particular multivariate patterns that may more accurately reflect mental disorders. What if the areas of overlap and the areas of distinction in symptomatology between different psychotic disorders, or across each of the spectral patterns seen in autism or ADHD, could be described in terms of the common or specific permutations in the genetic-neurodevelopment-neural systems matrix? Lofty as this ideal may sound, it is a central, transformative idea behind RDoC. "RDoC is an attempt to create a new type of taxonomy for mental disorders by bringing the power of modern research approaches in genetics, neuroscience, and behavioral science to the problem of mental illness. … RDoC is a new, comprehensive effort to redefine the research agenda for mental illness" (Insel and Lieberman 2013). Simmons and Quinn (2014) have described RDoC as representing a potentially new classification system for research on mental illness. RDoC is clearly a working model, dynamically structured, and fully open to modifications. Constructs and domains can be reorganized and refined, units of analysis can be added, and the criteria for construct definition can be revisited.

As is the case with any multi-leveled data integration project in biology and medicine (see Chap. 15), critical to the RDoC initiative is a data sharing and data integration platform. Bioinformatics tools and infrastructure are central to this agenda—searching for patterns among diverse sets of data and integrating data so as to make data-driven discoveries. RDoC's data platforms are necessarily federated data repositories, and these are elaborated in Sect. 15.1.

2.3.2 RDoC's Circuit-Level Pitch

As an operational model, RDoC necessarily rests on a few postulates and assumptions about the nature of mental illnesses. A central assumption is that these illnesses are rooted in dysregulation of brain circuitry (Cuthbert and Insel 2010a; Morris and Cuthbert 2012). This then provides the basis for other assumptions or hypotheses as follows: Variations of a circuit phenotype can account for variations of a disorder; developmental and environmental effects on the brain can be inferred at the circuit level in that they modify the circuit phenotype; neuroscience methods such as functional imaging and electrophysiological assessment can be used to profile the circuitry; and, intervention and treatment can target the circuit-expressed mechanism. Since the same set of cognitive or emotional processes may differentially play out in related disorders (accounting for overlapping symptomatology), studying the circuit representation of a process may also give insights into underlying circuit variations in a subset of disorders. For example, the "fear circuit" expressing fear potentiation may have distinct signatures for OCD and generalized anxiety.

As a practical, strategic constraint, a manageable reference point centering the approach at the circuit level enables bidirectional data integration—drilling downward to cellular and molecular levels or upward toward behavioral manifestations. Having a central organizing point of reference makes for a simpler integrative strategy as opposed to the specification of all possible neural/cellular constructs, which could be proliferative and unwieldy.

RDoC does not delve explicitly into notions or conceptions of neural circuits, but certain notions are implicit in the discussions in RDoC. Circuits as currently conceptualized in RDoC can be traced to a few familiar influences: The 2008 NIMH Strategic Plan Statement on RDoC references a few developments such as optogenetics and MR tractography that were emerging at that time tied to neuron labeling and white matter tracing, respectively. The NIMH Draft Statement on RDoC (version 3.1, June 2011) indicates that ' "Circuits" can refer to measurements of particular circuits as studied by neuroimaging techniques, and/or other measures validated by animal models or functional imaging (e.g., emotion-modulated startle, event-related potentials)–.' At a NIMH workshop on cognitive systems (October 23–25, 2011), convened to clarify constructs in RDoC's Cognitive Systems Domain, elaboration was also given to the various units of analysis. The workshop proceedings (revised May 2012) describe working models of circuits for a number of broad cognitive domains (e.g., attention, perception, and memory). The corresponding circuits listed reflect the contemporary influence of cognitive neuroscience and functional imaging. The referenced circuits are for the most part large-scale neuroanatomic projection systems or cortical parcellations. They are systems such as the "dorsal attentional network (superior parietal lobe, frontal eye fields, DLPFC)"; sensory projection pathways such as the magnocellular and parvocellular systems in vision; major sensory association systems such as the ventral and dorsal extra-striate projections in vision ("what" and "where" pathways); the

tri-synaptic loop of the hippocampus; and various well-documented cortical nodes (e.g., the frontal eye fields, the nucleus accumbens.) Bearing in mind that this represents an initial instantiation of a working model that is yet to be elaborated, some of the postulated circuits still lean heavily toward a particular neuroanatomic system when more than one candidate system exists. For example, the cognitive processes of response selection, inhibition, or suppression were associated by the workgroup overwhelmingly with cortical (prefrontal and posterior parietal) areas and with minimal reference to the striatum.

Another shaping force of the circuit-level pitch in RDoC is the candidate gene approach to phenotypes which has aided in the linking of genes to circuits to cognition in the G-P explanatory matrix (see Insel and Cuthbert 2009). Among the many known examples of genes that have been linked to cognition via factors expressed at the neuronal/synaptic level are those described below (see Craddock et al. 2006; Owen et al. 2004; Sabb et al. 2009). And while the strength of these G-P associations, especially the links from circuits to cognition, are generally weak or unclear, they may signal firmer associations: (a) The association of the val158met polymorphism with significant increases in catechol-*O*-methyltransferase (COMT) activity (dopamine catabolism) in the dorsolateral prefrontal cortex in patients with schizophrenia, and subsequent effects of neuropsychological tests of set switching and other aspects of "executive" function. (b) The association of various risk haplotypes with dystrobrevin-binding protein 1 (DTNBP1 or "dysbindin"), and presynaptic reductions of dysbindin glutamatergic neurons in cortical and hippocampal sites in schizophrenia with a range of effects on cognitive tasks. (c) The association of a variant of the Taq1 allele with the dopamine D2 receptor (DRD2), reduced D2 binding in all areas of the striatum, and possible effects on cognitive measures.[5]

In view of such developments, RDoC has reasonably set the "neural circuit" as the central point of reference for describing cognitive processes and mental disorders. Implicit in RDoC's circuit-level pitch are certain models of circuits—some being large-scale cortico-cortical or cortico-subcortical projection systems, some operationalized as neural/cortical nodes of the kind presented by functional imaging, and some defined at the synaptic level. RDoC clearly also makes allowance for finer elaboration of neural circuits as may be relevant to the cognitive processes set forth by RDoC. Nevertheless, there is a difficult line to be straddled in making both accommodations—purveying some particular notions of circuits while also trying to be open to other renditions of circuits. The assumption that RDoC makes that psychopathology can largely be traced to biology, spelled out in terms of neural circuitry, has been well critiqued in the research literature on RDoC (see, e.g., Nesse and Stein 2012). And any a priori assumption about

[5]In most such studies attempting to link a neural phenotype to a cognitive phenotype, major confounds arise with the use of established neuropsychological tests and batteries, as these measures compound numerous neural processes and cannot be parsed neatly to neural circuits; ironically, this problem, writ large, provided the impetus for this book. See also Chap. 15.

the nature of mental disorders inevitably shapes the kinds of research questions and models designed to study the disorders (Berenbaum 2013). In the same vein, assumptions about neural circuits, their form, size, functional properties, genetic drivers, etc., and assumptions shaped heavily by popular ideas in cognitive neuroscience, will give focus to a mere sliver of circuit forms and features in the immensely broad spectrum of circuit definitions in neuroscience.

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