Book chapter

Methodological considerations: Integrating measures across assessment modalities

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Summary

Large-scale multimodal data have never been more accessible in neuroscience, providing an unprecedented opportunity to study interindividual differences. Integrating these data across assessment modalities, as opposed to treating each modality in isolation, requires careful consideration of both theoretical and practical nature. This chapter provides an overview of key concepts essential for truly integrative clinical neuroscience. Successful translation of basic research into clinical knowledge requires a common reference framework that accounts for dimensional phenotypes organized at multiple levels in a dynamically interacting system. At the same time, clinical care relies on relatively simple categories to enable efficient prevention, diagnosis, and treatment of pathological conditions. An appropriate framework must bridge both, with particular emphasis on aspects that are important for understanding the occurrence and developing treatment of dysfunctional states. Neuroscience methodology is embedded in this hierarchical organization, with different recording and stimulation methods targeting processes at different levels. Challenges remain in the actual integration of data obtained at different biological levels, on different timescales, at different spatial resolutions, and often in different species. In particular, cross-species translation of (clinical) research can only succeed if both the measurement methodology and the process to be measured are well conceived and have clear counterparts in humans and the respective animal models. Finally, we show how "deep multimodal phenotyping" represents an ideal case of neuroscience research crossing multiple levels of organization in single individuals. Emerging tools for complex multivariate data analysis should aim to successfully integrate these data into real-world knowledge.

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Conflicts of interest

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1 Introduction

Rapid methodological advancements in the fields of neuroscience and "big data" analytics, along with the emergence of deeply characterized, population-level study cohorts, have led to a continuously increasing amount of information on human behavior, brain physiology, and pathology. Considering these developments, the question arises as to why this gain in information and technology has translated only slowly into deeper understanding and improved diagnostics and therapy of psychiatric disorders (Stephan, Bach, et al., 2016; Stephan, Binder, et al., 2016).

In this chapter, we first introduce why and how theoretically well-grounded assessment methods and techniques for integrating multimodal data can help to translate our ever-increasing "raw" knowledge into clinical progress (section 1). In subsequent sections, we then discuss theoretical and practical aspects of multimodal analytics that we consider especially relevant to the aims of this book. Specifically, we provide an overview on theoretical concepts underlying the idea of multimodal data integration (section 2), follow this with a discussion of methodological considerations for cross-species translational research (section 3), and then close with an overview of the "deep phenotyping" approach in neuroscience (section 4).

1.1 Frameworks for integrative neuroscience

Neuroscience relies strongly on theoretical concepts necessary to describe and categorize associations and interactions between ordered as well as disordered brain function and behavior. From a psychiatric point of view, theoretical frameworks seek to characterize clusters of behaviors and symptoms along with their (patho-)physiological representations to facilitate standardized diagnosis and treatment of mental illness. Neuroscientific research on mental health related processes can take various forms, involving investigation of neurobiological phenomena in different settings and species using various methods that assess different biological levels of organization (Figure 1). To enable effective translation of basic and clinical research into clinical practice, a theoretical framework is needed to facilitate the integration of these multimodal data. Existing research and clinical approaches, such as the concept of neurobehavioral trait dimensions discussed in this book, the Research Domain Criteria (RDoC) (Insel et al., 2010), the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017), and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), approach this challenge in different ways. The contrasting approaches employed by these frameworks reflect an ongoing debate as to whether

psychiatric disorders are best characterized in the form of dimensionally scaled traits (as in RDoC or HiTOP) or by categorical labeling (as in the DSM).

In section 2, we discuss theoretical concepts that are relevant to the integration of multimodal data, thereby providing an overview of current clinical and research concepts pertaining to dimensional phenotyping and multimodal data integration. In addition, we further discuss how the concept of network neuroscience can provide a basis for an integrative and clinically meaningful framework.

1.2 Biological levels of organization

When explaining neurobiological phenomena, we traditionally assume a hierarchical organization of increasingly complex systems, ranging from interacting physical particles to social interaction between humans (Figure 1, *Level*). Each of these *biological levels of organization* or *analysis* arises from its preceding system but may exhibit unique characteristics not present in its predecessor (Novikoff, 1945; Cacioppo & Berntson, 1992; Breedlove & Watson, 2013)**.** In the context of *network neuroscience* (section 2.4), brain organization is usually divided into the *microscale* level of individual neurons and synapses, the *mesoscale* level of local neuron populations, and the *macroscale* level of brain regions and their connections (Sporns et al., 2005). Psychiatric symptoms and neurobehavioral traits could be simultaneously represented as (patho-) physiological processes at these biological levels. Identification and characterization of these processes along with their interactions may provide valuable knowledge on the origin of disordered cognition and behavior. Especially important features, either being identified as causally related to the outcome or constituting "hubs" in process-interactions occurring across levels, may have value as potential biomarkers and treatment targets.

Taking an evolutionary perspective, the concept of a hierarchical organization of biology provides a theoretical basis for the assumption that findings derived from research with non-human animals can be extrapolated to humans (Figure 1, Species). Considering that human biology is organized hierarchically and that humans have continuously evolved and share common ancestry with other species, it is plausible to assume that biological levels present in humans will – up to a certain level – have counterparts in many other animal species. Studying these counterparts in non-human animals, using methods from human research along with (non-)invasive methodologies that are not applicable to humans, may help to generate hypotheses and provide insights into human biological organization, e.g., through comparative evolutionary approaches (Friedrich et al., 2021). Section 3 of this chapter discusses such methodological considerations and potential pitfalls that

should be taken into account when conducting translational research and integrating data across species.

1.3 Translating laboratory research into real life understanding

The majority of neuroscientific research in humans takes place in lab settings, in front of computer screens, or in specialized contexts such as neuroimaging devices (Figure 1: *Setting*). Within these settings, highly abstract stimuli are often used to isolate the cognitive process(es) under investigation. When the main goal of psychopathology-directed research is to improve patient care, the question arises as to what extent findings generated by such research relate to behavior and functional impairments occurring in the "real" world. This relationship is described by the *ecological validity* of an experiment. Three main factors contribute to ecological validity: the nature of the setting, the stimuli applied, and the subject's response (Schmuckler, 2001). For example, in the case of neuropsychological test performance, prediction of real-life functioning has been shown to be generally modest, because standardized and objective measures of real-life functioning itself are often missing (Chaytor & Schmitter-Edgecombe, 2003; Lahnakoski et al., 2021)**.** How**ever,** recent developments in methodologies such as ecological momentary assessment (Shiffman et al., 2008), and the increasing use of naturalistic stimuli in neuroimaging research (Sonkusare et al., 2019), constitute promising steps toward enhancing neuroscience-based prediction of real-life function and dysfunction.

Along with the question of ecological validity, another aspect to be considered is the degree of *objectivity* associated with the acquired data. Measures derived from neurophysiological processes tend to be viewed as relatively *objective*, whereas self-report measures are often considered *subjective*. However, the subjective aspect of self-report data may provide unique insights into individuals' inner states that cannot be acquired by putatively more objective methods. It is nevertheless important to acknowledge the limited generalizability and susceptibility to bias of self-report, and interview-derived data, which also relies on participant report (Althubaiti, 2016).

Multimodal, longitudinal assessment of the same individuals followed by integrative data analysis may offer possibilities for increasing the explained portion of observed variability in "real world" phenomena and thus improving ecological validity of specific measures. A multimodal-integrative approach may also provide a way to evaluate measurement objectivity and bias by comparison of data within subjects. In the closing section of this chapter, we discuss the deep phenotyping approach along with its recent applications.

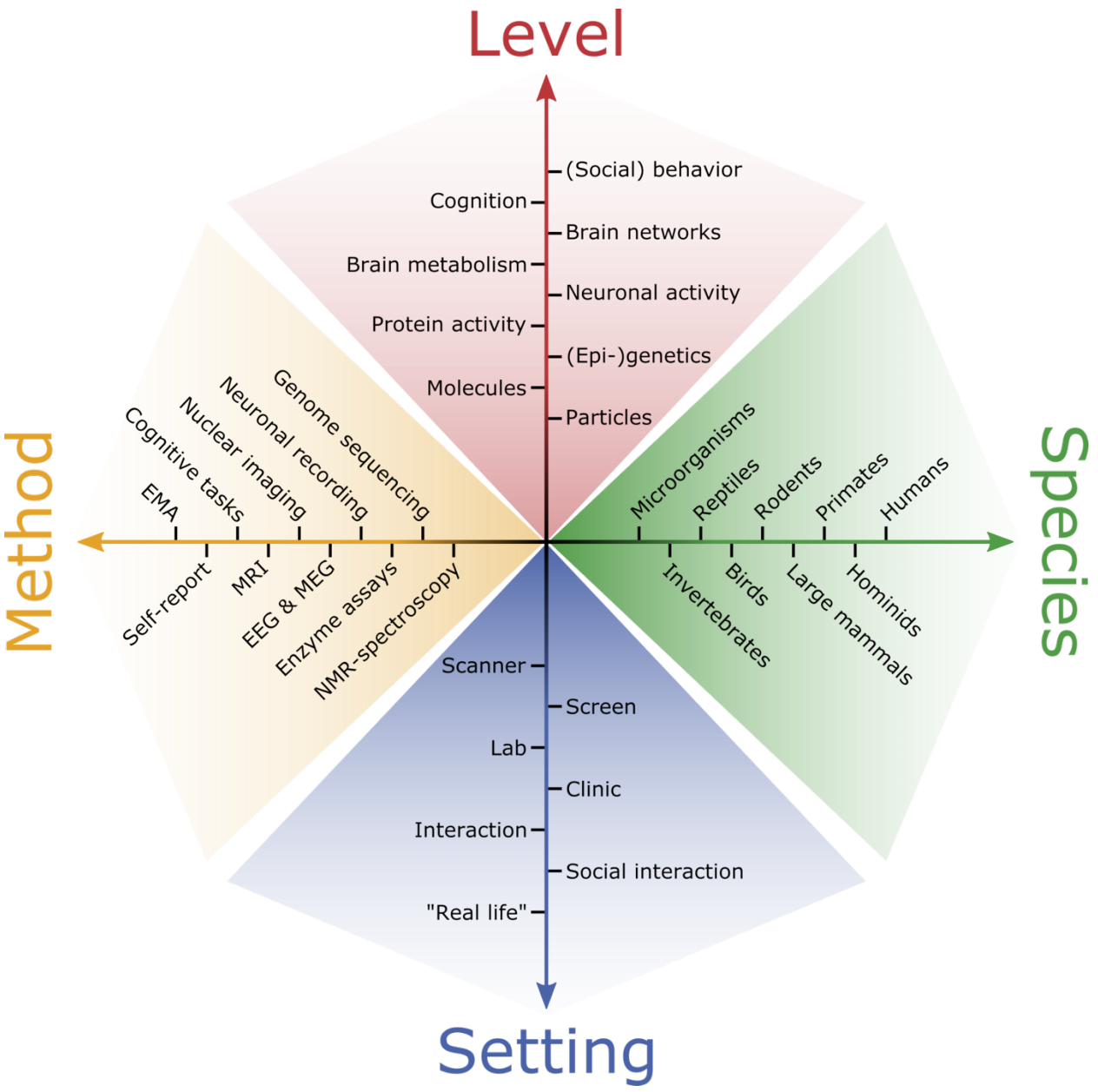

Figure 1: Dimensions of multimodal assessment

Each axis represents a single dimension of multidimensional data assessment. Any specific study will touch on at least one element of each dimension; for example, a study might use a behavioral task with functional MRI measurement (Method and Setting) to assess brain networks and their cognitive functions (Level) in humans (Species). Note that the figure should primarily be considered as an example, both in terms of dimensions and individual elements. EMA = ecological momentary assessment, MRI = magnetic resonance imaging, EEG = electroencephalography, MEG = magnetoencephalography, NMR = nuclear magnetic resonance.

2 Theoretical concepts

2.1 Categories and dimensions

Three prominent descriptive frameworks used in contemporary clinical research, the DSM (American Psychiatric Association, 2013), the RDoC (Insel et al., 2010) and the HiTOP (Kotov et al., 2017), are based on contrasting assumptions regarding the definition of psychiatric disorders. The DSM mainly relies on a categorical approach that classifies individuals into either having or not having a disorder based on whether a certain number of symptoms is exceeded. In contrast, RDoC and HiTOP are dimensional systems that view psychiatric symptoms and affiliated traits as being scaled from lower, more normative levels to severe manifestations having significant impact on affective, cognitive, and social functioning in certain individuals.

However, it is important to acknowledge that these approaches are closely connected and that the appropriate choice of research tools depends on the specific context in which they are applied. First, it is worth noting that a *diagnosis* can be either categorical or dimensional, whereas a *disorder* in most cases is both. Disorders may either be present or not (categorical) - often based on whether they have significant impact on everyday functioning - while also showing clinically meaningful variability, for example, in respect to symptom severity or functional impairment (dimensional) within patients and within non-clinical populations (Chmura Kraemer et al., 2004). In clinical contexts, categorical classifications provide the obvious advantage of allowing for straightforward, easily standardized allocation and evaluation of treatment options. Researchers, in contrast, may prefer dimensional over categorical approaches for hypothesis testing, as dichotomization of continuously distributed data often depends on arbitrarily defined cut-off criteria and generally leads to decreased statistical power (MacCallum et al., 2002). It can be noted that the relationship between the two approaches relates to the use of cut-off criteria: Categorical classifications are usually derived by dichotomization of a continuous-score variable (e.g., number of symptoms) and are thus informed by dimensional systems. On the other hand, categorization in terms of more than two ordered categories – as seen, for example, in the DSM sub-classification of major depressive disorder into *mild*, *moderate,* and *severe* forms – reflects a dimensional approach (Chmura Kraemer et al., 2004).

2.2 Evolving frameworks

Considerable research demonstrates that genetic, physiological, and environmental risk factors and mechanisms relevant to development of psychiatric disorders actually extend across DSM

boundaries rather than being specific to a certain disorder (Kotov et al., 2017). Indeed, the fifth edition of the DSM responded to this evidence by incorporating secondary, "boundary-crossing" dimensional measures in its diagnostic categories (American Psychiatric Association, 2013). However, the concept in its core is based on empirically derived clinical phenotypes, rather than on a "bottom-up" effort to connect disturbances at the neurophysiological level to disordered cognitions and behaviors. As such, the DSM may ultimately not be suited to integrating knowledge from different levels of biology and neurophysiology into a general concept of mental dysfunction. In contrast, the RDoC initiative represents the above-mentioned biological levels (here, "units") of organization as columns in a matrix system, in which the main mechanism of action in *neural circuits* is shaped by genetic, molecular, and cellular levels and progresses up to levels of interpersonal behavior. *Construct domains* (such as *negative* and *positive valence,* or *cognitive systems*) are represented as rows that intersect with the biological levels (columns), which influence one another. Of note, the RDoC matrix system is designed to evolve with new evidence and is thought of as an open, general framework, rather than a fixed model of brain (dys-)function (Kozak & Cuthbert, 2016). In its basic conceptualization, the RDoC system provides a promising framework for the integration of multimodally acquired data. It remains to be seen, however, how the RDoC conceptualization can be integrated into clinical practice.

Recently, Michelini et al. (2021) formulated a promising approach bridging from the biobehaviorally oriented RDoC to potential clinical application by mapping RDoC *construct domains* to the *spectra* and *subfactors* defined by the clinically focused HiTOP. Like RDoC, HiTOP applies a dimensional approach that attempts to create a hierarchy from psychopathological symptoms and their patterns of co-occurrence. On top of this hierarchy are *spectra* (such as *internalizing*, *externalizing*, or *thought disorder*) that subsume *subfactors* (such as *fear* or *distress*) which in turn are mapped to specific symptoms and DSM disorders (Kotov et al., 2017). From a clinical viewpoint, HiTOPs central advantage is its focus on clinical phenotypes defined from empirically measurable symptom dimensions which could easily be translated to clinical practice (Latzman et al., 2020). A systematic mapping between biobehavioral RDoC and clinical HiTOP constructs could provide a biological foundation for the HiTOP hierarchy while offering clinical testable targets for the RDoC matrix system (Michelini et al., 2021). If empirically grounded, such an integrated framework could bring considerable progress to future psychiatric research and care.

2.3 Integration

The term neuroscience does not refer to a specific discipline but rather to a field encompassing many different sub-disciplines, each aiming at understanding a different level of human neurophysiology, psychology, or behavior. In order to categorize knowledge derived from this multidisciplinary environment and embed it in a larger context, neuroscientists traditionally adopt a reductionist approach (Bickle & Hardcastle, 2012). Reductionism here refers to the view that all the complexity of human psychology and behavior, and the data acquired in corresponding research fields, can be reduced to neurophysiological processes. As we are still unable at this time to deduce most psychological phenomena from neurophysiological function, the reductionist view is opposed by pluralism: Different sub-disciplines, and the theories derived from their research efforts, coexist in awareness of their potentials, as well as their methodological and explanatory limits. However, following Kotchoubey et al. (2016), a purely pluralistic approach may not suffice either for establishing global explanations of neurobehavioral phenomena. Effective integration of knowledge will require not just a combination of theories, but rather a global theoretical conceptualization incorporating ideas and findings from different disciplines (Kotchoubey et al., 2016).

2.4 Endophenotypes, neurobehavioral dimensions, and network neuroscience

Never before have we had a larger amount of empirical information regarding human brain functioning than in the current age of "big data". Methodologically advanced neuroimaging and extensive phenotypic data have become available at population-scale. "Simple" accumulation of data, however, cannot bridge the explanatory gap between knowledge about neurophysiological processes on one side, and what is known about human psychology and behavior on the other. In the context of psychiatry, the endophenotype concept was established to bridge the pathway between dysfunctional behavior and associated genetic findings. Endophenotypes were originally referred to as distinct, measurable, heritable, and state-independent components associated with both behavior and genetics, placed on any possible intermediate level of analysis (Gottesman & Gould, 2003). In a broader context, the endophenotype concept can be widened to encompass sets of clustering components, now extending across biological levels (Insel & Cuthbert, 2009). These broader defined endophenotypes are closely related to the RDoC domains, the HiTOP spectra or subfactors and to other dimensional frameworks describing category-crossing clusters of associated neurobehavioral functions or dysfunctions. Neurobehavioral trait dimensions, such as, for example, the inhibition-disinhibition construct connecting frontal-executive functioning with antisocial and addictive behavior (Patrick et al., 2013; 2019; Venables et al., 2018), provide frameworks for the

integration of data acquired multimodally on different biological levels, but within the same theoretically defined functional area.

While neurobehavioral dimensions could be the concept of choice within a certain functional domain, going one step further, the need for an overarching concept arises. This general framework should be based on dimensional concepts but serve the goal of providing reliable and clinically meaningful classification of disorders. To allow for multimodal data integration, an effective framework should specifically account for the coexistence of interacting biological systems distributed across levels of analysis in humans and animals. We close this section with a description of how the concepts of systems science might be equipped to provide a basis for an integrative neuroscientific framework with the ability to transform bench research into clinical practice.

The aim of systems science is to describe complex systems consisting of interconnected elements in which each element and each connection has certain attributes. Within a system, the elements are connected more tightly with one another than with the external environment, but the system as a whole communicates with the environment (Flood & Carson, 2013). Common general characteristics of complex systems, such as stability, balance, and feedback-loops, can be applied to all neuroscientific sub-disciplines – suggesting that systems science can serve as a universal theoretical framework for the neurosciences (Kotchoubey et al., 2016). The neuroscientific adaptation, commonly referred to as network neuroscience, describes biological levels of organization as networks with nodes (e.g., proteins, neurons, brain regions, organisms) connected through edges (e.g., molecular interactions, synapses, structural and functional connectivity, social behavior). These networks can interact with, and modulate, each other not only in a bottom-up, but also a top-down fashion as seen, for example, in the influences of the (social) environment on patterns of gene expression (Bassett & Sporns, 2017).

Practical applications that build on this theoretical foundation for level-crossing interactions range from integrative analyses of gene expression and brain connectivity in human and non-human animals (Bassett & Sporns, 2017), over multi-layer analyses of functional and structural brain connectivity (De Domenico, 2017), to multivariate analyses of brain-behavior relationships (Mišić & Sporns, 2016). Recently developed models bridging from neurobiological to social levels promise new insight into biomarkers of, and treatment targets for, neuropsychiatric disorders (Bassett & Sporns, 2017).

3 Translational methodology: Integrating data across species

A key aspect required for successful cross-species translation of knowledge on (patho)physiology of psychiatric diseases is the availability of methods to compare and translate human and non-human animal findings in both directions. A variety of methods – from genetics, to the study of molecular pathways, to in vivo and in vitro physiology, to neuroimaging and behavior sampling – are now available for use as translational tools (Figure 2). In this section, we introduce these methods in the cross-species context, and discuss limitations and pitfalls associated with their application as cross-species translational tools.

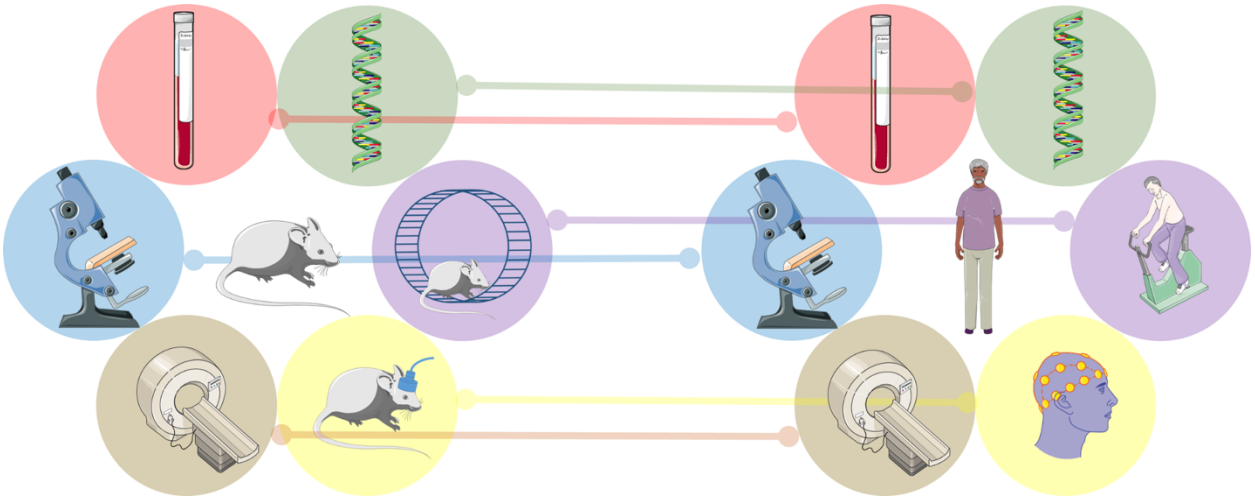

Figure 2: Cross-species translation

Advances in whole genome sequencing in recent decades have enabled genome-wide association studies with large clinical and healthy populations to discover various rare deletion and duplication factors contributing to the occurrence of psychiatric symptoms, as well as identification of numerous common risk alleles that are linked to increased risk for specific mental illness conditions. These discoveries have in turn triggered the development of genetic-modification models with animals (mostly mice and rats) in which gene sequences are altered to mimic specific disease conditions based on research with humans. Studying such genetically altered organisms from micro- to macroscales provides information of unprecedented richness about pathways from molecular influences to observed phenotypes. In addition, such animal models are valuable for generating

novel hypotheses about disease pathways and aiding efficient evaluation of pharmacological interventions aimed at reducing the occurrence of specific phenotypes.

Technological advances contributing to the emergence of the foregoing genetic models of specific mental health conditions are paralleled by the development of various cross-species tools and methods for studying underlying biological influences from micro- through macro-levels to behavior and environment. Such cross-species tools are not limited to measurement at specific biological levels, but also extend to invasive and non-invasive stimulation techniques for modulating brain activity in various ways to map behavioral effects.

An overview of some of the available tools for cross-species translation is provided in Table 1. From the perspective of studying neurobehavioral traits, the translation from human to animal models and back provides the means to link specific traits to underlying biology in a much more detailed manner, through application of invasive technologies not amenable to human use in combination with much shorter neurodevelopmental periods in animals (e.g., rodents), allowing for more rapid experimental sequences.

Table 1: Overview of cross-species tools available at different evaluation levels

Level	**Example tools**	**Application scenarios**	**Available in**	
			Human	**Animal**
Genes	Study of deletion and duplication syndromes	To study the effects of specific genes associated with specific mental health conditions, genetically modified animals	yes	yes
Genes/ Tissue properties	mRNA quantification	To quantify mRNA expression is specific tissues as a measure of local gene activity to approximate quantity of specific proteins	yes	yes
Tissue properties	Biosamples	To quantify molecules/proteins associated with specific mental health conditions	yes	yes
Tissue properties	Induced pluripotent stem cells and brain organoids	To mimic early brain development	yes	yes
Tissue properties	Neuroimaging (i.e. structural magnetic resonance imaging, positron emission tomography)	Estimating brain structural tissue properties	yes	yes

Brain activity	Neuroimaging / electrophysiology / positron emission tomography	Estimating brain activity and connectivity	yes	yes
Brain activity	Transcranial magnetic stimulation / Deep brain stimulation	Modulating local brain activity	yes	yes
Behavioral	Tasks / naturalistic behavior	Tasks measuring specific cognitive functions / observing behavior in natural or controlled environment	yes	yes
Environmental	Controlled experiments	Systematic modulation of environmental factors	yes	yes

Importantly, whilst many of the tools and methods listed in Table 1 allow for comprehensive cross-species comparisons and translational applications, they are also subject to a number of limitations. One is that animal-genetic models are often selected to represent phenotypes that are presumed to reflect a certain human disease condition. Yet, particularly in psychiatry, the validity of such a model is limited by the understanding of the respective human disease condition and by virtue of the fact that most psychiatric conditions represent a complex combination of features that are specific in important respects to the human species (e.g., deficits in language, theory of mind, or complex social emotions such as shame or guilt). It is therefore often questionable whether or to what extent more rudimentary behaviors in animals indeed reflect the complex features or states observed in the corresponding mental disorders. Moreover, the validity of an animal model relies heavily on the assumption that single gene and polygenic effects contributing to the counterpart phenotype in humans have similar functions in the animal model, which is not necessarily the case. This issue is also reflected in the substantial differences in brain anatomy and function across animals and humans. Whilst the function and organization of many brain areas such as sensory and motor cortices is comparable in many respects across mammalian species, other brain structures such as the prefrontal cortex that are essential for higher cognitive and executive processing exhibit salient discontinuity. In that sense, the validity and extent of any cross-species translation must be carefully considered for any specific application in the context of clinical research, keeping in mind the above limitations.

4 Deep phenotyping: Multimodal assessment of real-life psychopathology in individuals

The concept of deep phenotyping largely emerged with the introduction of novel technologies allowing for characterization of biological systems at different levels, from genes sequences to various tissue properties to resulting behavior (Figure 3). Rather than focusing on quantification of a few measures in large populations, the main objective of deep phenotyping is to acquire as much information as possible at the individual organism level. In the context of psychiatry, the aim is to identify biological, behavioral, and environmental factors contributing to development of specific mental conditions and associated neurobehavioral traits (Meyer-Lindenberg & Weinberger, 2006). For example, in addition to the use of various fluid biomarkers and genotyping, it is now possible to quantify the expression of genetic information in specific tissues to study local gene activity and how it relates to specific mental health conditions. Moreover, with the development of technologies to induce pluripotent stem cells (iPCS), it has become possible to generate brain organoids (i.e., simplified in vitro versions of organs that show realistic microanatomy) derived from individuals with mental health conditions that to some extent mimic early normal or pathological brain development.

Similarly, advanced neuroimaging technologies allow for visualization of various brain structural and functional tissue properties ranging from micro- (e.g., single cell recordings during surgery) to meso- (e.g., neural population recordings using implanted electrodes) to macroscales (e.g., MRI and EEG measurements). However, tools at the micro- and mesoscale levels in particular are still often limited to specific mental illness conditions requiring invasive interventions. Also at the behavioral level, the recent boom in the development of wearables and smart devices now provides a technological framework for collecting various biosensor measures as well as ecological momentary assessment data, allowing for investigation of disease-related variability along with the role of environmental factors contributing to specific mental conditions in daily life.

The large amounts of heterogeneous data collected using such a deep phenotyping framework also presents major challenges with respect to dealing with big complex data resources. For example, an effective integration of the abovementioned assessment levels, from genetics through neuroimaging to behavior, remains a major challenge in current research. In this respect, emerging machine learning respectively artificial intelligence approaches may offer a promising toolbox for achieving the desired comprehensive integration needed to maximize the advantages of deep phenotyping in understanding clinically-relevant neurobehavioral differences.

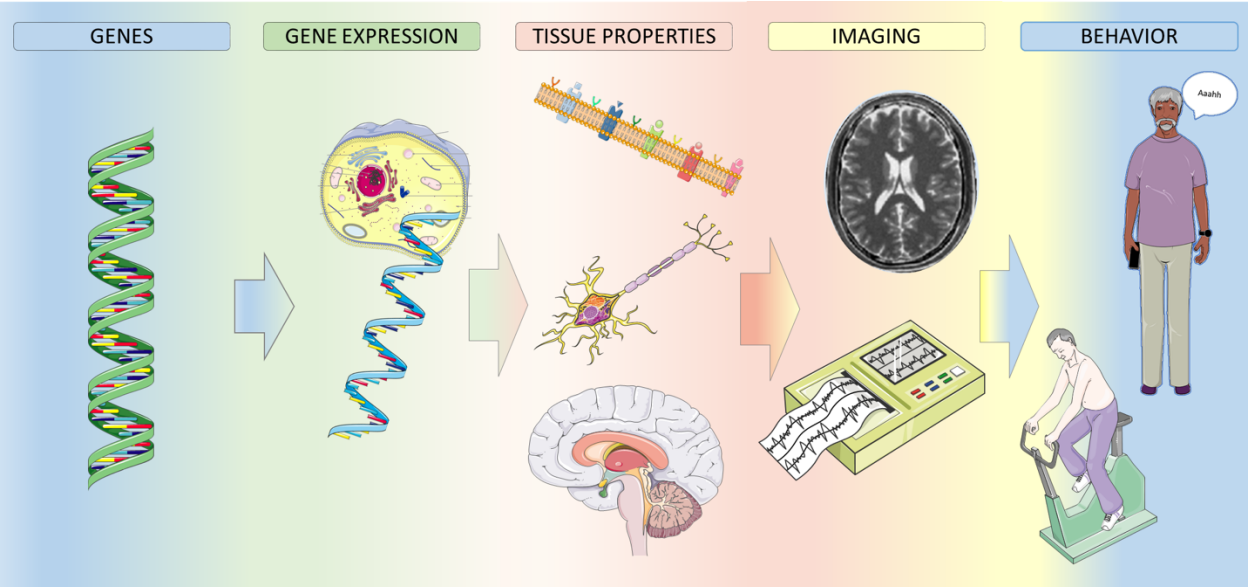

Figure 3: Deep phenotyping

The deep phenotyping approach aims at characterizing and integrating multiple measures from different dimensions (cf. Figure 1) in single individuals, ultimately following the goal to capture all representations a trait in question might have on different biological levels. Icons used for this figure were downloaded from smart.servier.com, licensed under a Creative Commons Attribution 3.0 Unported (CC BY 3.0) license.

5 Conclusions

In this chapter, we have discussed the role of evolving methods and frameworks for assimilating complex multimodal data for purposes of studying neurobehavioral differences in the context of clinical science. Pertinent concepts encompass different taxonomic systems for describing clinical phenotypes – ranging from traditional diagnostic categories, to dimensional and hierarchical characterizations of psychopathology, to hybrid approaches. Deep phenotyping-based integration of evidence across species and across biological levels of analysis holds promise for improving our understanding of behavioral heterogeneity observed within and across diagnostic entities. Parallel advances in technology-based collection of "big data" along with improved ecological validity of specific measures can further facilitate this development. Major challenges remain, particularly with respect to how best to integrate information from different levels to maximize insights gained into the neurobiology of behavior. However, progress is being made in this direction and appears likely to continue given emerging new ideas and research methods.

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