VIEWPOINT

Between Nothing and Everything: Phenomenology in Movement Disorders

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In movement disorders, phenomenology refers to the science and art of classifying abnormal movements. Traditional clinical practice has been based on phenotype-driven investigation, diagnosis, and management. However, many have questioned our continued reliance on phenotype. Phenotype has been repeatedly demonstrated to be an unreliable guide to the precise lower-level pathophysiological process. After all, a single phenotype can be caused by multiple diseases and a single genetic disorder can be associated with varied phenotypes. There has been a growing call for molecular subtyping to have priority in scientific research.

In this Viewpoint, we redebate the relevance of phenotype, arguing that we may be using phenotype in the wrong way. We discuss how a better appreciation of this many-diseases-to-few-phenotypes process can allow our experimental literature to be more effectively understood. We suggest that the convergence of many diseases onto a limited number of phenotypic patterns may reflect the fact that the sensorimotor system can only "break" in a limited number of ways. Therefore, if we can understand the system-level processes that underpin specific phenotypes, this could unlock novel phenotype-specific therapies regardless of the specific underlying disease process. Encouragingly, many existing therapeutic tools such as neuromodulation already target system-level processes.

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Phenotype in Clinical Practice

The term phenotype (from the Greek φαινο-, (faino-), "showing," and τύπος, (túpos), "type") refers to the observable physical properties of an organism.[1,2] These include the organism's appearance, development, and behavior and are determined by interactions between genetic, environmental, and stochastic factors.[3] In movement disorders, phenotype is generally used as a label for an abnormal category of movement derived from our examination and observation of a patient. Bradykinesia,[4] chorea,[5] dystonia,[6] myoclonus,[7] tics,[5] and tremor[8] make up the major categories and descriptive definitions capture the essence of each phenotype (Fig. 1).[9] This clinical categorization is a vital part of our clinical formulation in movement disorders with classic textbooks organized by phenotype-driven differential diagnosis and treatment selection.[10] Phenotype often dictates how we group patients in experimental research and clinical trials and how we evaluate the success of therapeutic interventions through use of phenotype-specific severity scores.[11–14]

A neurologist training in movement disorders develops the skill of identifying and correctly subclassifying phenotype through experience and supervision by specialists in movement disorders. This movement pattern recognition task is imperfect and subjective. When movement patterns are more subtle, labeling can become dependent on personal thresholds for when to "call" a particular disorder as present. However, the relative preservation of phenotypic classification through generations of movement disorders practice suggests that phenotypic categories convey something meaningful. Often the precise pattern or distribution of a phenotype has nuances that are specific to an individual, but the classification of the

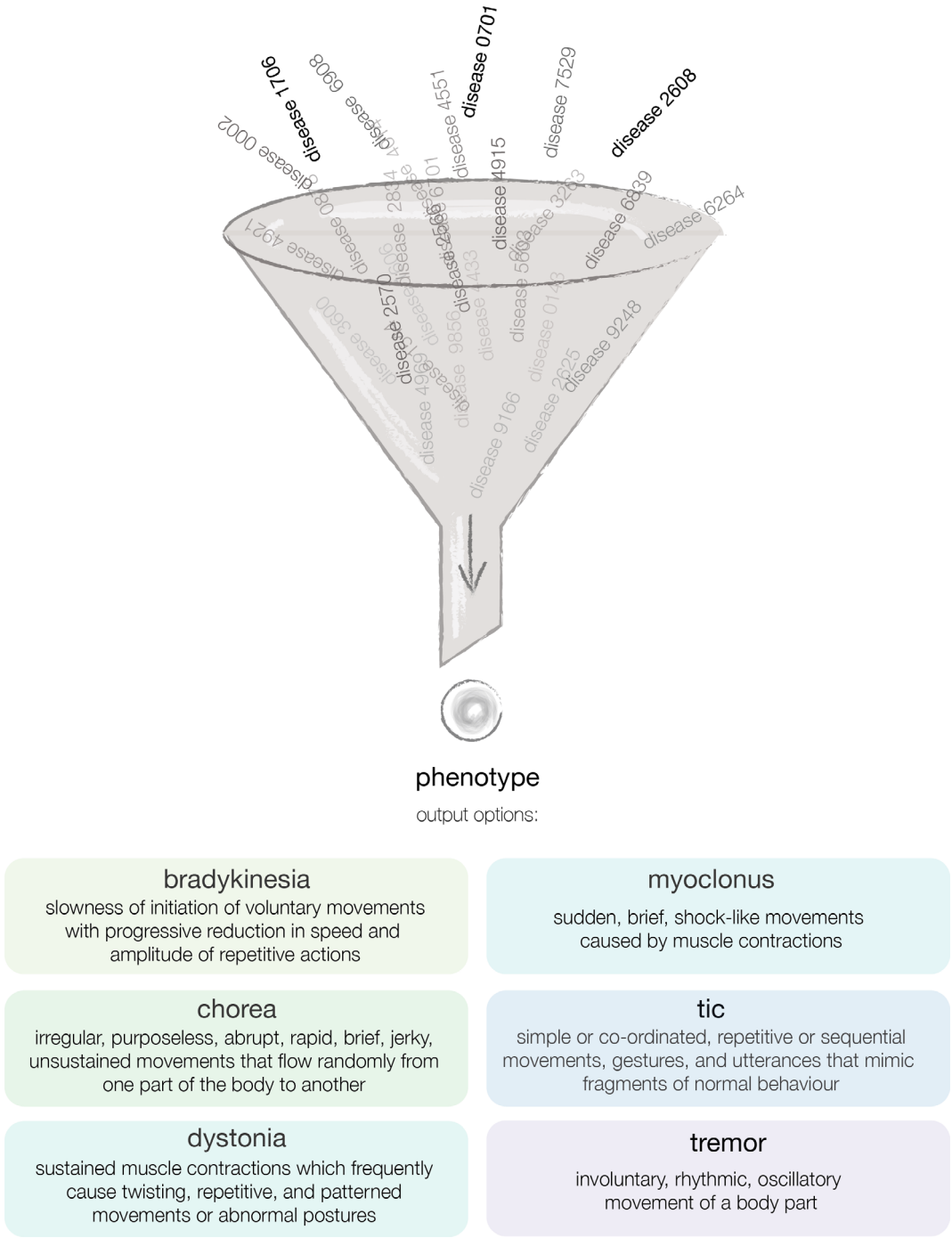

FIG. 1. Core movement disorder categories. Thousands of different disease processes cause a limited number of phenotypes. Each phenotype appears to represent a stable substate of disordered movement with specific characteristics which can be descriptively summarized: bradykinesia,[4] chorea,[5] dystonia,[6] myoclonus,[7] tic,[5] and tremor.[8] [Color figure can be viewed at wileyonlinelibrary.com]

overriding core phenotype is usually clear. Therefore, a consistent movement architecture defines the behavioral features of each phenotype. In neurodegenerative conditions, different stages of disease can be associated with different phenotypes. For example, in early Huntington's disease choreiform movements are typical, whereas later a Parkinsonian phenotype is more commonly seen. Phenotype therefore appears to be responsive to evolving patterns of system-level dysfunction caused by accumulating neurodegeneration. In non-degenerative disorders the phenotype is usually stable: once the nervous system has failed in a particular way, it does not usually change.

Understanding the Limitations of Phenotype

Historically, astute clinical phenotyping was our main point of access to pathophysiology and was the foundation of the clinico-pathological method. However, we now know this mapping is unreliable as a single phenotype can be caused by multiple diseases and a single genetic disorder can be associated with varied phenotypes.[15] Our current phenotype groupings are hugely useful in guiding our clinical practice but do not precisely reveal lower-level molecular etiology. Therefore, research driven by molecular subtyping from which we can develop molecular therapeutics strategies is important and should be welcomed.[15] However, this does not mean that we should abandon scientific interest in phenotype. Instead, we need to understand the reasons why there is a disconnect between disease and phenotype and the architecture of this disconnect. This is where the biologically fundamental concept of *degeneracy* is important and useful. The word degeneracy in this context has a different meaning from the more familiar use of the word to describe cellular degeneration as in neurodegenerative diseases. Instead, degeneracy can be defined as "the ability of elements that are structurally different to perform the same function or yield the same output."[16] Describing a many-to-one mapping degeneracy is distinct from *redundancy* which occurs when the same function is performed by identical elements.[17] Degeneracy is a ubiquitous properly of biological systems at all levels of organization.[16] For example, genetic code is degenerate with different codons (nucleotide triplets) specifying the same amino acid.[18] Even in the nervous system of simple organisms (such as the crustacean stomatogastric ganglion which has only 26 neurones), similar network performance can arise from diverse combinations of neuronal activity.[19–23] Degeneracy is thought to improve the resilience of biological systems to disease or damage and is a key mechanism of adaptability that drives natural selection.[24] The collapsing of many diseases onto few common patterns of movement dysfunction is a many-to-one mapping, an example of a degenerate architecture.

The degeneracy of phenotype in clinical movement disorders has many repercussions for how we should use phenotype both clinically and experimentally. For interested readers, supplemental material to this article simulates how degeneracy might affect the interpretation of experimental data in fundamental ways (Supplementary Fig.). Indeed, many of the current very reasonable criticisms of phenotype-driven research can be distilled down to our failure to appreciate the importance of degeneracy.[9] For example, it is common to give the clinical phenotypic classification of an illness primacy in experimental studies by using it as a "gold standard" categorical variable. This means that we constrain and bias our analysis of experimental data by an assumption that all the participants in our study have the same disease because they share phenotypic characteristics. Experimental markers will continue to mislead if used interchangably as markers of both lower-level (specific disease) and higher-level (common phenotype) dysfunction (Fig., Supplementary Fig.). Furthermore, the primacy of the clinical phenotypic classification often implies an unbroken chain of causality from any biological measure in our population of interest to the movement phenotype. The way experimental data are typically described in research publications demonstrates this causality assumption and Krakaeur et al. detail various examples of "filler verbs" used to this effect in research papers ("underlies," "produces," "mediates," "plays a role in," "reflects," "encodes," "regulates.")[25] Research papers often imply that an observe change in an experimental variable is *directly related in a mechanistically relevant fashion* to the movement disorder phenotype. This leads to the inevitable conclusion that normalizing the experimental variable should improve the clinical phenotype and therefore the quality of life of the patient. The degeneracy of phenotype in movement disorders tells us that this assumption is often incorrect as changes in an experimental marker at lower levels may not be causally related to phenotype generation.

Multilevel understanding of movement disorders

We therefore need to break from the legacy of descriptive neurology in which clinical phenotype is considered to be a window directly opening onto lower-level pathophysiological processes. Instead, phenotype is a system-level dysfunction that is linked only in a highly complex manner with underlying disease-level dysfunction. To reach a fuller understanding of movement disorders we need to be able to explain how the nervous system dysfunctions at multiple levels of organisation. Each level of investigation has different experimental and conceptual tools needed to capture the patterns and rules underwriting function and dysfunction and which level one investigates will depend on the question being asked.[25,26]

Interestingly, different levels of organization may have relative independence and lower-level process may not have complete explanatory power for higher-order processes (Fig. 2B). Correspondingly, characterization of the molecular machinery responsible for a disease may not give us the knowledge to explain why movement breaks down to cause specific phenotypes. This also has ramifications for those trying to develop animal models due to the differences between human and other animal brains.

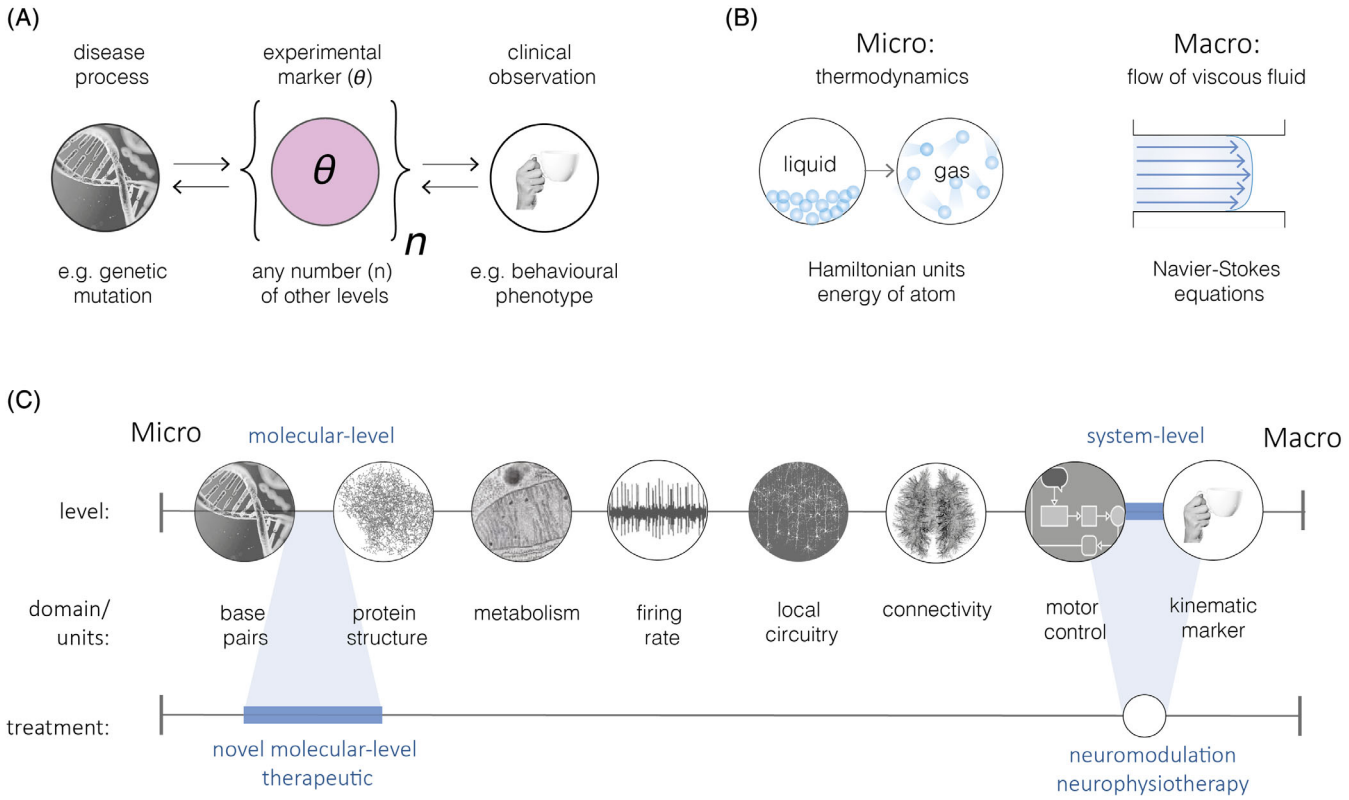

FIG. 2. Multilevel explanations for movement disorders. (**A**) Many experimental markers are used imprecisely as markers of both disease and phenotype. As a single metric is unlikely to be able to explain both phenomena, such imprecise usage is likely to limit progress in understanding. (**B**) Often components at each ascending level are some kind of composite of the entities present at the level below. However, different levels can also be autonomous. To take an example from physics, the thermodynamic boiling point of water is usually defined by phase transition equations expressed in Hamiltonian units which represent the total energy of the system at the level of atoms (microscopic level). If one wants to explain the flow of viscous fluids (macroscopic level) then Navier–Stokes equations are used. A complete and comprehensive explanation of the flow of water can be made without reference to the atomic level, and the information from the atomic level explanation has no utility in explaining the flow of water.[29] (**C**) To explain a system's behavior at both higher and lower levels, different parameters or units are often needed. In this figure, intermediary levels between a genetic mutation and a behavioral phenotype are arbitrarily subdivided into further levels along an approximate axis of scale. By better appreciating the different levels of organization we can then sculpt research efforts to be reactive to the actual and anticipated landscape of future viable therapies. For example, neuromodulatory and neurophysiotherapy interventions are much more likely to be informed by understanding at a system level. [Color figure can be viewed at wileyonlinelibrary.com]

The optimal approach to investigate different movement disorders will vary. For some diseases we are beginning to have the knowledge and methods to allows us to try to reverse causal genetic or molecular deficit. However, the pragmatic reality is that curative, affordable molecular therapies for all movement disorders remain a distant prospect.[27,28] Furthermore, in any disorder that involves an interplay between genetic, environmental, and stochastic factors, a pure molecular "fix" may never be available. There is therefore still a great need for other forms of treatment that build on knowledge of dysfunction at alternative levels of the nervous system.

A new perspective on phenotype

Clinical observation tells us that a relatively invariant and stable pattern defines each phenotype. This suggests that specific types of "system failure" underpin the observed behavior. One priority is therefore to understand the network parameters that underwrite the production of each phenotype, recognizing that this is a different process from understanding the underlying disease. If we take tremor as an example, this is the "easiest" phenotype to reliably identify as we can reliably extract oscillatory movements. Such behavioral markers can be used to characterize the defining system-level mechanism such as abnormal oscillatory activity in the cortico-cerebello-thalamo-cortical network.[30,31] Furthermore, therapeutic interventions that treat tremor at this system-level origin, such as with lesions or deep brain stimulation (DBS) surgery, can improve tremor (almost) regardless of the disease process causing the tremor. The invariant behavioral features of other phenotypes will also be underwritten by specific neural dynamics within the brain. Advances in technology such as motion capture allows us to characterize patterns of phenotype

dynamically over time. This, and other data that are closely linked to the actual production of movement such as data reflecting coordinated network function, are most likely to reflect the specific network dysfunction that underwrites specific phenotypes. Phenotype signatures could then be used in many ways. Most simply, quantification can help us objectively monitor change in movement disorders. Reliable quantitative biomarkers could also be used to feed back into interventions, for example, as a feature to be minimized within adaptive DBS. Scientifically, the dynamic statistics of each phenotype can then be powerfully paired with experimental techniques such as continuous neurophysiological recordings to correlate behavior with neural process, refining our understanding of phenotypic mechanisms.

Such information will hopefully also take us further in understanding why there is a limited range of phenotypic patterns. The relative stability of phenotype suggests that once the sensorimotor controller has failed in that particular manner it is very difficult, without intervention, to claw back normal motor control. One way to conceptualize these observations is to consider phenotype as a stable state of sensorimotor dysfunction (Fig. 3A). The favorable response of phenotype patterns to interventions such as DBS tells us that it is possible to move the system to a more optimal state. Interestingly, returning circuit function to a healthier state may not require a reversal of underlying disease. It may be more practical to find a new network state that improves function rather than trying to undo all the various component changes that have accumulated from a specific underlying disease (Fig. 3B).[32]

The fact that multiple diseases converge onto a limited number of stable phenotypic patterns makes phenotype and its corresponding circuit level failure an obvious target for therapeutic development. It reduces our problem list by orders of magnitude as there are thousands of diseases and many fewer phenotypes. Furthermore, prioritising phenotype also fits with the current and anticipated landscape of viable therapies. We already have many system-level interventions and if we are looking to define a particular mode for DBS or design-targeted neurophysiotherapy, system-level knowledge will better equip us to design specific interventions (Fig. 2C). Such system-level approaches are enticing, as higher-level processes that are "closer" to clinical manifestations are more likely to have a more predictable effect on the symptomatic motor phenotype. This contrasts with lower-level data that may reflect variables that are not relevant to higher-level function.[33]

An Evolving Use of Phenotype

Currently, phenotypes are imprecisely defined. Inter-rater reliability in classification of phenotypes can be low and we have all witnessed debates between two specialists about whether something is predominantly "phenotype A" versus "phenotype B." As is often the case in frank disagreement, it may be that both are "partially" true, that is, that there are overlapping

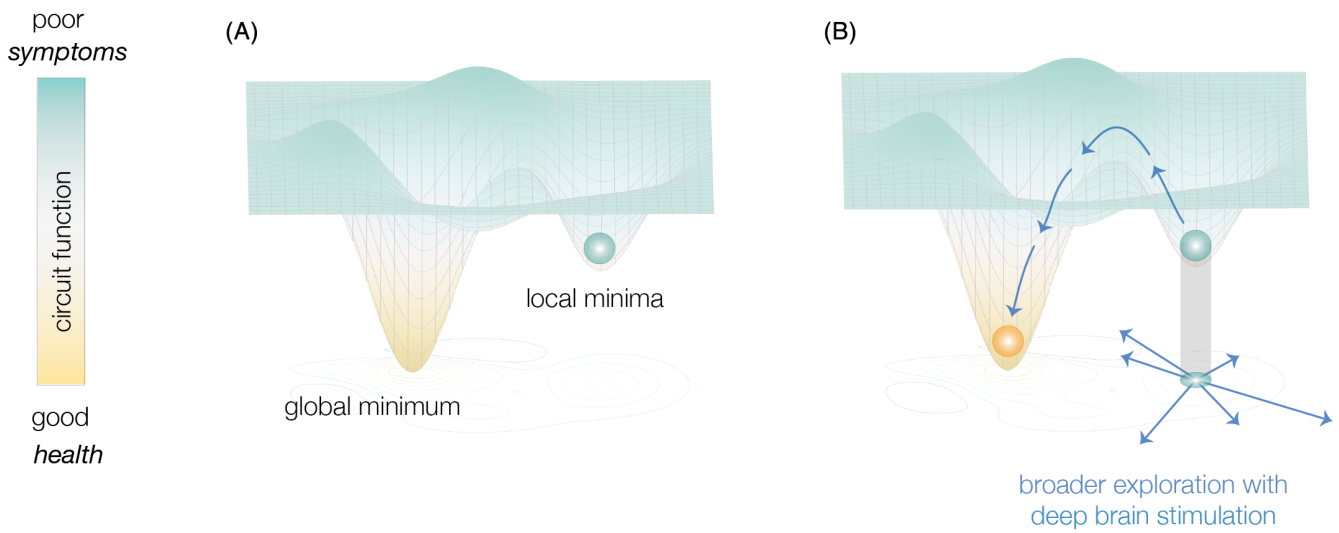

FIG. 3. Why are phenotypes stable? In health, we can assume that the process of evolution will have led to the development of a sensorimotor control system that operates relatively optimally for the repertoire of motor behavior required for normal human life. This is likely to be a dynamic equilibrium with mechanisms that allow the system to maintain function in the event of the inevitable perturbations over a dynamic control space. (**A**) The invariant and stable nature of phenotype is suggestive of a sensorimotor system that has become stuck in a suboptimal state. This is similar to an optimization process that has become trapped within a local minimum that it is difficult to climb out of as no better solutions lie in the neighborhood. (**B**) Response to deep brain stimulation (DBS) tells us that it is possible to move the system to a more optimal state. If DBS is injecting noise/variability into the system across multiple parameter dimensions, this may allow the control system to explore a wider space and to find better solutions to the disease perturbation. [Color figure can be viewed at wileyonlinelibrary.com]

distributions of certain features across both categories. By moving towards the objective quantification of movement disorder phenotypes we should be able to be more precise about what quanta of dysfunctional movements are relevant. It is also highly likely that there are meaningful, stable phenotypic subcategories that branch from our main categories. With the ability to sample phenotype over extended time periods and within more naturalistic everyday settings there will be a huge expansion in the amount and nature of the data that we have available to guide categorization. Data-led approaches governed by the statistical properties of the movement features will also likely reveal factors hidden from clinician-led pattern recognition. Such information on phenotype was not available when phenotype divisions were first carved out. As a community we will need to create methods by which to validate alternative groupings of movement, rooted in their clinical utility and/or their ability to shed light on mechanism, and continue to evolve our clinical practice in response to such outcomes.

Conclusions

The convergence of diverse diseases onto a limited number of phenotypic patterns suggests that the sensorimotor system breaks in a limited number of ways. This discrete number of stable phenotypes displayed in movement disorders can therefore be viewed as an opportunity. If we can better understand the rules that underwrite phenotype itself, we can develop system-level interventions with greater efficacy and utility across a range of diseases. The end goal is to build models for movement disorders that bridge levels. However, until we better understand a broader scope of organizational levels, and their relative hierarchical independence, it is difficult to make headway with such an aim. Using a multipronged approach across levels is likely to be the most fruitful to accelerate discovery and unlock new axes to drive therapeutic innovation. We advocate a focus on phenotype, recognizing it as an important organizational level for scientific and therapeutic discovery.

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Data Availability Statement

Not applicable

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A.S.: 3A, 3B.

M.J.E.: 3A, 3B.