Phenotypic plasticity and the perception–action–cognition–environment paradigm in neurodevelopmental genetic disorders

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ABBREVIATIONS

GABA	γ-Aminobutyric acid
PACE	Perception–action–cognition–environment

Careful study of the phenotype can have implications at several levels, namely clinical diagnosis, pathophysiological reasoning, management planning, and outcome measurement. Behavioural phenotypes involve cognition, communication, social skills, and motor control. They can be documented in a host of neurodevelopmental conditions and approached with the recently refined perception–action–cognition–environment (PACE) paradigm, which focuses on the neurodevelopmental processes that underlie learning and adaption to the environment through perception, action, and cognitive processing. Although this paradigm was originally developed in the context of cerebral palsy, it can be applied along developmental trajectories in several neurogenetic conditions, including Down syndrome, fragile X syndrome, Rett syndrome, Angelman syndrome, and Williams syndrome, to name but a few. It must be recognized, however, that relevant, valid tools for assessment and management strategies still need to be developed.

The notion of phenotype has always been central to clinical practice. Etymologically, it refers to 'what shows', hence the characterization of observable properties that can relate to clinical knowledge and serve its methodology. The common use of the term phenotype links it with the notion of genotype, which is understood as the genetic basis that is expressed as the phenotype. However, the general concept can be much wider than the implied focus on genotype–phenotype relationship. First, careful phenomenological observation of a patient's phenotype is the only way to make a clinical diagnosis. Secondly, this approach is a 'royal road' to pathophysiological reasoning, which may of course incorporate the molecular dimension of the genotype where applicable. Observed features can tentatively be explained by known physiology and gene function. For example, the propensity for more severe neurological impairment in patients with Angelman syndrome associated with 15q11-q13 microdeletion than with imprinting defect or uniparental disomy has thus been hypothesized to be due to hemizygosity of γ-aminobutyric acid $(GABA)_A$ receptor subunits impairing GABA-related neural synchrony.[1] Another example concerning genotype–phenotype discordance *HPRT1* mutations associated with Lesch–Nyhan syndrome has called for more refined reflection on reported discrepancies in neurogenetic disorders.[2] Potential explanations for discordant phenotypes relate to clinical ascertainment, age at evaluation, and patient categorization. In addition, phenotype can serve as a starting point to investigate physiological pathways, as exemplified for language, face processing, or visuospatial skills in Williams syndrome. Third, the phenotypic approach is important for management planning, as some of the features may constitute targets, constraints, or facilitating opportunities, for example self-injury in Lesch–Nyhan syndrome, impaired manipulative function in Rett syndrome, or social skills in Angelman syndrome, respectively. The idea that phenotypic features can be modified through management stems from the phenotypic plasticity paradigm,[3] which has gained broadening significance and appeal in a variety of domains including developmental medicine. Phenotypic plasticity was originally defined as environmentally sensitive production of alternative phenotypes by a given genotype.[4] In the broader perspective outlined above, the emphasis is placed on environment-dependent clinical expression, functional ecology, reaction norms, and adaptation. Fourth, as a corollary to this paradigm, the phenotypic approach can serve for outcome measurement.[5]

The framework in which the perception–action–cognition–environment (PACE) approach described in this supplement was conceived is consistent with this view of phenotypic plasticity. This approach focuses on the neurodevelopmental processes that underlie learning and adaptive strategies with respect to the environment through perception, action, and cognitive processing. PACE was originally developed for cerebral palsy (CP) as an

integrative and developmental approach, and the tools it has striven to build up may find wide application in other neurodevelopmental disorders as well. Indeed, CP is primarily defined as a phenotype with possible links to pathophysiology. The term cerebral palsy describes 'a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain; the motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, behaviour, epilepsy, and by secondary musculoskeletal problems'.[6] Among these accompanying disturbances, sensation, perception, cognition, communication, and behaviour are at the core of the PACE approach.

As mentioned above, fine description of the phenotype can promote pathophysiological reasoning and eventually link to genotyping. In recent years, rapid technological improvements in DNA analysis have brought about new insights into the role that molecular biology might play in CP, although it is often regarded as being essentially secondary to extrinsic factors. The direct contribution of several genetic abnormalities has been documented to interfere with specific aspects of brain maturation. Single gene mutations have been identified in individuals with CP associated with cerebral dysplasia, microcephaly, hydrocephalus, or extracerebral abnormalities. Single gene mutations have also been documented in families with recurrent presentations consistent with CP. These include genes encoding glutamate decarboxylase 1 (*GAD1*),[7] whose product catalyses the conversion of glutamic acid to GABA. They also include the *KANK1* gene, whose product, KN motif and ankyrin repeat domains 1, has a known role in cytoskeleton formation.[8] And mutations in genes encoding four different subunits of the adaptor-related protein complex 4 (*AP4M1*, *AP4E1*, *AP4B1*, *AP4S1*) have been associated with presentations of CP. This protein complex is involved in the sorting of cargo proteins from the trans-Golgi network to the endosomal–lysosomal system. Another inherited form of CP concerns the *ADD3* gene, which encodes γ-adducin.[9] These findings have implications for diagnosis and counselling. They have expanded existing gene panels that are increasingly used in clinical practice to screen multiple known genes associated with CP at much the same cost as single gene analysis. In parallel, the relevance of these genotype–phenotype associations to the understanding of CP is currently being studied. For selected gentoypes, vulnerability hypotheses have been suggested.[10] In particular, the contribution of genetic vulnerability interacting with environmental stressors, such as intrauterine exposure to maternal infection or inflammation, has improved the understanding of causative factors. More generally, improved understanding of the interaction of genetic and environmental factors has led to a better appreciation of the substantial role played by genetics and epigenetics in the phenotype of CP.

What this paper adds

- Neurobehavioural phenotypes can be described specifically in selected neurogenetic disorders.
- The perception–action–cognition–environment paradigm applies to other conditions than cerebral palsy.
- Valid tools must be developed for assessment and management strategies in these conditions.

Phenotypic studies have increasingly recognized the importance of behavioural features. A behavioural phenotype represents a distinctive association of abnormalities in domains such as cognition, language, social skills, and motor control, which is consistently accompanied by a biological disorder.[11] Clinical descriptions of conditions characterized by a behavioural phenotype have thus been linked to specific genetics. Examples of conditions clinically characterized some 50 years ago are still highly relevant and include Williams syndrome (1961), Lesch–Nyhan syndrome (1964), Angelman syndrome (1965), and Rett syndrome (1966). All of these can serve as models for the phenotypic approach in terms of diagnosis, pathophysiology, management, and outcome. Molecular characterization of these conditions has allowed the development of animal models that provide important insights into the pathophysiological mechanisms and targets for the study of phenotypic plasticity. This has, for example, been a focus of research using environmental enrichment paradigms in mouse models of Rett syndrome.[12–14] Most models, however, replicate only selected features owing to pathophysiological complexity. Modelling efforts should therefore concentrate on multiple models, each addressing specific experimental questions. Such efforts have led to suggesting avenues for the development of specific therapeutic approaches in several genetic neurodevelopmental conditions,[15] including fragile X syndrome, Rett syndrome, Angelman syndrome, tuberous sclerosis complex, and Down syndrome.

In patients, PACE paradigms can be developed similarly to the CP context. For management, it must be recognized that these conditions cannot be cured. Like CP, the functioning of individuals can, however, be modified; this is the task of all professionals working with people with this condition who need to identify what can and cannot be modified.

Although studies have been conducted in most of these syndromes, methodological issues have limited reproducibility and generalization to a large extent. To assess cognition, researchers often use tests that have not been validated in the studied populations. Specific biases may be difficult to overcome. For example, motor deficits may significantly interfere with testing. They might do so differentially in different syndromes. Selected language skills may be correlated with intellectual ability in some conditions, including Down syndrome[16] and Williams syndrome,[17] but language characteristics may not parallel cognitive impairment, as exemplified in Angelman syndrome[16] and Rett syndrome.[18] Some authors have relied on selected strategies to design cognitive tasks, such as eye-tracking in Rett syndrome.[19] This

approach is of potentially great interest but may not avoid some important biases. Rose et al.[20] have addressed these to evaluate attention as well as face and pattern recognition in a group of patients with Rett syndrome. They concluded that attention was 'less mature', with fewer and longer fixations, and restricted gaze focus tending to ignore nose and mouth. Similar difficulties at deciphering the complexity of human behaviour in the setting of severe intellectual disability have been noted when studying Angelman syndrome. Issues such as the contextual significance of laughter, aggressiveness, stereotypies, and other 'autistic features' have yielded diverging interpretations, although specific studies have greatly contributed towards clarification.[21] Moreover, any exploratory or intervention study conducted in this context in the framework of PACE should be designed to keep appropriate emphasis on dynamic developmental trajectories.[22,23] This holds true when studying animal models. Behavioural phenotypes vary across ages, cohorts, and genetic backgrounds of mouse models, calling for caution when interpreting the findings. For example, mice with an inactivated maternal *Ube3a* gene on either a 129S7/SvEvBrd-*Hprt*$^{b\text{-}m2}$ or C57BL/6J background studied across a range of functional domains and ages showed several differences.[24] Motor and spatial deficits were seen at 16 weeks but not at 8 weeks. Abnormal startle reactivity and sensorimotor gating were seen only in adolescent C57BL/6J mice.

Overall, the current state of research offers documentation of the phenotype of many neurodevelopmental genetic conditions. For selected conditions, for example Down syndrome and Williams syndrome, the level of analysis of the phenotype is sound enough to provide a good basis for testing intervention in the PACE perspective. This type of study should be strongly encouraged as there is an urgent need for tools for assessing informative groups of patients with such conditions. There is a need for finer clinical and laboratory studies along a multidimensional typology, delineating relevant functions and avenues for modulation. Similarities and differences between conditions should be better documented. Animal models should be designed to test hypotheses that might be relevant to human patients. So far, few powerful intervention studies directed at inducing phenotypic changes have been conducted. This field is wide and multilevelled, expanding from pharmacological modulation of gene expression to behavioural and cognitive intervention.

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