OPINION

Environmental enrichment, new neurons and the neurobiology of individuality

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Abstract | 'Enriched environments' are a key experimental paradigm to decipher how interactions between genes and environment change the structure and function of the brain across the lifespan of an animal. The regulation of adult hippocampal neurogenesis by environmental enrichment is a prime example of this complex interaction. As each animal in an enriched environment will have a slightly different set of experiences that results in downstream differences between individuals, enrichment can be considered not only as an external source of rich stimuli but also to provide the room for individual behaviour that shapes individual patterns of brain plasticity and thus function.

Experience and behavioural activity continuously alter the brain, and enriched environments (ENRs; alternatively referred to by the abbreviations EE or EC for 'enriched condition') are tools to study these effects in the laboratory. Mark Rosenzweig, one of the pioneers of environmental enrichment, defined enrichment as the "combination of inanimate and social stimulation"[1]. The basic experimental set-up has hardly changed over decades[2,3]: animals, normally rats or mice, that are kept in a larger group and in a larger cage, often equipped with additional toys, nesting material and tubes to hide, are compared with what are considered 'standard housing' animals in the laboratory (FIG. 1; BOX 1). Rosenzweig's minimalist definition already emphasizes the point of a 'combination': enrichment is always multifactorial and multimodal (FIGS. 1,2). The specific set-ups might vary considerably: sometimes, for example, the cage size is kept constant but group size is varied; in other cases, only toys are used as enrichment in standard cages, enrichment might be for only short intervals daily as opposed to representing the living conditions for a longer period of time and so on. This variability makes direct comparisons difficult[2,3], and it is surprising that such a poorly standardized paradigm has yielded, by and large, such consistent overall results. The paradigm is about complexity and the reduction in complexity for the sake of the experiment. Differences do matter of course, but there is something fundamental at the core of the paradigm that is fairly invariant to modifications across a wide range of settings.

Since its beginnings more than 75 years ago, the ENR paradigm has become one of the most successful general concepts in experimental biology and psychology because it enables the experimental capture of the fundamental link of plasticity between structure and function. A number of general reviews have summarized the state of the field and its history[4–8]. By contrast, the current Perspective article aims at outlining a non-exclusive vision of where the paradigm might be taken in the future.

Experience and behavioural activity leave structural traces that over time substantially contribute to defining our individuality and personality. The resulting interindividual differences have rarely been in the focus of ENR research, which always emphasized between-group comparisons. With the rise of personalized and precision medicine, however, there is a growing general interest in exploring sources and mechanisms of interindividual variability and within-group effects[9,10]. Indeed, the ENR paradigm could also be developed to take on a lifespan perspective, to combine longitudinal with cross-sectional analyses and to become multivariate. For example, as large cohort studies in humans search for biological markers of 'successful ageing', complementing animal studies based on the ENR paradigm could help to unravel the underlying mechanistic complexity.

In this article, I discuss how some of these opportunities are exemplified by studies on adult hippocampal neurogenesis, a phenotype of brain plasticity that shows a sensitive response to environmental stimuli[11] and, as suggested by data obtained from animal studies, a potential role in the individualization of the dentate gyrus[12] and in its functions (including behavioural pattern separation, the avoidance of catastrophic interference, clearing and forgetting as well as the ability to flexibly integrate novel contents into pre-existing contexts). A short summary of ENR effects on the brain and of proposed underlying mechanisms will set the stage for these considerations. When discussing adult neurogenesis in this context, emphasis will be placed on functional aspects, because behaviours are both the cause and the consequence of activity-dependent plasticity. Activity-dependent regulation of neurogenesis implies that it is behaviour that regulates the production of new neurons, which change the neuronal basis for certain relevant aspects of future behaviour and close the feedback loop. From there, I discuss the general relevance of the ENR paradigm for the human situation, including translational implications regarding healthy cognitive ageing and Alzheimer disease (AD) as a condition, for which preventive measures frequently make direct reference to the ENR concept. Finally, on the basis of this, I describe future opportunities for the ENR paradigm that lie in shifting the focus from 'enriching heredity' to 'enriching plasticity', and thereby from static end point differences to effects on dynamic processes.

General effects and mechanisms

Effects of ENR on the brain. The ENR paradigm was originally introduced by Donald Hebb in the 1940s, resonating with his quest for understanding the role of experience in brain development[13].

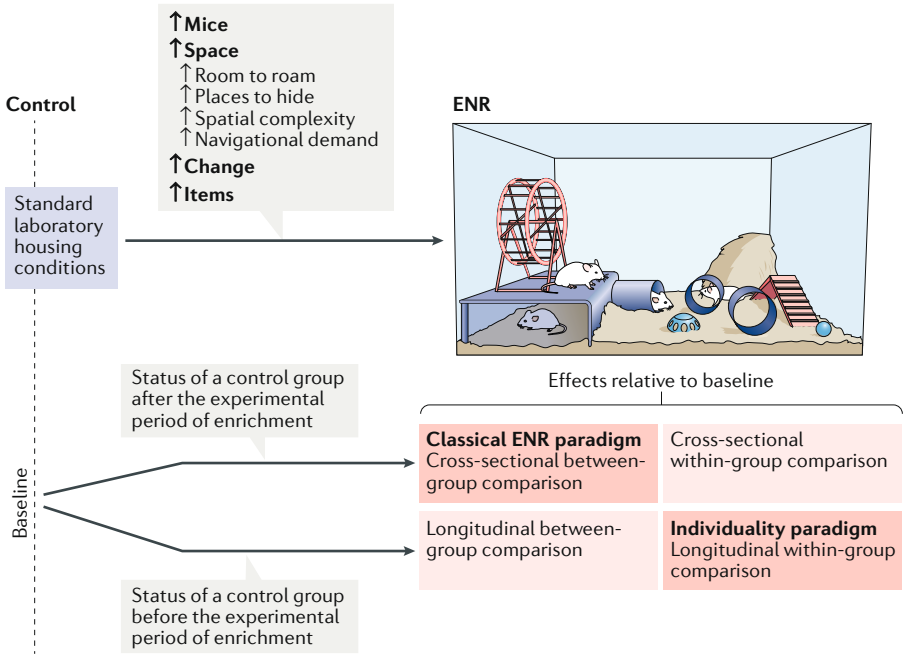

Fig. 1 | **The enriched environment paradigm and its variations.** The precise paradigm implemented in studies of enriched environments (ENRs) varies, but key features are that inbred, that is, genetically identical, animals (mice or rats) are exposed to a larger cage with more animals and a selection of toys and structures on which to climb and hide. Experimentally, physiological and behavioural effects are compared between a control group in standard housing and the enriched group. In the classical ENR paradigm, data analysis consists of a cross-sectional comparison of group means for the parameters of interest. The paradigm can also have a longitudinal domain, in which the baseline is the status of the experimental group before ENR. This enables longitudinal analyses and the assessment of diverging trajectories (the individuality paradigm). Both cross-sectional and longitudinal perspectives allow between-group and within-group comparisons, extending the conventional view of the paradigm.

At that time, intelligence had been largely considered an innate trait, not amenable to environmental influences. Famously, Hebb compared rats reared as pets at his home with rats living in the laboratory[2,3].

With this perspective, the ENR paradigm had, at least to some extent, been a reductionistic attempt to respond to the even more reductionistic framework of behaviourism, an influential school of thought that for decades dominated theories about learning. B. F. Skinner and other proponents of behaviourism believed that essentially all cognition could be reduced to conditioned responses and "psychic reflexes"[13]. Behaviourism treated the brain as a black box and focused on input–output relationships. The initial question was thus: would behaviour also change when this strict relationship was resolved in the richness of general experience? The answer was yes: enrichment had lasting, generalizing effects on behaviour, including learning. Since then, this has been confirmed in many studies using a wide array of behavioural tests[14–17]. These insights had rather immediate and far-reaching societal impact, providing one of the scientific rationales for the Head Start programme in the United States in the 1960s, designed to 'enrich' the life of low-income children in order to improve their school readiness[18].

Importantly, the rat studies following Hebb's initial work also showed that the behavioural impact was associated with substantial effects on brain structure[19,20]. In the days before magnetic resonance imaging, which would later make such observations almost commonplace, this was a revolutionary insight. Key investigators in the field, most notably Marian Diamond, Edward Bennett, David Krech, Mark Rosenzweig and later William Greenough, further developed the idea of how experience actually shapes the brain structure and thereby brain function (reviewed for example in REF.[4]).

Together, the data available today imply that ENR has a considerable number of specific effects (FIG. 2). ENR promotes growth and increases the size and weight of the brain itself (as well as substructures) and across many domains of brain function (but usually decreases body weight)[19,21]. ENR has remarkable effects across scales — from molecular and cellular to behavioural and social. There are, throughout the brain, also substantial effects on cell proliferation and cell genesis, suggesting widespread cell-based plasticity[20,21].

These effects might be, in part, explainable by the finding that ENR also affects gene expression in many cells and tissues[22–24], alters protein production[25] and modulates the biochemical processes of, for example, neurotransmitters[26], neurotrophic factors[27], hormones[28] and immune factors[29], often on timescales that last beyond the time window of the actual stimulus and are sometimes very long lasting[30,31].

ENR also ameliorates chronic disease phenotypes, increases recovery from acute conditions by itself and as adjuvant manipulation[32] and is effective throughout life into oldest age[33,34], and some effects are even transmittable to the following generation[35–39].

The scope and the strength of effects that result from what is a rather straightforward, non-invasive — and upon first impression simple — intervention is remarkable and raises important questions about the nature of the relationship between cause and consequences and about the mechanisms mediating this relationship.

Genetic background. By and large, the ENR paradigm treats the genetic background as a constant and systematically varies the environment in order to study the effects on the brain under the assumption that the resulting effects are in turn causative for later function and behaviour.

When applied to genetically identical, inbred strains of mice and rats, ENR has the theoretical potential to help in deciphering interactions between genes and the environment ('gene × environment interactions') that underlie plasticity. The paradigm can achieve this by means of controlling the genetic influence through the use of genetically defined and varying the environment (FIG. 1). Strictly speaking, however, in order to address the gene × environment interaction, one would have to systematically vary the genetic background as well. In experiments with one genetically defined strain, only the impact of 'environment' on a fixed genetic background is analysed.

By contrast, many classical studies in the field have been done on outbred strains of rats (for example, Long Evans or Sprague Dawley), which show considerable within-strain genetic variation[40]. This within-strain genetic variation limits the power to ascribe any observed effect specifically to environmental influences. In outbred

Box 1 | **Is enrichment really rich or only reversing impoverishment?**

The enriched environment (ENR) paradigm is an abstraction and a highly reductionistic construct. A classical critique has been that the setting might not so much reflect a true enrichment over control conditions but rather represent a reversal of the impoverishment that is found in the standard housing of laboratory animals compared with the situation in the wild[45]. This critique is an important and critical point. However, the two evoked comparisons (ENR–control and ENR–wild) are conceptually quite different: first, the comparison ENR–wild has rarely been tested experimentally (for a detailed discussion, see REF.[120], as well as REFS[121,122] and their discussion in REF.[5]); second, common laboratory strains of mice have not experienced feral conditions in hundreds of generations (for C57BL/6, since 1905) and are genetically distinct from wild mice (for example, see REF.[123]). They have been bred for captivity and the laboratory. The experiment is thus reductionistic with respect to the genotype of the animals, their physiology[124], their 'habitat' (see point 1) and their resulting behaviours[125]. Standard laboratory conditions are both more stressful (for example, with respect to the ambient temperature in most facilities[126]) and much less stressful (for example, with respect to predators, abundance of food and so forth) than wild conditions, suggesting that defining the baseline as adverse conditions might also fall short. These issues constitute inbuilt caveats of the paradigm but are not an argument against using it per se. To the contrary, the key point in favour of the ENR paradigm is that it is about a relative change over a baseline and that absolute conclusions about feral conditions should neither be intended nor drawn post hoc. This emphasis on relative change, however, needs to be taken into account, and discussion of the baseline will always be as important as the consideration of the relative deviations from that baseline.

strains, the genetic variation is random and not known. Genetic variability contributes to interindividual phenotypic variability, which a priori is not desired.

However, there have been first attempts to exploit the variability of outbred stocks. A variation on the ENR paradigm based on 'sibling interventions' in outbred CD1 mice made use of the genetic heterogeneity to estimate the heritability and malleability of a trait. Importantly, that study did not find gene × environment interactions that would explain the change in heritability of 'intelligence' between control and enriched mice but saw environmental variance as the main driver[41].

The fact that some effects of ENR can be transmitted not only to the immediate offspring of the living animals exposed to ENR but also sometimes across several generations has spurred interest in the genetic, behavioural and especially epigenetic mechanisms underlying these effects. Interestingly, both paternal and maternal enrichment have an impact on the offspring, suggesting the coexistence and interaction of several routes of transmission[35–39].

Nested mechanisms of enrichment. As yet, there is no generally accepted mechanistic model of ENR and no unifying theory of the paradigm. Although on one hand this is not surprising given the scope of the effects and of the parameters that constitute the enrichment, there is, on the other hand, a much-felt need to integrate the available data and concepts. Historically, one can distinguish four main lines of thought that have emphasized motor[42], sensory[43], cognitive and emotional[5] or social stimuli[44] as drivers of ENR effects (FIG. 2), resulting in generalizing effects such as 'arousal'[43] or 'learning'[5], which in turn lead to differential development[45]. In fact, effective key elements of ENR, which together might explain how ENR works, appear to be physical activity, social interaction and mental or cognitive stimulation as a result of exploration or play (FIGS. 2,3a). These elements are not independent of each other, however, and will have to be considered together and in their interactions. Highly reductionistic theories miss this complexity and thereby what makes the ENR paradigm so particular. For example, physical activity alone results in some effects that at first appear highly similar to those of ENR[46], but detailed analysis can reveal how different these seemingly identical effects actually are, for example, on learning and memory[15]. It is no trivial task to distinguish general locomotion from physical activity in a more sportive sense, to appreciate sensory (especially proprioceptive) enrichment due to exercise and to specify the relative contribution of arousal compared with a boring standard laboratory cage.

On the other end of the spectrum, effects on gene transcription have been interpreted as reflecting some basic molecular causality. Although candidate-based approaches have revealed a potential prominent function of certain molecular mediators of ENR effects (see review in REF.[47]), the overall explanatory power has been low.

The reason for this is that, from a molecular perspective as well, ENR is a quintessentially complex context with emergent properties. Almost by definition, susceptibility to the effects of ENR must be highly polygenic and individual genes may have very small effect sizes. Zhang et al. showed that environmental enrichment increased differences in DNA methylation between the dorsal and ventral hippocampus, prominently including binding sites for neurogenic transcription factor NeuroD1 (REF.[23]). That study was a first step in the direction of more integrative analyses, but how to move from such results to advanced mechanistic insights and understandable 'mechanisms' still remains open.

Generally, mechanisms in complex contexts are nested, requiring interfield and interlevel integration (FIG. 3b). Craver and Darden have used the words of economist Herbert A. Simon to point out that these are 'nearly decomposable systems' in that "biological systems are composed of more or less independent mechanisms assembled into higher-level mechanisms, and so on"[48]. Theories that have the power to explain complex relationships in biology bridge between such levels, facing either upward or downward. Starting from transcriptomics, one will be tempted to build integrative mechanisms from the most basal layer, but extrapolation across layers remains difficult. Adding layers raises questions about the interfaces and relationship between these. Brain-derived neurotrophic factor (BDNF) is an example of such an upward-looking 'mechanism' of ENR effects for which unequivocal evidence exists at several levels[49]. However, it is also obvious that no single factor will ever explain the complexity that is the key point of the paradigm. A more integrative view on mediators such as BDNF is required[50].

Environmental influences directly or indirectly act upon processes at multiple layers, often relying on complex intermediate processes in such a nested model. The resulting vertical (between layers) and horizontal (within layers) network of interdependencies is difficult to articulate and consequently to understand.

Mechanisms are to be found at all the different levels and in their interactions. At the same time, to regard the relationship of mechanisms as simple hierarchy and layered in the first place might be profoundly misleading. In the end, what we are looking at is a high-dimensional network of direct and indirect causes. Within that causality space, many different mechanistic perspectives on ENR are possible.

How to achieve a broad, yet sufficiently reductionistic, mechanistic approach is

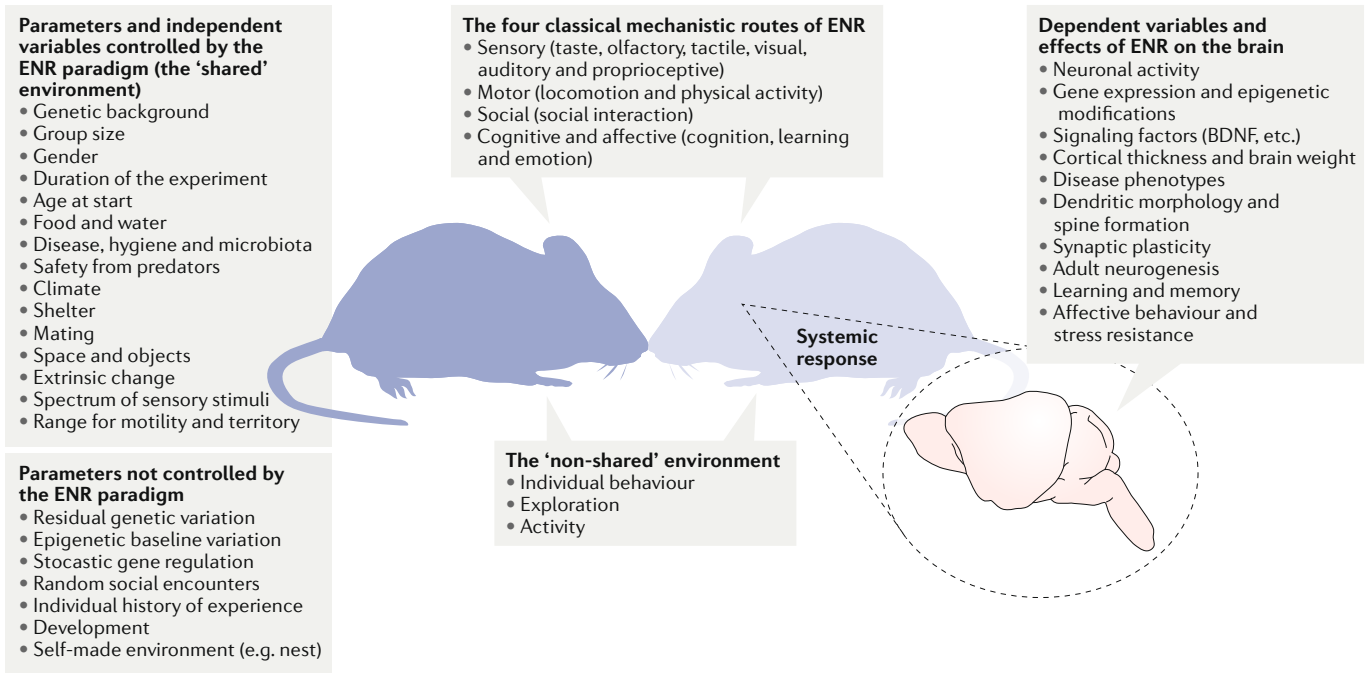

Fig. 2 | **Parameters, mechanisms and variables in the enriched environment.** Despite being highly reductionistic, the enriched environment (ENR) paradigm is characterized by a wealth of obvious or hidden variables and parameters. It is not possible to completely control the parameters and independent variables in ENR experiments, and the behaviour of the animals creates a 'non-shared' environment that is an emerging variable in the concept. The individuality paradigm emphasizes this aspect and relates it to interindividual, within-group effects of ENR. Four classical mechanistic routes of ENR (sensory, motor, social, and cognitive and affective) intersect with the 'non-shared' environment but are not identical to it. ENR has a wide range of effects on the brain that might or might not be related to systemic responses. The relationship between these two domains and the underlying causalities has hardly been explored thus far. Here again the effects of ENR on the brain are found across scales from molecular to behavioural. Adult hippocampal neurogenesis is an exemplary readout that captures this complexity in nucleo. BDNF, brain-derived neurotrophic factor.

not clear from the present-day literature and state of the field. What exactly creates a relevant 'mechanism' is very difficult to define, and there should generally be more debate in biology about the nature and limits of what we consider mechanistic insight (see REFS[48,51]). The systems affected by ENR are all nonlinear, best approximated as high-dimensional networks of dynamic interactions, but in terms of tangible insight, this characterization is hardly helpful.

More and richer data (for example, from omics studies) will help to solve that problem (for example, in machine learning approaches) but will also continue to amplify the complexity. Data alone do not generate insight. However, in the end, this will create new opportunities. Approaches from 'big data' science and systems biology, especially 'causal inference', are developed for exactly this type of problem[52]. Longitudinal analyses introduce a temporal, dynamic dimension but again pose additional challenges. Within the reductionistic, controllable qualities of the environment of ENR, some fundamental, highly complex questions can be addressed because they can be tested experimentally.

ENR has always been dominated by the neurosciences, but the percentage of studies outside the brain, almost absent until well into the 1980s, is steadily increasing. This expansion offers the opportunity to open the analysis to interaction effects between different body systems. In order to peer into the black box of mechanisms of enrichment, such multivariate approaches will be necessary.

To start doing so, it will be very helpful to have exemplary processes at hand, which allow a description across scales, both vertically from genes to behaviour and social structure and temporally from acute events to lifespan perspectives. On the basis of the animal literature, adult hippocampal neurogenesis appears to be a process that fulfils these characteristics and can be used as a model. As with all models, adult neurogenesis also has many limitations: its exact prevalence and role in humans still remains to be established and it represents just one small, specialized aspect of hippocampal plasticity. Nevertheless, keeping such limitations in mind, the combination of ENRs and adult hippocampal neurogenesis provides a model system with great potential.

Adult neurogenesis: a key phenotype

ENR effects on the hippocampus. The very nature of the ENR effect directed early attention to the hippocampus as a key structure involved in learning and memory as well as in emotions. In a monumental review, Smith and Jones summarized the knowledge of ENR in 1980 and called for more work on the hippocampus[53]. Publications in this area have surged since then. Ohline and Abraham have, for example, recently reviewed the impressive number of studies describing the full range of electrophysiological changes in the hippocampus in response to ENR[54]. The discovery that ENR produced lasting increases in the sparseness of place cell representations in the hippocampus, presumably increasing the processing efficiency in (spatial) learning, underscores how specific the analyses have become and how profound ENR changes can be[55].

The state of the art today includes reports on numerous effects of ENR on both cognition and affective behaviours[56] and, correspondingly, on the dorsal and ventral anatomical subsections of the hippocampus, which take leading roles in processing cognitive or affective

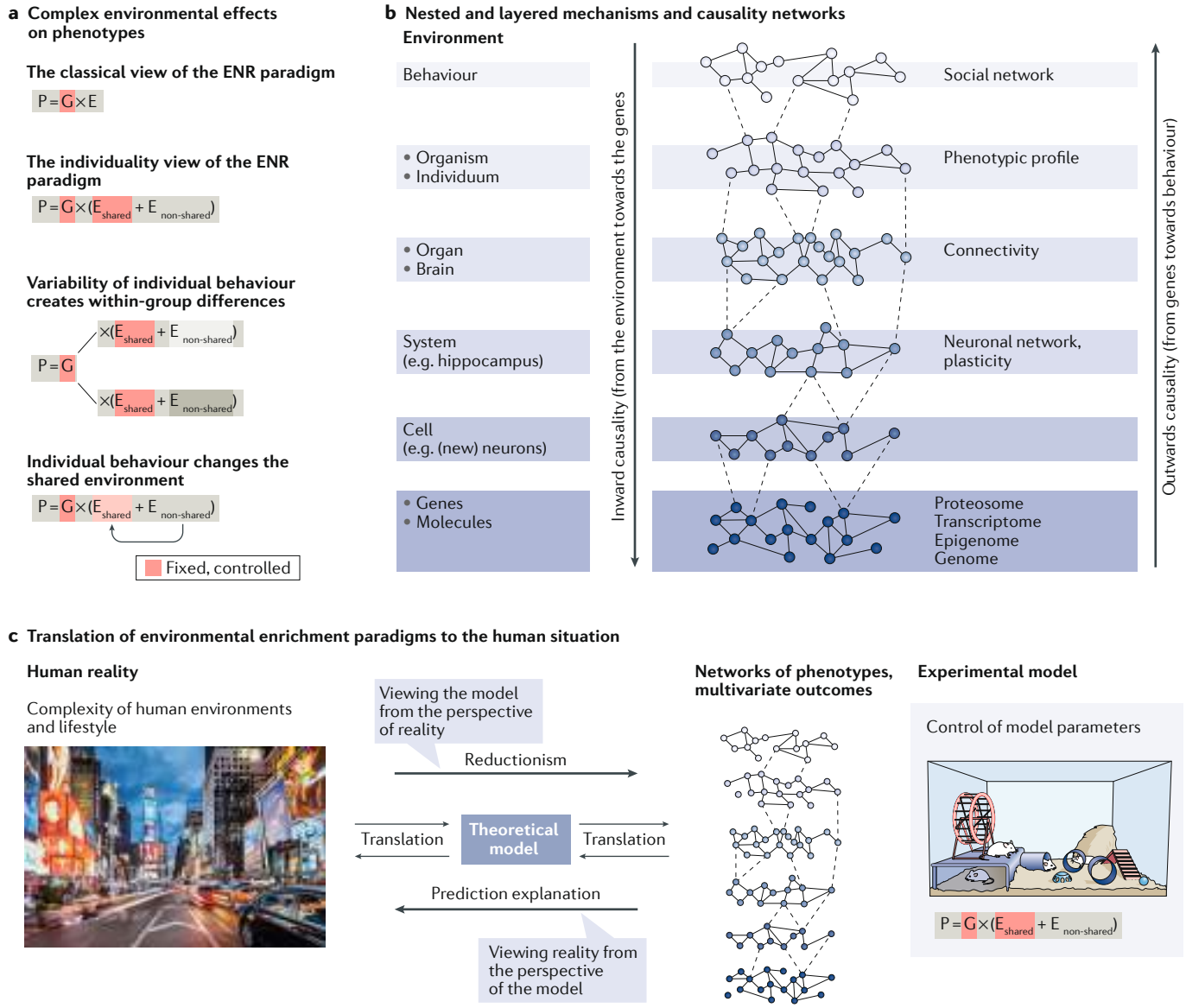

Fig. 3 | **Mechanistic perspectives on enriched environment. a** | The enriched environment (ENR) paradigm is traditionally seen as an experimental strategy to address the effects of environment (E) on phenotypes (P) when the genetic background (G) is fixed. As detailed in this article, this view is not quite complete because individual animals within the ENR cage also behave and form their own environment, as do the other animals. This 'non-shared' environment has a substantial impact on the phenotype and prevents the E part of the equation from being fully controlled, even if in the experimental situation the nominal environment for the subjects is identical. Behaving animals change the environment of their cage-mates, for example, by altering the social structure. **b** | A mechanistic description of the ENR paradigm faces the challenge that effects of the environment are across scales and domains so that mechanisms are both nested and layered. Interlevel and within-level integration of causality networks are necessary. There is an inward causality from the environment down to the molecular basis and an outward causality towards behaviour within that environment. **c** | Translation of the ENR paradigm to the human situation involves the formation of a theoretical model that becomes the 'rosetta stone' of translation. Importantly, this translation must be bi-directional in order to become successful.

functionalities, respectively[57,58]. These effects and their supposed connection within the hippocampus have also raised important hypotheses about activity-dependent and environmentally induced plasticity in the context of neurological and psychiatric disorders (see reviews in REFS[32,50]).

In many of such conceptualizations, adult hippocampal neurogenesis plays an important role, integrating current thinking about the functional contribution that the new neurons make to both cognition and affective behaviour in health and disease. ENR robustly stimulates adult hippocampal neurogenesis, which might be part of the structural basis of preventive or therapeutic effects of lifestyle and activity in such conditions[59]. Many studies that have looked at interaction effects of environmental enrichment and disease phenotypes in rodent models included adult neurogenesis as a proposed mechanism (see for example REF.[60]). As discussed below, this focus lends mechanistic face validity to many studies, but the actual causality often remains correlative and ultimately speculative.

The translational relevance of such findings has also sometimes been questioned as part of the discussion whether adult hippocampal neurogenesis occurs in humans. This debate was recently re-ignited by two prominently placed reports[61,62] that came to exactly opposite

conclusions. The dissenting study could not reproduce the previous studies on proxy marker expressions as indication of adult neurogenesis in humans[63]. Hard evidence of adult neurogenesis in any species, however, had not been based on proxy markers in the first place but on birth dating studies[64–66]. If despite this evidence, the critiques were correct, this would of course limit the translational relevance of adult hippocampal neurogenesis. However, at present, the available evidence supporting adult neurogenesis should not be discounted, although it is likely that adult neurogenesis in humans will show some considerable differences from rodents. The equivocal marker expression might in part reflect that the process of adult neurogenesis might have a considerably different dynamic in humans, resulting in a pool of 'neurons in waiting' as a reservoir for cellular plasticity that is not fully captured with the markers used in rodent studies[67].

Neuronal development in the adult. The discovery that ENR stimulates adult hippocampal neurogenesis[11] also gave a new twist to the ENR paradigm because adult hippocampal neurogenesis is not an end point but represents a complex yet circumscribed developmental process with definable functionality. ENR here visibly interacts with neural development (in the adult) and does so at different stages of the neurogenic process with, for example, effects on cell survival[11,68], precursor cell proliferation and maintenance[31,33], dendrite and spine formation and maturation[69], as well as functional integration[70]. ENR also induces the persistence of Cajal–Retzius neurons, the output of which steers development of the dentate gyrus, further suggesting that ENR indeed prolongs development into adulthood[71].

Most visibly, ENR promotes the survival of adult-born neurons in the dentate gyrus with no or limited effect on the proliferation of precursor cells[11,68]. This selectivity, however, is genetically determined and hence variable[72], which is important for translational inspirations. In addition, physical activity increases precursor cell proliferation (see below) so that the availability of a running wheel in the cage might also mask this distinction. The activity-dependent recruitment mostly takes place once the cells have exited from the cell cycle[70,73] but, interestingly, well before they are functionally fully integrated.

The young immature, postmitotic neurons in the adult hippocampus go through a phase of increased synaptic plasticity[74–77], which biases network activity towards the new cells[78] and might drive their recruitment into the existing network. That it is the encoding of experience that promotes the integration of new neurons has been shown directly by means of optogenetics[79]. The exact quantitative contribution this mechanism makes to the overall effect on experience encoding is not yet known, but these findings provide further support for the notion that the key enrichment effects depend on neural activity (as opposed to merely systemic and nonspecific effects).

The transient early-postmitotic role and the lasting network function are linked, and presumably the former instructs the latter. Because a survival-promoting effect in these neurons is also found in response to an induction of long-term potentiation (LTP) and after specific learning stimuli[80–83], ENR itself might represent relevant learning stimuli. This would also be in line with the 'learning theory' of environmental enrichment as a whole, proposed by Edward Bennett and colleagues and discussed elsewhere[5]. The problem with this idea is that what might specifically constitute 'learning' in the paradigm has largely remained elusive.

However, because adult neurogenesis is regulated by behaviour and leads to changes in measurable behaviour, it allows a model to be built of the complete feedback loop encompassing the bi-directionality of plasticity, rather than the conventional one-way-route of 'environmental influence on …'. This description can incorporate the full range of relevant potential stimuli.

One of these seems remarkably nonspecific: physical activity (which, in the laboratory situation, usually involves voluntary wheel running) is often considered a part of environmental enrichment and increases adult neurogenesis, but it does so by strongly inducing precursor cell proliferation[46]. The effects of physical activity and environmental enrichment are additive[84], which indicates that increasing the potential for neurogenesis is sufficient to increase the actual use of the recruitable cells in the case of cognitive stimulation. In addition, it seems to be the active, not passive, participation in an ENR that results in a pro-neurogenic and related functional effect[85].

In older age, adult neurogenesis is decreased, but there is a very strong, relative response to ENR[86]. Upon prolonged exposure to the ENR stimulus, a maintenance effect on precursor cells becomes apparent[33] that is also strongly visible in a physical activity paradigm[87], which together emphasize the critical role that general activity and locomotion play in maintaining neurogenesis potential. In turn, this observation is of great relevance for 'brain maintenance' concepts that aim to explain the individual ability to cope with the adverse effects of cognitive ageing.

The idea that adult neurogenesis can convey resilience has also been suggested for affective behaviours[88], and in an impressive set of experiments it was shown that new neurons build resilience to chronic stress by specifically inhibiting the ventral dentate gyrus[89]. The potential role of environmental stimuli in this context has not yet been studied, but the whole scope of possible influences of behavioural activity in the broadest sense and experience on 'reserve' formation already becomes visible.

ENR effects on gene expression have also been studied in the context of adult neurogenesis, but the resulting lists of genes in which their expression was significantly altered were surprisingly short and no discernible patterns emerged[90]. Lacar et al. (2016) used a single, short, 15-minute exposure to ENR as stimulus and investigated gene expression at the single-cell level in the dentate gyrus[91]. However, in such an acute situation, ENR effects on neurogenesis substantially differ from long-term effects in that not only the postmitotic cells but also the precursor cells respond[92], and we have proposed previously that such early and acute effects are fundamental for triggering the lasting changes (see below)[93]. In any case, these results suggest that the initial exposure to a novel environment is one critical aspect to environmental enrichment but distinct from the sustained ENR situation, in which novelty invariably must wear off.

Given that at least in rodents, essentially all measurable LTP in the dentate gyrus can be attributed to the new neurons[74,75,94] and that adult neurogenesis appears to be instrumental for functions that have been considered hallmarks of the dentate gyrus (for example, behavioural pattern separation[95,96]), the hypothesis could be developed that adult neurogenesis indeed provides critical contributions to hippocampal function.

A more complete picture: individuality

A key point of the classical ENR paradigm is that the actual intervention is limited to providing the setting of the experiment; in most cases the experimenter does not interfere further with the course of the experiment (except for husbandry purposes or a limited rearranging of toys and so forth).

There are exceptions to this rule, but they are rare. Thus, by and large, in the ENR paradigm both genetic background and environment are held constant (FIG. 3a). However, this applies only to what is called the 'shared environment': the classical ENR paradigm addresses the effect of an enriched pre-set environment in the absence of genetic variation (FIGS 2,3). The shared environment is the outer environment that is nominally identical in the ENR paradigm, but there are other aspects to 'environment' that deserve more attention.

An interesting simple question leads to these aspects: does ENR also increase phenotypic variation within the enriched groups? Walsh and Cummins described in 1979 that variance of nuclear diameter in the granule cell layer was greater in enriched living rats (with unaltered means) and proposed a differential 'developmental restriction' of these neurons[97]. With few notable exceptions[98–100], the ENR literature was more concerned with mean differences between groups than with variance between individuals and the question whether ENR would generally increase variability was not systematically addressed. If so, the question was mostly asked from the perspective of animal welfare: would a certain amount of enrichment interfere with the desire for controlled and standardized conditions and reproducibility of the results[98–100]? A massive recent study at the German Mouse Clinic investigated 164 variables in three cohorts from two strains of mice of both sexes and under three different housing conditions and came to the conclusion that simple enrichment (that is, nesting material, shelter and so forth) did not affect the reproducibility of the results and had mostly small mean effects with little or absent effects on variability[99].

With respect to the ENR effects on adult hippocampal neurogenesis, we noted that in addition to an increase in the mean number of new neurons, individual longitudinal trajectories of 'roaming entropy' (a measure of active exploration and territorial coverage in the ENR cage) explained one-fifth of the interindividual variance in adult neurogenesis at the end of a 3-month experiment. Some ENR animals did not differ from controls whereas others had almost five times as many new neurons[12]. A related study also suggested that there is a social component to this individualization process in that high roamers tended to be socially more 'individualistic', showed less non-social exploration and were possibly less playful[101]. Torquet et al. automated the analysis of social interactions in a similar approach and could show that dopaminergic signalling mediated effects of this aspect of enrichment on emerging individuality[102].

At a conceptual level, these findings imply that ENR is actually an experimental paradigm to explore in animals the so-called 'non-shared' environment — that is, the differential experience of each individual animal in the shared ENR environment (FIGS 2,3a). In the literature on twin studies, the 'non-shared' environment has been an important construct but difficult to assess directly and experimentally[103]. The ENR paradigm effectively controls for both the genetic background (because the animals inbred) and the nominal environment (because they are all living in the same cage and all changes to that environment equally apply to all of them), but not the non-shared environment.

The implications appear twofold: first, the factor of individual behavioural activity has become a definable parameter (or variable) in the ENR paradigm that enables a more complete assessment that drives ENR effects; second, ENR can now be turned into a model that is suitable to investigate the (neuro)biology of individualization. In turn, these implications have consequences on concepts such as personalized medicine, which thus far suffers from the fact that essentially all standard animal experiments aim at minimizing intragroup variance.

Translational, medical implications

A thorough review of the topic of enrichment models and disease was published in *Nature Reviews Neuroscience* in 2006, and although it by now would certainly benefit from an update with respect to the specific studies that are covered, the general, and largely positive conclusions about the opportunities of enrichment models in the context of disease have hardly changed[32]. Despite many shortcomings, the results of ENR studies in disease models are generally promising and have therefore been used to justify more or less immediate translation to the human situation. In the case of acute impairment such as in stroke or traumatic brain injury, where ENR has massive effects, this is plausible, albeit more by association and face validity than on the basis of very concrete mechanistic hypotheses.

In the case of chronic and degenerative disease, the findings have been often less clear. This is exemplified by the surge of experiments studying animal models of AD (or more correctly, of cerebral amyloidopathy) under ENR conditions (as well as other neurodegenerative diseases), including several among them, which hypothesize adult neurogenesis as a mediator of functional effects[104,105] (see REF.[106] for a summary of the underlying rationale). The conceptual background is that educational status, cognitive activity as well as physical activity reduce the risk of AD in humans. Lifestyle factors in total explain about one-third of the risk[107]. ENR thus promises to be a straightforward animal model system to examine the influence of environment and activity on disease development in AD. Although by and large, positive effects on all kinds of measures could be observed, clear interaction effects indicating a causal interference with the pathology itself have not been discovered. One explanation has been that the transgenic overexpression of a mutant form of the human *APP* gene might have overridden any physiological regulation so that only general compensatory effects could be seen, if at all[108]. Another issue is that many studies have further decreased their power by exploring additional parameters (for example nutrition), resulting in complex factor designs that would call for advanced modelling.

The ENR paradigm has an important and concrete limitation in the use of monogenic models of sporadic (and chronic) disease such as AD, because the gene × environment interactions that lie at the centre of ENR are here confounded a priori. The genetic intervention has massive reverberations throughout the genome, creating a complex new molecular background upon which the behavioural intervention acts (see a more general discussion of such issues in REF.[51]).

On the other side one might envision studies that turn this constraint into an advantage, when additional dependent variables and the time course of the disease are put into the centre of the investigation to establish a larger, data-rich picture. However, for this we must learn to understand how animals respond to environmental enrichment over time with the fullest range of variables and we must include the fact that 'environment' is also actively made by the animals, not just passively experienced. Constraining disease-related genotypic variation allows useful experimental reductionism, especially if, or perhaps only if, the complexity of the response is made the topic of the investigation.

Enrichment in humans. In the human literature on the subject, there are the concepts of cognitive reserves, brain reserves and brain maintenance[109,110] that capture different perspectives of individual differences in the vulnerability to cognitive

decline. How exactly these ideas relate to the experimental paradigm of ENR has not yet been fully explored from either side, although links are highly suggestive[10,111,112]. The face validity of the approach is thus high, but beyond the basic setting there is rarely specific translation in the sense that the intervention would have been fine-tuned on the basis of insight into the interaction effects that conceptually lie at the centre of the ENR paradigm. On the other hand, enrichment concepts have their own long history and development in psychology, only partially overlapping with the neurobiological approach emphasized here. An extensive and very insightful review by Hertzog et al. (2008) defined the state of the art mainly, although not exclusively, from a psychological perspective[113]. A comparable overview from biology and an interdisciplinary synthesis of enrichment concepts are still missing today.

ENR in animals is a relative model, comparing two artificial situations and defining an arbitrary baseline. It is the relative richness of experience that is central. This point is crucial when results from animal studies are extrapolated to the human situation (FIG. 1) because, under most circumstances, the baseline can hardly be defined and controlled in humans. Humans will generally enter any related study with a poorly quantifiable history and, thus, undefined baseline of preceding enrichment. The extrinsic stimuli also cannot be dosed as effectively.

The immediate clinical translation of ENR, as promoted, for example, in the rehabilitation after stroke[114,115], thus shares with the animal studies only the key manipulation that involves a relative increase in 'social and inanimate stimulation' and 'activity' and the human situation poses considerable additional challenges[116]. On the other hand, lifestyle in humans is highly individual, so that the paradigm could be used to assess the variable range of influence that any individual has to influence trajectories of health and disease.

However, the key difference between ENR in human and animal research is that the genetic influence cannot be controlled. Unless one were able to somehow assess the genetic contribution to the observed effects, the result remains a complex interaction of exactly the environmental and genetic factors that animal research attempts to dissect. However, this creates an opportunity for well-designed and well-analysed translational or comparative studies.

In some conditions (for example, in cerebral palsy[117]), ENR-inspired clinical application of 'enrichment' has already impressively demonstrated the potential of such an approach, but very often the term in such conditions is used in a rather narrow sense, amounting more to a rich, yet specified training paradigm. A key idea of ENR, however, has always been that the stimuli are defined only broadly via a few key settings.

Nevertheless, the combination of 'enriched rehabilitation' with task-specific training and physiotherapy seems a logical step over current standard approaches to neurorehabilitation[118]. This potential could be exploited further with the help of systems medicine techniques; for example, in skillfully designed longitudinal cohort studies with defined 'enrichment', the inability to control genetics is replaced by a broad assessment of genetic, epigenetic and other factors. Computational models would have to be developed that allow the integration and interpretation of these complex data sets. Lifestyle interventions, for example, in the context of preventing dementia, have often shown mixed results in clinical studies. However, lifestyle intervention studies are hardly clinical studies in the classical sense. They are difficult to design because of limits to randomization and blinding, and the massive interdependency of identifiable single lifestyle factors together with large interindividual variation prevents simple conclusions. A translated and extended ENR design could overcome this, and parallel human and animal studies in point-by-point translation might lead the way. For this, translation has to be bi-directional (FIG. 3c).

Because in the ENR paradigm the amount of extrinsic manipulation is actually limited (amounting only to the exposure to the environment with some change over time) and the key process is driven by the activity of the animals themselves, ENR has indeed some potential to be developed into a biological approximation for 'lifestyle risk and resilience'. ENR embraces the complexity of lifestyle-based interventions and does not make unwarranted mechanistic a priori assumptions. The lifestyle of a mouse in a cage is obviously far from what we do consider lifestyle in humans, but certain core elements are still applicable so that an attempt to build a reductionistic model seems feasible. The key point is that individuals seek and shape their own environment on the basis of genotype, chance and past experience[119].

The future of the ENR paradigm

The ENR paradigm has thus far largely been one of comparing end points, not of the developmental processes that ultimately cause differences in the selected end points (FIG. 1). Nevertheless, the ENR paradigm has helped shape the current neurobiological view that the brain's fine structure and connectivity are influenced by our experience of and — as much as we are influencing what we experience and how we respond to it — our activity in the world. ENR is thus a paradigm of 'active experience'. This is a continuous iterative process: the altered structure leads to new behaviours, which in turn might further affect the structure, which is responsible for performing similar actions in the future. This process itself can be explored. An emphasis on individual rather than group effects and the increasing inclusion of longitudinal phenotypes would allow this to be done (FIGS 1,3). Experiments based on ENR could become much richer in their production and usage of data and acquire an added translational value that lies in the emphasis on a process rather than only a comparison of end points.

A famous book by one of the pioneer researchers in the field of ENRs, Marian Diamond, carries the telling title *Enriching Heredity*[7], and the main line of thought, summarizing the state of the field at the time, is exactly this: how does

Glossary

Adjuvant manipulation
A supportive treatment that is applied alongside a primary (therapeutic) intervention.

Behaviourism
A school of thought in cognitive psychology that treated higher brain functions and especially learning as consequence of more or less simple input–output relationships ('psychic reflexes').

Emergent properties
Properties that arise in complex systems and go beyond what can be predicted from knowing the functions of the parts of that system.

Enriched environments
(ENRs). Defined housing conditions for laboratory animals that are richer in stimuli than standard conditions.

Individualization
The processes by which members of a population become different from each other.

Outbred strains
Laboratory strains of animals that preserve a certain level of genetic inhomogeneity (as opposed to inbred strains, in which animals are genetically identical).

enriched living act upon the immutable genetic background in order to generate phenotypic variation? Ironically, despite all the impact of the paradigm, the exact nature of the gene × environment interaction that is supposedly targeted with the paradigm has remained elusive to this day. This elusiveness is not too surprising given the immense complexity of that interaction and the only recent advance of technologies and methodologies to approach that complexity.

Today, we can take the general truth of gene × environment for granted, but with new methods we can apply essentially the same set of questions and general approach to the interaction itself and its temporal dynamics. Hence, we should move to 'enriching plasticity' that is enriching the process and not the preconditions. An interesting question at this point would be the often desired outcome specificity in medical contexts and the caveat of potentially maladaptive plasticity. In any case, focus on the process would be, presumably, an important shift for which only the very first steps have been taken. Progress has become possible and necessary by the advancement of epigenetics, next-generation sequencing and the range of other omics technologies and advanced modelling. Some of the questions addressed in past studies, well ahead of their time, can and will now be asked again with modern methodology and a systems approach. If systems biology is the biology of complexity, environmental enrichment as a model of complexity has many prerequisites to become a quintessential experimental paradigm for systems biology. This will require a closer interaction between modellers and experimentalists; a multivariate, individual and longitudinal perspective; and new ideas about what constitutes mechanisms in biology.

Ultimately, this might extend to systems medicine and personalized medicine. The large face validity of ENR for disease conditions would be substantiated by experimental models that capture the essence of one key aspect — that genetic preconditions and the shared environment affect complex phenotypes in a processual rather than a static manner. This development would involve individualizing self-amplifying trajectories of activity that build upon initial sets of factors and parameters, including genetics and environment. Life can be seen as being composed of a multitude of such parallel threads and trajectories, including the co-development of disease and plasticity.

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