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PERSPECTIVE

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Integrating regenerative biology with developmental psychobiology to understand behavioral recovery

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Abstract

Developmental psychobiology (DPB) is a sub-discipline of developmental biology investigating the roles of physiology, biomechanics, and the environment on behavioral development. Regenerative biology is also a sub-discipline of developmental biology, studying how tissues and organs heal and regenerate after injury. One aspect of healing and regeneration is the behavioral recovery of the whole organism, involving the nervous system and coordinated movements in three-dimensional space. Behavioral recovery is often a secondary measure in many regeneration studies, primarily focusing on molecular and cellular mechanisms involved in structural recovery. Studies and frameworks in DPB, however, suggest that behaviors may have an active role in the regeneration process, and integrating regenerative biology with DPB would provide a basis for behavioral research on regenerative systems as a separate biological question to increase our understanding of behavioral recovery. Here, I introduce the probabilistic epigenesis framework from DPB and elaborate on how it reveals gaps in our knowledge concerning regeneration and behavioral recovery. I close with an initial regenerative history framework to guide regenerative biologists and bioengineers studying behavioral recovery to address these gaps and optimize behavioral recovery with regenerating tissue.

KEYWORDS

development, neuroplasticity, probabilistic epigenesis, regeneration quality, structural regeneration

1 | INTRODUCTION

Regenerative biology aims to understand how regenerative-competent animals regrow tissues and organs without scarring. For example, how does a salamander regrow a limb after amputation? After over a century of studies, we have made significant strides in understanding the molecular and cellular processes underlying limb regeneration. Yet, we know little about how behaviors like walking recover during tissue regeneration, whether such behaviors affect structural recovery, and how we can optimize behavioral recovery alongside tissue regeneration. This is a crucial area of research because understanding how behaviors recover after injury is essential for successfully applying regenerative biology in human medicine. Moreover, insights from developmental psychobiology (DPB) suggest that behaviors play an equal and active role in tissue regeneration as molecular and cellular activity.

Behaviors are conventionally defined as an organism's observable actions and reactions within its environment in three-dimensional space.[1] For example, walking, swimming, catching prey, mating, and so forth. These actions and reactions are controlled by an organism's sensory and motor systems, which are restricted by their

anatomy, neural system, musculature, and environment. These systems define an animal's "action space"[2] or *Umwelt*,[3–5] and any changes to a system will alter the action space. For example, an optic nerve transection will blind the animal, immediately disrupting its action space. After transecting the optic nerve in salamanders, vision is restored 40 days after the retina regenerates and the optic nerve is reconnected with the brain.[6,7] Behavioral tests during structural regeneration of the retina and nerve can determine if vision is restored. Some tests include the optokinetic interactions of the eyes, the approach and capture of prey on a lure, and escape reactions.[7–9] Here, it is essential to consider the animal's entire action space across testing because minor manipulations like cool water temperature may make a cold-blooded salamander nonresponsive to visual stimuli. Or, measuring a response to a lure underwater can shorten response time compared to a lure on land because the object may appear closer due to the refractive index of water. Note that transcription, physiology, biomechanics, and the external environment are also limited by their own "spaces," which impinge on the behavioral action space of an organism.[2]

DPB is a subdiscipline of developmental biology that integrates psychology to understand how behaviors develop.[10–13] Some relevant research topics include the development of animal behaviors like swimming,[14–16] social interactions,[17] feeding,[18] stepping,[19] behaviors across metamorphosis,[15,20] and learning[21]; and human behaviors like reaching,[22] grasping,[23] walking,[24] language,[25] learning,[26] and stroke recovery.[27–29] To understand the development of these behaviors, DPB takes a dynamic systems approach. It investigates the contribution of physiological, biomechanical, and environmental processes underlying the development of a behavior. The contribution of these three processes holds equal weight and coact as a team, much like the area of a rectangular prism depends 100% on the length, width, and height. This dynamic systems perspective is understood under a framework called probabilistic epigenesis[30,31]—which will be discussed later. Also, DPB traditionally disparages traditional dichotomies from other fields, like gene–environment, innate–acquired, nature–nurture, and hardwired–plastic. From the DPB perspective, the development of a phenotypic trait results from the contributions of various physiological, biomechanical, and environmental processes coacting with one another during development. The goal of DPB is to identify and specify how each of these processes contributes to the developmental expression of any behavioral attribute/trait. This is an important perspective because DPB allows us to understand all processes involved during each developmental phase to understand any behavior's induction, transformation, and maintenance—which will also be discussed later.

In this manuscript, I propose that general principles from DPB can help us understand how the regeneration of any structure that mediates behavior recovers the behavior. For example, the spinal cord and locomotion (e.g., swimming and walking),[32,33] the skin and sensation,[34] muscle and movement,[35] the optic nerve and vision,[36] the axolotl brain and memory,[37] the planaria pharynx and eating,[38] breathing of the lungs,[39] and so forth. Also, the perspective of DPB will focus attention on some ignored processes underlying regeneration because behaviors can play an active role in regeneration, similar to molecular and cellular signals. To elucidate the value of DPB for regenerative biology, I will describe two general principles from the probabilistic epigenesis framework: (i) probabilistic coactions and (ii) inductive, facilitative, and maintenance experiences. I will apply them to studies in regenerative biology using a "probabilistic regenesis" framework to show their value in addressing some knowledge gaps. I will then provide an initial framework of "regenerative history" for future research to improve our understanding of behavioral recovery. The aim of proposing the integration of DPB with regenerative biology is to stimulate research on these knowledge gaps to enhance our understanding of regenerative biology and promote the successful application of regenerative biology in human medicine.

2 | THE DPB PERSPECTIVE

2.1 | Probabilistic coactions

DPB ascribes a framework of probabilistic epigenesis (Figure 1) to understand the developmental history of a behavior. This framework was proposed by Gilbert Gottlieb[30,31,40] from the developmental theories of the embryologists Paul Weiss[41] and Ludwig von Bertalanffy, population geneticist Sewall Wright,[42] and other DPB scientists like Zing-Yang Kuo, T. C. Schnierla, and Daniel Lehrman.[43] It begins with a critique of predetermined epigenesis—the central dogma or modern synthesis, which states that DNA codes for RNA, RNA codes for proteins, proteins lead to structures, and structures lead to function, activity, or experience. Simply, DNA → RNA → protein → structure → function. Here, environmental factors may permit or disrupt the unrolling of this program across development to be "normal" or "pathological." Instead, probabilistic epigenesis proposes that bidirectional coactions of biological levels construct phenotypes across development (Figure 1). Simply, DNA ↔

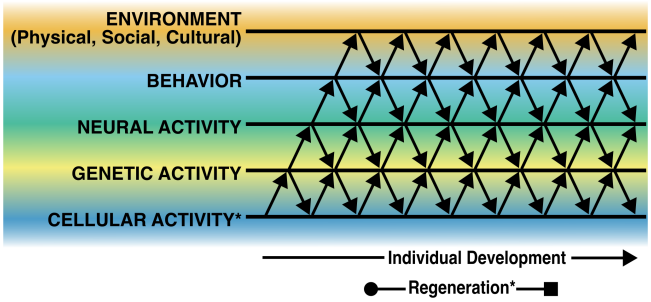

FIGURE 1 Bidirectional influences in probabilistic epigenesis and regenesis. This is a modified framework of the one proposed by Gilbert Gottlieb[30,31] that can be applied to regeneration. The asterisks denote that cellular activity and regeneration have been added to the original framework. Each factor of environment, behavior, neural activity, genetic activity, and cellular activity interact across individual development and regeneration. Note that development continues with a directional arrow. At the same time, regeneration has a designated initiation from the injury (denoted by the circle) and an ending when regeneration is theoretically complete (denoted by a square). The listed factors are not exhaustive.

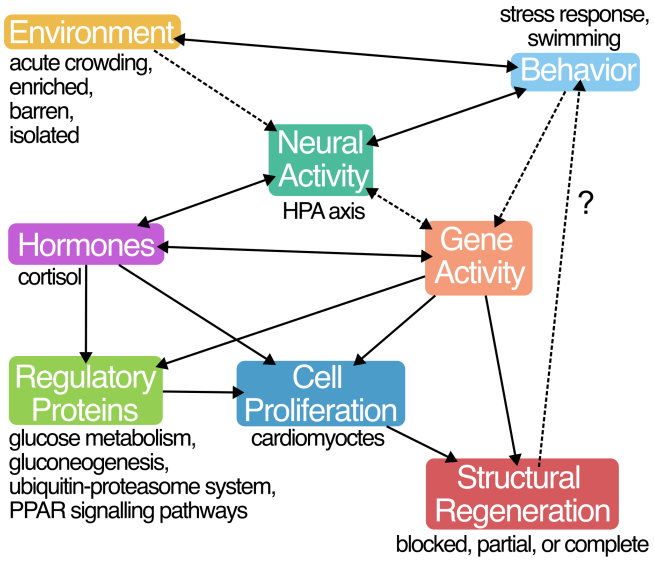

FIGURE 2 Interactive diagram of heart regeneration in zebrafish in response to environmental stressors. This is a visual representation of the interactions that take place in reference to "probabilistic regeneration" and published studies on how environmental stressors affect and interact with heart regeneration.[49–51] Solid arrows denote interactions known to occur, while dotted lines denote hypothesized interactions.

RNA ↔ protein ↔ structure ↔ function. Thus, instead of a unidirectional view of DNA serving as a blueprint for structure and function, the bidirectional view proposes that functions, experiences, structures, proteins, RNA, and gene activity interact equally in an open and dynamic system to construct a phenotypic trait.

Modern molecular biology, epigenetics, and ecological developmental biology strongly support the probabilistic epigenesis framework.[44,45] They broadly indicate that each level is inseparable from the organism's development, and variability in coactions of these levels leads to a range of phenotypes (i.e., a norm of reaction). For example, incubation temperature affects the sex ratio in reptiles,[46] gravity affects body axis formation in *Xenopus*,[47] and monozygotic identical twins reared together can have significant phenotypic differences.[48] When Gottlieb proposed probabilistic epigenesis, incubation temperature, gravity, and other normally occurring aspects of the environment were frequently neglected when considering the role of gene activity. Thus, Gottlieb proposed that they should be incorporated into research on behavioral development and have equal weight in constructing a phenotype (Figure 1). Here, horizontal coactions occur at the same level (gene ↔ gene, cell ↔ cell, behavior ↔ behavior, etc.), and vertical coactions occur across levels (gene ↔ neural ↔ cell ↔ environment ↔ behavior ↔ gene, etc.) throughout an individual's development. The relation between a seller and a buyer nicely illustrates the inseparable nature of these vertical coactions; a seller can only sell if there is a buyer, and a buyer can only buy if there is a seller. Gene activity and neural activity, and so forth, have the same type of relationship.

Evidence of the probabilistic epigenesis framework can be found throughout developmental and regenerative biology. For example, studies on the role of the environment and behavior on zebrafish heart regeneration nicely demonstrate these horizontal and vertical coactions[49–51] (Figure 2). In one study, zebrafish were exposed to 1 h of crowding (i.e., 10 fish per 250 mL) daily for 30 days after ventricular cryoinjury to the heart.[49] Only 30% of those exposed to crowding regenerated their hearts, while 100% of the control condition exposed to standard housing regenerated their hearts. Thus, the environment directly affected the regeneration of structures and associated functions (i.e., environment → structure and function).

This failure to regenerate (i.e., collagen deposition and scarring in the heart) was linked to a two-fold reduction in cardiomyocyte proliferation. Follow-up studies with the stress hormone agonist dexamethasone suggested that increased levels of stress hormones were a driving factor in the reduction of cardiomyocyte proliferation. Thus, the environment affected hormone release, altering cell proliferation during regeneration (i.e., environment → hormones → cell proliferation). RNA-sequencing analysis showed that at least three genes were significantly downregulated: *ankrd9*, *nr4a1*, and *igfbp1b*. This demonstrated that the environment also affected gene expression (i.e., environment → gene expression).

Other studies on the effect of group, enriched, or barren housing also suggested that stressed zebrafish maintained proteins in their heart associated with a stress response.[51] Thus, the environment affected proteins, which later affected cell proliferation, and so forth, (i.e., environment → protein → cell proliferation). Overall, this research, in conjunction with more traditional themes in developmental biology (i.e., predetermined epigenesis or the modern synthesis), would support the bidirectional relationships between the processes underlying regeneration (i.e., DNA ↔ RNA ↔ protein ↔ structure ↔ function ↔ environmental experiences) (Figure 2).

An important aspect missing from these examples on the effect of the housing environment on zebrafish heart regeneration[49] is what behaviors were disrupted by the heart injury and how these behaviors recovered and contributed to regeneration. Human patients suffering from a heart attack (i.e., myocardial infarction) engage in lower levels of behavioral activity (i.e., are more sedentary) because their heart pumps less blood, increasing muscle fatigue. However, slowly increasing exercise (i.e., increasing active behavior) over many weeks after injury increases heart recovery in humans[52] and can increase cardiomyocyte proliferation and lead to less scarring (i.e., collagen deposition) in zebrafish[50] (Figure 2). Thus, different behavioral experiences across regeneration, like exercise, may promote better heart regeneration in those with stressful environments.

In summary, like development, the processes underlying regeneration coact with one another across regeneration in a form of "probabilistic regenesis." These processes traditionally include DNA, RNA, proteins, cells, the immune system, etc. However, they should also include behavior and environmental experiences and consider the inseparable nature of all the underlying systems during regeneration (Figure 1). Recent reviews on the role of the environment on regeneration provide further examples.[53–56] However, these reviews often neglect these systems' coactional and inseparable nature (e.g., buyer and seller relationships) and how the behavioral "action space" instantly changes after injury.

2.2 | Inductive, facilitative, and maintenance experiences across development

In DPB, behavioral experiences across development are categorized as *inductive*, *facilitative*, or *maintenance experiences*, and individuals can each have their own trajectory of when these experiences occur, which will impact the development of the behavior[30] (Figure 3). *Inductive experiences* are experiences that are necessary to alter the

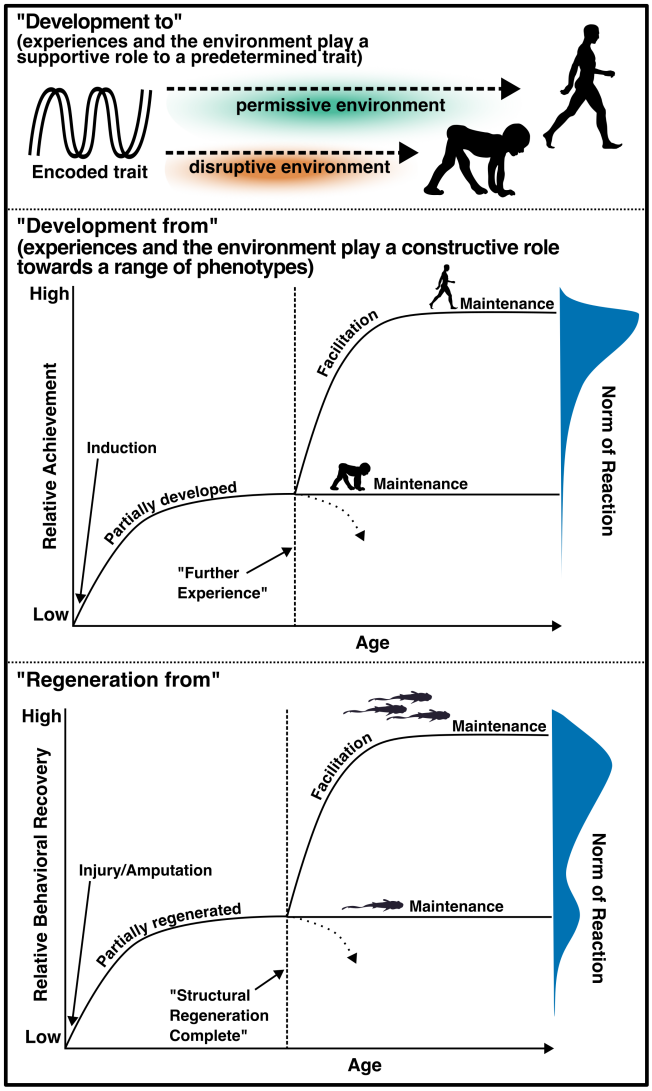

FIGURE 3 Inductive, facilitative, and maintenance experiences in development. This is modified from Gottlieb's "Roles of Experience"[30] to include a diagram of "Development to" and the "Norm of Reaction." In the "Development to" section, an encoded trait symbolized by DNA unrolls in a permissive environment to allow for normative walking, or unrolls in a disruptive environment leading to pathological walking like "Uner Tan" Syndrome. In the "Development from" section, developmental trajectories are plotted across age on the *x*-axis depending on the relative high or low achievement on the *y*-axis. First, there is induction, perhaps leading to spontaneous movements, which then increase in coordination over time. Further experience from birth allows for more sensory experiences to facilitate the development of walking. Or a specific behavior (e.g., crawling) never transforms and is maintained. These walking behaviors are neither normative nor pathological but occur on a norm of reaction, as shown by the imaginary distribution of walking behavior from the green bell curve on the far right. "Regeneration from" follows a similar trajectory with the injury being the inductive event and structural regeneration contributing to further experience. Some experiences after regeneration may facilitate the recovery of shoaling behavior (i.e., group swimming), while others may maintain more solitary swimming.

expression of a trait; *facilitative experiences* are those that regulate the rate of trait development; and *maintenance experiences* are those that sustain the behavior. Some individuals may have the same phenotype despite divergent individual trajectories (i.e., equifinality), while others have similar trajectories yet divergent phenotypes (i.e., multifinality). This is similar to the open systems theory of teleonomy or goal-directedness, where the intrinsic dynamics of the system (i.e., probabilistic coactions) allow it to continue moving toward some attractor basin (i.e., norm of reaction).[57] This contrasts with the more closed system, central dogma, wherein an encoded trait unrolls across development, and experiences and the environment play a permissive or disruptive role toward a predetermined target trait (e.g., an instinct) (Figure 3).

A classic example of these experiences in DPB is the development of walking behaviors in humans (Figure 3). The central dogma would assert that a set of genes codes for walking and that you can observe the innate reflex of stepping at birth by supporting the infant under their arms and holding them upright to elicit well-coordinated stepping. As the infant grows and begins to support themselves, the innate stepping reflex allows them to walk.[58] Simply, the infant "develops to[59]" a prespecified innate trait. However, studies following a probabilistic epigenesis framework have shown that different facilitative and maintenance experiences construct walking behavior. For example, infants lying on their back kick or "air-step" before crawling on their bellies, transforming to classic crawling before walking.[60] These motor experiences construct the muscles and neural feedback loops for coordination. However, heavier babies often have a later onset of walking because it is more challenging to kick heavy limbs.[61] Ankle weights can also decrease air-stepping while submerging the legs underwater increases stepping.[24] Moreover, Jamaican parents expect their children to walk around 10 months, and most do so, with a third skipping the crawling stage. English parents, in contrast, expect their children to walk around 12 months, and most do so, with only 7% skipping the crawling stage. Patients with 'Uner Tan' syndrome, in contrast, maintain their crawling behavior into adulthood.[62] Thus, walking "develops from[59]" sensorimotor experiences constructing and facilitating the transformations of air-stepping to kicking to crawling to walking. These experiences are just as important to the development of the phenotype as gene activity, cell activity, neural activity, etc., and all factors are inseparable from one another across development.

The timing of different sensorimotor experiences like air-stepping and crawling across development can also differentially affect biomechanical loading, which has a direct effect on skeletal morphology. Consider developmental studies on *Polypterus* fish, which can walk in terrestrial environments and swim in aquatic environments using their pectoral fins. *Polypterus* fish raised on land intermittently pick up their nose and significantly twist their body when walking. In contrast, those raised in aquatic environments keep their nose level, and the body only moves slightly from side to side.[63,64] This leads to differences in biomechanical loading across development wherein land-raised *Polypterus* had more narrow and elongated bones in the fins and pectoral girdles than control animals raised in aquatic environments. Also, classic studies in embryology paralyzed chick embryos during development and found improper joint development with bone fusions.[65,66] This paralysis was linked to differences in gene expression of mechanosensitive signaling pathways like *Wnt*, *Bmp*, and *Hippo*.[67,68] Whether paralyzing limbs or providing different biomechanical loading during regeneration affects bone and joint regeneration remains unclear, but imperfect skeletal morphologies occur in salamander limb regeneration, and the specific regulators remain unclear.[69–72]

These studies on *Polypterus* and paralyzed chick embryos indicate that the movement of joints and limbs (i.e., behaviors) during development can affect bone development. But when does a regenerating limb begin moving? It is established in mice and rats that walking begins in utero with spontaneous limb movements that begin to have coordination due to sensorimotor feedback and the biomechanical restrictions of the uterine environment.[73,74] Are developmental pathways associated with walking also involved in anatomical and behavioral recovery after injury—similar to de novo molecular and cellular signaling? When is the onset of coordinated stepping after limb amputation? How does this affect the regeneration of joint and skeletal morphology? Can the onset of stepping be manipulated via practice stepping? How does a salamander change its behavior and biomechanical loading to compensate for losing a limb and then continually recalibrate its nervous system as the limb regrows and begins to receive sensory input? Do biomechanical restrictions (e.g., weights or water) during regeneration affect the behavioral recovery of walking and the structural construction of the limb? What is the range of variability (i.e., norm of reaction) in the functional sensorimotor recovery of regenerated limbs? The answers to these types of questions remain unknown.

3 | INTEGRATING DPB WITH REGENERATIVE BIOLOGY

DPB research reveals significant gaps in our understanding of tissue regeneration, and research in this domain

could improve behavioral and structural regeneration outcomes for animal models and patients. As an initial starting point, we should use a "regenerative history" framework to consider how the degree of structural regeneration, environmental constraints, and neuroplasticity coact to affect behavioral recovery across the time required to regenerate the tissue (Figure 4). Any changes to these four factors (structure, environment, neuroplasticity, or time) will directly impact behavioral recovery. For example, delaying or increasing regeneration time may lead to differences in structural regeneration.[75–77] Altering the regeneration time and quality of regenerated structures could also alter the degree of environmental experiences during regeneration. All these factors (i.e., time, structural regeneration, and environmental experiences) would also affect how much neuroplasticity or brain reorganization could occur to compensate for the injury and the recovery of the structures. However, before empirically manipulating these factors, it is important to understand the entire history of regeneration from injury to behavioral recovery because regenerative animals may adopt novel regeneration-specific behaviors or neuroplasticity to facilitate behavioral recovery.

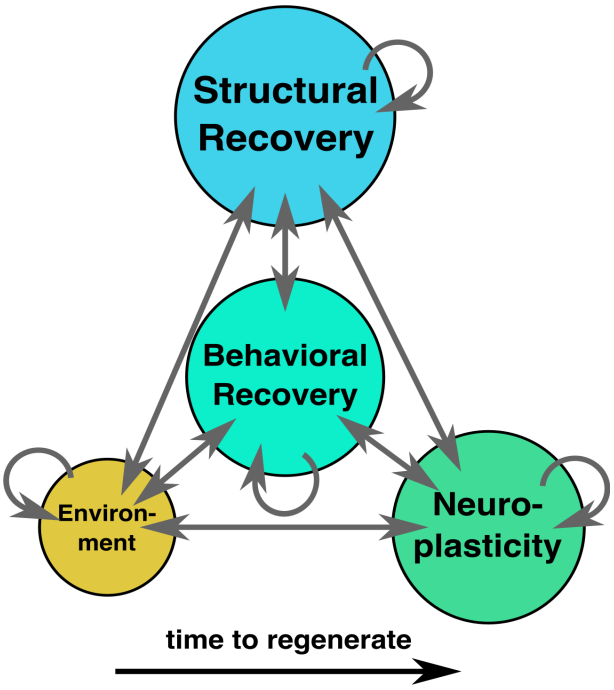

FIGURE 4 Initial framework for regenerative history research. Each circle within an interconnected nodes diagram represents structural regeneration (blue), the environment (orange), neuroplasticity (green), or behavioral recovery (teal). Horizontal, reciprocal interactions are noted by circular arrows, while vertical interactions across levels are noted by straight lines. Each circle has a different area to illustrate different "degrees of x" (e.g., degrees of structural regeneration). The time to regenerate is represented below the circles as an arrow. As the animal regenerates, the area of the circles will flux across regeneration time as the degree of each circle (i.e., the area) also changes. Understanding this relationship across regenerative time/history will be the first step in understanding behavioral recovery.

We can model current research in regenerative biology and behavioral neuroscience to measure structural regeneration, the environment, neuroplasticity, and behavioral recovery across the entire regenerative history of this tissue. Research on structural regeneration must consider variability in the structural properties of the tissue in comparison to uninjured or developmentally comparable controls. This can be done with comparative quantitative histology[72,78] and physiology (e.g., in vivo torque and in situ force to measure muscle recovery).[79] Throughout regeneration, the environment, or *Umwelt*, will change because the animal will likely interact with it differently when the structure is damaged and slowly becoming functionally competent. Moreover, a host of environmental factors may impact regeneration.[54–56] Thus, we must test our regenerative species across a host of environments (e.g., variable temperatures, seasons, light cycles, social groupings, etc.) to understand the norm of reaction. Neuroplasticity can be measured by quantifying how many peripheral nerves have regenerated and reintegrated with the tissue via retrograde and anterograde axon tracing.[80] Then, differences in brain activation throughout regeneration can be measured using brain histology and immediate early genes like *c-fos* or *arc*,[81,82] or using resting-state functional magnetic resonance imaging (rsfMRI).[83] Behaviors must also be tracked throughout the regenerative history following an ethogram[1] of all possible behaviors affected by the injury and tissue regeneration. Such work may require single experiments on one facet of the framework (e.g., structural recovery) before other facets can be studied and incorporated.

We can also consider how different experiences induce, facilitate, or maintain behaviors or states during regeneration. One attempt to modify—or facilitate—the outcome of regeneration with behavioral experience comes from a study on hindlimb regeneration in newts.[84] One hindlimb of the newt was amputated mid-femur, and they were forced to walk on a wet surface 48 h after amputation, for 5 min, twice daily, 5 days a week, for 8 months.[84] With a DPB or "development from" perspective, one may predict that this locomotor training would facilitate the recovery of stepping behavior. However, the newts with locomotor training had delayed regeneration and heterogeneous digit formation. Thus, the experience of stepping, which could theoretically increase stepping recovery, also led to poor structural regeneration. The authors note that the friction of the wound epidermis with the ground did not disrupt limb regeneration. One aspect this study failed to examine was the set of behaviors

and neural recalibration the control newts participated in that aided in the limb's synonymous regeneration and behavioral recovery. That is, they did not study the compensatory, maintaining, inductive, and facilitative behavioral experiences that occurred in relation to behavioral recovery in the control newts. This could reveal what factors are important for the behavioral recovery of stepping behavior in newts and where we may implement behavioral modifications to optimize recovery. Indeed, most newts appear to behave normally after limb regeneration, but the specific behaviors that guide their recovery during regeneration remain unknown.

This research may also require basic studies on the behavior of the regenerative species without injuring them. Here, scientists may consider studying the adaptive function of the behavior, the proximate causes of the behavior, its evolutionary history, and its developmental history (i.e., Tinbergen's four questions, which form the framework for research in animal behavior[1,85,86]). From this, we can study whether adaptive behavioral functions are restored, whether similar proximate stimuli cause the behavior after regeneration, and whether the regenerative history relates to the evolutionary or developmental history of the behavior. For example, it would be important to understand the locomotor movement of newt limbs across a substrate[84] and the sensory thresholds of mechanoreceptors in their manus and digits for sensorimotor responses (i.e., some proximate causes of stepping behavior). Or their responses to prey and predators (i.e., some adaptive functions of behaviors). Such behaviors may be disrupted by an injury and have specific neural underpinnings (i.e., proximate causes) that are not fully restored after regeneration. This would require understanding the neural underpinnings of the behaviors themselves prior to injury.[87,88] Once the behavior, sensorimotor, and neural underpinnings are somewhat understood in an uninjured animal, they can be monitored immediately after injury and throughout the regeneration process—which has been done in the field of vision restoration after optic nerve transection.[8] If we know the developmental history of the behaviors and what experiences induce, transform, and maintain the behaviors, we may then modify those experiences along the regeneration period to alter or optimize behavioral recovery and measure impacts on the process of regeneration itself.

Insight from behavioral or environmental manipulations across regeneration would allow us to develop behavioral therapies that work in tandem with regenerative cellular, molecular, and bioengineering therapies to improve post-injury outcomes in humans. These behavioral therapies would fit within the environment portion of the initial framework I have provided (Figure 4). They could also affect neuroplasticity and the degree of structural regeneration, which together would affect behavioral recovery. This requires an immense amount of work and shows how significant the gap is in our knowledge of behavioral recovery in regenerative animals.

4 | CONCLUSION

Integrating DPB into regenerative biology provides new research questions on behavioral recovery after injury and the role of behavior in regeneration. A "probabilistic regenesis" framework will allow behavior to contribute equally with molecular, cellular, and environmental components to the processes underlying regeneration. A "regeneration from" perspective will help identify experiences that induce, facilitate, or maintain behavioral recovery and the construction of the regenerated organ. The "regenerative history" framework I provided is the first step in understanding this gap in our knowledge. Since DPB and regenerative biology are both subdisciplines of developmental biology and include a focus on behavior, their integration would likely promote significant advancements in each.

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