Integrating Neuroplasticity and Evolution

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Abstract

Neuroplasticity and evolutionary biology have been prominent fields of study for well over a century. However, they have advanced largely independently, without consideration of the benefits of integration. We propose a new framework by which research can begin to examine the evolutionary causes and consequences of neuroplasticity. Neuroplasticity can be defined as changes to the structure, function, or connections of the nervous system in response to individual experience. Evolution can alter levels of neuroplasticity if variation in neuroplasticity traits exists within and between populations. Neuroplasticity may be favored or disfavored by natural selection depending on the variability of the environment and the costs of neuroplasticity itself. Additionally, neuroplasticity may affect rates of genetic evolution in a myriad of ways. For example, it could decrease rates of evolution by buffering against selection. It could also increase rates of evolution via the Baldwin effect, by increasing genetic variation, or by incorporating evolved peripheral changes to the nervous system. These mechanisms can be tested using comparative and experimental approaches and by examining patterns and consequences of variation in neuroplasticity among species, populations, and individuals.

Introduction

Neuroplasticity, also called neural plasticity or brain plasticity, has been of interest to scientists since the late 19th century. The history of the concept in neurobiology is not well documented, however the first wide use of the concept is attributed to Santiago Ramón y Cajal in a series of lectures and papers in the early 1890s[1]. Despite wide use of the term throughout neurobiology, neuroplasticity does not have a universally accepted definition. Two definitions are common. First, neuroplasticity is sometimes defined very broadly as any "change in the nervous system" within an individuals' lifetime, as was done by Shaw and McEachern in *Toward a theory of neuroplasticity*[2]. Similarly, Costandy[3] defines it as "a catch-all term referring to the many different ways in which the nervous system can change". The second definition narrows neuroplasticity to refer to change in the nervous system that results specifically from experience. This definition is exemplified in Kolb et al.[4], who define neuroplasticity as "the organization of brain circuitry changing as a function of experience", and Cramer et al.[5], who define it as "the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections".

One consequence of not having a clear definition of neuroplasticity is a lack of integration of this concept with knowledge and hypotheses from other fields. For example, the integration of evolution with phenotypic plasticity, with phenotypic plasticity defined as a change in phenotype due to individual experience[6], has been a focus of theoretical and empirical work by evolutionary biologists for decades now. However, neuroplasticity has not been included in this integration. There may be ways that neuroplasticity is distinct from other forms of plasticity in terms of its interaction with evolution, particularly because of its links to learning and memory[7,8,9] and the important role of behavior in establishing and maintaining reproductive isolation[10,11]. Thus, integrating neuroplasticity and evolution may yield novel insights.

In this paper we provide a definition of neuroplasticity that allows for integration across the fields of neurobiology and evolutionary biology. We then develop links for hypotheses and questions that would be best served by the integration of these fields. We propose that neuroplasticity be strictly defined according to the narrow description above, as changes to the structure, function, or connections of the nervous system in response to individual experience. This narrower definition closely aligns with the broader term description of phenotypic plasticity used by evolutionary biologists. “Individual” in this definition refers to an individual organism rather than an individual neuron or component of the nervous system. The focus should be on this level of biological organization because evolution by natural selection occurs at the population level due to variation in individual fitness. “Experience” here refers to environmental features that an organism encounters in its lifetime. Under this definition, changes to the nervous system that arise purely from genetically determined developmental trajectories would not be considered neuroplasticity.

To understand this distinction, consider the development of visual cortical sensory pathways in mammals. Visual information is first processed in the retina within the eyes. This information is next transmitted though the ocular nerve to the thalamus, and then to the visual cortex. The sequence of this particular visual pathway appears to be universal among mammals, regardless of their experience during development, and so the neural connections formed during development that produce this anatomical pathway would not be considered neuroplasticity. However, the strength and distribution of the connections within this pathway can be strongly influenced by

experience. Consider the development of ocular dominance columns. Both sides of the visual cortex receive inputs from both eyes, and neurons that receive input from one particular eye tend to be grouped together in the visual cortex, forming columns of cells that all receive input from the same eye, so-called ocular dominance columns[12]. Visual experience during ontogeny can alter the development of these columns[13,14]. For example, blocking visual input from one eye in ferrets during development leads to an underrepresentation of ocular dominance columns for that eye and an overrepresentation of ocular dominance columns for the other eye[15]. Thus, while the overall connectivity of this visual pathway in the brain is genetically determined, the wiring and synaptic connectivity of cells within this pathway is affected by neuroplasticity.

One limitation to the integration of neuroplasticity with evolution is how these fields conceptualize plasticity. In evolutionary biology, plasticity is typically represented as a reaction norm (Figure 1), which visualizes the potential phenotypic manifestations of traits caused by exposure to different environments. For example, water fleas (*Daphnia pulex*) develop a predator resistant morphology only if they are reared in water with predator cues[16]. By contrast, in neurobiology, plasticity is typically viewed as change over time in response to environmental exposures. For example, Irvine et al.[17] found that rats put in enriched environments showed increased neuronal activity over time, indicative of long term potentiation in the dentate gyrus. These approaches differ in their uses, as the former approach examines the outcomes of phenotypic change, and the latter studies the processes of that change. The latter approach is useful for understanding the mechanisms that generate plastic variation, while we propose the former is more useful for evaluating the evolutionary causes and consequences of that plasticity. The reaction norm approach is useful for the integration of neuroplasticity and evolution because it allows for comparison of the direction and level of plasticity between genotypes. This will facilitate comparisons to prior work on phenotypic plasticity, easing the integration between phenotypic plasticity and neuroplasticity.

There are two major questions in integrating neuroplasticity and evolution (Figure 2). First, how does evolution affect neuroplasticity? More specifically, is neuroplasticity itself an evolvable characteristic on which natural selection can act and that can affect fitness? Second, is there a reciprocal causal relationship, namely can neuroplasticity in return affect genetic evolution?

How can evolution change neuroplasticity?

An important first question in the study of the evolution of neuroplasticity is: what specific characteristics of the nervous system do we consider to be the trait that is evolving? Nervous systems are hugely complex, including up to billions of neurons and orders of magnitude more synaptic connections between those neurons. The scope of what specific aspect of neuroplasticity could be under selection ranges from the nature of the whole integrated neural system to the strength of an individual synapse. Examples of commonly studied neuroplasticity traits include short-term changes such as facilitation/depression at synapses that are repetitively active, intermediate-term changes such as spike-timing dependent plasticity and long-term potentiation or depression, as well as broader longer-term developmental changes such as improved auditory processing in blind humans[18]. This is by no means a comprehensive list. For a trait to evolve under selection, it needs to meet three criteria. It needs to have variation, that variation needs to covary with fitness, and the trait needs to be heritable across generations. The key to understanding what aspects of neuroplasticity are important targets of selection requires testing traits for these criteria.

Though research explicitly addressing the interaction between neuroplasticity and evolution is currently lacking, inter-individual differences in levels of neuroplasticity, a requirement for natural selection, have been noted. For example, Mes et al.[19] found that wild and hatchery-reared Atlantic Salmon differ in their levels of BDNF (brain derived neurotrophic factor), suggesting different levels of neuroplasticity. Similarly, Stewart and Cramer[20] note genetic polymorphisms for BDNF, dopamine, and apolipoprotein in humans, all of which can impact levels of neuroplasticity. Chen et al.[21] found inter-individual differences between humans in levels of neural adaptation after performing an inhibitory control task. These examples demonstrate that levels of neuroplasticity are not always homogenous across individuals, indicating the possibility for natural selection.

Neuroplasticity is widespread and may be ubiquitous across animals with complex nervous systems, suggesting that either it is critical for survival or that it is an inherent part of nervous systems (or both). Neuroplasticity could affect fitness by allowing individuals to respond to

changing external conditions. Greater levels of morphological plasticity have been hypothesized to increase fitness when environmental conditions vary within the lifetime of an individual or between generations. This variation selects for individuals who are flexible in their phenotype, allowing them to perform well regardless of shifts in environmental conditions[6]. For example, Fallis et al.[22] showed that fruit flies (*Drosophila melanogaster*) from areas with more variable climates showed higher levels of physiological plasticity in response to temperature variation. Neuroplasticity can similarly be hypothesized to influence fitness under changing environmental conditions, when the ability to adjust the nervous system in response to such change increases individual survival or reproductive success (Figure 1). The timeframe of environmental change that selects for neuroplasticity might be shorter than for morphological plasticity because of how rapidly neuroplasticity can change phenotypes. Evidence for this effect of neuroplasticity is lacking, however one form of environmental influence on fitness that may be affected by neuroplasticity is disease. Increased neuroplasticity has been shown to reduce the likelihood of developing cardiovascular disease in humans and mice[23], suggesting a possible benefit of neuroplasticity when disease is common.

Neuroplasticity can also be linked to fitness through behavioral plasticity and learning because these processes likely occur as a result of some form of neuroplasticity. This link was most famously established in *Aplysia californica* (a species of sea slug) by Nobel-prize winning neuroscientist Eric Kandel and his research team, who showed that learning and memory are reflected in changes in the molecular and cellular machinery of the brain[24,7]. Research since then has only further supported this link[8]. Perhaps the best evidence for a causal link between neuroplasticity and memory formation are studies that demonstrated false memories can be artificially created in mice by stimulating plasticity in the brain[25]. Memories can even be inactivated and reactivated by artificially manipulating synaptic plasticity[26]. A more recent simulation study using virtual organisms suggests that neuroplasticity underlies aspects of the evolution of learning and behavior[27]. Adaptation to highly variable environments has also been linked to greater levels of learning and behavioral plasticity in several animal groups[28], including mammals[29], amphibians[30], and insects[31]. In each of these cases selection for increased levels of neuroplasticity may occur as it affords greater potential for behavioral plasticity and learning.

High levels of neuroplasticity may reduce fitness under certain circumstances. This could be due to the metabolic costs of maintaining the neural machinery needed for plasticity or if plasticity is functionally maladaptive. If plasticity is costly, and provides little functional benefit, then selection is expected to reduce plasticity[32]. Empirical support for this potential pattern was found in wood frogs, *Rana sylvatica,* where increased plasticity was shown to reduce fitness in response to predation[33]. However, other examples and theory have shown that the costs of plasticity can be minimal or absent[34], and so may not be strong drivers of the evolution of plasticity. Neuroplasticity may be selected against if it is maladaptive, such as when environmental conditions are very stable, resulting in phenotypic changes that reduce performance and fitness[32] (Figure 1). For example, neuroplasticity has been observed to sometimes be harmful in the context of neurological responses to injury[35]. At this point more research and empirical examples are needed regarding the metabolic costs of neuroplasticity and the importance of maladaptive neuroplasticity.

Moving forward, the method by which the evolution of neuroplasticity can be tested is by quantifying variation in neuroplasticity between individuals or populations of organisms and comparing that variation to environmental variation and fitness. Ideally, quantifying levels of neuroplasticity can be done using the reaction norm approach described above, where a particular feature of the nervous system is measured under different experimentally controlled environments. This can be done sequentially on a single individual if the trait can continuously change, or it can be done on different individuals of the same genotype (clones, same family, same population). Variation in neuroplasticity can also be estimated by comparing proxies for levels of neuroplasticity, such as levels of neural growth hormones, neurotransmitter or receptor levels, neuron numbers, dendritic spine densities, or indicators of neurogenesis. Differences in levels of neuroplasticity between populations would indicate evolution between those populations, as this suggests that the ecological factors in the populations have selected for different optimum levels of neuroplasticity. Variation in neuroplasticity can also be more directly linked to fitness by comparing neuroplasticity levels to measures of fitness such as survival or reproduction. This could be done with common garden or transplant experiments between populations with different levels of neuroplasticity. We would expect individuals from high neuroplasticity populations to show better survival and reproduction in their habitat than

individuals from low neuroplasticity populations. Finally, comparing levels of neuroplasticity between parents and offspring, particularly in a controlled breeding common garden design, can be used to estimate heritability of neuroplasticity, a requirement for evolution by natural selection. Thus far, explicit tests of the heritability of neuroplasticity are lacking.

How can neuroplasticity affect rates of genetic evolution?

The ability for individuals to shift their neural circuitry in response to experience, and resultantly shift aspects of their perception, behavior, or cognition, may increase or decrease rates of genetic evolution depending on the specific nature of the neuroplasticity and the patterns of selection in the system in question. Phenotypic plasticity has been hypothesized to reduce rates of genetic evolution when plasticity increases performance of individuals and thus buffers populations against selection. Much theoretical work has supported this hypothesis[36–39]. For example, Lalejini et al.[39] used digital organisms to measure the strength of selection on traits that vary in their level of adaptive phenotypic plasticity. They found that higher levels of plasticity reduce rates of evolution because plasticity buffers populations against selective sweeps from variable environments. Empirical work demonstrating this phenomenon is, however, lacking. Neuroplasticity may also reduce rates of genetic evolution because it allows nervous systems to remain fully functional in response to a shifting selective landscape without the need for evolved changes.

On the other hand, there are at least three theoretical ways that high rates of neuroplasticity could increase rates of genetic evolution. First, the Baldwin effect[40,41] proposes that phenotypic plasticity can lead to genetic evolution by allowing individuals to survive in new or changing environments. Under this theory, more plastic individuals in a population are more likely to survive when environments, and therefore conditions of natural selection, change. Only the individuals that survive can subsequently undergo selection to the new conditions. An empirical example of this mechanism is shown in Yeh and Price[42], where they examined plasticity and colonization in dark-eyed juncos. They demonstrated that individuals with more flexible breeding season length were more successful and had higher fitness in a novel coastal environment when compared to their ancestral mountain territory. Survival in the novel coastal environment then allowed for selection on other traits. This theory could apply to neuroplasticity

as well, particularly given the behavioral context of this example. If individuals with a greater ability to reorganize their nervous system are more likely to thrive under new conditions, they will then be able to evolve, both in their nervous system and other traits.

A second way neuroplasticity may increase the rate of genetic evolution is by increasing available trait variation or strength of selection. The greater the available trait variation, the greater potential there is for natural selection and evolution to shift trait values. Plasticity can increase this available variation and generate adaptive variation in new or changing environments that was not present in previous generations (Figure 3). This can then result in plasticity leading to rapid evolution of the new trait variation. Increased variation also occurs if the population includes individuals that express non-adaptive plasticity. When plasticity operates in the opposite direction to optimum trait values, rates of evolution are expected to increase[43–45] due to increased selection and increased trait variation. This process could operate with neuroplasticity as well. Although neuroplasticity is generally expected to be adaptive, shifting the nervous system towards the optimum state, this may not always be the case, particularly under novel conditions. An example of this form of plasticity affecting evolution can be seen in Ghalambor et al.[45]. They examined how plasticity and rapid evolution interact by transplanting Trinidadian guppies (*Poecilia reticulata*) from high to low predator environments. They measured sequence evolution of genes in the brain and the plasticity of those same genes by looking at gene expression patterns. Adaptive plasticity was inferred when gene expression changes occurred in the same direction as evolutionary change. On the other hand, maladaptive plasticity was inferred when gene expression changed in the opposite direction as evolutionary change. They found that genes that showed maladaptive plasticity also tended to show rapid evolution in response to the transplant. Demonstrations of maladaptive neuroplasticity are rare in the literature. One area it has been noted is in response to spinal cord injuries, where neuroplasticity can lead to organ and muscle dysfunction[46]. Future research examining the fitness consequences of variation in neuroplasticity are needed to understand the prevalence and evolutionary consequences of maladaptive neuroplasticity.

A third way neuroplasticity may increase the potential for genetic evolution, and one that may be particular to neuroplasticity in comparison to other forms of plasticity, is by accommodating

evolved changes to nervous system traits. This mechanism, like the Baldwin effect, involves the evolution of traits other than the focal neuroplasticity trait. This theory has been described primarily with respect to peripheral sensory or behavioral control aspects of nervous systems[47]. Nervous systems are highly complex and integrated. In order for aspects of sensory perception to evolve, not only do the sensory organ and peripheral nerves need to change, but the circuit of neurons within the central nervous system that processes the incoming sensory signals needs to change as well. Neuroplasticity in those central pathways may allow for evolutionary change in sensory systems due solely to changes in the sensory periphery, without the need for additional evolution of the central components of an integrated system. Evidence for this hypothesized effect of neuroplasticity has been shown in color vision of transgenic mice that were modified to express extra photopigments in the retina, with no genetic modifications to central visual pathways in the brain. Despite these photopigments being completely novel to mice, they showed segregation of opsin genes among photoreceptors[48], leading to novel perceptual color discrimination abilities[49]. A similar effect occurred when introducing a novel photopigment into the retina of squirrel monkeys[50]. The underlying neuroplasticity that allowed for this novel color vision has been proposed as a mechanism for the evolution of trichromatic (or greater) color vision[47].

To further illustrate how this mechanism could lead to evolution, imagine two populations of animals, one with high levels of neuroplasticity in the visual processing system, and one with low levels of neuroplasticity. If a mutation leading to an extra color sensory input occurred in both these populations, it would likely have no effect or be strongly selected against in the low plasticity population because no added sensory information could be processed, and thus no evolution of that population would occur. The high plasticity population on the other hand could gain additional sensory information because neuroplasticity in the visual system would allow for processing of the added sensory input. This added input could be selected for, leading to evolution. Much remains to be studied about the potential, or even necessity, for neuroplasticity to facilitate evolutionary change.

Conclusion

Throughout the history of science, the integration of separate fields has often served as a catalyst for major advancement. Perhaps the most famous of these was when Charles Darwin combined information from the fields of geology and economics to develop his theory of evolution by natural selection[51]. Recently, integrative studies in the field of neuroscience have highlighted the enormous potential and benefit in considering ecology and evolution[52,53]. These have provided insight into the mechanisms that lead to the massive diversity of nervous systems among animals, as well as the role of nervous systems in mediating adaptive evolutionary change. Thus far, this approach has not been extended to include the integration of the centuries-old fields of evolution and neuroplasticity. We argue that this integration is necessary to advance our understanding of the causes and consequences of neuroplasticity in nature. Theodosius Dobzhansky famously wrote that "nothing in biology makes sense except in the light of evolution", and it is time we bring neuroplasticity into that light.

Acknowledgments

B.A.C acknowledges support from the National Science Foundation (IOS-1755071 and IOS-2203122). S.P.G and C.J.A acknowledge internal support from Cornell University.

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Figure Legends

Figure 1. Example of theoretic reaction norms and how selection could influence population level neuroplasticity.

The Y-axis represents any aspect of nervous systems that could undergo plasticity. The X-axis demonstrates two different environments that could lead to different phenotypes. Lines represent different genotypes within a population. Each line shows what trait value would be manifested by a particular genotype when exposed to each individual environment. Flat lines indicate rigid genotypes that do not express neuroplasticity. Steeper lines indicate greater amounts of neuroplasticity. The figure on top represents a population before any selection. The bottom figures represent populations after selection, when only favored genotypes survive. Arrows represent alternative patterns of natural selection. The left arrow represents selection in a variable environment where more plastic individuals are favored because low trait values are favored in environment 1 and high trait values are favored in environment 2, selecting for more plastic genotypes. The right arrow represents selection in a stable environment when the same trait values are favored in both environments. In this case, less plastic genotypes are favored, particularly if plasticity is costly.

Figure 2. An integrative framework for studying the evolutionary causes and consequences of neuroplasticity.

The top arrow indicates mechanisms by which evolution can change levels of neuroplasticity. The bottom arrow indicates mechanisms for how neuroplasticity can affect rates of genetic evolution. Plus and minus signs indicate the direction each mechanism is expected to influence either levels of neuroplasticity (top) or rates of genetic evolution (bottom).

Figure 3. An integrative framework for studying the evolutionary causes and consequences of neuroplasticity.

Example of theoretical reaction norms for two populations (left: low neuroplasticity, right: high neuroplasticity) demonstrating how higher levels of neuroplasticity can increase trait variation in novel environments. The Y-axis represents any aspect of the nervous system that could undergo plasticity. The X-axis represents two environments: 1) a prior environment where selection has

shaped trait variation; and 2) a novel environment where selection has not yet shaped trait variation. Lines represent different genotypes within each population. The population with higher neuroplasticity generates greater trait variation in the novel environment, resulting in increased strength of selection.