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Harnessing Plasticity to Understand Learning and Treat Disease

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Abstract

A large body of evidence suggests that neural plasticity contributes to learning and to disease. Recent studies suggest that cortical map plasticity is typically a transient phase that improves learning by increasing the pool of task relevant responses. Here, I discuss a new perspective on neural plasticity and suggest how plasticity might be targeted to reset dysfunctional circuits. Specifically, a new model is proposed in which map expansion provides a form of replication with variation that supports a Darwinian mechanism to select the most behaviorally useful circuits. Precisely targeted neural plasticity provides a new avenue for the treatment of neurological and psychiatric disorders and a powerful tool to test the neural mechanisms of learning and memory.

Keywords

vagus nerve stimulation; rehabilitation; neuropathology; sparse coding; neuromodulation; tinnitus

Introduction

Neurological and psychiatric disorders account for one third of the total disease burden in the developed world[1]. Current surgical, behavioral, and pharmacological treatments generally lack the power and precision necessary to modify aberrant circuits and restore normal function. Effective treatments are possible if tools can be developed that operate at the same temporal and spatial scales as the brain (i.e. milliseconds and micrometers). The first half of this article summarizes the evidence that precisely timed release of neuromodulators may prove to be a valuable tool to manipulate fine scale neural connectivity in humans. In the second half, I propose a new perspective on brain function which may explain a range of apparently contradictory observations related to cortical map plasticity associated with learning and disease.

Reversing Pathological Brain Plasticity

Although neural plasticity is generally viewed as an adaptive process, there is considerable evidence that plasticity can also be maladaptive[2-5]. For example, brain changes in response to nerve damage or cochlear trauma appear to be responsible for many types of chronic pain and tinnitus. Significant injury-induced changes in map organization, spontaneous activity, neural synchronization, and stimulus selectivity have been observed in multiple regions of

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the central nervous system[2, 4]. In some but not all studies, the severity of phantom limb pain and tinnitus is well correlated with the degree of map reorganization in somatosensory and auditory cortex, respectively[6-8]. The ideal method to test whether pathological plasticity is directly responsible for these sensations would be to reverse the plasticity and evaluate the perceptual consequence[9].

Studies in animals have shown that repeatedly pairing sensory stimuli with electrical stimulation of the cholinergic nucleus basalis (NB) of the basal forebrain generates precise, powerful and long lasting changes in cortical organization[10-19]. In principle, this method could be used to reverse the effect of pathological plasticity[20]. However, NB stimulation is highly invasive and thus not practical for clinical use. The vagus nerve is more readily accessible, and a recent study reported that pairing brief bursts of vagus nerve stimulation (VNS) with sensory inputs can generate highly specific, long lasting, and therapeutic neural plasticity[9].

The efficacy of VNS in enhancing plasticity appears to lie in the synergistic action of multiple neuromodulators, including acetylcholine, norepinephrine, serotonin, and brain derived neurotrophic factor[21-23]. VNS improves learning and memory of associated events in rats and humans using the identical stimulation parameters[24, 25]. Repeatedly pairing a single tone with VNS is sufficient to generate specific, powerful, and long lasting changes in the auditory cortex map of tone frequency (Fig. 1A)[9]. Importantly, VNS-directed plasticity is temporally precise. Map expansion was specific to the tone frequency paired with VNS and no changes were observed in response to another tone frequency that was separated by several seconds from the frequency paired with VNS[9]. Pairing VNS with sensory stimuli is a potentially attractive method of modifying neural circuits without significant side effects. VNS is well tolerated in the 60,000 patients who currently receive VNS therapy for epilepsy or depression[26]. By pairing tones with a brief burst of VNS, it is possible to drive plasticity in rats with only 1% of the intensity of the VNS that is delivered clinically[9, 26]. Pairing trigeminal nerve stimulation with tones failed to generate map plasticity[9], which suggests that VNS is particularly well suited to direct neural plasticity.

Directing plasticity to reverse pathological changes associated with chronic tinnitus

If appropriately targeted, VNS-directed plasticity can be used to normalize pathological plasticity caused by injury to the nervous system. The first proof of concept experiment to show that VNS-directed plasticity can be therapeutic was conducted in an established animal model of chronic tinnitus[27]. Tinnitus is the perception of sound in the absence of a corresponding external acoustic stimulus and is often caused by prolonged exposure to loud noise. Severe tinnitus is disabling for more than one million Americans[28]. The dominant theory is that chronic tinnitus is the consequence of abnormal neural activity caused by pathological neural plasticity following damage to the cochlea[29].

Exposure to intense high frequency noise increases the number of neurons tuned to mid-frequency tones, degrades frequency selectivity, and increases excitability and synchronization of auditory neurons in rats[9, 29]. Noise exposure also eliminates the ability of rats to detect a gap in a mid-frequency tone, presumably because the tinnitus sensation fills in the gap[27]. The rationale for the VNS-based tinnitus therapy was that increasing the number of cortical neurons tuned to frequencies other than the tinnitus frequency would reduce the overrepresented tinnitus frequency and eliminate the tinnitus[13, 30]. Eighteen days of exposure to different tones paired with VNS was sufficient to completely eliminate the neural and behavioral correlates of tinnitus in noise exposed rats (Fig. 1B,C)[9]. There was no sign that tinnitus returned even months after the end of therapy. Sham therapy consisting of VNS alone or tones alone had no effect on behavioral or neural correlates of tinnitus. These results confirm that appropriately directed plasticity can be used to reverse the pathological plasticity associated with nervous system damage and could be the basis of a new form of therapy. Tests of VNS-tone pairing in patients with severe tinnitus are ongoing and initial results are encouraging (clinical trial identifier NCT01253616; http://www.clinicaltrials.gov)[31].

Other Forms of Externally Directed Neural Plasticity

In principle, VNS paired with other experiences could be used to reverse pathological plasticity in other disease states[3]. The first experiment to demonstrate that VNS-event pairing could be used to drive plasticity outside of the sensory cortex was conducted in the primary motor cortex. VNS was repeatedly triggered by movements of the lower forelimb in one group of rats and the upper forelimb in a different group (Fig. 1D). After five days of VNS-movement pairing (~300 pairings per day), the region of primary motor cortex associated with the paired movement was more than doubled[32]. Rats receiving identical motor training without VNS pairing did not exhibit motor cortex map plasticity. These results support observations in the auditory system that VNS-event pairing results in long-lasting plasticity that is both spatially and temporally precise. The effectiveness of VNS-directed plasticity in treating tinnitus suggests that VNS-movement pairing might be useful for treating motor disorders, in which regions of the motor system are damaged (e.g. stroke) or in which a particular movement is over exaggerated (e.g. focal dystonia)[3].

Temporal processing abnormalities are observed in many neurological and psychiatric diseases[33-36] and it might prove useful if VNS-event pairing could modify temporal properties of neural networks. The first experiment to demonstrate that VNS-event pairing can drive temporal plasticity was conducted in the auditory system[37]. VNS was repeatedly paired with rapid tone trains in one group of rats and with slow tone trains in a different group. VNS-tone train pairing was able to increase or decrease both the number of action potentials evoked by rapidly modulated sounds as well as the degree of neural synchronization to these sounds[37]. In contrast, passive exposure to modulated sounds without VNS had no effect on temporal response properties. These results suggest that pairing VNS with specific events may act as a general method for modifying neural response selectivity. Based on earlier studies, it is expected that VNS-event pairing also alters the sensitivity and selectivity of subcortical structures as well as higher cortical regions[14, 38].

A Functional Role for Map Plasticity

An important factor limiting the potential of directed plasticity to treat neurological and psychiatric conditions is our inadequate understanding of neural coding and the role that neural plasticity plays in learning and in disease. For example, despite the key historical role of map plasticity studies in advancing our understanding of neural plasticity, the function of map plasticity in associative or skill learning remains uncertain.

A few weeks of training of humans or animals on a task that activates a small region of primary motor or sensory cortex can lead to a significant expansion of the brain region engaged by the task[5, 39-45]. The degree of map reorganization is often correlated with the degree of learning in individuals[39, 45]. Drugs, brain lesions and mutations that block learning also block cortical map plasticity[46-53]. These results suggest that map plasticity may be directly responsible for learning[54].

However, there is a growing body of evidence that map plasticity is not directly responsible for learning. The role of map plasticity in learning was initially questioned because such large scale changes seem to predict that learning one task could potentially undo learning on another. Clearly, humans and animals can store an enormous number of memories and skills with little interference[55-57]. The observation that cortical map plasticity is often associated with clinical pathologies, including amblyopia, tinnitus, phantom limb pain, and focal dystonia, indicates that map plasticity is not always adaptive[6, 7, 58-60]. The most recent and compelling evidence that map plasticity is not causally related to learning is that training-induced cortical map plasticity can reverse without loss of ability (Fig 2A) [61-66]. These studies suggest that map plasticity can be a transient phenomenon that is not required for the expression of learning.

A recent study definitively demonstrated that map plasticity can significantly accelerate learning, but is not necessary for improved performance[12]. Large-scale and long-lasting map plasticity generated outside of a behavioral context by pairing tones with NB stimulation was shown to significantly enhance learning on a tone frequency discrimination task[12]. Beginning training with an expanded map appears to give rats a head start such that they learn faster. By the end of a few weeks of training all the rats exhibited the same high level of performance, but there was no longer any sign of the map expansion. These results demonstrate that map plasticity plays an important role in learning, but the transient nature of map plasticity in this study indicates that it cannot be the mechanism for storing improved perceptual abilities or other skills (Fig 2A). The most plausible explanation for these results is that map plasticity is involved in learning but not memory.

The Expansion-Renormalization model (Fig 2B) proposes that map expansion is usually a transient phenomenon that serves to expand the pool of neurons that respond to behaviorally relevant stimuli so that neural mechanisms can select the most efficient circuitry to accomplish the task[12]. During the first stage of the Expansion-Renormalization model, neuromodulators are repeatedly released at the same time as task specific stimuli. The resulting map expansion increases the number of neural circuits throughout the brain that respond to task stimuli (Fig $2C_{1-3}$). Later processes select the most efficient circuitry from this new and heterogeneous population (Fig $2C_4$). As subjects learn the task, they associate the activity of different neural circuits with task outcome. In this model, learning results when subjects select the most efficient circuits and associate activity of these circuits with the appropriate behavioral response. By the end of learning, performance relies on responses from a dedicated circuit of neurons (black circle in Fig 2B) rather than requiring large-scale map plasticity to store the new skill (Fig $2C_5$). These circuits are likely to be distributed across many brain regions, including cortical and subcortical structures[67, 68].

Learning as a Darwinian Process

The Expansion-Renormalization model is based on principles of Darwinian selection. In ecosystems and market economies, the Darwinian two-step model [i.e. (i) replication with variation and (ii) selection] is highly effective at generating robust and complex networks[69, 70]. Given the power and flexibility of evolutionary algorithms, it is surprising that map plasticity has not been seriously entertained as a source of replication with variation upon which reinforcement based selection could operate as a possible neural basis for adaptive behavior[71].

Two of the three traits necessary for selection-based learning to operate are well known and there is growing evidence of the third. The first trait that is necessary for an evolutionary algorithm to operate in the brain is diversity. Early expectations that the brain might resemble a well ordered bank of filters have been replaced by compelling evidence that response diversity is the rule among neurons, even in topographically organized regions of the brain. For example, primary auditory cortex is organized into a one dimensional map based on sound frequency, but nearby neurons can differ greatly in their sensitivity to the intensity, direction, bandwidth, modulation envelope, harmonic organization, local contrast, and many other features of sound[72-80]. Responses of a significant fraction of primary auditory cortex neurons are shaped by inputs from other modalities, reward signals, and attention[81, 82]. Similarly high levels of response diversity are found at high and low levels of the visual and somatosensory pathways[83-86]. Earlier hypotheses about Darwinian selection in the brain emphasized neural diversity, but were not widely embraced because they did not provide a specific mechanism for replication with variation that could support progressive learning[87-89]. The Expansion-Renormalization model posits that map plasticity accelerates learning by generating useful diversity (Figure 2B-C and Figures S1 and S2 in the Supplementary material online). Although studies of receptive field plasticity often emphasize the net effect (i.e. shift toward the relevant stimulus), the changes observed are so diverse that few individuals (cells or subjects) change in a manner that reflects the mean receptive field change[11, 39, 90, 91]. By expanding the pool of neurons that respond to novel behaviorally relevant stimuli, map plasticity provides a mechanism to increase circuit diversity without any assumptions about what constellation of features may contain useful information.

The second trait that is necessary for an evolutionary algorithm to operate in the brain is selection. The molecular, cellular, and systems level mechanisms for identifying temporal associations between neurons are among the best studied phenomena in neuroscience. Circuit selection is likely shaped by release of neuromodulators, including acetylcholine, norepinephrine, and dopamine, and involves many of the molecular mechanisms that are known to be useful in associative learning, including NMDA receptors, Ca2+/Calmodulin(CaM)-dependent protein kinase II (CaMKII), activity-regulated cytoskeletal protein (ARC), post-synaptic density protein 95 (PSD-95), and cAMP response element binding protein (CREB)[92-94].

The third trait that is necessary for an evolutionary algorithm to operate in the brain is circuit stabilization. Genetic mutations are stable due to the chemical characteristics of DNA. It is much more difficult to explain the stability of memories because neural circuits are highly plastic and embedded in large scale non-linear networks in which changes to a few can have large consequences. Circuit stabilization is especially problematic in the context of large-scale map renormalization. After finding a circuit that exhibits a particularly useful motor sequence or a set of sensory response properties that was able to solve a difficult task, it is hard to imagine how these rare characteristics could be maintained if the vast majority of nearby cells change their characteristics during map renormalization. Since the majority of synaptic inputs arise from nearby cells, large scale map plasticity would be expected to wipe out the useful characteristics of the circuit.

Useful response properties would be stable if they were stored as a sparse code in a distributed circuit of neurons with strong coupling (Figure S1 in the Supplementary material online). Past experiments have provided compelling evidence that “the local cortical network structure can be viewed as a skeleton of stronger connections in a sea of weaker ones”[95]. The strongest cortical synapses appear to be much more stable [i.e. resistant to long-term plasticity (LTP) or long-term depression (LTD)] than the majority of synapses[96, 97]. Behavioral studies have shown that even a single cortical neuron can drive behavior[98]. Collectively, these findings suggest that reinforcement learning could be used to select and stabilize small networks of distributed neurons with behaviorally useful properties by generating highly reliable and stable connections. If this Darwinian account of learning is confirmed, the primary value of map plasticity would be the increased probability of finding rare, but behaviorally useful, neural circuits.

Darwinian evolution has proven to be a powerful strategy in ecological, immunological, and economic systems. Although the mechanisms differ greatly across these systems, the core traits of replication with variation to generate diversity, selection to pick winners, and stabilization to maintain progress are present in the nervous system. Modeling studies are likely to prove valuable in understanding how rules such as spike-timing dependent plasticity and homeostatic mechanisms alter the excitatory-inhibitory balance and shape plasticity in normal learning and in pathological conditions[99].

Model Predictions

This new model is able to account for a diverse set of findings that were poorly explained by earlier models of learning and plasticity and makes specific testable predictions.

i. A Darwinian system explains how map expansion speeds learning without being necessary for task performance[12].

ii. This model explains why blocking map plasticity slows, but does not prevent, new learning[46].

iii. Storage of new skills and memories in small stable networks can explain the low degree of interference among large numbers of memories and skills[55-57].

iv. The expansion and selection of circuits based on neuromodulator timing explains how learning can occur even for subtle stimulus features that subjects cannot perceive[100].

v. Darwinian learning helps explain why humans and animals can so effectively learn complex sensory, cognitive, and motor tasks that evolution could never have specifically prepared the species for[101]. For example, rodents rapidly learn to categorize human speech sounds and their performance is as robust to background noise and other forms of degradation as human listeners[37, 102, 103].

vi. Map expansion may persist under conditions that lead to high levels of focused attention, such as ever-changing task demands[39, 40, 104] or distress[6, 7], because these conditions continue to trigger release of neuromodulators and prevent normalization.

vii. The model predicts that manipulations that reduce response diversity can impair performance. Repeated exposure to a tone during the auditory cortex critical period expands the representation of the tone and reduces the diversity of frequency selectivity (bandwidth) for neurons near the exposed tone by 40% [105]. This diversity reduction is associated with impaired ability of adult rats to discriminate between tones near the exposed frequency. Other manipulations that cause map expansion that includes a rich diversity of response tuning are associated with improved perceptual learning[12, 39, 90, 91]. These results confirm that the diversity of task relevant neural responses can be more important than the number of task relevant neural responses.

viii. The model makes the clear and testable prediction that small stable neural circuits can drive both skilled behavior and pathological states. Recent advances in optogenetics and imaging will soon make it possible to identify, record from, activate and inactivate the small and distributed neural circuits proposed in this model[106, 107]. Light-responsive proteins could be expressed in the small fraction of neurons responsible for a given memory through a combination of endogenous and exogenous factors (e.g. a plasticity related-promoter, activity-related promoter and a short acting drug that leads to rapid gene expression[108]). The theory proposed here would be supported if: (a) activation of a small number of neurons was sufficient to drive behavior (e.g. the perception of tinnitus, generation of a skilled movement or recollection of an earlier memory[108]), and (b) inactivation of the same small number of neurons was sufficient to block the corresponding memory or skill. These techniques will also make it possible to study the physiological properties of the cells involved in these traits - first in *in vitro* and later in *in vivo* (ideally awake behaving) preparations. A recent study using 2-photon in vivo calcium imaging confirmed that associative fear learning enhances sparse population coding and robustness of the conditional stimulus, yet decreases total network activity[107].

Concluding remarks

New insights about the regulation and expression of neural plasticity are likely to aid the refinement of plasticity-based therapies to treat a variety of brain disorders. It is possible that the neural exploration mechanisms that support learning can sometimes lead to pathological networks that are maladaptive. Depending on the connectivity of neurons in the network, pathological spontaneous activity in a small population could trigger disturbing phantoms sensations such as tinnitus, pain, spasticity, and even perseverative thoughts. The brain has likely evolved regulatory mechanisms to prevent the formation of strong networks capable of producing pathological activity, but given the huge neural solution space that must be explored to support robust learning, it may not be possible to maximize learning without risking the development of pathological networks. Sensory deprivation, such as amputation or high frequency hearing loss, reliably cause map plasticity but only results in pathology (e.g. phantom limb pain or tinnitus) in about half of the affected individuals[6-9, 89, 109]. If strong circuits drive disturbing experiences, they would be expected to trigger the release of neuromodulators that maintain map expansions, which might be only a sign but not a cause of network dysfunction and disability. Other conditions, including obsessive-compulsive disorder, phobia, schizophrenia, dystonia, and epilepsy, may in part be due to small brain circuits with strong coupling that are not eliminated because their activation consistently leads to neuromodulator release that prevents the pathological circuits from being eliminated. If small networks can trigger disease states, it is possible that many of the most reliable biomarkers of brain disease are not directly related to the core pathology. The treatment of many disorders will require first understanding and eventually controlling the factors that regulate neural plasticity[110]. VNS-event pairing provides a powerful tool to trigger the precisely timed release of a powerful cocktail of neuromodulators that can drive therapeutic plasticity[3, 9].

Finally, the Darwinian perspective on brain plasticity suggests that the earlier view that each brain region performs a specific computation [e.g. orientation tuning in V1, color processing in V4, motion analysis in medial temporal (MT) area, short term memory in hippocampus, etc.] may have been overstated. An alternative view is emerging which suggests that each brain area (by virtue of its unique connectivity and physiological specializations) contributes to the unified process of learning by providing neurons to specialized circuits that generate valuable behaviors. This view that sparse coding is used for heavily rehearsed problems (Figure $2C_5$) (as recently observed in well trained monkeys[111]) and coarse coding is used as a first-pass solution to a new problem (wisdom of the crowds[86, 102, 112, 113], Figure $2C_1$) could resolve the long debate about whether the brain uses a coarse or a sparse coding strategy. Two of the key observations that have been interpreted as favoring coarse coding (widespread neural activity evoked by even simple tasks and large-scale changes associated with learning) are also consistent with a Darwinian view of brain function using sparse coding. In this view, widespread neural activity and large-scale plasticity are both needed to generate sufficient response diversity to support Darwinian evolution of behaviorally useful brain circuits. This proposal will be supported if future optogenetic studies reveal that small populations of neurons are necessary and sufficient to generate a wide range of learned behaviors.

More than ten years after the end of the “Decade of the Brain”, neuroscience remains an exciting field in which new theories and technologies are likely to overturn long held notions about how our brains operate and how best to repair them when they malfunction (Box 1). Over the coming decades, a Darwinian perspective on learning may turn out to be a dead end, but for now this perspective is worth pursuing since it offers new experimental predictions, new modeling opportunities, and new hope for the treatment of neurological and psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOX 1. OUTSTANDING QUESTIONS

- How much overlap is there between the cells of neural circuits involved in different tasks?
- How are neurons in different brain regions identified as belonging to a particular circuit?
- How is the effectiveness of different circuits compared in order to optimize selection?
- What are the most important sources of the diversity in neural circuits?
- How are the most behaviorally useful circuits selected and stably maintained?
- How is the set of available neural circuits biased by prior learning?
- What is the size of the minimal circuit that can store a memory?
- What role does temporal coding play in memory storage and retrieval?
- What is the optimal method to direct clinically useful neural plasticity?
- How does the relative amount and timing of different neuromodulators shape the expression of map expansion and circuit selection?

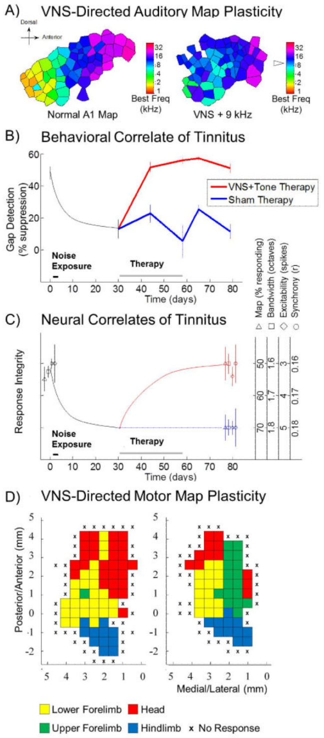

Figure 1.

Examples of VNS-directed plasticity. A) Repeatedly pairing VNS with a tone increases the number of neurons in primary auditory cortex (A1) that are tuned to the paired frequency[12]. Each polygon represents a single microelectrode recording site and the color indicates the preferred tone frequency at that location. The left panel shows the A1 map of tone frequency in a normal rat. The right panel shows the map after a brief burst of VNS was repeatedly paired with a 9 kHz (blue) tone over twenty days. B-C) Repeatedly pairing VNS with different tones surrounding the tinnitus frequency eliminated the behavioral and neural correlates of tinnitus, including map distortion, frequency broadening, increased excitability and increased synchrony, in an animal model[12]. Tinnitus was documented by the inability to detect a brief gap in a sound matched to the tinnitus frequency with no impairment in detecting gaps in other sounds[27]. Degraded values are plotted lower on the x-axis to match the impaired behavior. The shape of the curved lines was inferred from earlier studies. Error bars show s.e.m. D) Repeatedly pairing VNS with a movement increases the number of neurons in primary motor cortex that generate the paired movement[44]. The map on the left is from a rat that received VNS paired with movement of the lower forelimb (yellow). The map on the right is from a rat that received VNS paired with movement of the upper forelimb (green). Movement training alone did not alter the maps compared to naïve rats. Data adapted, with permission, from [9] (panels A-C), [32] (panel D).

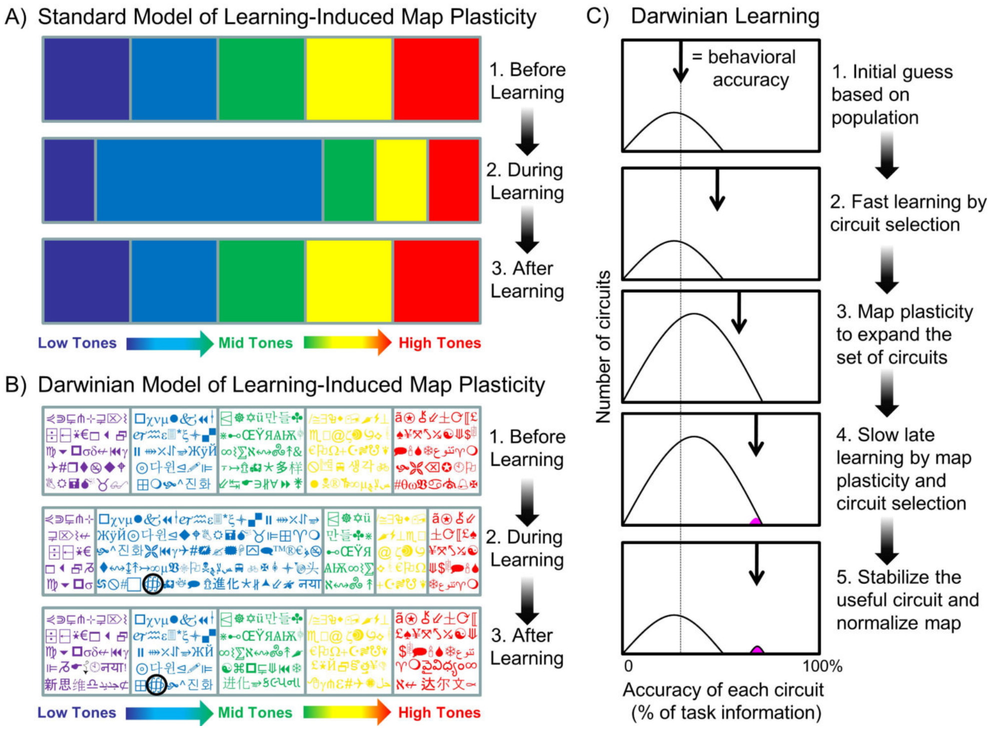

Figure 2.

Schematic diagrams comparing the standard model and the Darwinian model of learning-induced map plasticity. A) Highly specific map plasticity is associated with learning, but is not necessarily maintained. This schematic shows that discrimination of low frequency (blue) tones increases the proportion of neurons that respond to these sounds. Recent studies show that map plasticity usually renormalizes after learning without a decrease in performance[12, 61-65]. Thus, it is not clear where the memory is stored. B) In the proposed Darwinian model of learning, map plasticity increases the diversity of neural circuits that could accomplish the task. Each symbol represents a neural circuit that responds differently. Although the circuits may be tuned to the same tone frequency, many other stimulus features influence the responses of individual circuits. Map plasticity is a form of replication with variation (neural exploration). If the best circuit could be selected and stabilized, maps could be returned to normal while new skills and memories are maintained. In this schematic, the black circle denotes the new circuit that persists and supports the memory. These circuits involve neurons from many brain regions. C) A schematic diagram in which the amount of information provided by neural circuits that respond to the task stimuli (e.g. the blue low frequency neurons in A and B) is plotted. For a novel task (1), judgments would be based on the average of many circuits (wisdom of crowds). Initial behavioral performance is indicated by the dotted line. With feedback (2), the brain would rapidly select the most effective circuit and improve behavioral performance (black arrow). Map expansion would increase the number of responsive circuits (3) and likely result in the selection of a new, more effective circuit and better behavioral performance (4). If that circuit were stabilized (pink), the rest of the map could return to the initial state (5) in order to support future learning[114]. If necessary, the process could be repeated. The presence of stabilized circuits would influence the set of diverse response characteristics generated by the next round of map plasticity, which could enhance learning by biasing the exploration of the neural solution space based on past learning (see Figure S2 in the Supplementary material online). In this schematic, circuit effectiveness is represented as the percentage of task information provided by each circuit, where the left edge is zero bits. The pink circuit corresponds to the black circled circuit in B).