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Network Modeling of Adult Neurogenesis: Shifting Rates of Neuronal Turnover Optimally Gears Network Learning according to Novelty Gradient

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Abstract

Apoptotic and neurogenic events in the adult hippocampus are hypothesized to play a role in cognitive responses to new contexts. Corticosteroid-mediated stress responses and other neural processes invoked by substantially novel contextual changes may regulate these processes. Using elementary three-layer neural networks that learn by incremental synaptic plasticity, we explored whether the cognitive effects of differential regimens of neuronal turnover depend on the environmental context in terms of the degree of novelty in the new information to be learned. In "adult" networks that had achieved mature synaptic connectivity upon prior learning of the Roman alphabet, imposition of apoptosis/neurogenesis before learning increasingly novel information (alternate Roman < Russian < Hebrew) reveals optimality of informatic cost benefits when rates of turnover are geared in proportion to the degree of novelty. These findings predict that flexible control of rates of apoptosis–neurogenesis within plastic, mature neural systems optimizes learning attributes under varying degrees of contextual change, and that failures in this regulation may define a role for adult hippocampal neurogenesis in novelty- and stress-responsive psychiatric disorders.

INTRODUCTION

Research on neurogenesis in the adult brain has overturned dogma that individuals are born with all the neurons they will ever have (Gould, Tanapat, Rydel, & Hastings, 2000; Eriksson et al., 1998). Given the well-established role of the hippocampus in learning and memory, stress responses, and neuropsychiatric disorders, grasping the functional role of hippocampal neurogenesis may be important to a deeper understanding of mental functioning in health and disease, and informative to therapeutic prospects of neural stem cell research (Ming & Song, 2005; Dziewczapolski, Lie, Ray, Gage, & Shults, 2003; Eisch, 2002). Although convincing evidence suggests that neurogenesis in the dentate gyrus of the hippocampus is regulated by stress hormones and psychiatric treatments (Malberg & Duman, 2003; Gould et al., 2000), the unique functional role of neurogenesis independent from, or not already accounted for, by traditionally defined mechanisms of transsynaptic plasticity has not been demonstrated (Kempermann, 2002). Numerous challenges exist for conclusively showing the specific functional purpose of neurogenesis in vivo (Kempermann, Wiskott, & Gage, 2004). Virtually all known interventions that robustly regulate neurogenic events also influence various processes supporting transsynaptic plasticity, and behavioral measures of learning and memory are non-specific to neurogenic versus transsynaptic plasticity. Additional uncertainties concern whether neuronal attrition plays a vital functional role in concert with neurogenesis and the direction of causality in the relationship between animal learning and rates of hippocampal neuronal proliferation and/or survival (Kempermann et al., 2004; Prickaerts, Koopmans,

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Blokland, & Scheepens, 2004; Dong, Csernansky, Goico, & Csernansky, 2003; Nottebohm, 2002).

While sacrificing the vast complexity of real neural systems, elementary neural network simulations can address or circumvent many of the uncertainties and methodological limitations of current in vivo approaches. Differential extents, timing, and locations of apoptotic and/or neurogenic events can be precisely controlled, and global network learning and memory performance may be quantitatively compared across experimental conditions. In computational studies using various neuronal characteristics, network architectures, synaptic weight change algorithms, and degrees of biophysical realism, neurogenesis has consistently been found to enhance the ability of information-bearing networks to learn new information (Crick & Miranker, 2006; Becker, 2005; Chambers, Potenza, Hoffman, & Miranker, 2004; Deisseroth et al., 2004; Wiskott, Rasch, & Kempermann, 2004; Cecchi, Petreanu, Alvarez-Buylla, & Magnasco, 2001).

We have used standard three-layer feed-forward pattern recognition networks to characterize the learning and memory effects of coordinated apoptotic–neurogenic events in the middle layer (Chambers et al., 2004). Networks of this type use gradient descent back propagation (Widrow & Lehr, 1998; Rumelhart & McClelland, 1986) as a powerful algorithm for mediating learning via transsynaptic connection strength change. Also known as perceptrons because of their ability to learn patterns that humans can perceive, these networks provide the basis for applied technologies in human voice and facial feature recognition (Haykin, 1999). Networks of this type are also useful in understanding fundamental observations in developmental cognitive neuroscience, such as how children show greater skill in learning new languages compared to adults (Spitzer, 1999). Thus, given two perceptrons with identical architectures subjected to the same transsynaptic learning algorithm while learning a new set of alphabetic characters, the network with the more immature connectivity structure tends to learn more efficiently (Chambers et al., 2004). Due to their relative simplicity and applicability in performing cognitive tasks that are generally conceptually accessible, these networks may provide a relatively transparent depiction of the fundamental learning and memory effects of neurogenesis.

In previous work using elementary pattern recognition networks, it was shown that neural turnover could be independently regulated from consistent, ongoing processes of synaptic plasticity, but interactive with these processes, as a rapid and potent mechanism for augmenting global network flexibility and new learning efficiency (Chambers et al., 2004). In “adult” networks that had achieved mature patterns of axodendritic connectivity after learning the Roman alphabet, the efficiency for learning new information (i.e., the Greek alphabet) was significantly enhanced in proportion to the rate of neuronal turnover in the middle layer. This acceleration of new learning also incurred an informatic cost in terms of degrading old memory, suggesting that more highly neurogenic brain regions involved in memory formation should share a cooperative relationship with relatively nonneurogenic regions to which long-term memories might be exported and stored. Given evidence characterizing the hippocampus as a region (a) that mediates short- versus long-term memory exchange in cooperation with the relatively nonneurogenic neocortex (Eichenbaum, 2000; McClelland, McNaughton, & O’Reilly, 1995) where (b) neurogenesis and neuronal attrition are modulated in part by stress hormones (Gould et al., 2000; McEwen, 2000), these results seemed salient to understanding fundamental functions of hippocampal neurogenesis. In particular, the results suggested that adult hippocampal neurogenesis and/or turnover may provide a mechanism for endowing the adult brain with some capacity for heightened neural flexibility, as in earlier developmental stages (i.e., childhood), without globally compromising the brain’s capacity for accumulating long-term memory storage necessary for adult life.

However informative this and other computational studies might have been regarding the basic functionality of neurogenesis, none have addressed questions on why and how neurogenesis might be dynamically regulated. Numerous in vivo studies have implicated a host of cellular and molecular systems in the regulation of neurogenesis, including but not limited to corticosteriods, serotonin, glutamate, neurotrophic factors, vascular growth factors, and proteins controlling cell cycling (Deisseroth et al. 2004; Heine, Maslam, Joels, & Lucassen, 2004a; Newton & Duman, 2004; Malberg & Duman, 2003; Cameron & Gould, 1996). Meanwhile, environmental–experiential contingencies such as various forms of psychosocial stress (Mirescu, Peters & Gould, 2004; Malberg & Duman, 2003) and exposure to complex, changing environments (Kempermann, Gast, & Gage, 2002; Van Praag, Kempermann & Gage, 2000) have been described as potent regulators of neurogenesis, possibly mediated by some or all of these neural substrates. In addressing the question of regulation in neural network models, we assumed that a general function of any form of regulation is to optimize performance according to changing performance demands. This assumption, in light of available in vivo evidence, led us to hypothesize that ongoing rates of neuronal turnover might be tuned to optimize future network learning according to the degree of novelty inherent to new contextual information presented to the learning system. The plausibility of this idea was reinforced by additional lines of evidence implicating the hippocampus in novelty recognition and encoding (Schmajuk, 2002; Gluck & Myers, 1996), where rates of neurogenesis may correlate with different behavioral responses to environmental novelty (Lemaire, Aurousseau, Le Moal, & Abrous, 1999). Thus, cortioco-steroids and other neural mediators of neurogenic regulation might be evoked with amplitudes or durations in proportion to the degree of stressfully novel environmental contextual change, appropriately preparing hippocampal networks for future learning demands of differential informational burdens.

To test this hypothesis, we used character-recognition networks in learning one of three new alphabetic data sets in addition to the original Roman that differed informatically from Roman in a graded manner by how much they contained new information (alternate Roman < Russian < Hebrew). Taking advantage of the ability of perceptrons to learn predetermined input/output pattern associations, we chose these data sets from a translational perspective so that quantifiable differences in informational novelty corresponded well with differences easily recognizable to the human eye, using alphabets known to have graded differences in geographical and linguistic origins. After networks had gained mature patterns of synaptic connectivity via learning the Roman alphabet, they were subjected to differential regimens of neuronal turnover and challenged with new learning on each of the new alphabets. Learning and memory performance indexed by degree of turnover and novelty of the new information provided topologies indicative of optimal performance maxima.

METHODS

Network Architecture

Simulations were performed using Neural Network Tool-box (MATLAB 6.0) using a Dell Dimension 2100 PC (1 MHz). All network architectural and functional attributes were set prior to the experiments consistent with Chambers et al. (2004), as recommended by MATLAB software documentation for optimal performance in alphabetic character pattern learning and recall. Networks were organized as three-layer feed-forward systems with complete connectivity between layers, but none within layers. The input layer comprised 35 neurons topographically ordered in a 5 × 7 grid allowing alphabetic character representations to be formed by firing rates of 1 or 0 at each neuron (Figure 1). Each input-layer neuron bears an axodendritic connection with each of the 10 middle-layer neurons forming a 35 × 10 array of input-to-middle layer (I–M) connections. In turn, each middle-layer neuron projects to each of the 26 output-layer neurons via a 26 × 10 middle-to-output layer (M–O) connection array. With

this architecture, networks learn to associate each of 26 independent input pattern representations (e.g., letters of the alphabet) with 1 of 26 independent and fully sparse output firing patterns (e.g., if “A” is presented to input layer, fire output-layer Neuron 1 only; if “B” is presented to input layer, fire output-layer Neuron 2 only, etc.).

Network Dynamics

As in biophysical neural networks, firing of middle- and output-layer neurons is determined by a summation of incoming signals from the previous layer. Each of these signals is generated by a multiplication of the firing rate of the inputting neuron from the previous layer with the corresponding axodendritic connection weight unique to that connection. This axodendritic weight serves as the computational equivalent of synaptic strength and is subject to incremental change during network learning. Summed input information plus a variable bias weight associated with each neuron is transformed by a standard sigmoidal input–output function (MATLAB code: “logsig” transforms input value x to output y where $y = 1/[1 + \exp(-x)]$). This function serves as the computational equivalent of somatodendritic activation of action potentials producing neuronal firing ranges from 0 (no firing) to 1 (maximal firing).

Prior to network learning, the axodendritic connection weight values are randomized to low values ranging (−, 1) for I–M connections and (−0.01, 0.01) for M–O connections. These initial connection weight ranges are chosen for optimality in character recognition learning in three-layer systems using back-propagation algorithms. Initial low-weight randomization provides optimality in learning patterns of potentially large informatic diversity, and simulated neurons initialized in this way may be thought of as being functionally immature neurons with minimal axodendritic arborization.

Network Learning

Gradient descent back propagation with variable learning rate (MATLAB code:trainFcn = “traingda”) was used as the fully deterministic incremental weight change algorithm during learning. In this form of supervised learning, input patterns generate a firing pattern in the output layer that is mathematically compared to the desired output as an error quantity. As formally described elsewhere (Widrow & Lehr, 1998), methods of differential equations are used to compute small changes in the axodendritic connection weight arrays that will incrementally minimize the error quantity (error gradient descent) proportional to a set learning rate. Repeated epochs of training allow networks to learn desired input–output representation with high accuracy (one epoch represents a single exposure to the entire data set and a corresponding round of incremental weight changes). The variable learning rate option allows slight variation in the size of the incremental weight changes according to the slope of the error gradient, enhancing learning efficiency.

Simulated Apoptosis/Neurogenesis

Neuronal turnover events were imposed strictly in the middle layer, which by analogy with hippocampal neurogenesis renders this layer loosely symbolic of the dentate gyrus, and the input and output layers symbolic of the entorhinal cortex and CA3 regions, respectively. Apoptosis and neurogenesis occurred in adult networks (that had previously learned Roman without neuronal turnover) as 1:1 events where an information-bearing neuron was obliterated and replaced with an information-naive neuron. A neuron selected for turnover had all of its associated I–M, M–O, and bias weights reassigned to newly randomized values ranging (−1, 1) for I–M connections and bias, and (−0.01, 0.01) for M–O connections. Thus, neurogenic neurons were defined by immature connectivity states, as was the case for all neurons in the network upon initialization prior to any learning.

Measures of Network Performance

Network memory after learning was measured as the error in the ability of networks to generate the desired output patterns associated with learned input patterns. Thus, after learning the desired 26 input–output associations of the Roman alphabet, memory is quantified as the sum of the squared errors (SSE) defined as

$$\mathrm{SSE}=\sum_{i=1}^{26}\sum_{j=1}^{26}(\mathrm{af}_j-\mathrm{df}_j)^2$$

where af = actual firing rate and df = desired firing rate indexed at the *j*th output-layer neuron, taken over the *i*th letter of the Roman alphabet presented to the input layer.

In this convention, lower SSE values indicate better memory, and learning performance plots decreasing SSEs, according to progressive epochs of training on a data set.

Analysis of Network Performance

Because the synaptic weight change algorithm was completely deterministic and consistently used across all experimental conditions during learning, the only source of random error in the simulations was the low random connection weight assignments to information-naive networks or neurogenic neurons. To ensure that this variability did not account for experimental effects, groups of networks composed of individuals each given independent initial weight randomizations were studied in cohorts by parametric analysis, as in routine biobehavioral research using groups of animals. One-way, two-way, and repeated measures analyses of variance (ANOVAs) (between factors: degree of turnover, alphabet; within factor: epochs of training) were used to measure network memory and learning performance followed by the post hoc Tukey procedure where indicated.

Alphabetic Data Set Design

The design and ordering of letters in the Romalt, Russian (Cyrillic) and Hebrew alphabets (Figure 1) was informed by several factors including the standard ordering of letters in each of the respective alphabets and consideration of phonetic and visual similarity. However, alphabet designs were ultimately guided by informatic considerations, including the need to only include 26 characters from each of the Russian and Hebrew alphabets (the true alphabets have 33 and 27 characters, respectively) and the aim to distribute informatic differences in a fairly even manner across the order of character correspondences.

The measure of informatic difference (novelty gradient) between Roman and the other alphabets was Hamming distance, which computes the total number of differing points between two representational firing patterns presented to the input layer (e.g., alphabetic letters). For this calculation, each alphabetic character in the Roman alphabet was assigned a corresponding character in each of the other three alphabets, where the Hamming distance could be calculated between whole alphabets as a mean of 26 character-to-character comparisons. The desired output representations of corresponding letters were the same (e.g., B [Roman], Б [Russian], and ב [Hebrew]: fire only output-layer Neuron 2). This approach allows the Hamming distance between Roman and each of the other alphabets to reflect a novelty gradient with respect to the Roman alphabet, specific to the degree of difficulty associated with learning novel input patterns after having first learned Roman.

Experimental Design

Eight nascent neural networks of the same architecture but with uniquely randomized low connection weights were generated (Figure 2). This group then underwent training on the Roman alphabet until each network learned to a high degree of accuracy (SSE = 0.1). Corresponding to this training, networks achieved significant axodendritic connection weight growth consistent with acquiring a mature, information-bearing network phenotype (see Chambers et al., 2004). This group of eight adult networks was then cloned into 11 new groups. Each one of these groups was then subjected to 1 of 11 differing regimens of neuronal turnover where from none to all 10 of the middle-layer neurons underwent turnover. The resulting 11 groups of networks were then challenged on recall of the original Roman alphabet (after turnover, before new learning). Then, they were cloned again into a total of 33 new groups indexed by regimen of turnover (11 regimens) and selection of new alphabet to be learned (Romalt vs. Russian vs. Hebrew). Using the same deterministic incremental synaptic weight change algorithm as that used in initial learning of the Roman alphabet, new learning curves were generated with exposure to the new alphabets. These curves represent progressive decreases in the values of the learning error (SSE), referential to the alphabet being learned, with increasing epochs (duration) of learning. After learning the three new alphabets, network groups were again challenged on recall of the old Roman alphabet.

RESULTS

Novelty Gradient: Quantification of Informatic Differences between Alphabets

As shown in Figure 1, the novelty gradient, taken as the mean Hamming distance between Roman and the other data sets, increased in an approximately geometric fashion according to Romalt (4.0 ± 0.1) < Russian (9.7 ± 1.2) < Hebrew (16.7 ± 0.8). To verify comparable informatic complexity between Roman and the other three alphabetic data sets, eight individualized information-naive networks were cloned into four groups where each group was independently challenged with initial learning of one of the four alphabets. This test (Figure 3) showed an overall difference in difficulty of learning the alphabets, $F(3,31) = 3.3$, $p < .05$ (ANOVA), as determined by the number of epochs required to reach the same level of learning proficiency (SSE = 0.1). However, post hoc analysis specified that only learning Russian was more difficult than learning Hebrew (Tukey, $p < .05$), whereas the difficulty in learning Roman relative to learning any of the other three alphabets was not different. This result ensured that novelty gradient rather than differing levels of informatic complexity was the critical factor determining the difficulty in learning new alphabets after networks had already learned Roman.

Informatic Costs of Neuronal Turnover: Old Memory Recall

After learning Roman to the same level of proficiency, networks were twice tested for recall of Roman, once immediately after undergoing turnover, and again after having been trained on each of the new alphabets after turnover (Figure 4). As expected from the elimination of information-bearing synaptic connectivity associated with neuronal turnover, increasing extents of neuronal elimination and replacement prior to new learning causes increasing degradation of Roman recall: degree of turnover, $F(10,87) = 77.5$, $p < .001$ (Figure 4A). The weakening of this effect with extreme rates of turnover (conditions of 9 and 10 neurons undergoing turnover) was also observed in our previous study (Chambers et al., 2004) and may be interpreted as a partial breakdown of the forgetting effects of the model under conditions that are also likely nonphysiological. This feature likely results from the retention of fragmented information in the intact axodendritic connections of remaining neurons after turnover of 4 to 9 neurons, which creates output patterns that are more different from the desired output than if all 10 middle-layer neurons are turned over. After undergoing turnover and learning one of each of the new alphabets (to a proficiency level of SSE = 0.1, or for up to 5000 epochs of training, whichever came first), networks remained impaired in Roman recall

(Figure 4B). This effect varied significantly (two-way ANOVA) with main factors of increasing turnover, $F(10,231) = 13.8$, $p < .001$, and new alphabet learned, $F(2,231) = 1067.9$, $p < .001$, and in their interaction, $F(20,231) = 1.99$, $p < .01$. Thus, both increasing extents of neuronal turnover and the learning of increasingly novel information contribute to degradation of old information recall. Moreover, the worsening of recall across increasing extents of turnover is most accentuated if the new information learned is most similar to the old information (Romalt).

Informatic Benefits of Neuronal Turnover: New Learning Performance

After undergoing neuronal turnover, networks exposed to repeated epochs of training on new alphabets drive SSE toward zero, consistent with learning under all experimental conditions (Figure 5). However, the efficiency of this learning is influenced both by extent of neuronal turnover and by the alphabet being learned in separate two-way repeated measures ANOVAs carried out for short- and long-term phases of learning. Over short-term learning (epochs 100–400), increasing rates of turnover, $F(10,231) = 71.9$, $p < .001$, generally enhanced learning, whereas learning of increasingly novel alphabets slowed it, $F(2,231) = 680$, $p < .001$. These main effects showed significant interactions, $F(20,231) = 33$, $p < .001$, such that the benefit of increasing neural turnover becomes more pronounced with increasing novelty of new information being learned. A significant three-way interaction (Epochs × Turnover × Alphabets), $F(60,693) = 2.8$, $p < .001$, is consistent with the overall superiority of low rates of neuronal turnover in learning the least novel information (Romalt), in the earliest epochs of learning. Similar results are observed over long-term learning (epochs 400–2800), where independent main effects of neuronal turnover, $F(10,231) = 40$, $p < .001$, and alphabet, $F(2,231) = 235$, $p < .001$, show significant interactions, $F(20,231) = 12$, $p < .001$. A significant three-way interaction here (Epochs × Turnover × Alphabets), $F(120,1386) = 1.8$, $p < .001$, is consistent with the overall flatness of both the low- and high-turnover-rate learning curves across all alphabets, whereas the intermediate turnover rates continue to produce gains in learning performance specifically in learning the Russian and Hebrew alphabets. The relative flatness of the low-turnover learning curves appears to represent a sustained lack of power in producing beneficial learning effects, whereas the flatness of the high-turnover learning curves is secondary to having reached the floor of maximal performance relatively early on.

In an alternate view of these data, it is instructive to transform learning performance (SSE) to *gradient performance* where

$$\text{Gradient Performance} = \frac{\text{novelty gradient}}{\text{SSE}}$$

and novelty gradient = 4.0, 9.7, and 16.7 for learning of Romalt, Russian, and Hebrew alphabets, respectively. Taken at discrete time points (epochs) in the learning process, gradient performance is a measure of the relative speed of learning after differing rates of neuronal turnover, normalized to differing novelty gradients. Mean gradient performance surfaces for groups of networks undergoing low, medium, and high rates of turnover (2, 5, and 8 middle-layer neurons turned over) on different novelty gradients indicate learning speed optima (Figure 6). At 100 epochs of learning, the lowest region of gradient performance (slowest learning speed) occurs where high turnover rates are applied to learning the least novel information. In contrast, low turnover rates produce the best gradient performance on the lowest novelty gradient, whereas high turnover rates produce the greatest speed overall on high-novelty gradients. With longer durations of learning (400 and 1600 epochs), overall advantage shifts to the medium and higher rates of neuronal turnover, where low rates of turnover are least optimally applied in the context of high-novelty gradients.

DISCUSSION

These findings build upon previous simulations suggesting that neuronal apoptosis/neurogenesis within information-bearing networks augments new learning capability primarily mediated by transsynaptic plasticity occurring throughout the network (Crick & Miranker, 2006; Becker, 2005; Chambers et al., 2004; Deisseroth et al., 2004). Furthermore, these results demonstrate for the first time that an additional aspect of neuronal turnover in elementary neural networks is that its informatic costs and benefits depend on an environmentally determined parameter: the degree of contextual novelty in the information to be learned compared to what is already known. Specifically, low turnover rates incur the least degradation of previously learned information and are best suited to learning relatively un-novel information over relatively short durations of learning. High turnover produces the greatest degradation of older memory but is most optimal for learning drastically novel information especially over long periods of learning.

Implications for Psychiatric Neuroscience and Neurogenesis Research

While depicting a functional role for neuronal turnover as a potent mechanism for enhancing global network flexibility, these findings also suggest the critical importance of the flexible regulation of turnover in the face of differential extremes of novel environmental informational demands. Such compound flexibility may be especially beneficial in primary neural systems of learning and memory thought to be exquisitely responsive to wide ranges of environmental contextual change such as the hippocampus (Freeman, 2003; Vyssotski et al., 2002). Ample evidence suggests that extreme changes in informational context as represented by severe psychosocial stressors (loss of loved one, geographical translocation, job change) represent powerful instigators of the corticosteroid system in both psychiatrically healthy and vulnerable populations (de Kloet, Joels, & Holsboer, 2005; Sousa & Almeida, 2002). It is at these times that relatively extreme forms of plasticity including neuronal elimination and neurogenesis in the corticosteroid-receptor-rich hippocampus may be appropriately invoked in healthy persons for rapid and accurate adaptive change to new informatic contexts transcending social–emotional and cognitive domains (Jacobs, Praag, & Gage, 2000). Analogous interpretations have been made in the study of adult songbirds, where regular temporal variations in rates of natural neuronal death and rebirth correspond to novel birdsong production associated with seasonal changes in social, survival resource, and sexual demands (Nottebohm, 2002). However, in mammals, and humans in particular, profound changes in psychosocial contexts often do not follow regular seasonal variation, but may instead be far more random and of differential durations and magnitudes. Although speculative, the current findings are consistent with the view that adaptive brain functioning entails sophisticated mechanisms for accurately detecting and/or estimating the onset, potential magnitude, and duration of stressful environmental contextual change. This information may then be transmitted via graded responses of the corticosteroid stress-response system for the appropriate regulation of neuronal turnover. Phasic increases of neuronal turnover of appropriate extent and/or durations would then optimally prepare hippocampal physiology for novel contextual learning while creating experimental conditions for identifying associations between learning and neurogenic neuronal survival in animal studies (Prickaerts et al., 2004).

Psychosocial stressors consistent with drastic environmental change are universally known to initiate or predispose to episodic worsening of numerous psychiatric conditions in which the hippocampus is implicated, including mood disorders, posttraumatic stress disorder, borderline personality, and schizophrenia (Brady & Sinha, 2005; Charney, 2004; Dimsdale, Keefe, & Stein, 2000). The current results suggest that stress-responsive psychiatric disorders putatively involving neurogenesis may not only entail abnormalities of the local cellular determinants of hippocampal cell loss or regeneration, but may also involve failures in distributed cortical–

limbic regions that connect and cooperate with the hippocampus in novelty assessment and encoding (e.g., prefrontal cortex, ventral striatum, and amygdala) (Charney, 2004; Chambers, Taylor, & Potenza, 2003; Schmajuk, 2002). It is interesting to speculate that various psychiatric phenotypes involving differential system failures of these novelty-responsive substrates might correspond to differential forms of dysregulated hippocampal neuronal turnover, where stressfully novel contextual change might instigate under- or overshooting of turnover, or epochs of cell loss and regeneration abnormally out of phase (e.g., in depression or mania, respectively). In vivo and behavioral explorations of these scenarios might entail more rigorous accounting for neuronal losses along with neurogenesis and attention to differential degrees of informational or stressful novelty occurring subsequent to or concurrent with learning paradigms. Studies of neurogenesis using lesion or genetic animal models of mental illness that entail abnormalities in novelty responsiveness would also be informative. Given the existence of multiple neural substrate mechanisms beyond corticosteroids, such as glutamate and neurotrophins that may mediate neural responses to novelty or stress, and/or regulation of neuronal death and regeneration (Eriksson & Wallin, 2004; Heine, Maslam, Joels, & Lucassen, 2004b; Newton & Duman, 2004; Chambers et al., 1999), further work is needed to clarify the potential independent or interactive roles of these systems in environmental novelty-and/or stress-induced regulation of neurogenesis.

Model Limitations and Implications for Computational Research

The use of neural network simulations in making broad predictions relevant to basic and clinical research has not been a typical avenue of progress in neuroscience and must be viewed with caution. The current study uses a network architecture and learning algorithm that is considerably reduced from the biological level of realism. These simulations use networks comprised of 71 neurons connected between three layers, with neuronal turnover occurring in the middle layer. This architecture can only be interpreted as grossly symbolic of the entorhinal, dentate gyrus, and CA3 layers of the hippocampus that collectively contain millions of neurons of differing phenotypes, including inhibitory interneurons, and show inter- and intralayer connectivity patterns far more complex than the classic trisynaptic feed-forward pathways (Witter, Wouterlood, Naber, & Van Haeften, 2000; Rolls, 1996). Moreover, back-propagation learning, although allowing artificial networks to learn information pattern association recognizable to humans, does not represent an entirely local (Hebbian) learning rule because incremental synaptic weight change occurring throughout the network requires information locally available only to the output layer. Nevertheless, the beneficial effects of neurogenesis in learning new information identified using three-layer perceptrons (Chambers et al., 2004) has been generally confirmed in more sophisticated networks using architectures and incremental weight change algorithms that more closely model hippocampal architecture and physiology including the use of more biologically relevant synaptic change rules (Becker, 2005; Deisseroth et al., 2004). In particular, recent work by Crick and Miranker (2006) has shown cognitive benefits of apoptosis/neurogenesis analogous to our findings in networks that incorporate both inter-and intralayer connectivity and learn to encode self-organized representations of alphabetic letters via local Hebbian synaptic change. These findings suggest that neither the type of incremental synaptic learning mechanism nor the specifics of network architecture are critical determinants in observing the functional efficacy of neuronal turnover. Instead, many of the fundamental aspects of neural turnover observed in simple systems could emerge from only a relatively simple set of network parameters and yet transcend higher order levels of complexity. However, it would be expected that the specific ways in which neurogenesis might affect learning and memory would be further refined by greater network sophistication. For example, Becker's (2005) model incorporates functional and anatomical data about the role of the dentate gyrus in extracting the unique features of new information from those that are shared. This effect, which is increased with neuronal turnover, may enhance the efficiency of new memory storage. Further simulation studies that use larger network

ensembles, more biologically plausible connection architectures, and cellular dynamics are needed to confirm the fundamental and/or universal nature of the present findings.

Most biological research on neurogenesis has not taken into account corresponding rates of apoptosis, in part due to methodological complications in identifying cell death. Recent reports do suggest that ratios of the rates of hippocampal cell death and neurogenesis are fairly tightly correlated across ages and different species (Amrein, Slomianka, & Lipp, 2004; Heine et al., 2004a). Although it seems clear that many newly generated neurons die before functional maturation (Heine et al., 2004b), the existence or role of death in older, functionally mature middle-layer neuronal populations, vis-à-vis neurogenesis, remains experimentally ill defined. Previous modeling approaches have examined neurogenesis with (Crick & Miranker, 2006; Becker, 2005; Chambers et al., 2004; Deisseroth et al., 2004) and without concurrent cell loss (Becker, 2005; Wiskott et al., 2004), where these approaches emphasize the functional importance of forgetting versus retaining larger memory stores, respectively. In the current study, both computational and neurobiological considerations inform our choice of modeling neuronal turnover as opposed to neurogenesis alone. Computationally, demonstrating the effects of increasing memory capacity (instead of learning efficiency) by addition of new neurons (without neuronal attrition) is fairly trivial (Haykin, 1999; Rolls & Treves, 1998) and does not seem to account for biological data indicating newly generated neurons show enhanced plasticity (favoring learning efficiency instead of increasing memory storage) (Schmidt-Hieber, Jonas, & Bischofberger, 2004). In addition, it remains unclear how if the accumulation of long-term memory is predominantly ascribed to the mostly nonneurogenic neocortex (McClelland et al., 1995), increasing memory capacity would be a major point of hippocampal neurogenesis. Neurobiologically, several lines of evidence provide at least circumstantial support to the view that apoptosis and neurogenesis occur in a coordinated fashion and share functional relationships. For instance, several studies indicate the neuronal population of the dentate gyrus appears to remain constant, or decrease across the adult life span of animals, although neurogenesis continues, albeit at a lower rate, into older age (McDonald & Wojtowicz, 2005; Schmitz & Hof, 2005; Heine et al., 2004a; Boss, Peterson, & Cowan, 1985). Interventions that can instigate a neurogenic response, including stress hormones, ischemia, neurochemical and mechanical injury, and even antidepressants, also appear to produce initial or concurrent phases of neuronal death (Sairanen, Lucas, Ernfors, Castren, & Castren, 2005; Dong et al., 2003; Kokaia & Lindvall, 2003; Gould & Tanapat, 1997). Studies of mature glial/neural cell interactions with neural stem cells suggest that local molecular events may serve to maintain a balance of glial/neuronal population counts in the face of potential neuronal losses (Ming & Song, 2005; Hastings & Gould, 2003; Song, Stevens, & Gage, 2002). Nevertheless, further biological research is needed to definitively rule in or out the existence or functional role of mature DG neuronal death in coordination with neurogenesis as assumed in this report. Future computational models should examine the informatic impact of independent or coordinated variation in neuronal attrition and neurogenesis.

Summary

The present study indicates that the functional benefit of neuronal turnover in elementary neural networks depends on the appropriate matching of rates of neuronal turnover with the degree of novelty of new contextual information to be learned. These findings not only emphasize the functional importance of the regulation of neurogenesis, but also suggest that this regulation should be flexibly governed by neural systems that detect differential degrees and durations of significant environmental change. Together with data indicating the role of corticosteroids and other neural systems in mediating adaptive or maladaptive responses to various extremes of contextual change and in regulating hippocampal neurogenesis, these results provide a novel

hypothesis concerning the functionality of adult neurogenesis that warrants further investigation using more sophisticated computational or biobehavioral approaches.

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References

Amrein I, Slomianka L, Lipp H. Granule cell number, cell death and cell proliferation in the dentate gyrus of wild living rodents. European Journal of Neuroscience 2004;20:3342–3350. [PubMed: 15610166]

Becker S. Computational principal for hippocampal learning and neurogenesis. Hippocampus 2005;15:722–738. [PubMed: 15986407]

Boss BD, Peterson GM, Cowan WM. On the number of neurons in the dentate gyrus of the rat. Brain Research 1985;338:144–150. [PubMed: 3896391]

Brady KT, Sinha R. Co-occurring mental and substance use disorders: The neurobiological effects of chronic stress. American Journal of Psychiatry 2005;162:1483–1493. [PubMed: 16055769]

Cameron HA, Gould E. Distinct populations of cells in the dentate gyrus undergo mitosis or apoptosis in response to adrenalectomy. Journal of Comparative Neurology 1996;369:56–63. [PubMed: 8723702]

Cecchi GA, Petreanu LT, Alvarez-Buylla A, Magnasco MO. Unsupervised learning and adaptation in a model of adult neurogenesis. Journal of Computational Neuroscience 2001;11:175–182. [PubMed: 11717533]

Chambers RA, Bremner JD, Moghaddam B, Southwick SM, Charney DS, Krystal JH. Glutamate and post-traumatic stress disorder: Toward a psychobiology of dissociation. Seminars in Clinical Neuropsychiatry 1999;4:274–281. [PubMed: 10553033]

Chambers RA, Potenza MN, Hoffman RE, Miranker W. Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. Neuropsychopharmacology 2004;29:747–758. [PubMed: 14702022]

Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. American Journal of Psychiatry 2003;160:1041–1052. [PubMed: 12777258]

Charney DS. Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. American Journal of Psychiatry 2004;161:195–216. [PubMed: 14754765]

Crick C, Miranker W. Apoptosis, neurogenesis, and information content in Hebbian networks. Biological Cybernetics 2006;94:9–19. [PubMed: 16372165]

de Kloet ER, Joels M, Holsboer F. Stress and the brain: From adaptation to disease. Nature Reviews Neuroscience 2005;6:463–475.

Deisseroth K, Singla S, Toda H, Monje M, Palmer TD, Malenka RC. Excitation–neurogenesis coupling in adult neural stem/progenitor cells. Neuron 2004;42:535–552. [PubMed: 15157417]

Dimsdale, JE.; Keefe, FJ.; Stein, MB., editors. Stress and psychiatry. 7. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2000.

Dong H, Csernansky CA, Goico B, Csernansky JG. Hippocampal neurogenesis follows kainic acid-induced apoptosis in neonatal rats. Journal of Neuroscience 2003;23:1742–1749. [PubMed: 12629178]

Dziewczapolski G, Lie DC, Ray J, Gage FH, Shults CW. Survival and differentiation of adult rat-derived neural progenitor cells transplanted to the striatum of hemiparkinsonian rats. Experimental Neurology 2003;183:653–664. [PubMed: 14552907]

Eichenbaum HR. A cortical–hippocampal system for declarative memory. Nature Reviews Neuroscience 2000;1:41–50.

Eisch AJ. Adult neurogenesis: Implications for psychiatry. Progress in Brain Research 2002;138:315–342. [PubMed: 12432777]

Eriksson PS, Perfilieva E, Bjork-Eriksson TB, Alborn A, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. Nature Medicine 1998;4:1313–1317.

Eriksson PS, Wallin L. Functional consequences of stress-related suppression of adult hippocampal neurogenesis—A novel hypothesis on the neurobiology of burnout. Acta Neurologica Scandinavica 2004;110:275–280. [PubMed: 15476455]

Freeman WJ. Neurodynamic models of brain in psychiatry. Neuropsychopharmacology 2003;28:S54–S63. [PubMed: 12827145]

Gluck MA, Myers CE. Integrating behavioral and physiological models of hippocampal function. Hippocampus 1996;6:643–653. [PubMed: 9034851]

Gould E, Tanapat P. Lesion-induced proliferation of neuronal progenitors in the dentate gyrus of the adult rat. Neuroscience 1997;80:427–436. [PubMed: 9284346]

Gould E, Tanapat P, Rydel T, Hastings N. Regulation of hippocampal neurogenesis in adulthood. Biological Psychiatry 2000;48:715–720. [PubMed: 11063968]

Hastings NB, Gould E. Neurons inhibit neurogenesis. Nature Medicine 2003;9:264–266.

Haykin, S. Neural networks: A comprehensive foundation. Upper Saddle River, NJ: Prentice Hall; 1999.

Heine VM, Maslam S, Joels M, Lucassen PJ. Increased P27KlP1 protein expression in the dentate gyrus of chronically stressed rats indicated G1 arrest involvement. Neuroscience 2004;129:593–601. [PubMed: 15541881]

Heine VM, Maslam S, Joels M, Lucassen PJ. Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus–pituitary–adrenal axis activation. Neurobiology of Aging 2004;25:361–375. [PubMed: 15123342]

Jacobs B, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: A novel theory of depression. Molecular Psychiatry 2000;5:262–269. [PubMed: 10889528]

Kempermann G. Why new neurons? Possible functions for adult hippocampal neurogenesis. Journal of Neuroscience 2002;22:635–638. [PubMed: 11826092]

Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Annals of Neurology 2002;52:135–143. [PubMed: 12210782]

Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. Current Opinion in Neurobiology 2004:186–191. [PubMed: 15082323]

Kokaia Z, Lindvall O. Neurogenesis after icshemic brain insults. Current Opinion in Neurobiology 2003;13:127–132. [PubMed: 12593991]

Lemaire V, Aurousseau C, Le Moal M, Abrous DN. Behavioral trait of reactivity to novelty is related to hippocampal neurogenesis. European Journal of Neuroscience 1999;11:4006–4014. [PubMed: 10583489]

Malberg JE, Duman RS. Cell proliferation in adult hippocampus is decreased by inescapable stress: Reversal by fluoxetine treatment. Neuropsychopharmacology 2003;28:1562–1571. [PubMed: 12838272]

McClelland JL, McNaughton BL, O'Reilly RC. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review 1995;102:419–457. [PubMed: 7624455]

McDonald HY, Wojtowicz JM. Dynamics of neurogenesis in the dentate gyrus of adult rats. Neuroscience Letters 2005;385:70–75. [PubMed: 15967575]

McEwen BS. Effects of adverse experiences for brain structure and function. Biological Psychiatry 2000;48:721–731. [PubMed: 11063969]

Ming G, Song H. Adult neurogenesis in the mammalian central nervous system. Annual Review of Neuroscience 2005;28:223–250.

Mirescu C, Peters JD, Gould E. Early life experience alters response of adult neurogenesis to stress. Nature Neuroscience 2004;7:841–846.

Newton SS, Duman RS. Regulation of neurogenesis and angiogenesis in depression. Current Neurovascular Research 2004;1:261–267. [PubMed: 16181076]

Nottebohm F. Neuronal replacement in adult brain. Brain Research Bulletin 2002;57:737–749. [PubMed: 12031270]

Prickaerts J, Koopmans G, Blokland A, Scheepens A. Learning and adult neurogenesis: Survival with or without proliferation? Neurobiology of Learning and Memory 2004;81:1–11. [PubMed: 14670353]

Rolls ET. A theory of hippocampal function and memory. Hippocampus 1996;6:601–620. [PubMed: 9034849]

Rolls, ET.; Treves, A. Neural networks and brain function. Oxford, UK: Oxford University Press; 1998.

Rumelhart, DE.; McClelland, JL. Parallel distributed processing: Explorations in the microstructure of cognition. Vol. 1. Cambridge: MIT Press; 1986.

Sairanen M, Lucas G, Ernfors P, Castren M, Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and adult survival in the adult dentate gyrus. Journal of Neuroscience 2005;25:1089–1094. [PubMed: 15689544]

Schmajuk, N. Latent inhibition and its neural substrates. Boston: Kluwer Academic; 2002.

Schmidt-Hieber C, Jonas P, Bischofberger J. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 2004;429:184–187. [PubMed: 15107864]

Schmitz C, Hof PR. Design based stereology in neuroscience. Neuroscience 2005;130:813–831. [PubMed: 15652981]

Song H, Stevens CF, Gage F. Astroglia induce neurogenesis from adult neural stem cells. Nature 2002;417:29–32. [PubMed: 11986650]

Sousa N, Almeida OF. Corticosteroids: Sculptors of the hippocampal formation. Reviews of Neuroscience 2002;13:59–84.

Spitzer, M. The mind within the net: Models of learning, thinking and acting. Cambridge: MIT Press; 1999.

Van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. Nature Reviews Neuroscience 2000;1:191–198.

Vyssotski AL, Dell'Omo G, Poletaeva II, Vyssotsk DL, Minichiello L, Klein R, et al. Long-term monitoring of hippocampus-dependent behavior in naturalistic settings: Mutant mice lacking neurotrophin receptor TrkB in the forebrain show spatial learning but impaired behavioral flexibility. Hippocampus 2002;12:27–38. [PubMed: 11918285]

Widrow, B.; Lehr, MA., editors. Perceptrons, adalines, and backpropagation. 1. Cambridge: MIT Press; 1998.

Wiskott, L.; Rasch, M.; Kempermann, G. What is the functional role of adult neurogenesis in the hippocampus?. Cognitive Sciences EPrint Archive (CogPrints). 2004. Retrieved from cogprints.org/4012/

Witter MP, Wouterlood FG, Naber PA, Van Haeften T. Anatomical organization of the parahippocampal-hippocampal network. Annals of the New York Academy of Sciences 2000;911:1–24. [PubMed: 10911864]

Figure 1.

Input/output representations of the alphabetic data sets and differences in informatic novelty. Input characters are defined by binary firing rates across the 5 × 7 neuronal grid of the input layer, and output numbers indicate which of the 26 output-layer neurons should fire corresponding to each alphabetic character in a fully trained network. Informatic differences between the input patterns of the Roman alphabet (top left) and the alternate roman (Romalt), Russian, and Hebrew alphabets (bottom) are qualitatively visible upon character-to-character comparisons, and quantified as Hamming distances. Novelty gradients of new alphabets (Romalt, Russian, Hebrew) relative to old data (Roman) are calculated as the mean Hamming distance (±*SEM*s) of assigned corresponding letters between alphabets.

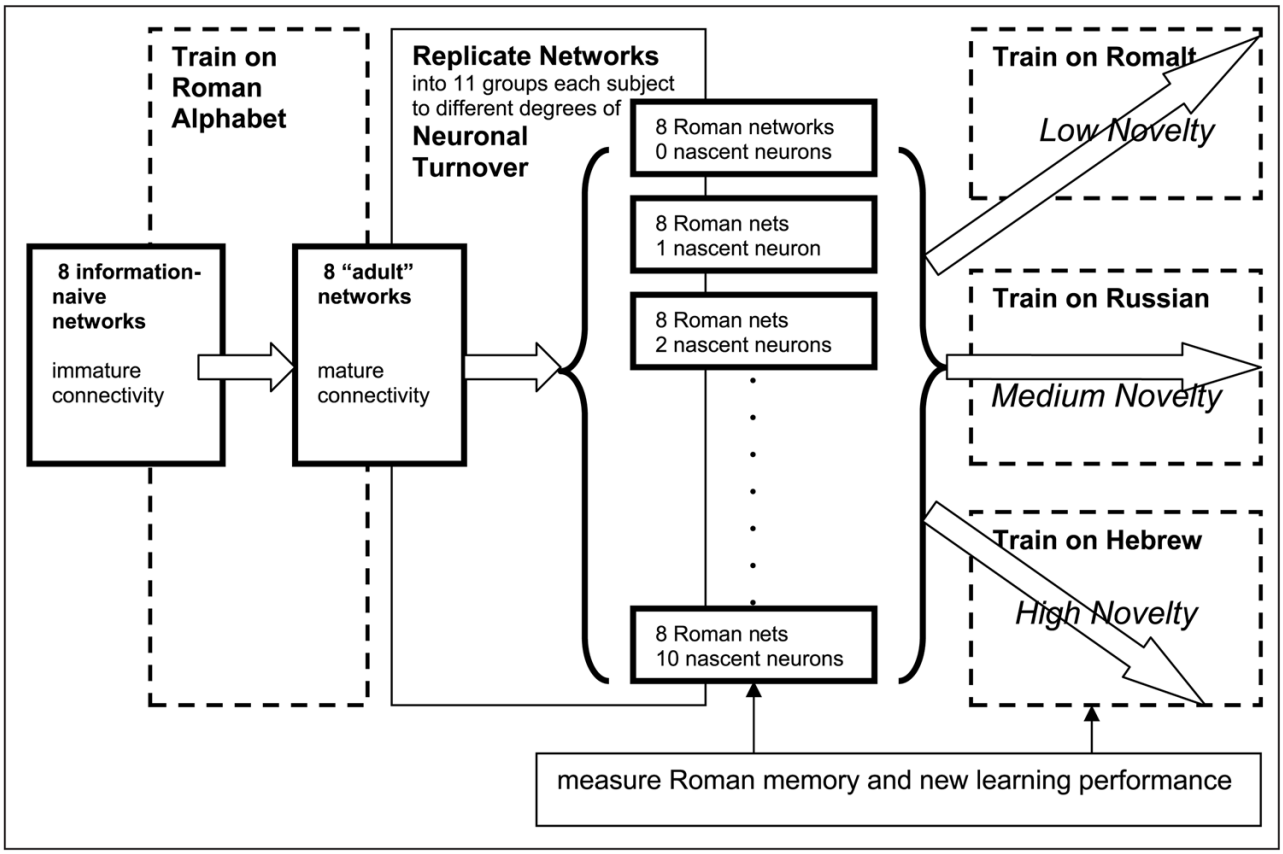

Figure 2.

Experimental design. Networks of differing genetic-like parameters (initial low connection weight randomization) all undergo the same environmental exposure during learning of the Roman alphabet, during which they show axodendritic connection weight growth. Networks then undergo (0%, 10%, 20%, …, 100%) turnover of middle-layer neurons and are cloned into three new groups for learning of each of the three new alphabetic data sets. The same deterministic axodendritic weight change algorithm was used at all steps of the experiment so that learning effects, although primarily mediated by synaptic change, were the result of differential degrees of neuronal turnover or new environmental conditions (data sets).

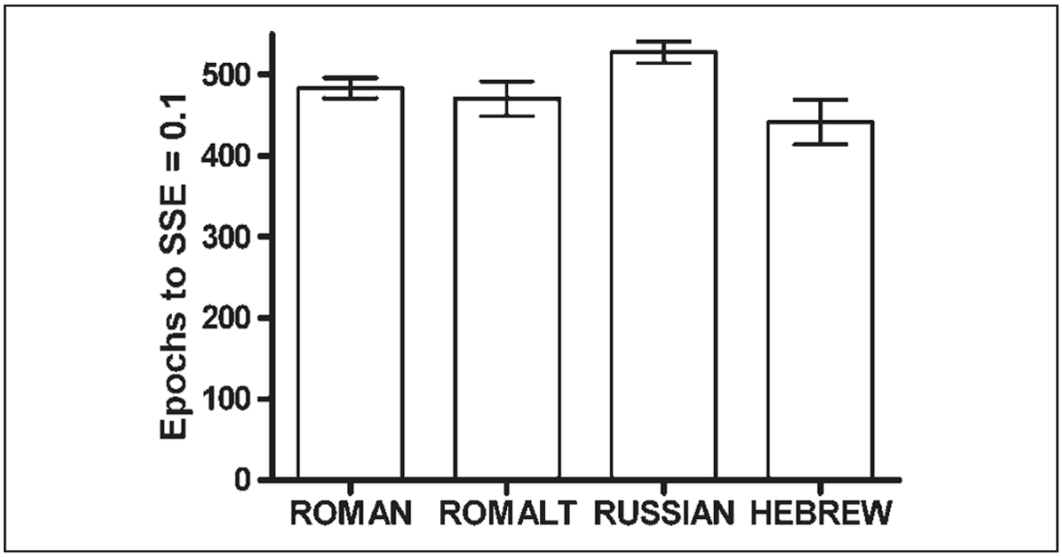

Figure 3.

Proficiency of learning (number of epochs of learning to reach SSE = 0.1) of a group of eight information-naive neural networks cloned and independently trained on each of the four alphabetic data sets. Data are presented as number of epochs of learning to reach SSE = 0.1 ± *SEM* for a group of networks. Although Russian was significantly more difficult to learn than Hebrew, the difficulty in learning Roman relative to the three other alphabets was not significant, indicating that novelty gradients between Roman and the other alphabets (instead of relative learning difficulty) was the critical parameter of interest.

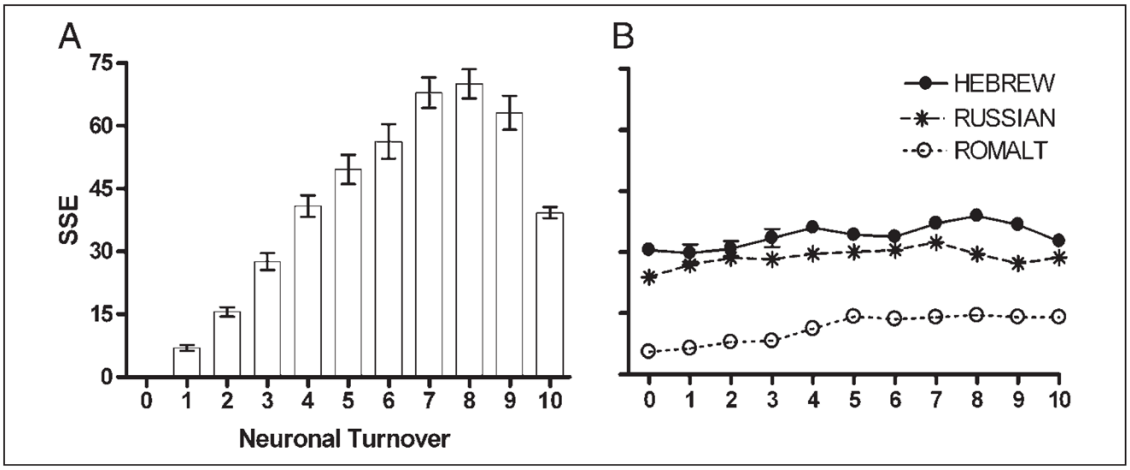

Figure 4.

(A) Recall of old information (Roman) after neuronal turnover, but before learning new information. The *x* axis plots the total number of middle-layer neurons undergoing turnover in independently treated groups of eight networks. Greater mean SSE (±*SEM*) indicates worsening Roman recall with increasing turnover. (B) Recall of old information (Roman) after turnover and learning new information (Romalt, Russian, Hebrew). Networks were trained on new information to a proficiency of SSE = 0.1, or for up to 5000 epochs of training, whichever came first. Roman recall suffers with increasing turnover and learning increasingly novel information as independent and interacting effects.

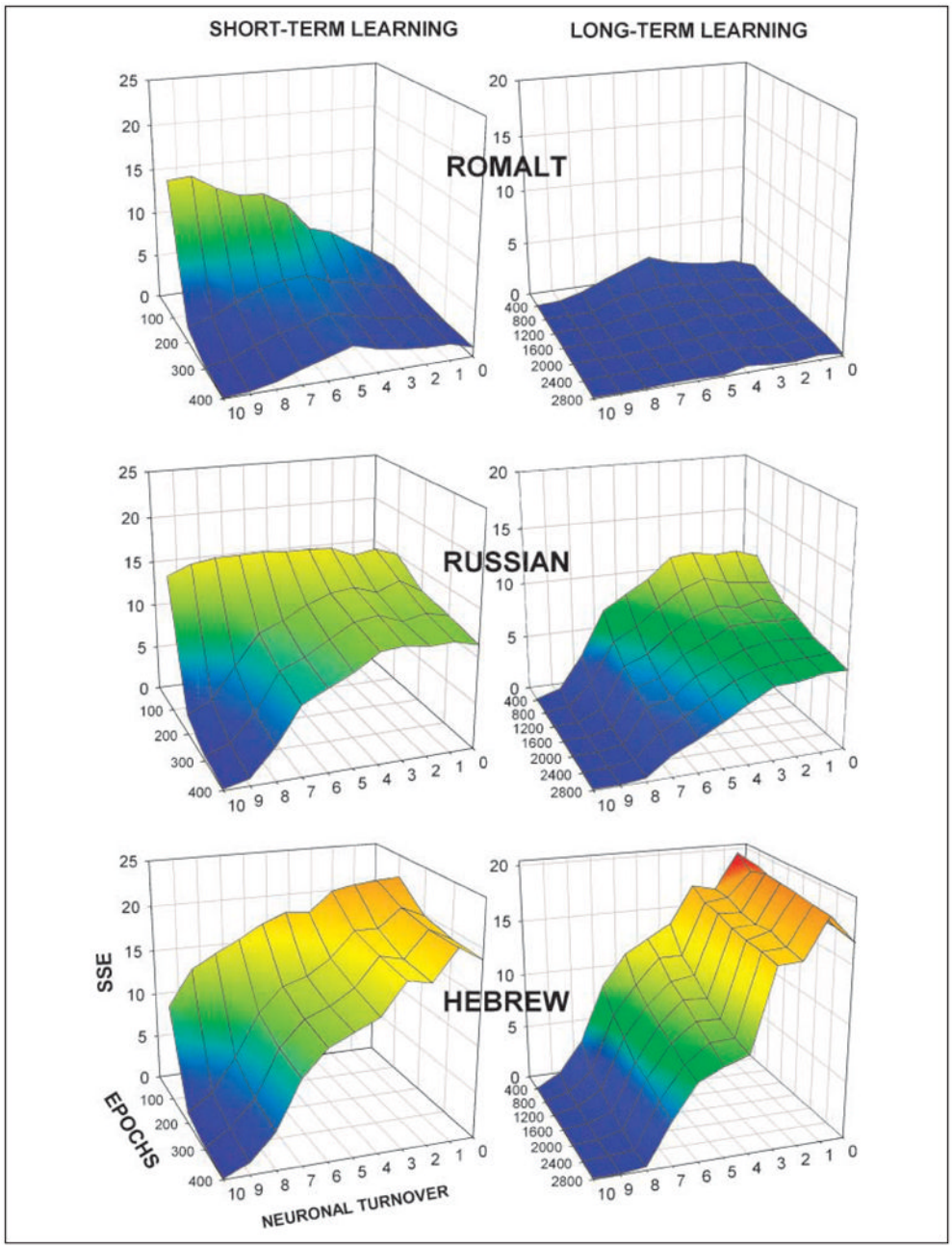

Figure 5.

Network learning curves plotted across increasing rates of neuronal turnover form surfaces that descend toward SSE = 0.1 with increasing epochs of training. Low points in these surfaces indicate greater accuracy of recall of new information. In repeated measures ANOVA for each new alphabet over short-term (epochs 100–400) or long-term (epochs 400–2800) training, neuronal turnover and alphabet being learned impacted learning as independent main and interactive effects, and in a three-way interaction with epochs of training.

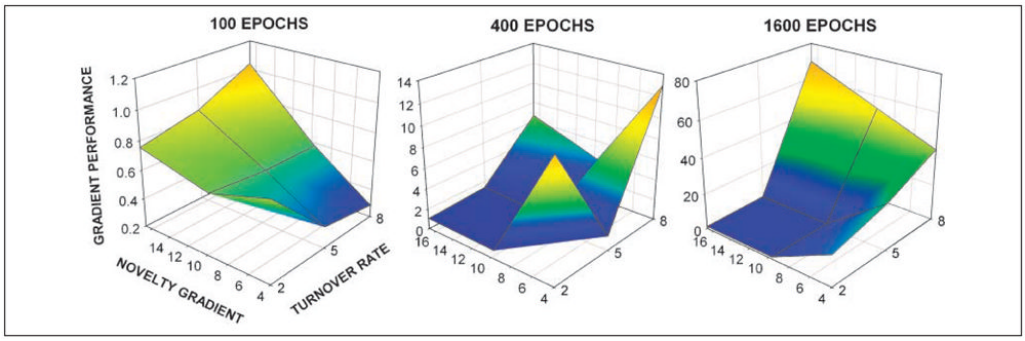

Figure 6.
Gradient performance as a measure of relative speed of learning on differing novelty gradients after different degrees of turnover, taken at 100, 400, and 1600 epochs of training. Low, medium, and high turnover rates (20%, 50%, and 80% of middle-layer neurons turned over) are compared on low-, medium-, and high-novelty gradients (4.0, 9.7, 16.7) where more optimal performance corresponds to higher surface maxima. Performance optima are localized to low turnover rates on low-novelty gradients early in learning (100 epochs), whereas high turnover rates are increasingly superior on high-novelty gradients over extended periods of learning (1600 epochs).