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White Matter Damage Impairs Adaptive Recovery More Than Cortical Damage in an In Silico Model of Activity-Dependent Plasticity

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Little is understood of how damaged white matter interacts with developmental plasticity. The authors propose that computational neuroscience methods are underused in this problem. In this article, they present a nondeterministic, in silico model of activity-dependent plasticity. Using this model, they compared the impact of neuronal cell loss or axonal dysfunction on the ability of the system to generate, maintain, and recover synapses. The results suggest the axonal dysfunction seen in white matter injury is a greater burden to adaptive plasticity and recovery than is the neuronal loss of cortical injury. Better understanding of the interaction between features of preterm brain injury and developmental plasticity is an essential component for improving recovery.

Keywords: white matter damage; cortical damage; activity-dependent plasticity

Developmental disabilities associated with preterm birth affect thousands of children each year. Cerebral white matter injury is the best current predictor of cerebral palsy and developmental delay following preterm birth. Recent theory[1] and studies[2] suggest a significant impact on cortical development as well.

Experimental models indicate that different patterns of early life brain injury may have very different recovery profiles.[3] In children, the correlation between damage and developmental profile is far from perfect. Although minimal white matter injury may result in profound disability, severe damage is sometimes associated with surprisingly favorable neurodevelopmental outcome.[4-6]

White matter injury occurs early in motor system development. The associated motor and cognitive abnormalities, however, become manifest only when neurodevelopmental mechanisms are superimposed on the initial brain injury. Although children's brains often exhibit remarkable adaptive plasticity, the cerebral white matter injury characteristic of prematurity remains frustratingly resistant to intervention despite such potential developmental adaptability. Indeed, very little is known about factors that may facilitate or inhibit developmental recovery.

We consider adaptive plasticity to be the persistent modification of the nervous system resulting from prior experience and influencing future behavior.[7] Extreme resilience has been observed after some types of cortical injury, including notable recovery of function following perinatal stroke[8] and the ability to redirect language function to the nondominant hemisphere after hemispherectomy.[9] This significant recovery of function may be due to the ability of the immature brain to modify and develop pathways.[10] Consistent with this concept of adaptive plasticity, dominant-side visual deprivation successfully restores binocular vision in children with amblyopia.[11] Yet the goal to restore function after premature white matter injury by inducing adaptive plasticity remains elusive.[12]

Our limited understanding of the interactions between features of brain injury and adaptive plasticity asks for

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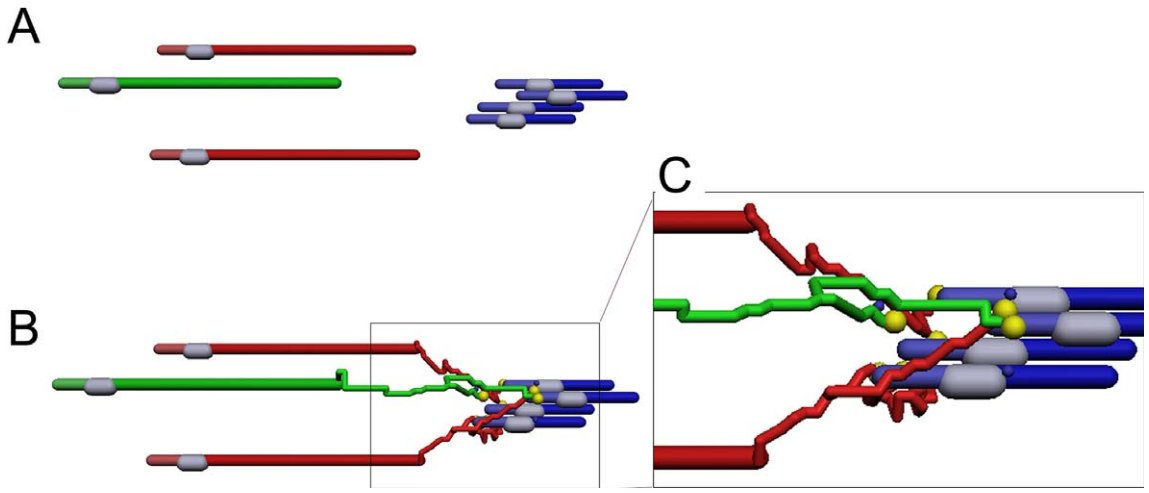

Figure 1. Demonstration of self-connecting, nondeterministic in silico model. In this example simulation, the green and red source neurons are identical and are all the same distance from the target neurons (blue). The positions of the neurons at the start of the experiment are set in a 3-dimensional virtual space and their parameters defined (A). No synaptic connectivity exists between the neuron groups at this point. Identical input signals are applied to each of the source neurons. After several million time cycles, multiple synapses (yellow spheres) are present and the blue neurons propagate signals (B, magnified in C).

novel research approaches to better understand adaptive plasticity following white matter injury early in development. In silico modeling may provide one such opportunity. Since Hodgkins and Huxley mathematically predicted ion channels in the squid axon, computational modeling has provided a valuable theoretical approach to experimentation in neuroscience research.[13,14] We hold that nondeterministic, computational models can help us better understand the theoretical impact of brain injury on adaptive plasticity.

We have used an in silico model that simulates the generation of synapses by neurons in the absence of predefined architecture or connectivity. The model incorporates extensive algorithms that simulate physiological processes. This allows in silico neurons to interactively self-define their synaptic connectivity. We propose that this general model can be used to study how different features of immature brain injury are likely to affect plasticity.

In this article, we present a specific application of this model to test the hypothesis that white matter injury affects adaptive plasticity differently from cortical injury. First, we simulate diffuse cell death in cortical injury by blocking the output of scattered neurons. Second, we simulate diffuse white matter injury by degrading action potential propagation in the axons of those same neurons. Third, we then compare the impact of neuronal loss or axonal dysfunction on subsequent adaptive plasticity. Because of the probabilistic nature of the algorithms, repeated trials of the same initial configuration will have similar but somewhat varied outputs. Thus, a system-level response to change in a single active mechanism can be evaluated.

In Silico Modeling of Network Formation

Our computational model is generated by placing neurons in a 3-dimensional virtual space, adding input activity to the first layer of neurons, and allowing the layers to form synaptic interconnections (Figure 1). The simulation starts with no initial connectivity. The neurons form and prune axons and synapses based on an independent set of algorithms for inputs, feedback, growth factors, and modulators.[15] The algorithms for each of the physiological parameters are based on specific implementations of a general algorithm developed by Bienenstock, Cooper, and Monroe in 1982.[16] Their model was based on the critical insight that neurons seek a target activation rate. The Bienenstock, Cooper, and Monroe model is based on the critical insight that neurons seek a target activation rate. This allows for the development of adaptive neuronal models using temporal competition between incoming action potentials. The assumption that neurons seek sufficient synaptic efficacy to maintain their target activation rate allows for a self-connecting and modifying system. Synapses will also terminate if they are unable to maintain a minimum activity level.

Synapse formation, efficiency, and termination are all defined by algorithms based on a modified application of the general algorithm. Neurons seeking connectivity release growth factors from their dendritic arbors based on these equations. Axons grow and branch in response to the growth factor gradient. A synapse is formed when an axon growth cone reaches a dendritic spine. The algorithms incorporate decay functions with known computational features of neurons, such as average firing rate and spontaneous firing rates, to model physiological neuronal

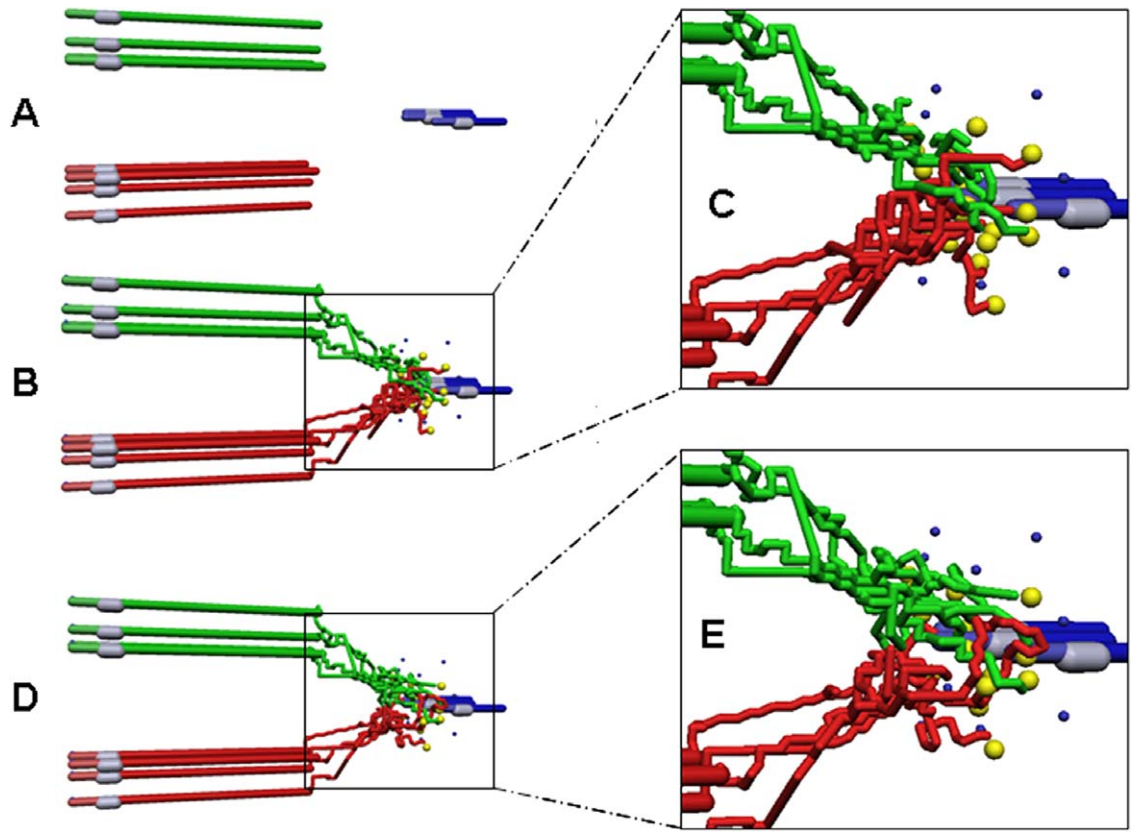

Figure 2. Images of a subset of neurons in activity-responsive in silico model. Two groups of identical source neurons, identified as green and red, compete for synaptic connections with target neurons (blue) in a 3-dimensional virtual space. At the start of the experiment (A), the positions and parameters of the neurons are set and no connectivity exists between neurons. Identical input signals are applied to the 2 clusters. At steady state (B, and C magnified), multiple synapses are present (18), evenly distributed between the red and the green source neurons. To evaluate the responsiveness of the system to changing inputs, the input activity to the red cluster is dropped by 50%. The resulting steady state (D, and E magnified) has a similar number of effective synapses (16) but now 70% are with the higher activity green cluster.

behavior in each of these areas. In a similar manner, additional algorithms consider action potential characteristics of neuronal firing rates, refractory periods, and propagation rates. Axon growth is limited by physical constraints such as space limitations, as may be seen in biological systems. Axons thus grow, branch, and reabsorb based on defined axonal properties applied to the environment of growth attractants modified by physical topology. Up to 20 different types of neurons can be delineated with definable variables including target and minimum activity rates, axonal and dendritic field characteristics, and whether resulting synapses are excitatory or inhibitory.

Methods

Defining the In Silico Model System

To simulate activity-dependent plasticity, we defined 2 distinct groups within the source neurons. The 2 neuronal groups compete for synaptic connections with a single group of target neurons. This is illustrated for a small group of neurons in Figure 2. The initial lack of connectivity stimulates growth factor release from the dendritic spines of the target neurons. Both groups of source neurons respond similarly to the growth factors by forming axonal branches each with terminal growth cones. The growth cones extend in the direction of the growth factor concentration gradient. Growth cones form synapses when they reach spines. When source and target neurons are connected by synapses, they are able to propagate action potentials. Given sufficient time cycles, the system reaches a steady state, where the synaptic connections remain fairly constant over time until some variable is changed. An even distribution of effective synapses results at steady state when the input activity to all source neurons is equal.

In Silico Model of Activity-Dependent Plasticity

We initiated the in silico model with a 2-layer system of 128 unconnected neurons (Figure 3A). Input activity to the 64 source neurons of the first layer stimulates the system to form connections between these neurons and the 64 target neurons in the second layer (Figure 3B). Although the system is stable at steady state (Figure 3C), it will self-modify the existing

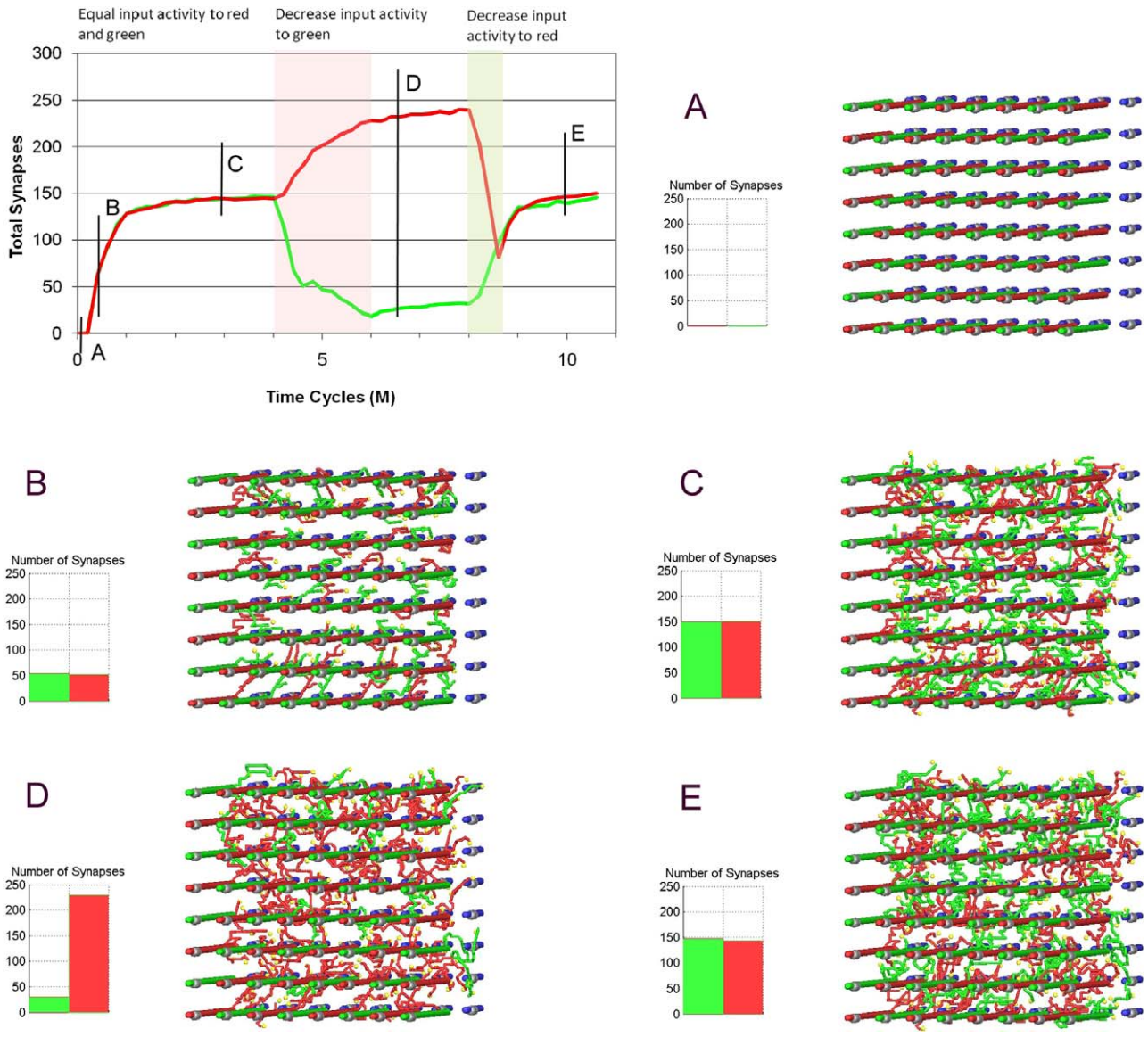

Figure 3. Graph and corresponding images of activity-dependent paradigm. Graph shows average number of synapses present in each subgroup (red and green) of 64-grid source neurons across time cycles for multiple experimental runs (n = 5). Captured images of selected time points from a standard experiment correspond to labeled time lines on graph. Bar graphs to the left of each image show actual number of synapses at that time point, color-coded. The input activity is modified as described in Figure 2. Initially, there are no connections with 64 blue target neurons (A). With equal input activity, synapses are acquired (B) and reach steady state (C). When the input activity of the green cluster is decreased by half (red-shaded), the synaptic density of the green subset decreases and recovers little when the input activity is returned to equal (D). A transient decrease in dominant-side (red) input activity to 50% (green shading) allows the nondominant group (green) to recover. With this protocol, the groups consistently return to equal synaptic representation with minimal terminal variability (E).

synaptic connections in response to changes in input activity. To evaluate the response of the model to competition between unequally stimulated neurons, we decreased the input activity to half the source neurons (green) by 50%. The distribution of synapses shifts in favor of the higher activity neurons. This is best appreciated by comparing the number of synapses for the 2 groups (Figure 3A-E). When the input activity is returned to equal, and the simulation is again allowed to run to a steady state, the new distribution of connections will again remain fairly constant over time (Figure 3D). Notably, a return to equal input is not sufficient to generate an increase in number of synapses in the nondominant neurons. (This simulates what happens when the vision is corrected in a child with amblyopia without eye patching. Dominant-side deprivation is a necessary feature of activity-dependent recovery of visual function.) Such dominant-side deprivation is then simulated by decreasing the input activity to the other

(red) half of the source neurons to 50%. After sufficient time in this configuration, the 2 groups attain equal synaptic connections and the input activities of both sets of neurons are returned to equal (Figure 3E).

In the activity-dependent protocol, numerical results are obtained by running multiple experiments with similar starting characteristics and determining the mean variability. The ability to acquire, prune, recover, and maintain a competitive number of synapses is reflected in the percentage variability in synapse number between competing neuronal groups at the termination of each experiment. The mean variability is then compared with the mean variability that results when the identical activity-dependent protocol is run with a single change in neuronal function.

Diffuse Brain Injury Model

Cortical infarction is defined, at least in part, by the death of functional neurons. Subcortical white matter injury impairs axonal function by direct action on axons or secondary to glial cell injury.[17,18] To compare the relative impact of axonal dysfunction or neuronal death on subsequent activity-dependent plasticity, we modeled each within an otherwise identical activity-dependent plasticity protocol. Complete loss of neuronal function would be expected with cell death from cortical damage. Disruption in signal propagation within scattered axons is an expected outcome of diffuse white matter injury.

We modeled diffuse cortical injury by blocking axonal function in a scattered subset of neurons and white matter injury by incrementally degrading the axonal signal propagation in the same neurons of an identical simulation. Because this process is nondeterministic, all runs will yield somewhat different results. Experiments were all run repeatedly, a minimum of 5 repetitions of each experimental protocol. The terminal variability was determined by calculating the difference in synapse number between the 2 neuron groups (red and green) at the end of the experimental protocol. Variability was normalized to a percentage of synapse number and analyzed for significance ($P < .01$) by a single factor analysis of variance.

Results

In Silico Model of Activity-Dependent Plasticity

In the clinical setting, input deprivation of dominant visual tracks is accomplished with eye patching. In our in silico system, patching can be modeled by decreasing input activity to the dominant neuronal group. As in the clinical application, the length of input activity restriction is critical to returning the model system to equilibrium. To generate a control protocol, we adjusted the length of decreased input activity to the dominant neuronal group. The final experimental protocol reliably generates a final steady state with equal synaptic representation by the 2 neuronal groups (Figure 3E). Multiple experiments with this protocol consistently demonstrated minimal terminal variability ($1.55\% \pm 0.71\%$, $n = 5$).

Response of the Activity-Dependent Protocol to Neuronal Dysfunction

In keeping with findings from rodent studies that recovery is inconsistently modified by different types of brain injury at different ages,[3] we simulated both neuronal death and dysfunction. We simulated diffuse neuronal death by blocking axonal function completely in a scattered subset of 25% of the source neurons. In this setting, there was only a slight increase in terminal variability that is not significantly different from control ($2.87\% \pm 2.56\%$, $n = 5$). However, when we modeled diffuse axonal dysfunction by incrementally degrading the propagation of action potentials in the same neurons of an otherwise identical simulation, the terminal variability of the activity-dependent protocol is significantly increased ($9.14\% \pm 2.64\%$, $n = 5$, $P < .001$). Taken together, the presence of scattered neurons with inefficient action potential propagation generates much greater deficits in pruning and recovery of functional synapses than scattered loss of neurons.

Further analysis of synapses per neuron over time (Figure 4) indicates that neurons with impaired signal propagation are able to initially compete for synaptic representation but are unable to effectively maintain connectivity. The excessive loss of synaptic connections even at steady state substantially attenuates the system response to input activity changes.

Discussion

White matter damage in the preterm brain that eventually results in motor and cognitive disabilities occurs at a time when motor system development is still ongoing. At least in part, the absence of normal adaptive plasticity and maturation may contribute to the etiology of disability.

Brain damage in newborns can be diffuse, focal, cortical, subcortical, predominantly gray or white matter, bilateral, or asymmetric. We wanted to investigate whether adaptive plasticity would be different in cortical versus white matter damage. This question is difficult to study in available model systems. Because adaptive plasticity is a response of the developing system, information from in vitro models is rather limited. Injury patterns overlap in most in vivo models, where the response of a system is better assessed. These limitations make it challenging to evaluate the functional impact of single variables.

In this article, we propose that in silico modeling may be a useful tool to study adaptive plasticity. We used a computational model that enables us to simulate the system-level response of neuronal function to a single abnormality. Our in silico modeling results indicate that white matter injury has a significantly greater impact on adaptive plasticity than does gray matter injury.

Activity-dependent plasticity in the visual columns is arguably the best understood and most effectively used

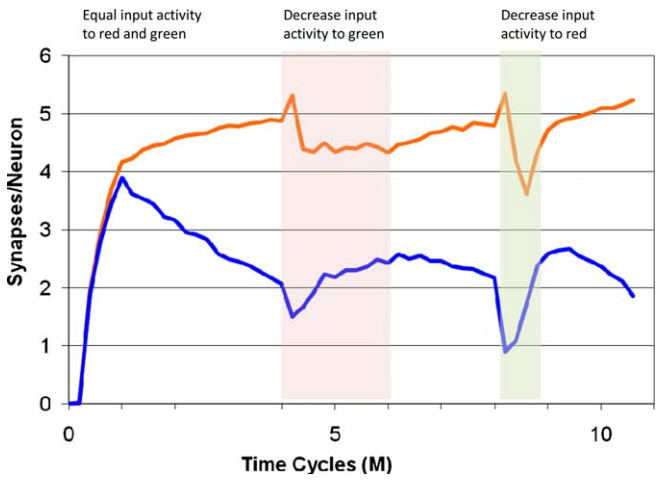

Figure 4. Effect of white matter injury on activity-dependent recovery. Graph compares average difference in number of synapses per neuron between all normal source neurons (orange) and all impaired neurons (blue) over the course of the activity-dependent protocol (n = 5). Shaded areas represent decreased input activity in the same protocol shown previously (Figure 3). The 25% of neurons with inefficient signal propagation initially compete for synaptic representation but maintain connectivity poorly. The excessive loss of synaptic connections in a subset of neurons diminishes the responsiveness of the entire system to the activity-dependent protocol, significantly increasing terminal variability.

example of adaptive plasticity.[19] Time windows exist within developing systems when such plasticity is more easily attained. Treatment of amblyopia by patching of the dominant eye is remarkably effective at restoring stereopsis in children if used within the time window of plasticity.[11] The in silico system we used in this article simulates the visual column response and consistently predicts well-described features of visual plasticity, such as a similar requirement for dominant-side deprivation.[15] Therefore, it is a potentially useful tool for studying the impact of injury on adaptive plasticity.

This neuronal simulation system is based on modeling the action and response of physiologically relevant parameters. In a nondeterministic fashion, each separate simulation generates unique results, even when run with identical starting parameters. Thus, as in most types of experimentation, multiple repetitions of the same protocol decrease the probability of a chance result. Additional experimental simulations can then be studied with a single change in a variable or starting parameter.

Using this in silico model of activity-dependent plasticity, we can simulate the impact of a specific feature of injury on the adaptive response of a system. By modifying axonal function to different degrees, we are able to compare the impact of disturbed signal propagation with the impact of neuronal loss, without introducing other potentially confounding variables. We degraded signal propagation in a subset of neurons within a standardized model system of activity-dependent plasticity. Moderate signal disruption generates a partial conduction block with less frequent, irregular action potentials as seen in white matter injury. This was compared with the more extreme condition of completely nonfunctional neurons, a common result of cortical injury. Elimination of functional neurons had only a minimal effect on the ability of the system to regain and maintain synapses within the activity-dependent model, whereas inefficient signal propagation significantly changed the adaptive response.

The nonfunctional neurons did not compete for synapses. The neurons with abnormal axonal function, however, did actively compete for and attain synapses but were unable to maintain them at the same rate as normal neurons. This interfered with the effective activity-dependent gain and loss of synapses and introduced substantial variability into the system. Thus, neurons with inefficient axonal signal propagation compete for synapses but are unable to maintain and use those connections over time. The inability of scattered neurons to effectively maintain synapses interferes with the ability of the whole system to respond permanently to changes in input activity. If white matter injury similarly affects the ability of cortical neurons to maintain effective connectivity, it could have a profound impact on adaptive plasticity.

These results are also consistent with multiple studies indicating a potential role for white matter in developmental adaptive plasticity. Under normal circumstances, differentiated oligodendrocytes form myelin by producing long, fine processes that seek out and selectively wrap axons in a highly controlled process.[20] Subsequently, electrical activity in axons initiates communication between astrocytes and oligodendrocytes to adjust myelin thickness.[21] Glia and axons interact to promote oligodendrocyte survival and effective myelination.[22] Thus, myelination is neither passive nor static, and axons are not simple recipients of indiscriminant myelination. This tightly controlled process is modified by experience from childhood through adult life.[18]

In summary, we have modeled the effect of diffuse neuronal death and dysfunction on activity-responsive plasticity in silico. We evaluated the difference between a complete loss of axonal function and a partial block in signal conduction. These results support our hypothesis that white matter integrity is a crucial component of effective adaptive plasticity.

An improved understanding of the impact of injury type on subsequent adaptive plasticity is essential to improving treatment. We suggest, indeed, injury-specific treatment interventions may be necessary to generate more effective recovery after preterm brain injury. In silico modeling systems such as ours may provide a helpful tool to increase our understanding of this complex problem.

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