National Eye Institute

2024 NEI Visual NeuroPlasticity Workshop

Introduction

The goal of this workshop was to identify cross-cutting principles emerging in the broadly inclusive field of visual neuroplasticity. Seventeen expert participants reported on studies ranging from retinal to cortical, and from molecular to behavioral.

Cortical Cellular Mechanisms

The study of visual neuroplasticity has made good use of events occurring during the postnatal development of binocular vision. During the period of head growth, a primary visual cortical (V1) neuron's receptive field (the area of space it responds to) must continuously remap to account for the gradually changing positions of the two retinas with respect to the visual scene. This process is of clinical interest due to the perceptual double vision that results from ocular misalignment in strabismus and amblyopia. It has also been widely impactful in neuroscience research due to the pioneering discovery (1) of a gradual closing of this type of plasticity during a "critical period."

Neuroscientists have identified numerous circuit, cellular, and molecular processes that are changing during the critical period. One useful concept in this study is the E/I ratio: Local circuits of interconnected excitatory (E) and inhibitory (I) cortical neurons homeostatically tend to seek the appropriate balance for optimal information processing. It is also useful to know that during early postnatal development, inhibitory interneurons and their connections mature more slowly than excitatory neurons. Experimental manipulations have targeted the parvalbumin (PV) interneuron and have established its causal role in an acceleration or delay in bringing the critical period to a close (2, 3).

Another handle on mechanism is the fact that during the critical period the *amplitude* of V1 miniature excitatory post-synaptic currents (mEPSCs) in pyramidal neurons gradually decreases (presumably to compensate for an increase in the *frequency* of mEPSCs due to the animal having more visual experience). Monocular deprivation can reverse this trend and reinstate the larger mEPSC amplitudes, thus restoring the balance (4). This restoration was linked to the classic textbook phenomenology of "Hebbian plasticity" by showing that monocular deprivation increases the expression of a hallmark of certain synaptic mechanisms: the GLuN2B subunit of the NMDA receptor (5). Thus, eye patching is a clear tool for inducing neuroplasticity.

In mouse V1, during the maturation of inhibitory interneurons, other cellular and extracellular events are occurring. The emergence of extracellular matrix, glia, and various signaling molecules is thought to stabilize synapses between the new inhibitory interneurons and the excitatory neurons. As with experimental manipulation of inhibitory interneurons, manipulation of these structural or molecular players can extend the critical period, or even rejuvenate neuroplasticity in the adult. However, as explained by Elizabeth Quinlan (University of Wisconsin-Madison) there are still many open questions as to whether visual deprivation and/or pharmacological manipulation will turn out to be the best clinical approaches to the recovery of the neuronal receptive field remapping that is needed to treat strabismus and amblyopia.

Beyond the critical period for ocular dominance plasticity, other forms of neuroplasticity come into play. Visual cortical neurons have spatial receptive fields as their most basic property. But they also have preferential sensitivities to other features of the visual scene (e.g., spatial frequency or direction of motion) and within each of these feature dimensions neurons are “tuned” around a particular center value (e.g., a best frequency or a preferred direction). These sensitivities are flexible to change during normal visual attention, prediction, and learning presumably as a mechanism also supporting the formation and use of visual memories.

The recent work of Lindsey Glickfeld and her group at Duke University is highlighting the involvement of short-term synaptic plasticity in the neuronal local network flexibilities that alter V1 tuning to support prediction/familiarity (6). But beyond the classic synaptic mechanisms of short- and long-term plasticity, Glickfeld hypothesizes that membrane phenomena intrinsic to all excitable cells may also play a role in the type of neuroplasticity that can strengthen or alter short-term preferences in the process of familiarity/memory.

Rafa Yuste, of Columbia University, put forward a theory that this process of neuronal flexibility via altered preferences, or strength of tuning, is best realized not at the single-neuron level, but at the level of collections of multiple V1 neurons that fire as groups, or ensembles. In their studies (7), the ensemble representation (as assessed by the calcium-indicated action potential frequency of group members) was orthogonal when the mouse viewed horizontally vs. vertically moving stripes, and thus the ensemble analysis also invoked an explanation involving the reciprocal excitatory/inhibitory nature of neural representations, in general. They showed that ensemble representations increased in strength over one week as the mice became familiar with the stimuli. Subsequently, the team was able to evoke a correct behavioral choice by stimulating the appropriate ensemble.

During the workshop discussion, Yuste entertained the possible involvement of parvalbumin (PV) interneurons in sculpting the ensemble collection, and a potential role of non-synaptic intrinsic mechanisms in strengthening the ensemble response to a familiar stimulus.

Several months after the workshop, Tirin Moore and his group at Stanford University published a highly relevant study (8), which supports the utility of ensemble representations and extends the familiarity/memory concept to “working memory” in non-human primates. They recorded from lateral prefrontal cortex as the monkeys held the memory of a briefly cued visual target location prior to a delayed saccade to the remembered target. Instead of maintained spiking in local cortical networks, as previously hypothesized, the subthreshold short-term synaptic (and/or intrinsic) plasticity of neuronal ensembles maintained the memory during the delay period.

To understand adult neuroplasticity more fully, it is interesting to ask exactly how the individual neurons within the ensemble can flexibly change their sensitivities. David Fitzpatrick (Max Planck Florida Institute for Neuroscience) has studied this issue at the level of individual synaptic inputs on the spines of the dendritic tree. He and his team have found a surprising amount of diversity in feature preferences across the large collection of synaptic inputs to a given V1 neuron.

In the Fitzpatrick laboratory, calcium imaging was used to measure the feature sensitivities of inputs onto individual dendritic spines, while at the same time imaging the activity of the soma. By definition, the soma was most active when its preferred stimulus was shown to the animal, in this case a ferret. The synapses that were maximally active for the same stimulus value would be the ones most effectively driving the soma to fire. One might expect most input preferences to match the soma preference, but remarkably, instead the Fitzpatrick team found that the inputs had a wide range of preferences. They looked for evidence that the matched inputs were the strongest inputs, seeking ultrastructural evidence that their synaptic efficacies had been strengthened though a process of long-term synaptic plasticity. But they found no evidence for this. Instead, they determined that synaptic

inputs drive the soma by virtue of being more numerous (9). This is a mechanism that can change the neuron's sensitivity very quickly, by shifting the collection of active inputs.

Thus, instead of neuroplasticity requiring a long-term molecular or structural change at the synapse, a neuron with a diverse set of synaptic inputs can momentarily change its preferences by receiving a different collection of inputs. As a simple example, a neuron normally selective for horizontally moving stripes can easily become a neuron tuned to a tilted orientation by getting more input though synapses with a tilted-stripe preference.

The Fitzpatrick team also tested whether V1 soma-matched inputs tended to have different origins than the group with more diverse preferences and found that inputs bringing feedback from another cortical area tended to be more diverse than those that came from within V1. This would support the hypothesis that corticocortical projections serve to bias the sensitivities of V1 neurons and could shift representations on a moment-to-moment basis, as might be needed to alter attention and prediction.

While the natural diversity of synaptic inputs provides a quick "strength in numbers" mechanism for plastic shifts in neuronal representations, this type of neuroplasticity undoubtedly occurs in conjunction with the intrinsic membrane phenomena and synaptic vesicle depletion-based mechanisms that are sensitive to the temporal pattern of the inputs. A fuller understanding of both intrinsic and synaptic mechanisms is a goal for future research.

Subcortical Mechanisms

The thalamus and the superior colliculus play major roles in visual processing and should be expected to be important for visual neuroplasticity. Hey-Kyoung Lee and her group at Johns Hopkins University have focused on the thalamocortical projection that brings visual information from the lateral geniculate nucleus (LGN) of thalamus, directly to layer 4 of V1. Building on the substantial body of knowledge gained from past studies of ocular dominance plasticity, they took a unique approach involving the thalamus itself, as well as the auditory system (10).

Professor Lee reviewed the fact that during the critical period even periods of brief monocular deprivation produce long-term synaptic changes in the direct thalamocortical inputs representing the deprived eye. This phenomenon is not seen in post-critical period adults. However, adult visual deprivation *does* induce layer 4 synaptic plasticity of the thalamocortical inputs to layer 4 primary auditory cortex (A1). The Lee group showed that this was due to an intra-thalamic mechanism: the circuits in the auditory thalamus responded to visual deprivation with disinhibition of thalamocortical projections to A1. Although not observed in visual areas of thalamus, this subcortical circuit, involving the thalamic reticular nucleus, may have a generally facilitative role in neuroplasticity.

In other experiments in the Lee laboratory, both A1 and V1 layer 4 synaptic plasticity was examined in deafened adult animals. Within one week of deafening the A1 thalamocortical synapses did not change, but remarkably, the V1 thalamocortical synapses showed significant synaptic long-term potentiation (LTP; blocked by NMDA receptor antagonists). In discussion lead by Jianhua Cang from University of Virginia, others wondered if signals to encourage V1 plasticity may have come from corticocortical projections. This is currently unresolved.

What is the mechanism for this deafening-induced V1 synaptic potentiation? Further examination suggested that it did not critically involve the V1 PV interneuron, and its V1 local inhibitory circuity. Since the thalamocortical synaptic change was at the excitatory neurons, but not the inhibitory neurons, Lee hypothesized that it impacted the E/I balance, which is a cortical phenomenon common to multiple brain area. Thus, changes in cortical E/I balance may be generally permissive to plasticity.

Chinfei Chen, from Boston Children's Hospital, described her working hypothesis for neuroplasticity at the retinogeniculate synapse in thalamus. She and her team have shown that the dorsal lateral geniculate nucleus (dLGN) neurons that project directly to mouse V1 (thalamocortical neurons) receive a diverse set of synaptic inputs from retina. They analyzed the feature preferences of individual synaptic boutons and found that even within a cluster on the same dendrite, the inputs came from multiple retinal ganglion cell (RGC) types, with multiple types of stimulus preference (11).

Professor Chen described experiments during the "thalamic sensitive period" (which overlaps with the cortical critical period). During this time, the type of visual experience can significantly bias the preferred feature values of the neurons. She hypothesized that having multiple different types of RGCs with varied input strengths represents an organizational structure with the potential for plasticity.

Her team performed other experiments to show that experience-dependent shifts in feature sensitivity did not depend on corticothalamic input from V1, which led her lab to a focus on the diverse bouton clusters themselves. These clusters also include neuromodulatory inputs from another subcortical structure, the dorsal raphe nucleus (12). Furthermore, the clusters are ensheathed in glial cells. Chen speculated that the glia might provide a mechanism for flexible compartmentalization of different feature values and types.

Jennifer Hoy (University of Nevada Reno) added to the discussion of subcortical modulation with her group's data from superior colliculus. She mentioned neuromodulatory inputs to superior colliculus from hypothalamus, noting sex and as well as age differences in behavior. The behavior her group studies involves binocular integration and presumably depth perception: live prey capture in freely-moving mice. Her behavioral paradigms where especially interesting to participants who seek collaboration between human studies and animal models.

Retinal Remodeling and Neuroglia

Studies of retina offer the opportunity for a closer look at structural and cell-signaling aspects of plasticity. As introduced by Alapakkam Sampath (University of California Los Angeles), these plastic changes may be viewed as adaptive or maladaptive. Sampath challenged the field to appreciate that the progression of maladaptive processes limits the potential for therapeutic rescue, e.g., via stem cell transplantation to replace photoreceptors or optogenetics to make various other retinal cells light sensitive.

Bryan Jones and his group at University of Utah have studied the series of events that occur following the stress and death of photoreceptors (PRs) in inherited retinal disease and age-related macular degeneration. Typically, the rod PRs die first, gradually followed by death of the cone PRs, as well other events known collectively as retinal remodeling (13, 14).

Professor Jones sought to identify a critical window of time where intervention might prevent remodeling from fully asserting its detrimental impact on function. Backing up in time from PR death, he defined a Phase I as PR stress and loss of some of the dendrites that contact the rods, i.e., those of the bipolar cells that get input from rods (the "rod bipolar cells"). Phase II then includes changes in all types of retinal neurons - so therapeutic intervention would most usefully occur before this point.

Prior to substantial photoreceptor loss, as the bipolar cells are changing their morphology they are also changing their neuropharmacology and connectivity, in a process called reprogramming. Whereas rod bipolar cells normally make chemical synapses with amacrine cells (on the way to their connection with RGCs), during Phase I they start to develop gap junctions with amacrine cells, through which they obtain unusual amounts of glycine (an inhibitory transmitter). This switches their function to be

more like cone bipolar cells. This population-level reprogramming tends to homogenize the functional balance between the various types of rod and cone bipolar cells and would be expected to result in clinical defects related to adaptation to different lighting environments (as is sometimes reported).

However, the retinal circuitry is remarkably resilient and well designed for preservation of function even at substantial levels of PR death. Greg Field (University of California Los Angeles) and colleagues (15, 16) have evaluated the visual information content of populations of RGCs recorded using multi-electrode arrays. In a mouse model of retinitis pigmentosa, they measured the RGC contrast response functions across various phases of retinal remodeling. Even when the cones showed marked morphological abnormalities and were able to generate only very small responses to light, the RGC responses were nearly normal. Field and his group attribute this preservation of function to a compensatory boost in signaling by the bipolar and RGC neurons that gather the information from the cones. Their analysis suggested that the mechanism should not necessarily be viewed as a novel form of neuroplasticity, but instead it is consistent with the multicellular homeostatic structure/function of the retina, that naturally boosts low contrast signals in normal vision. Further experimental and computational modeling work will clarify this balance.

The Phase I process by which bipolar cells start to change their dendritic contacts with degenerating PRs is of interest. Daniel Kerschensteiner (Washington University) explained that to preserve function during developmental or experimental depletion in the numbers of bipolar cells, these cells make coordinated adjustments in dendritic territories and synapse configurations (17). The shift from doublet synapses toward single synapses is particularly striking, as an extreme example of synaptic neuroplasticity. Kerschensteiner defined homeostatic plasticity as “the drive of a neural system, be it individual neurons or populations or circuits of them, to return their activity to a set point following perturbations, and the mechanisms by which this is accomplished.” Many aspects of this ability decline with age.

In retinal remodeling, glial cells are largely viewed as having a negative role, with gliosis being clearly visible in the later stages when structural damage is most apparent. However, the retinal Müller glia clearly play a positive role in young and healthy retinas – a role that is similar to that of astrocytes in the brain.

Cagla Eroglu and her group at Duke University have studied astrocytes in rodent primary visual cortex and in cell culture. She views astrocytes as a major regulator of the balance between excitatory and inhibitory activity in cortical circuits. Astrocytes connect to one another via gap-junctions, and they also secrete specific synaptogenic proteins at synapses.

In V1 the development and balance of inhibitory signaling is especially significant to ocular dominance plasticity (e.g., by the parvalbumin, PV, interneuron). Thus, it is important to understand the regulation of inhibitory synapses onto the excitatory neurons. Eroglu’s laboratory recently discovered a notable player in this process. Neurocan is the name of the full protein, and it has separable N- and C- terminal fragments. The Neurocan N-terminus is associated with perineuronal nets, which are thought to stabilize newly formed synapses. In contrast, the Eroglu group showed that the Neurocan C-terminus may be involved in synapse formation – perhaps of the PV interneuron but especially of another class of V1 inhibitory interneuron: the somatostatin-expressing neuron (the SST interneuron) (18).

Given this demonstrated synaptogenic role of cortical astrocytes, can they be employed to help rejuvenate V1 plasticity after the end of the critical period? Neurocan is especially abundant in young astrocytes and is secreted as a whole, i.e., including the N- and C-termini. But once secreted, it is cleaved by specific proteases in the extracellular space, and this is especially relevant in older animals. Workshop participants discussed whether locally introducing the Neurocan C-terminus near synapses might potentially rejuvenate plasticity in adults. Alternatively, manipulating the abundance of specific

proteases should also impact visual neuroplasticity by allowing more synaptogenesis. However, these therapeutic manipulations might need to be precisely applied and combined with sensory training.

Functional Reorganization in Humans

Bringing knowledge gained from basic science to clinical rehabilitation is a major challenge. Marlene Behrmann (University of Pittsburgh) led an intensive discussion on this at the workshop. Her own studies have focused on plasticity in cases where children have undergone removal of large sections of cortex due to drug-resistant epilepsy (19). Recovery is remarkably good and the Behrmann group seeks to understand how the remaining brain areas reconfigure their functional connectivity to compensate for the lost tissue. A general question is to how best to frame functional magnetic resonance imaging (fMRI) and other non-invasive studies in ways that allow neuroscientists to connect the results of human studies to the more extensive neuroplasticity literature based on animal (mostly rodent) models.

As a framework for her studies of human oculomotor convergence insufficiency, Tara Alvarez (New Jersey Institute of Technology) described three theories of potential mechanisms of neural rehabilitation. First, there may be improved *synchronization* of the brain areas involved in the perception/behavior. Second, there may be *recruitment* of additional groups of neurons not normally involved. Third, the network of brain areas normally involved in the task may improve their *functional connectivity*. Alvarez and her group are doing a study of patients with double-vision issues due to traumatic brain injury (concussion). Their main metric is the point at which a high-acuity visual target moved closer to the face is perceived as double (i.e., at the "near point of convergence"). Using fMRI, they observed that the brain areas most involved were the frontal and supplementary eye fields, the parietal eye field, and the oculomotor area in the vermis of cerebellum. In concussed patients, there was less activity in these areas and after rehabilitative oculomotor training, which did improve performance, there was a significant recovery in the fMRI response (20). Thus, a change in neural network activity can serve as a biomarker for treatment efficacy.

Ione Fine and her group at University of Washington have used sophisticated auditory motion tasks to address the neural underpinnings of the enhanced auditory motion processing capabilities in individuals who were blind in early life (21). In these individuals, the cortical area that normally processes visual motion, the middle temporal area (MT), instead processes auditory motion. Furthermore, the right planum temporale, which is involved in processing auditory motion in sighted individuals, fails to show fMRI activity selective to the direction of auditory motion. Thus, remarkably, in these individuals, auditory motion processing has been entirely moved to area MT, an area not normally involved. Early blindness involves a significant reorganization of auditory brain areas: *recruitment* of additional groups of neurons, as well as changes in *functional connectivity* within nonprimary auditory cortex. Fine also reported that in two early-blind subjects with vision restored later in life, area MT showed overlapping areas of activity for visual motion and auditory motion. However, the auditory cortical reorganization in early-blind development was maintained and did not reveal new adaptation to visual experience. This large-scale type of plasticity that could be so well documented using fMRI in humans is not something a rodent model would be expected to capture. However, it may eventually be possible to develop non-human primate models with similarly remarkable plastic shifts in functional cortical representations.

Another opportunity to study the recovery of early-blind humans is after the removal of congenital cataracts. Corrective surgeries ideally occur in infancy, but in countries with inadequate health-care systems these dense cataracts have resulted in significant numbers of children growing up functionally blind. Pawan Sinha (Massachusetts Institute of Technology) has developed a program based in India (Project Prakash), to support lens replacement surgeries in children of various ages. Sinha and his

team have discovered interesting patterns of brain recovery which have led to new ideas for visual rehabilitation.

In a study of 19 cataract patients aged 7-16 years (mean age = 11 years), Sinha and Rokers and their groups (22) reported that visual acuity improves during the first few days after surgery but never fully recovers, leaving the patients at about 20/200. This behavioral result is consonant with imaging results showing a lack of plasticity in the white matter tracts that bring inputs from the optic nerve to LGN and superior colliculus (optic tract) and from LGN to occipital cortex (optic radiation). Thus, in humans the critical period for plasticity in the input to occipital cortex (V1 layer 4) apparently ends by around age 11 or so. However, when these same patients were tested on a task comparing pictures of faces to pictures of objects, their classification accuracy was above chance shortly after surgery and, especially for the younger patients, it continued to improve after surgery. There were also significant changes in the white matter tracts connecting occipital cortex to its contralateral partner, as well as to ipsilateral frontal, parietal, and temporal cortices, with the later projection presumably supporting the improvement in face vs. object discrimination. Furthermore, fMRI results showed gradual improvement in the face vs. object comparison across one week, one month, and six-month time points following surgery.

Professor Sinha theorized that a fuller understanding of constraints and possibilities for plasticity might usefully consider normal brain development. He compared the time course of visual experience in continuously sighted children with that of those with a sudden surgical opening of sight around age 10 or older. Normally after birth/eye-opening, infant color vision gradually develops over the first six months due to the delayed development of cones. But when the Prakash-project surgery occurred, the children already had fully developed cones. Taking a computational approach, Sinha and colleagues (23) trained deep neural networks (DNNs) to contrast these two developmental trajectories for face/object recognition. The results supported an interesting interpretation: DNNs initially trained on monochromatic images are more robust to face/object recognition. DNNs trained in full color do worse, as did all the post-surgical Prakash children when color was removed during an object discrimination task. This led Sinha to propose the Adaptive Initial Degradation (AID) hypothesis – "that normal development might actually be nature's clever ploy to put in place the robust strategies that the brain needs in order to deal with degradations later on."

Professor Sinha's AID hypothesis, and its support via DNN modeling, open up a new avenue for computational rehabilitation. DNN modeling is very good at capturing multi-stage information processing in the primate brain, especially for visual object recognition. DNNs are also very useful for the decoding of intended speech sounds in humans unable to articulate. The AID hypothesis goes one step beyond in suggesting that ideal therapeutic interventions could be computationally determined. For example, the Prakash children might initially use glasses with monochromatic filters. Optimal sensory degradation filters could be based on the biological principles of neuroplasticity and could be tuned to the recorded parameters of individual patients.

Cross-cutting Concepts

In search of recurrent themes and emerging concepts, we reviewed a broad range of studies. We initially defined neuroplasticity as a strengthening of communication across neurons, and we strove to go beyond the well-established textbook phenomenology of short- and long-term synaptic plasticity. Thus, we considered circuit and perceptual changes -- during early postnatal development and during normal attention/prediction/memory. We also reviewed retinal adaptation/remodeling and functional rehabilitation in humans. We identified the following principles:

- Neuroplasticity is driven by biological mechanisms that work to restore the local circuit balance of excitation and inhibition (E/I balance).
- Sensory deprivation acts as a perturbation to the E/I balance.
- Homeostatic processes work toward maintenance of function and they decline with age.
- Non-neuronal cells and gap junctions contribute to and provide structural and molecular support for change.
- Representational shifts occur via polysynaptic reweighting and involve neuronal ensembles.
- Redundancy and reciprocity are hallmarks of resilience and agents for change.
- Polysynaptic reweighting may occur within subcortical structures, and in thalamocortical or corticocortical projections, with the later exhibiting the most obvious adult plasticity.
- Calculated sensory degradation stimuli may encourage neuroplasticity by taking advantage of biological reweighting algorithms.

We can now define visual neuroplasticity as a process by which neuronal ensembles alter their sensory representations, in the retina or in the rest of the brain. This process may involve polysynaptic reweighting as well as cell and circuit-level engagement of homeostatic mechanisms, which may be triggered by visual input deprivation or degradation. Therapeutic approaches should seek to encourage relearning in ways that take advantage of the nervous system's natural tendencies for redundancy.

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