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Symposium

Removing Brakes on Adult Brain Plasticity: From Molecular to Behavioral Interventions

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Adult brain plasticity, although possible, remains more restricted in scope than during development. Here, we address conditions under which circuit rewiring may be facilitated in the mature brain. At a cellular and molecular level, adult plasticity is actively limited. Some of these “brakes” are structural, such as perineuronal nets or myelin, which inhibit neurite outgrowth. Others are functional, acting directly upon excitatory-inhibitory balance within local circuits. Plasticity in adulthood can be induced either by lifting these brakes through invasive interventions or by exploiting endogenous permissive factors, such as neuromodulators. Using the amblyopic visual system as a model, we discuss genetic, pharmacological, and environmental removal of brakes to enable recovery of vision in adult rodents. Although these mechanisms remain largely uncharted in the human, we consider how they may provide a biological foundation for the remarkable increase in plasticity after action video game play by amblyopic subjects.

Introduction

Neural circuits are shaped by genes and environment during early windows of brain development. Since the classic work of Hubel and Wiesel (1970) on visually deprived cats, most cortical systems are thought to be molded by experience during a “sensitive period” in early life. Considerable evidence supports this view. For example, abnormal visual input during infancy caused by misaligned eyes or congenital cataracts produces a permanent deficit in visual acuity, known as amblyopia (Lewis and Maurer, 2009). Unmatched input from the two eyes early in life not only results in loss of vision in the amblyopic eye but also disrupts the typical binocular organization of thalamo-cortical afferents, also known as ocular dominance columns. If the perturbation occurs later or in adulthood, the deficits are milder or nonexistent (Hubel and Wiesel, 1970). The notion of heightened periods of brain plasticity during development is not limited to sensory systems, but also extends to motor functions or cognition such as language acquisition (Newport et al., 2001). Here, we focus on amblyopia (from the Greek, *amblyos*—blunt; *opia*—vision) as an example of enduring changes in response to early experience (Ciuffreda et al., 1991).

Recent work has begun to unravel the cellular and molecular constraints that limit recovery from amblyopia, identifying two main classes of “brakes” that emerge with development (Fig. 1).

On the one hand, new structures established as the animal matures (e.g., myelin or perineuronal nets) drastically curtail neurite outgrowth in the adult brain. On the other hand, functional changes in the balance between excitation and inhibition (E/I) directly regulate the plastic potential of the established neural network. To date, this work has been predominantly performed in animal models. Yet, in addition to its theoretical importance, it is of high practical significance for humans, as it paves the way for new approaches to functional rehabilitation following cortical damage in adulthood and to promote learning by education and in job training. A challenge is to translate the biological manipulations shown to be effective in rodents into feasible and safe interventions in humans. With this aim, we consider the impact of perceptual learning and entertainment video games as tools that may promote brain plasticity.

“Brakes” on plasticity and how to lift them

An emerging view is that the brain is intrinsically plastic, and one of the outcomes of normal development is then to stabilize the neural networks that are initially sculpted by experience during the sensitive period. In the case of early vision, a key role of one such period is for visual experience to consolidate spatial acuity and to enforce the matching of orientation preference in binocular cells through the two eyes (Wang et al., 2010). More generally, a reduction in plasticity as development proceeds is likely to allow greater adaptability of the organism to variable conditions early in life, while ensuring an efficient neural architecture for known conditions by adulthood.

Early in development, excitation appears to dominate cortical circuits, but accumulating evidence supports a pivotal role for late-developing E/I circuit balance in the initiation of sensitive periods (Fig. 1). For example, the onset of visual cortical plasticity is delayed by genetic disruption of GABA synthesis or a slowing

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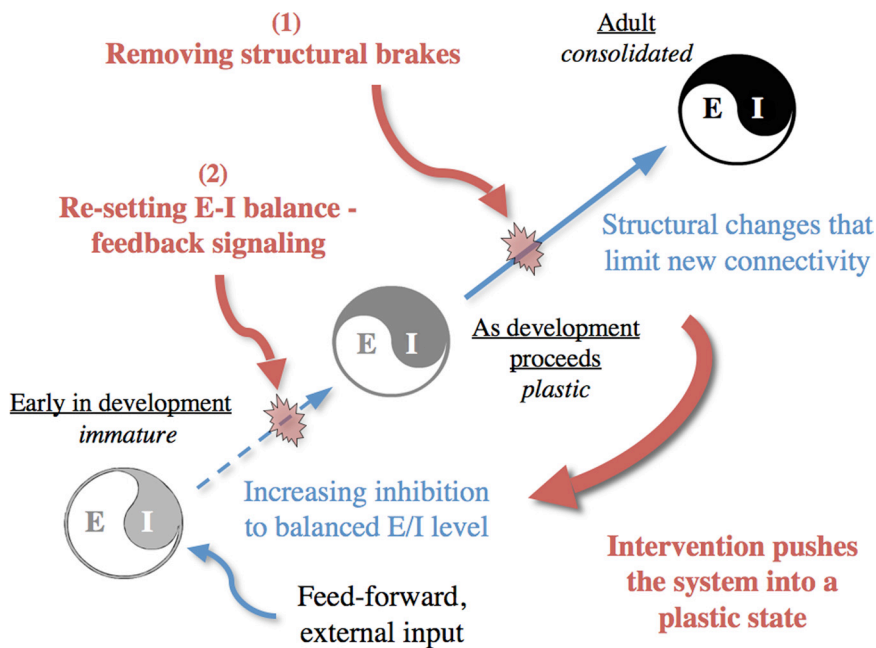


Figure 1. Evolving plastic capacity across the lifespan (blue arrows) (E/I, Excitatory-inhibitory circuit balance) suggests possible mechanisms for enhancing learning and recovery of function in adulthood (red). (1), Removing structural barriers to rewiring by targeting, for example, perineuronal nets, myelin, or epigenetic status. While effective in resetting brain plasticity in animal models (Table 1), their potential utility in humans remains elusive. (2), Resetting local E/I to a juvenile state where excitation dominates can also effectively promote plasticity in adulthood (Table 1). Noninvasive manipulations, such as the immersive and enriched conditions of video game play, may elicit various neuromodulatory responses, perhaps through feedback signals from higher control centers, to engage brain plasticity and learning in adults.

down of the maturational state of perisomatic inhibition (Hensch, 2005). Conversely, the application of benzodiazepines or other treatments that accelerate GABA circuit function triggers premature plasticity (Di Cristo et al., 2007; Sugiyama et al., 2008). These manipulations are so powerful that animals of identical chronological age may be at the peak, before, or past their sensitive period, depending on how the maturational state of their GABA circuitry has been altered.

Once induced, synaptic rewiring appears to be executed by the action of extracellular proteases (Mataga et al., 2002; Oray et al., 2004), which induce dendritic spine motility and pruning before regrowth. Notably, these effects proceed in a laminar sequence (Oray et al., 2004) consistent with the progression of plasticity through the thalamocortical circuit (Trachtenberg et al., 2000). Likewise in barrel cortex, a brief sensitive period for whisker receptive field tuning emerges concurrent with an increase in experience-dependent spine motility (Lendvai et al., 2000; Stern et al., 2001). Such abrupt and transient circuit reconfiguration is eventually recalibrated by homeostatic processes (Pozo and Goda, 2010), involving cell-intrinsic transcription factors (Greer and Greenberg, 2008; Chang et al., 2010) or surrounding glia-derived factors such as tumor necrosis factor α or the complement cascade (Stevens et al., 2007; Kaneko et al., 2008). It is notable in this context that one of the first successful approaches to reintroduce juvenile plasticity in the adult visual cortex was the direct transplantation of immature astrocytes (Müller and Best, 1989).

In addition, GABA circuits themselves exhibit synaptic plasticity that appears distinct from that of neighboring excitatory neurons (Yazaki-Sugiyama et al., 2009; Kameyama et al., 2010; Maffei et al., 2010). Whereas the classically studied pyramidal cell gradually shifts its responsiveness away from a deprived input,

interneurons do so only later (Gandhi et al., 2008), and in the case of fast-spiking interneurons, after an initial shift toward the deprived input (Yazaki-Sugiyama et al., 2009). Remarkably, direct transplantation of embryonic GABA precursor cells in the postnatal brain also supports a second sensitive period (Southwell et al., 2010). Similar to normal development (Sugiyama et al., 2008), the second wave of plasticity only emerges once the transplant matures to a critical stage of connectivity, and not before or after.

Neural networks thus sculpted by early experience ultimately become more hard-wired (Shatz and Stryker, 1978; Knudsen, 2004; Feldman and Brecht, 2005). Plasticity gradually winds down with a characteristic duration proportional to a species' lifespan (Berardi et al., 2000). Effects of early experience are thus actively preserved throughout life as a consequence of late-appearing molecular factors. The establishment of new connectivity may in part be under the control of "structural" factors that regulate axonal growth (Fig. 1), such as myelin-related proteins inhibiting axonal sprouting (NgR, PirB) (McGee et al., 2005; Syken et al., 2006) or chondroitin sulfate proteoglycans. The latter may restrain synaptic inputs by

forming tight perineuronal nets (PNNs) (Pizzorusso et al., 2006; Carulli et al., 2010) around the basket-type GABA cells which normally initiate a sensitive period (above). Directly removing such physical barriers to plasticity enables recovery from amblyopia (Table 1) (H. Morishita, M. Chung, H. Miyamoto, Z. He, M. Fagioli, and T. K. Hensch, unpublished observations).

Alternatively, the plastic potential of neural networks can be engaged late in life by acutely regulating "functional" E/I transmitter release. Manipulations that locally reduce inhibition in adulthood have been found to restore a heightened visual plasticity (He et al., 2007; Sugiyama et al., 2008; Harauzov et al., 2010) (Fig. 1). One action of endogenous neuromodulator release such as norepinephrine, acetylcholine, serotonin, or dopamine may be to adjust a favorable E/I balance (Bear and Singer, 1986; Kasamatsu, 1991; Kilgard and Merzenich, 1998; Bao et al., 2001; Weinberger, 2007; Maya Vetencourt et al., 2008; Goard and Dan, 2009). In a striking example, chronic treatment with the serotonin reuptake inhibitor (SSRI) fluoxetine restores visual function in amblyopic adult rats apparently by resetting E/I balance (Maya Vetencourt et al., 2008). This neurochemical milieu can act in a cell-specific manner during periods of heightened arousal or focal attention (McCormick, 1989; Gil et al., 1997; Kawaguchi, 1997; Kawaguchi and Shindou, 1998; Xiang et al., 1998; Hsieh et al., 2000; Froemke et al., 2007). Neuromodulatory tone also underlies sleep-wake state, fluctuating with a diurnal rhythm and providing a potential link to the regulatory role of sleep on brain plasticity (Frank et al., 2001; Steriade, 2004).

Interestingly, even these permissive factors are tightly regulated throughout the lifespan. Intense stimulation of neuromodulatory systems during infancy leads to impaired ability to augment learning later in life (Liang et al., 2006). In the mature brain, brake-like molecules further limit the role of neuromodu-

Table 1. Summary of invasive and noninvasive interventions that either induce ocular dominance shifts in adults with normal vision (“Adult ODP”) or restore visual acuity in adulthood (“Recovery”)

Intervention	Mechanism	Adult ODP	Recovery	Species	References
Invasive					
Astrocyte transplant	Structural	✓	n.t.	Cat	Müller and Best (1989)
NGF infusion	Structural	✓	n.t.	Cat	Gu et al. (1994); Galuske et al. (2000)
chABC	Structural	✓	✓	Rat	Pizzorusso et al. (2002, 2006)
Crt1 KO	Structural	✓	n.t.	Mouse	Carulli et al. (2010)
NgR KO	Structural	✓	✓	Mouse	McGee et al. (2005); H. Morishita, M. Chung, H. Miyamoto, Z. He, M. Fagiolini, and T. K. Hensch (unpublished observations)
PirB KO	Structural	✓	n.t.	Mouse	Syken et al. (2006)
dnNgR	Structural	✓	n.t.	Mouse	H. Morishita, M. Chung, H. Miyamoto, Z. He, M. Fagiolini, and T. K. Hensch (unpublished observations)
Focal demyelination	Structural	✓	✓	Mouse	H. Morishita, M. Chung, H. Miyamoto, Z. He, M. Fagiolini, and T. K. Hensch (unpublished observations)
Locus ceruleus stimulation	E/I	✓	n.t.	Cat	Kasamatsu et al. (1985)
cAMP activation	E/I	✓	n.t.	Cat	Imamura et al. (1999)
MGE transplant	E/I	✓	n.t.	Mouse	Southwell et al. (2010)
Lynx1 KO	E/I	✓	✓	Mouse	Morishita et al. (2010)
Noninvasive					
Valproic acid/TSA	Structural	✓	✓	Rat/mouse	Putignano et al. (2007); Silingardi et al. (2010)
AChase inhibitor	E/I	✓	✓	Mouse	Morishita et al. (2010)
Fluoxetine	E/I	✓	✓	Rat	Maya Vetencourt et al. (2008)
L-threo-DOPS	E/I	✓	n.t.	Cat	Mataga et al. (1992)
Dark exposure	E/I	✓	✓	Rat	He et al. (2007)
Enrichment	E/I	✓	✓	Rat	Sale et al. (2007)
Perceptual learning	E/I	n.t.	✓	Human	Levi and Li (2009b)
Video games	E/I	n.t.	✓	Human	Li et al. (2010)
TMS	E/I	n.t.	✓	Human	Thompson et al. (2008)

Proposed mechanism is categorized as disruption of structural or functional brakes. n.t., Not tested; chABC, chondroitinase ABC; NGF, nerve growth factor; L-threo-DOPS, L-threo-dihydroxyphenylserine; KO, knockout; Crt1, cartilage link protein; NgR, Nogo receptor; PirB, paired immunoglobulin-like receptor B; dnNgR, dominant-negative NgR; MGE, medial ganglionic eminence; TSA, trichostatin A; AChase, acetylcholinesterase; TMS, transcranial magnetic stimulation.

lators on brain plasticity. One such factor is the prototoxin Lynx1 acting on nicotinic receptors to dampen the response to acetylcholine. Removal of Lynx1 restores plasticity and allows recovery from amblyopia in adulthood (Morishita et al., 2010). Plastic changes induced in adulthood can be qualitatively different from those of the juvenile (Frenkel and Bear, 2004; Sato and Stryker, 2008), and may not always be enduring or capable of fully overcoming the structural limitations established earlier during sensitive periods. Yet, under certain conditions, they are adequate to restore enough plasticity to reverse amblyopia (Table 1).

Lessons for brain plasticity in adult humans

There is no doubt that humans demonstrate marked learning as a result of practice even in adulthood; yet when compared with children, adult learning appears qualitatively and quantitatively different. It is effortful, often quite narrow in its scope, and most of the time incomplete compared with the learning children may exhibit (Newport et al., 2001). Recent animal studies focused on augmenting plasticity in the visual cortex have identified means to recapitulate juvenile forms of learning in adulthood (Table 1). Achieving the same in humans would be a significant clinical advance as amblyopia is not always reversed when treated early in development, and conventional strategies (patching and penalization) are generally not undertaken in older children and adults. Here, we ask how the brakes identified in animal research might be lifted in humans, keeping in mind the possible costs of inducing exuberant plasticity in a mature nervous system.

One rather drastic example of adult plasticity in the case of amblyopia comes from “experiments of nature” whereby amblyopic patients have lost vision in the “good” eye. Under these conditions, visual acuity in the amblyopic eye sometimes spontaneously improves (Vereecken and Brabant, 1984; El Mallah et al., 2000; Rahi

et al., 2002). These few reports are consistent with the notion that the connections from the amblyopic eye may be weakened, inhibited, or unattended, rather than destroyed. Loss of the fellow eye would allow these existing connections to be reactivated. This could be the result of unmasking (Restani et al., 2009) or higher brain areas learning to attend to the previously inhibited signals from the amblyopic eye.

While direct pharmacological manipulations in humans are theoretically appealing, indiscriminately tampering with brakes on plasticity throughout the brain may cause more harm than good (see Pascual-Leone et al., 2005 for the two sides of plasticity). Interfering with brain chemistry, as in most animal studies, raises significant ethical and safety concerns. At the same time, many FDA-approved drugs are already administered with potentially informative side effects. This is the case, for example, of valproic acid and benzodiazepines. Recovery from stroke is enhanced by factors hypothesized to promote brain plasticity (Moskowitz et al., 2010), and could therefore potentially benefit from such a pharmacological approach.

Drugs that alter the “epigenome” also hold promise given recent discoveries of how environmental changes alter brain chromatin status (Zhang and Meaney, 2010). Epigenetic modifications, such as the acetylation of histones, are a common target of cancer biology (Stimson et al., 2009), and may have profound impact on the regulation of behavior. Histone deacetylase inhibitors promote synaptic plasticity (Levenson and Sweatt, 2006), reactivate critical periods, and rescue amblyopia in adult rodents (Putignano et al., 2007; Silingardi et al., 2010). More generally, the use of drugs that specifically target transcriptional regulatory processes known to be altered in neurodevelopmental disorders, such as Down’s syndrome, fragile X, or Rett’s syndrome, to cite a few, has proven strikingly efficient at alleviating cognitive deficits even when administered in adulthood (Chahrour and Zoghbi,

2007; Ehninger et al., 2008; Greer and Greenberg, 2008). Consistent with the theme developed here (Morishita and Hensch, 2008), one purported mechanism of action of these drugs may be to restore a more normal E/I balance (which is commonly impaired in such disorders) (Rubenstein and Merzenich, 2003; Polleux and Lauder, 2004; Gogolla et al., 2009).

Results from animal studies reviewed in Table 1 further suggest a need to systematically document psychotropic medications (e.g., SSRI antidepressants). In a close parallel with the animal literature, clinical trials to treat amblyopia with fluoxetine are underway in Finland, India, and New Zealand (L. Maffei, personal communication). Likewise, direct enhancement of cortical processing by cholinesterase inhibitors (Silver et al., 2008), such as those prescribed for Alzheimer's disease, offers another opportunity. Yet, it would be ideal to endogenously recapitulate brain states conducive to plasticity in a noninvasive but targeted manner. One potential route is through the endogenous release of permissive factors in response to altered environments.

The proposal that brain plasticity and learning are fostered by environmental factors is far from new (Greenough et al., 1987). As early as the 1960s, Bennett et al. (1964) had noted that adult rats housed in enriched cages had a greater cortical weight than those housed in individual, standard laboratory cages. Two seemingly opposite manipulations in adult rats illustrate the power of environment. Oddly, amblyopic rats subjected to complete visual deprivation by dark exposure for 10 d recover significant vision once allowed to see binocularly (He et al., 2007). Translation of this treatment to humans is questionable as the proportional length of dark exposure required is likely to be on the order of months rather than days, which may be too disruptive for most.

Arguably, a second, more promising approach for humans is environmental enrichment. Rats forced to use their amblyopic eye after reverse suture benefit from an exercise wheel, larger social groups, daily repositioning of food hoppers and various objects, and weekly cage changing (Sale et al., 2007). In both cases, a common mechanism is implicated—a change in E/I balance through reduced GABAergic inhibition in the visual cortex. In a parallel to these findings, recent work in humans has identified behavioral interventions that may heighten brain plasticity, above and beyond that observed under a normal lifestyle.

One such environment is aerobic exercise. The positive effects of aerobic exercise are particularly well known in the field of aging, with individuals who normally exercise outperforming those who do not on tasks as varied as dual-task performance, executive attention, or distractor rejection (for recent reviews, see Colcombe and Kramer, 2003; Kramer and Erickson, 2007; Hillman et al., 2008). In addition to its well documented impact on neurogenesis in animal models (Kempermann et al., 2000; Nithianantharajah and Hannan, 2006), aerobic fitness also leads to neuroanatomical and neurophysiological changes in older adults, including increased gray matter volume in the prefrontal and temporal areas (Colcombe and Kramer, 2003) and functional brain activity in a variety of areas such as superior parietal areas and the anterior cingulate cortex (Colcombe et al., 2004). Whether aerobic exercise can enhance brain plasticity in healthy, young adults unfortunately remains undocumented.

Another type of enriched environment extensively studied in humans, especially in the case of vision, is perceptual learning and, more recently, immersion in video games. During perceptual learning using only their amblyopic eye, patients are required to practice a variety of visual tasks. A review of the extant studies (almost 200 amblyopic subjects distributed over 14 papers) reveals that such practice results in a long-lasting improvement in

performance in amblyopic eyes (Levi and Li, 2009a). It is generally strongest for the trained eye, task, stimulus, and orientation, but appears to improve over a broader spatial frequency bandwidth than in normal vision, indicating some level of transfer (Huang et al., 2008). So far, perceptual learning has had limited impact on clinical practice, however, because of its limited transfer and the rather dull nature of the training, leading to compliance issues. Yet, the mechanisms by which it operates—a reduction of internal neural noise and/or more efficient use of the stimulus information by retuning the weighting of the information—are central to changing information processing in the visual cortex (Li et al., 2008; Levi and Li, 2009a).

Similarly, recent studies indicate that enhancements after action video game play are also due to observers being better able to select and use the most reliable information for the task (Li et al., 2009a). Yet, unlike perceptual learning, whereby the observer typically learns the best template just for the trained task, this work suggests that action gamers learn to find the best template on the fly as they are faced with new visual stimuli and new environments (Green et al., 2010b). Accordingly, fast-paced, action-packed games have already been documented to have potent positive impact on an array of skills, including perception, visuo-motor coordination, spatial cognition, attention, and decision making to cite a few, illustrating the powerful effect of action game play in reshaping the adult brain (Gagnon, 1985; Dorval and Pépin, 1986; Greenfield et al., 1994; De Lisi and Wolford, 2002; Green and Bavelier, 2006; Quaiser-Pohl et al., 2006; Greenfield, 2009; Li et al., 2009b).

Having access to a training regimen that naturally leads to improvements across many different visual tasks would be highly beneficial, as amblyopes suffer not only from low-level vision losses, but also from higher-level vision losses (for review, see Kiorpes, 2006; Levi, 2006). With an eye toward these mechanisms, adults with amblyopia were recently asked to play an off-the-shelf action video game (Medal of Honor: Pacific Assault) with their fellow eye patched (Li et al., 2010). This resulted in a substantial improvement in a wide range of fundamental visual functions, from low-level to high-level, including visual acuity, positional acuity, visual attention, and stereopsis.

Interestingly, improvement in amblyopic vision was also noted after playing non-action video games such as SimCity, which are not efficient in boosting normal vision (Li et al., 2009b). This observation is consistent with a primary principle in the field of learning wherein the learner should be faced with the “just-right” challenge to produce the greatest benefits. While the high demands of action games may be needed to push the limits of normal vision, less visually intense games may be a sufficient challenge to enhance amblyopic vision (see, for example, Vygotsky's (1978) *Zone of Proximal Development*). Consistent with this, normal rats do not improve their vision further in the same enriched cages that adequately restore acuity to their amblyopic siblings (Sale et al., 2007), and may rather require more extreme enrichment. The possibility of immersing rats into virtual environments should open the door to such studies (Harvey et al., 2009).

Action video game play may therefore improve the efficiency of probabilistic inference in neural circuits, which in turn would provide a mechanistic explanation for the broad transfer such training engenders (Green et al., 2010b). These plastic changes have been shown to be long-lasting, with beneficial effects noted 6 months to 2 years after the end of intervention (Feng et al., 2007; Li et al., 2009b). As with enriched cages, the factors that conspire to induce brain plasticity within the action game expe-

rience remain to be systematically assessed. As a training paradigm, gaming differs from more standard methods on several dimensions. First, gaming tends to be more varied in the skills it requires than standard training, which typically focuses on just one aspect of performance, as exemplified in the field of perceptual learning. Such variation during training enhances transfer across tasks (Schmidt and Bjork, 1992; Kornell and Bjork, 2008). Second, unlike standard training paradigms, gaming is an activity that is highly engrossing and also extremely rewarding. Reward, and the drive to perform as many correct responses per unit of time (Dye et al., 2009a), is likely to engage dopamine and possibly opiates and other neuromodulators. The relationship between game play and the reward system remains, however, an understudied domain. An early PET study indicated a large release of striatal dopamine during the play of a toy video game (Koepp et al., 1998), but significant experimental bias can affect the estimated size of the effect, calling for further replications (Egerton et al., 2009). Third, action games constantly require divided attention and its efficient reallocation as task demands change, most likely engaging neuromodulatory systems such as acetylcholine and dopamine (Rueda et al., 2005; Dye et al., 2009b), which are also known to enhance sensory processing and brain plasticity (Kilgard and Merzenich, 1998; Bao et al., 2001; Goard and Dan, 2009).

Finally, gaming is also associated with “flow” or the sense that one is able to meet the challenges of one’s environment with appropriate skills (Csikszentmihalyi, 1990). Flow is also characterized by a deep sense of enjoyment which goes beyond satisfying a need, and rather occurs when a person achieves something unexpected that has a sense of novelty. Playing entertainment video games is likely to increase flow. Accordingly, older adult stroke survivors report that participating in a virtual reality rehabilitation program leads to increased involvement, enjoyment, and sense of control over the environment (Farrow and Reid, 2004). The physiological bases of flow remain largely unknown, yet it would seem key for further studies to understand how it engages neuromodulatory systems as well as the regulation of the autonomous nervous system (Tang et al., 2007; Lutz et al., 2008).

Concluding remarks and future directions

Biology of the brain is heavily invested in the optimal timing and duration of plasticity, having evolved numerous molecular checks and balances to ensure an adaptable yet efficient organism. As we gain better knowledge of these mechanisms, we can assess the extent to which a sensitive period can be safely and noninvasively recapitulated by behavioral training such as perceptual learning (Levi and Li, 2009b), video game play (Green et al., 2010a), targeted pharmacological manipulation (Fluoxetine), or even brain stimulation to alter E/I balance directly (Fregni and Pascual-Leone, 2007; Thompson et al., 2008). A main challenge will be the ability to foster plasticity and relearning in one domain, while leaving unaltered cortical functions in other domains.

Physically constraining neuronal networks in a “sea” of molecular brakes after an early sensitive period may ensure that the widespread functional tuning driven by experience during development is maintained. Yet, the nervous system retains the ability to further retune its functional specificity even in adulthood, albeit in a more local and specific manner, through permissive, feedback factors such as neuromodulators (Fig. 1). Higher-level brain circuits involved in attention, executive function, and behavior regulation may play a pivotal role in adult plasticity by

their ability to modulate the coding efficiency of lower-order networks.

For instance, endogenous GABA circuits in superficial cortical layers seem to retain a latent plasticity throughout life (Lee et al., 2008; Kameyama et al., 2010). These may be poised to tap top-down feedback from higher cortical areas to sensory-motor structures such as during attentional tasks (Chen et al., 2008). Similarly, cholinergic projections from the basal forebrain to the neocortex, which have been shown to enhance the efficiency of sensory coding (Goard and Dan, 2009), may act by selectively modulating different GABAergic subtypes (Kawaguchi, 1997; Xiang et al., 1998; Kruglikov and Rudy, 2008). Such top-down control of adult plasticity would allow for fine-tuning of network connectivity as experience and demands from the environment varies, while still maintaining the overall circuit stability that typically follows the sensitive period.

The widespread learning and plasticity observed in response to action video games may provide a shared model system with which to study adult plasticity in animals and humans. A viable working hypothesis is that action game play primarily impacts top-down, attentional systems (Hubert-Wallander et al., 2010), possibly altering the E/I balance to allow heightened plasticity. Simulations of artificial networks of spiking neurons accordingly indicate that the efficiency of neural coding is enhanced thanks to changes in synaptic weights (Green et al., 2010b). It will be essential to learn, however, whether video games are engaging a top-down unmasking (Yang and Maunsell, 2004; Wandell and Smirnakis, 2009), perhaps variably effective depending on the circuitry established by each individual’s past experience, or in fact truly allow for plastic reorganization. In particular, whether structural brakes (gray matter myelin, PNNs) are lifted by video game training, enabling the physical pruning and growth of new axons in V1, remains uncertain and will require the improved resolution of imaging techniques (Karaarslan and Arslan, 2003; Thomas et al., 2008; Bock et al., 2009).

The links between action video game play and the molecular and cellular factors that control plasticity in animal models are quite preliminary. Human studies of learning and brain plasticity typically focus on changes in information processing and its efficiency, whereas animal studies characterize the molecular and cellular mechanisms that allow changes in connectivity. A more complete understanding of brain plasticity calls for bringing together these two levels of investigation within the same model system. These should be fruitful steps to further our understanding of the physiological states that promote brain plasticity and learning.

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