Published in final edited form as:

Neuroscience. 2014 December 26; 0: 4–16. doi:10.1016/j.neuroscience.2014.04.029.

Adult cortical plasticity following injury: Recapitulation of critical period mechanisms?

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Abstract

A primary goal of research on developmental critical periods is the recapitulation of a juvenile-like state of malleability in the adult brain that might enable recovery from injury. These ambitions are often framed in terms of the simple reinstatement of enhanced plasticity in the growth-restricted milieu of an injured adult brain. Here, we provide an analysis of the similarities and differences between deprivation-induced and injury-induced cortical plasticity, to provide for a nuanced comparison of these remarkably similar processes. As a first step, we review the factors that drive ocular dominance plasticity in the primary visual cortex of the uninjured brain during the critical period (CP) and in adults, to highlight processes that might confer adaptive advantage. In addition, we directly compare deprivation-induced cortical plasticity during the CP and plasticity following acute injury or ischemia in mature brain. We find that these two processes display a biphasic response profile following deprivation or injury: an initial decrease in GABAergic inhibition and synapse loss transitions into a period of neurite expansion and synaptic gain. This biphasic response profile emphasizes the transition from a period of cortical healing to one of reconnection and recovery of function. Yet while injury-induced plasticity in adult shares several salient characteristics with deprivation-induced plasticity during the CP, the degree to which the adult injured brain is able to functionally rewire, and the time required to do so, present major limitations for recovery. Attempts to recapitulate a measure of CP plasticity in an adult injury context will need to carefully dissect the circuit alterations and plasticity mechanisms involved while measuring functional behavioral output to assess their ultimate success.

Introduction

Critical periods in mammalian cortical development comprise temporal windows when neuronal physiology and morphology are most sensitive to changes in afferent sensory input or experience (Lorenz, 1935, Hubel and Wiesel, 1963). A central goal of research on developmental critical periods is the recapitulation of a juvenile-like state of malleability in

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the adult brain that might confer enhanced learning and/or recovery from injury. Considered within this framework, investigations into the underlying mechanisms for this robust period of early postnatal plasticity seek to uncover the key components that differentiate a relatively ‘plastic’ critical period brain from a relatively ‘static’ mature brain. The hope is that these same plastic processes might be reinstated following adult cortical injury to allow better recovery, effectively replacing synaptic connections lost following brain damage with new functional connections.

Developing such interventions requires a thorough understanding of the differences between critical period and adult cortical plasticity, as a first step in teasing out the key factors that drive or restrict plasticity in the uninjured brain. Cortical plasticity is sometimes framed as a privileged event, where a brain is either capable of altering its physiology and connectivity or is not, depending on developmental state. We will argue that the cortex displays a significant measure of plasticity at every stage of an animal’s lifespan, and that the direction of change, as well as the mechanisms that underlie the induction/expression of a particular form of plasticity, are the appropriate metrics for understanding changes in cortical malleability across ages. This view of developmental plasticity emphasizes the role of overlapping plasticity mechanisms with a continuum of modes and strengths that shift as an animal matures.

Despite the existence of this continuum of plasticity mechanisms during development, ample evidence exists linking short temporal windows in early postnatal development with a greater magnitude of plasticity and more permanent alterations of both cortical anatomy and physiology than in adult brain (Hubel and Wiesel, 1970, Shatz and Stryker, 1978, Antonini et al., 1999, Prusky and Douglas, 2003, Sawtell et al., 2003, Pham et al., 2004, Hofer et al., 2006, Heimel et al., 2007). Interestingly, after an acute injury or stroke in the adult brain, maximal neuronal plasticity and recovery occur during a sensitive period that follows the cortical insult (Nudo R.J. et al., 1996, Kolb et al., 2000, Villablanca and Hovda, 2000, Coq and Xerri, 2001, Biernaskie et al., 2004, Barbay et al., 2006, Salter et al., 2006, Rushmore et al., 2008, Nielsen et al., 2013), and as we will explore below, the cascade of events that reconfigure cortical circuitry following deprivation-induced plasticity and plasticity following cortical injury are strikingly similar (see these excellent reviews on plasticity following cortical injury/stroke (Wieloch and Nikolic, 2006, Cramer, 2008, Murphy and Corbett, 2009, Overman and Carmichael, 2013).

As both deprivation-induced plasticity and injury-induced plasticity show sensitive periods where changes are maximally expressed, and both processes have similar “trademark” effects on cortical circuits, comparisons between these two forms of plasticity seem to hold merit in the search for interventions that can reinstitute a measure of developmental plasticity in the mature injured brain. Here we aim to provide an analysis of the similarities and differences between deprivation-induced critical period (CP) and injury-induced plasticity by reviewing the literature detailing specific assays for cortical plasticity in juvenile, adult and mature injured brain. We will highlight the major effects of these parallel processes on cortical circuitry, with an emphasis on the correlations between anatomical alterations, functional circuit output and the age/state of the primary visual cortex.

Deprivation-induced plasticity in visual cortex: Differences between Juvenile and Adult

Ocular Dominance Plasticity during the Critical Period

Following the landmark studies by Hubel and Wiesel in kittens and adult cats that first delineated the notion of developmental critical periods in sensory cortex (Hubel and Wiesel, 1963, Hubel and Wiesel, 1970), the study of deprivation-induced plasticity is now mostly performed in rodents, in large part due to the powerful mechanistic questions that can be addressed through microcircuit analysis in these animals, as well as the use of transgenic mouse lines. In this review, we will primarily discuss studies using rodents that have explored the effects of deprivation-induced plasticity in the monocular and binocular primary visual cortex (V1m and V1b) of juveniles and adults.

Before eye opening and the onset of patterned visual experience, thalamocortical (TC) axons originating from relay cells in the dorsal lateral geniculate nucleus (dLGN) have arrived in V1 and synapsed with neurons predominately located within layer 4 (Shatz and Luskin, 1986). Although TC afferents in rodents do not form columns representing eye-specific inputs (termed ocular dominance columns) as they do in higher-order mammals (Wiesel et al., 1974, Shatz and Stryker, 1978, Crowley and Katz, 2000), after eye opening cells in rodent V1 preferentially respond to light driven by the contralateral eye (termed ocular dominance) in a similar manner to mammals possessing columnar segregation of thalamic input (Drager, 1978, Gordon and Stryker, 1996). Following monocular deprivation (MD) of the contralateral eye, single neurons within V1b shift their responsiveness away from the light-deprived contralateral eye and toward the open ipsilateral eye, a phenomenon termed ocular dominance plasticity (ODP) (Hubel and Wiesel, 1963). Although they will not be discussed at length here, MD and activity-dependent process also regulate distinct critical periods for the development and maintenance of cortical orientation and direction selectivity (see (White and Fitzpatrick, 2007) for review), as well as binocular orientation matching (Wang et al., 2010).

Moreover, while we will focus on the CP for ODP in light of the intriguing parallels to plasticity following injury, sensitive periods for maximal neuronal malleability have been established for numerous other sensory systems in cortex. For example, in the auditory system a CP exists for rapid and permanent alterations of cortical sensory representations in response to sound (Eggermont, 2013, Kral, 2013), with implications that inform cochlear implantation (Kral and Sharma, 2012). Furthermore, in primary somatosensory and auditory cortices critical periods are thought to be regulated via balances in excitatory/inhibitory network activity (Froemke and Jones, 2011, Xiong et al., 2011, Zhang et al., 2011), a suggestion that has been made for the modulation of the CP in V1 as well (Hensch and Fagiolini, 2005, Chen and Nedivi, 2013). While these topics present fascinating parallels with ODP, we refer readers to the citations listed above for an in depth review.

Recordings of neuronal population responses in V1 using visually evoked potentials (VEPs) and two-photon calcium imaging have shown a biphasic response profile during MD. After 3 days(d) of MD, neurons in V1b initially decrease their responsiveness to the contralateral

eye, however after 7d of MD neuronal responses to both the open-eye and deprived contralateral eye are increased (Frenkel and Bear, 2004, Mrsic-Flogel et al., 2007). These findings have been corroborated and extended by two recent papers, performing in vivo long-term single unit recordings in V1m of freely-behaving rats (Hengen et al., 2013) and in vivo cell-attached recordings in V1b of mice (Kuhlman et al., 2013), both finding an initial decrease in putative fast-spiking (FS) inhibitory cell firing rate after 1d of MD. These findings and those in the experiments described below were performed in the hemisphere contralateral to the deprived eye, unless otherwise noted. Following this rapid decrease in FS cell firing rate, chronic in vivo recordings revealed a reduction in putative pyramidal cell firing rate after 2d of MD, and a homeostatic increase returning FS cells to baseline by day 2 and pyramidal cell firing rate to baseline by day 4 of MD (Hengen et al., 2013). Hence, CP plasticity in V1m and V1b of rat and mouse is characterized by a rapid reduction in fast-spiking inhibition, a subsequent loss of deprived eye responses by 3d MD, followed by potentiation of responses to both eyes by 6d MD. The net effect of these biphasic changes within V1 is that total drive to V1 neurons is restored after several days of MD, but (in V1b) the relative drive from the two eyes has shifted to favor the open eye.

This biphasic response in deprivation-induced cortical plasticity is thought to rely on mechanisms that are separable and distinct. There is a reasonable consensus that the loss of cortical responsiveness to deprived eye stimulation after 2–3d MD involves some form of Hebbian-like long-term depression (LTD) (Rittenhouse et al., 1999, Heynen et al., 2008, Lambo and Turrigiano, 2013), as well as a coordinated strengthening of pre- and postsynaptic FS to pyramidal cell inhibition (Maffei et al., 2006, Maffei et al., 2010, Lefort et al., 2013, Nahmani and Turrigiano, 2014, Wang and Maffei, 2014). After 4–6d of MD, cells in V1 increase their responsiveness to both the open ipsilateral eye and the deprived contralateral eye (Frenkel and Bear, 2004, Mrsic-Flogel et al., 2007), and as mentioned above this synaptic depression followed by homeostatic potentiation are correlated with changes in firing measured in freely behaving rodents (Hengen et al., 2013).

Several lines of evidence suggest that this delayed synaptic potentiation (and correlated recovery of firing) is due to homeostatic, rather than classic Hebbian synaptic potentiation mechanisms such as long-term potentiation (LTP). First, the drop and rebound happen in both V1m and V1b, and also occur in response to binocular deprivation in V1b, indicating they do not require competitive interactions (Mrsic-Flogel et al., 2007, Lambo and Turrigiano, 2013). Second, the homeostatic increase in synaptic strength between 3 and 6d MD requires GluA2 C-tail interactions, a signature of homeostatic synaptic scaling but not of LTP (Gainey et al., 2009, Lambo and Turrigiano, 2013). Third, in mice deficient in tumor necrosis factor- α (TNF α), a protein necessary for homeostatic synaptic scaling but not for LTP (Stellwagen and Malenka, 2006, Steinmetz and Turrigiano, 2010), the initial MD-induced closed-eye depression response is expressed normally, but these mice fail to show a homeostatic increase in open-eye potentiation after 6d of MD (Kaneko et al., 2008). In sum, MD-induced plasticity during the CP is characterized by LTD and an increase in FS to pyramidal cell inhibition following brief deprivation that together depress neocortical firing, and these events then trigger a homeostatic process that works to restore V1 cortical firing as deprivation continues. This homeostatic response to continued deprivation suggests that the “aim” of V1 microcircuits in employing this array of plasticity mechanisms is to reestablish

a measure of functional output when faced with an imposed pathological state. While abundant evidence supports the important role of LTD-like and homeostatic processes in the biphasic response to MD, other forms of plasticity (e.g. long-term potentiation (LTP), spike timing-dependent plasticity, plasticity of intrinsic excitability) are likely to contribute to the microcircuit changes induced in V1 following deprivation (Nelson and Turrigiano, 2008)

ODP during the CP is also accompanied by anatomical alterations that are often temporally correlated with the onset of physiological changes in responsiveness, and these changes in morphology become increasingly pronounced as the length of MD increases. For example, brief (3d) MD during the CP induces a decrease in TC bouton density in V1b (Coleman et al., 2010) that parallels synaptic depression at TC synapses (Khibnik et al., 2010, Wang et al., 2013), but retraction or reduced growth of deprived axonal arbors and growth of axons serving the non-deprived eye only appear following longer periods of MD (Hubel et al., 1977, Shatz and Stryker, 1978, Friedlander et al., 1991, Antonini et al., 1998, Antonini et al., 1999). Similarly, spine motility from the apical dendrites of layer 5 pyramidal neurons is increased after brief (2–3d) MD in V1b (Oray et al., 2004), yet 4d of MD results in a decrease in spine density from apical dendrites of layer 2/3 and 5 pyramidal neurons in deprived hemispheres (Fifková, 1968, Rothblat and Schwartz, 1979, Mataga et al., 2004). Moreover, just as functional visual response properties do not recover if vision is restored after the critical period of ODP (Hubel and Wiesel, 1970, Prusky and Douglas, 2003, Wang et al., 2010), morphological changes induced by prolonged MD also do not recover if vision is not restored until after the CP. These findings highlight the essential role that developmental timing plays in regulating both morphology and functional circuit output in V1.

Critical Period vs. Adult Plasticity in V1

Foundational studies of CP plasticity using cats and monkeys (Hubel and Wiesel, 1970, Hubel et al., 1977) advanced the idea that the window for inducing major alterations in cortical anatomy and physiology in V1b ends after a short period in early postnatal life. Indeed, in these species TC relay cells and their afferents show little change following MD induction in adulthood (Vital-Durand et al., 1978, LeVay et al., 1980). However, it has been clear for decades that MD-induced plasticity in cat and in rodent is not a restricted binary (plasticity vs. no plasticity) CP event, but wanes incrementally with age (Daw et al., 1992, Antonini et al., 1999, Guire et al., 1999, Lehmann and Lowel, 2008). In addition while it takes longer to produce, OD shifts in carnivores and primates can occur in adulthood (Blakemore et al., 1978, Jones et al., 1984, Issa et al., 1999). Along these lines, relatively recent studies in rodents have probed the effects of MD in adulthood and found that neurons in V1b are able to show a shift from contralateral to ipsilateral eye responses, yet via a distinctly different mechanism than during the CP.

Although some labs have failed to see significant changes in ODP in adulthood, others have readily revealed OD shifts in adult mice (see these in depth reviews on adult ODP in V1 (Morishita and Hensch, 2008, Espinosa and Stryker, 2012, Levelt and Hubener, 2012)). Differences between these studies have been attributed either to (1) whether the assays used to measure OD shifts during adulthood were measuring synaptic sub-threshold vs. spiking

events (Morishita and Hensch, 2008), or (2) whether ODP assays were conducted in awake animals, animals anesthetized with halothane/urethane, or animals anesthetized with benzodiazepines which might affect the OD assay itself (Levelt and Hubener, 2012). Regardless, it is clear that in awake or lightly anesthetized rodents it is possible to reveal a significant measure of deprivation-induced physiological and morphological plasticity in adult V1.

Adult MD-induced plasticity has at least six essential differences from juvenile plasticity (Table 1): (1) Induction and/or expression threshold: It requires at least 4d, and often 7d or more of MD to observe a significant OD shift (Antonini et al., 1999, Sawtell et al., 2003, Pham et al., 2004, Tagawa et al., 2005, Hofer et al., 2006, Heimel et al., 2007, Hofer et al., 2009, Heimel et al., 2010); (2) Magnitude of change: In studies that have simultaneously looked at juvenile and adult MD-induced plasticity, the results from multiple assays (e.g. VEPs, optical intrinsic signal imaging and single unit recordings) show 50% of the magnitude of change in adults when compared to brief MD during the CP (Antonini et al., 1999, Pham et al., 2004, Hofer et al., 2006, Heimel et al., 2007). Interestingly, repeated exposures of the same eye to MD may strengthen deprivation-induced plasticity in adulthood (Hofer et al., 2006, 2009); (3) Mechanistic differences: While MD-induced plasticity during the CP is characterized by a biphasic loss of deprived eye responses followed by open and closed eye potentiation (see above), adult ODP shows a single dominant open eye potentiation response (Sawtell et al., 2003, Pham et al., 2004, Hofer et al., 2006). Under the assumption that visual stimulation through the closed eye primarily transmits “noise” to V1 microcircuits, the lack of a prominent decrease in cortical responsiveness to deprived eye stimulation in adult appears maladaptive (discussed at length below); (4) Functional recovery: Long-term MD begun before and lasting longer than the CP results in a seemingly permanent reduction of visual acuity and binocular orientation matching, whereas even longer stretches of MD during adulthood result in reversible changes (Prusky and Douglas, 2003, Wang et al., 2010); (5) Excitatory morphology: Longitudinal in vivo imaging of dendritic spines in mice have shown that spine motility decreases from approximately three weeks of age into adulthood (Holtmaat et al., 2005, Zuo et al., 2005). However, while MD induces an increase in spine motility and a later reduction in spine density during the CP, in adulthood the same manipulation produces decreased spine motility and either no change in spine density (Mataga et al., 2004, Oray et al., 2004), or an increase in spine density (Hofer et al., 2009) depending on the cell type and lamina examined. Moreover, while a decrease in TC synaptic terminal density and slowed axonal growth/retraction are hallmarks of MD-induced plasticity during the CP (Shatz and Stryker, 1978, Antonini et al., 1999, Coleman et al., 2010), no such changes have been reported after adult MD; (6) Inhibitory morphology: In vivo imaging has revealed that in adulthood, spiny inhibitory neurons in layers 1 and 2/3 of cortex show dynamic growth and retraction of their dendritic branch tips under basal conditions (Chen and Nedivi, 2013) and that 4d MD reduces the length of these dendrites (Chen et al., 2011) and decreases inhibitory synapses with stable spines in V1b (van Versendaal et al., 2012). It is currently unknown whether these forms of inhibitory morphological plasticity exist during the CP. However as detailed below, an appropriate level of inhibition is necessary and sufficient to engage the

mechanisms responsible for opening the CP for ODP and therefore, may be necessary in any effort to reinstitute CP plasticity in adulthood.

Initially the opening of the CP (i.e. the ability to reveal the normal shift in MD-induced ODP) relies heavily on the proper development of cortical inhibition (Hensch et al., 1998, Iwai et al., 2003, Fagiolini et al., 2004). Specifically, FS interneurons have been implicated as key regulators of CP initiation, because: (1) a precocious increase in FS interneuron morphological development via BDNF-overexpression results in an early CP for ODP (Huang et al., 1999, Chattopadhyaya et al., 2004), (2) cortical infusion of the transcription factor OTX2 is able to accelerate FS cell maturation, and OTX2 is necessary for CP initiation (Sugiyama et al., 2008), (3) degrading components of the extracellular matrix preferentially surrounding FS cell terminals results in increased ODP in adulthood (Pizzorusso et al., 2002), and (4) MD induces an increase in FS to pyramidal cell inhibitory synaptic strength during the CP in V1m, but not during the pre-critical period or in knock-out animals unable to express ODP (Maffei et al., 2004, Maffei et al., 2006, Nahmani and Turrigiano, 2014). Thus, something about the development of FS cell inhibition is necessary for either the induction or expression of ODP in V1. Hypotheses about what this “something” could be range from the impact of FS cell inhibition on excitatory cell physiological output (Kuhlman et al., 2013) and cortical rhythms (Levelt and Hubener, 2012), to a change in FS cell inhibitory synaptic strength that allows for the expression of the initial decrease in deprived-eye responses (Maffei et al., 2006, Maffei et al., 2010, Lefort et al., 2013), to increased suppression of spontaneous relative to visually evoked activity (Toyozumi et al., 2013); and these mechanisms need not be mutually exclusive. However, since an in vivo causal demonstration linking specific aspects of FS interneuron development and the normal MD-induced shift in OD during the CP has not yet emerged, it remains unclear as to whether or how FS interneurons permit CP initiation or if an increase in FS cell inhibition might allow for greater adaptive plasticity in adulthood or after injury.

Critical period for injury-induced adult cortical plasticity

After a focal ischemic stroke or acute injury to the cortex, a CP for maximal recovery exists during which early intervention seems to have most beneficial effects in both rats and humans (Nudo R.J. et al., 1996, Coq and Xerri, 2001, Biernaskie et al., 2004, Lee et al., 2004, Barbay et al., 2006, Salter et al., 2006, Nielsen et al., 2013). The onset and closure of this optimal period for rehabilitation after injury are correlated with a sequence of molecular and anatomical changes that progress from growth-promoting to growth-inhibiting (Wieloch and Nikolic, 2006, Overman and Carmichael, 2013), suggesting that they may underlie aspects of functional recovery.

Here we will review the plastic changes during the CP for recovery in rodent models of adult cortical injury and stroke, and compare the similarities and differences between this window for malleability and those present during the developmental CP for deprivation-induced plasticity. Our aim is not to frame plasticity after adult injury as identical to that of the CP but rather to use this comparison to uncover central events during the canonical CP that may be lacking after injury. Furthermore, a comparison of CP and adult deprivation-induced plasticity with that of adult injury-induced plasticity may help pinpoint which

features of injury-induced plasticity recapitulate developmental sequences (likely to be functionally adaptive) and which share commonalities with the mature brain's ability to compensate for sensory deprivation. We will examine the effects of acute injury or stroke to the cortex, rather than retinal or peripheral lesions, to sharpen our focus on mechanisms thought to be of cortical origin: that is, where cortical activity is the predominant factor driving subsequent plasticity after a reduction in input.

Sequence of events following adult cortical injury

Immediately following acute injury or focal ischemic stroke, the cortex is challenged by a host of factors including cell death, inflammation, gliosis, oxidative stress and ischemic loss of nutrients (Wieloch and Nikolich, 2006, Doyle et al., 2008, Murphy and Corbett, 2009). After stroke, neurons within the penumbra (area of reduced blood flow that surrounds the damaged core) may survive but only if sufficient reperfusion occurs (Lo et al., 2005). However just outside this area, in the region undamaged by injury or ischemia (termed peri-infarct), neurons begin to engage plasticity mechanisms that may establish the building blocks for functional recovery.

In the first few days to weeks after focal stroke there is a decrease in markers of neuronal metabolism in the peri-infarct region (Carmichael et al., 2004), followed by a loss of pyramidal cell dendritic spines (Zhang et al., 2005). In addition, focal cortical injury and ischemia lead to a rapid and profound reduction in cortical inhibition (reviewed in (Imbrosci and Mittmann, 2011)). A decrease in paired-pulse inhibition (Domann et al., 1993) and peak inhibitory conductance (Mittmann et al., 1994) are seen after 1d post injury, followed by a decrease in GABAA receptor (GABAAR) expression that begins approximately 1 week post injury (Schiene et al., 1996, Neumann-Haefelin et al., 1998, Qu et al., 1998) and continues for up to two months. Moreover, pyramidal cells within peri-infarct cortex display positive shifts in the reversal potential for GABAA synaptic responses (EGABA) (Neumann-Haefelin et al., 1995, Mittmann et al., 1998), possibly due to an impairment in the KCC2 Cl⁻ transporter (Jin et al., 2005), leading to an overall reduction in inhibitory tone. As might be expected, concomitant with this reduction in cortical inhibition (1–2d post-lesion) there is an observed increase in putative pyramidal single unit spontaneous firing rate in V1 (Schiene et al., 1996, Eysel et al., 1999), returning to baseline between 7–30d post-lesion. This rapid increase in excitation is associated with an enlargement in receptive field size (Eysel and Schweigart, 1999), an increase in theta-burst driven NMDA receptor-dependent LTP (Huemmeke et al., 2004), and impaired layer 2/3 LTD in rat V1 (Imbrosci et al., 2010). This rapid decrease in inhibition is reminiscent of the observed decrease in FS cell firing after 1d of MD during the CP (Hengen et al., 2013, Kuhlman et al., 2013). Indeed, the time period necessary to observe both the decrease in inhibition (~1d), and the transition to increased cortical excitation and growth (4–7d, see below), are identical for these two forms of plasticity. These findings suggest that there are mechanistic parallels between juvenile deprivation-induced plasticity and plasticity following injury in the mature cortex.

After approximately 7d, neuronal plasticity seems to shift toward a period of growth and synaptogenesis. For example, spine loss after focal ischemic insult is rapidly recoverable to near baseline levels following tissue reperfusion (Zhang et al., 2005). Moreover, dendritic

spines on layer 2/3 and 5 pyramidal cells and axon terminals in peri-infarct cortex that persist after injury show increases in length and density exceeding pre-ischemic levels (Ito et al., 2006, Brown et al., 2008, Mostany et al., 2010). Indeed while spine, bouton and synapse density decline until 4d after ischemic insult, both populations increase in both percent volume and cortical density from 7d until at least 12 weeks post injury (Stroemer et al., 1995, Ito et al., 2006). Similarly, the growth cone marker GAP-43 increases in the peri-infarct zone of both rat and humans between 3 and 14d after injury (Stroemer et al., 1995, Li et al., 1998, Ng et al., 1998), whereas significant changes in synaptic markers and axonal sprouting do not appear until approximately 1–4 weeks post-infarct (Stroemer et al., 1995, Stroemer et al., 1998, Carmichael et al., 2001, Lee et al., 2004, Ito et al., 2006). Furthermore, this progression mimics the expression profile for growth-inhibiting and growth-promoting genes in the peri-infarct cortex (Carmichael et al., 2005, Li et al., 2010). Interestingly, these growth-promoting genes appear to be enriched later and in a reduced manner following infarct in the aged brain compared to juvenile cortex, suggesting a less permissive milieu for growth in adulthood (Li and Carmichael, 2006).

Taken together, these data reveal a biphasic response profile of cortical microcircuit physiological and anatomical plasticity to focal injury in mature cortex: an initial period of cell death, synapse loss and decreased GABAergic output give way to increased pyramidal cell excitability, neurite expansion and synapse gain (Figure 1). This progression is thought to underlie some of the features of cortical sensory and motor map plasticity that follow a focal cortical infarct (Carmichael, 2003, Dancause and Nudo, 2011). In this scenario, following injury cortical disinhibition unmasks subthreshold inputs, creating a permissive environment that allows for the inappropriate activation of adjacent motor maps (Jacobs and Donoghue, 1991). In the ensuing weeks, activity-dependent cortical remapping occurs in the peri-infarct region, as both dendritic and axonal growth (Carmichael et al., 2001) are likely key players in reshaping cortical response properties (Carmichael, 2003, Brown et al., 2009). These biphasic alterations in cortical plasticity are strikingly similar in terms of temporal sequence, and the primary effect on circuit dynamics, to the changes induced by MD during the CP.

Recapitulation of developmental mechanisms?

A conspicuous pattern emerges from a comparison of deprivation-induced CP plasticity and plasticity following focal injury in adult. In both model paradigms an initial decrease in GABAergic inhibition and synapse loss transitions into a period of neurite expansion and synaptic gain. This biphasic response profile highlights how the cortex transitions from a period of protection and healing to one of reconnection and recovery of function. Intriguingly, this pattern of decreased activity and neurite loss followed by increased neuronal excitability is more reminiscent of deprivation-induced plasticity during the CP than in adult, as MD-induced plasticity in adult lacks the rapid prominent deprived eye response depression and spine loss seen during the CP (Espinosa and Stryker, 2012, Levelt and Hubener, 2012). Indeed, the loss of responsiveness to the deprived eye after brief MD during the CP makes intuitive sense, since the deprived eye transmits a noisy unpatterned visual stimulus that would act to drive V1 neurons with a very low signal:noise ratio. Thus, a circuit designed to optimize its drive to allow for the faithful transmission of information

flow would want to reduce this noisy stimulus in favor of the patterned input coming from the open eye. Under this scenario, the decrease in cortical responsiveness to the closed eye after brief MD is adaptive (e.g. reallocation of limited resources to shore-up cortical response properties), while a lack of acute plasticity after MD in adult is likely maladaptive – or at least lacks the adaptive benefit present in the first stage of both CP MD-induced and adult injury-induced plasticity. These “phenotypic” similarities between CP and adult injury-induced plasticity raise the question of whether these parallels are also evident at the level of cellular and molecular mechanisms.

Opening of the CP and inhibition

The opening of the CP for ODP relies on the appropriate level of GABAergic inhibition (Hensch et al., 1998, Iwai et al., 2003, Fagiolini et al., 2004), likely originating from the maturation of FS interneuron connections (Huang et al., 1999, Pizzorusso et al., 2002, Chattopadhyaya et al., 2004, Maffei et al., 2006, Sugiyama et al., 2008, Maffei et al., 2010). Exactly how this maturation of inhibition triggers CP plasticity remains unclear. MD during the CP induces an initial decrease in FS cell firing after 1d, followed by increased FS cell firing (Hengen et al., 2013) and increased pre- and postsynaptic FS to pyramidal cell synaptic strength after 3d (Maffei et al., 2006, Maffei et al., 2010, Nahmani and Turrigiano, 2014, Wang and Maffei, 2014). The parallel drop in GABAergic firing and postsynaptic GABAARs beginning 1d after cortical injury in adult cortex (Imbrosci and Mittmann, 2011) suggests that cortical disinhibition is an initial step gating a suite of plasticity events that follow cortical pathology in both adult and CP brains. However, it is still unclear whether cortical disinhibition is permissive or instructive for increases in cortical excitation and changes in cortical response properties during the CP or in adulthood. Importantly, while the reinstatement of CP-like plasticity after adult cortical injury (possibly through manipulation of FS-mediated inhibition) is a promising line of investigation, it is essential to keep in mind that engaging CP mechanisms within an adult-injury context may result in maladaptive or harmful consequences. For example, during the CP FS interneuron circuitry is still in the midst of a protracted development, whilst in adult cortex FS interneuron physiological and synaptic phenotypes have plateaued (Okaty et al., 2009, Lazarus and Huang, 2011, Pangratz-Fuehrer and Hestrin, 2011, Nahmani and Turrigiano, 2014). Accordingly, degradation of perineuronal nets surrounding FS cells (Pizzorusso et al., 2002) may not simply reengage an appropriate measure of FS inhibition, but lead to deleterious effects on cortical information processing due to the age and/or pathological state of the cortex. It will be important to employ assays of both circuit plasticity and functional behavioral output to assess the appropriateness of interventions intended to provide for adaptive plasticity in the injured adult brain.

Homeostatic Mechanisms

During the CP, MD induces an initial response depression to the previously closed-eye by 2d, followed by potentiated neuronal responses to both eyes by 6d (Frenkel and Bear, 2004, Mrsic-Flogel et al., 2007), and this second phase is regulated by homeostatic processes (Kaneko et al., 2008, Hengen et al., 2013, Lambo and Turrigiano, 2013) that precisely restore activity to baseline levels in vivo despite continued deprivation (Hengen et al., 2013, Keck et al., 2013). Homeostatic readjustment in neocortical networks thus appear to function

to keep neuronal firing within a desirable range, and a prolonged decrease in net drive is hypothesized to produce a compensatory increase in circuit excitability in order to reestablish the baseline firing rate set-point (Turrigiano and Nelson, 2004). Along with decreased net inhibition, these intrinsic and synaptic homeostatic processes may help explain the observed increase in neuronal excitability after adult cortical injury (Schiene et al., 1996, Eysel et al., 1999), which in turn leads to enlarged receptive fields (Eysel and Schweigart, 1999, Winship and Murphy, 2008). Moreover, it has been suggested that homeostatic mechanisms contribute to the initial (1–4 week) recovery of synapse density and cortical responses following focal cortical stroke (Murphy and Corbett, 2009). Whether the same homeostatic mechanisms (e.g. synaptic scaling) are present following adult cortical injury is unclear. This possibility could be tested by using manipulations that are known to block homeostatic synaptic scaling (Gainey et al., 2009, Lambo and Turrigiano, 2013) in vivo, and/or by performing long-term in vivo recordings in behaving animals in the week(s) following cortical injury/ischemia to monitor firing rates. The possibility that homeostatic mechanisms are critically involved in the recovery from cortical injury represents an intriguing avenue of exploration in the search for tools that can enhance adaptive plasticity and recovery after injury.

Hebbian and Molecular Mechanisms

In addition to homeostatic mechanisms, competition-based homosynaptic mechanisms (i.e. LTP) are thought to play a role in the cellular response to deprivation-induced plasticity during the CP. For example, in vivo expression of constitutively-active forms of H-ras accelerate ODP and are associated with enhanced LTP (Kaneko et al., 2010), and layer 4 to layer 2/3 theta-burst LTP has been implicated in maintenance of open-eye response potentiation after 6–7d of MD (Smith et al., 2009). Similarly, in cortical injury and infarct-induced plasticity models an increase in theta-burst driven NMDA receptor-dependent LTP (Hagermann et al., 1998, Huemmelke et al., 2004), and impaired layer 2/3 LTD (Imbrosci et al., 2010) are seen approximately 7d after injury. While correlative, these results suggest that 1 week after an induced pathology cortical circuits are capable of robust LTP that may play a role in the enhancement or maintenance of neuronal excitability and axonal rewiring.

Distinct commonalities between deprivation and injury-induced plasticity are also evident in the dynamic molecular changes in myelin-associated ligand and receptor expression. Focal ischemia up-regulates paired-immunoglobulin-like receptor B (PirB), a member of the myelin-associated protein receptor complex and a major histocompatibility complex class I (MHC1) receptor, in sprouting neurons (Li et al., 2010) and PirB knock-out mice show enhanced ODP and spine density during the CP and in adulthood (Majdan and Shatz, 2006, Djurisic et al., 2013). Furthermore, another myelin-associated ligand receptor, Nogo receptor complex-1 (NgR1), is upregulated after adult stroke, and mice lacking NgR show increased axonal connections after focal infarct (Li et al., 2010) and enhanced ODP in adulthood (McGee et al., 2005). Interestingly, many other MHC1 genes and proteins are upregulated in sprouting neurons after ischemia (Li et al., 2010), and these genes regulate both retinogeniculate connectivity and limit ODP (Coriveau et al., 1998, Datwani et al.,

2009), suggesting they may instruct proper circuit formation in the developing and injured brain.

Similar but Distinct

Taken together, these findings point to convergent pathways recruited after sensory deprivation in developing brain and by injury in adult, that work to homeostatically enhance cortical network activity and establish appropriate synaptic connectivity via activity-dependent learning rules. Yet while the mechanisms underlying deprivation-induced CP plasticity occur during a period of robust developmental circuit refinement, activity-dependent plasticity after injury is embedded within a framework of ongoing inflammation, excitotoxicity (Doyle et al., 2008), glial scarring and acidosis (Rossi et al., 2007, Beppu et al., 2014). Unsurprisingly then, there are clear differences in CP deprived vs. adult cortex after injury, likely owing to the increased severity of the underlying pathology in the latter. Specifically, while the time course for maximal synapse loss is similar between these two paradigms, the time needed to see significant gains in bouton and synapse density is much longer in the case of adult injury. For instance, after cortical ischemia synaptic terminal and spine density within peri-infarct cortex drops to ~20–30% of pre-injury levels by 4d, and recovers to ~100–200% of baseline by 6–12 weeks post injury (Ito et al., 2006). Yet, 3d of MD only decreases TC synaptic terminal density in V1b to ~70% of pre-deprivation levels, and recovers to ~100% after 1 week of MD (Coleman et al., 2010), while spine density similarly only shows a drop to ~70–75% of pre-MD levels by 4d (Fifková, 1968, Rothblat and Schwartz, 1979, Mataga et al., 2004). This temporal disparity in synaptogenesis and recovery may highlight the limits of activity dependent plasticity mechanisms working within an ischemic/injured milieu, rife with potent inhibitors of axonal growth and de novo synapse formation (Overman and Carmichael, 2013). Identifying the particular intracellular and circuit mechanisms responsible for the healing response following injury/ischemia, and those recruited specifically to promote functional circuit formation, will be key in attempting to recapitulate a measure of juvenile plasticity in the adult injured brain.

Conclusions

Although not an absolute predictor of functional recovery (Kolb et al., 2000, Giza and Prins, 2006, Dennis, 2010), it has long been appreciated that juvenile brains are often more resilient to injury than mature brains (Broca, 1865, Kennard, 1936), however the underlying mechanisms for these profound differences in neuronal plasticity and functional recovery are just beginning to be understood.

Deprivation-induced plasticity during the CP and injury-induced plasticity in adult both appear to require a measure of cortical disinhibition to allow for an ensuing increase in cortical excitability and morphological plasticity. Mechanisms serving both forms of plasticity shift from a period of decreased metabolism and cortical depression by 3–4d, followed by a longer period of neuronal excitability, synaptogenesis and growth. The temporal correspondence of the initial depression phase present in both of these biphasic response profiles is highly suggestive of parallel processes that gate neuronal malleability via cortical disinhibition (see Table 1). Using CP MD-induced plasticity as a model for an

adaptive response, it will be important to investigate FS interneuron connectivity following injury in adult to see whether similar effects are seen to those that are thought to permit the opening of the CP for ODP. Targeted manipulation of subsets of interneuron connections and/or GABAARs to mimic the consequences of brief MD during the CP will elucidate the role of inhibition in the early stages of adult cortical injury/ischemia.

Whereas the second phase of increased neuronal excitability and anatomical plasticity after MD and cortical injury both occur by approximately 6–7d, the time needed to see commensurate changes to those seen during the CP in pyramidal cell excitability and recovery of synapse density is 5–6 times longer following cortical injury. Interventions aimed at shortening this recovery period might examine whether homeostatic plasticity mechanisms contribute to this second phase of adult injury-induced plasticity, and if so, act to enhance the specific factors responsible for returning neuronal firing to baseline. These experiments will require a more comprehensive understanding of the relationship between perturbations of activity and the underlying signaling machinery responsible for the various flavors of neuronal homeostasis. Moreover, a comprehensive understanding of the functional expression of myelin-associated ligands and receptors after injury and ischemia will be paramount in promoting de novo synapse formation and axon sprouting. These experiments will require careful dissection of myelin-associated receptor activation during the biphasic response to adult cortical injury/ischemia, as these complexes are capable of both growth-limiting and promoting functions depending on the context of their induction (Carmichael et al., 2005, Overman and Carmichael, 2013).

While injury-induced plasticity in adult shares several salient characteristics with deprivation-induced plasticity during the CP, the degree to which the adult injured brain is able to functionally rewire remains limited. Attempts to recapitulate a measure of CP plasticity in an adult injury context will need to dissect the circuit alterations and plasticity mechanisms involved while measuring functional behavioral output to assess their ultimate success. These investigations will best be able to compare across these disparate developmental and brain states if they: (1) study both juvenile and adult animals of the same genetic background with the same experiment, (2) investigate multiple measures/levels of cortical plasticity (e.g. genetic, molecular, morphology, and physiology), and (3) analyze specific neuronal subsets within defined microcircuits possessing well characterized functional outputs.

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Highlights

- A significant measure of neuronal plasticity exists at every stage of the lifespan.
- Adult deprivation-induced cortical plasticity displays ~50% the magnitude of juvenile.
- A biphasic response characterizes cortical plasticity after injury and deprivation.

Figure 1.

Diagram of the biphasic response profile for deprivation-induced plasticity during the critical period (CP) in visual cortex, and injury/ischemia-induced plasticity in adult sensory cortices. This simplified cartoon illustrates the major changes in excitatory (red) and inhibitory (blue) neuronal population firing rate from 1 – 7+ days after deprivation or injury in the cortex. Note the prominent disinhibition common to both processes, followed by a relatively rapid (in the case of injury) or delayed (deprivation) increase in excitatory cell firing rate. This general trend of a biphasic response is paralleled by alterations of inhibitory and excitatory cell morphology after deprivation and injury (see Table 1).

Table 1

Comparison of the effects of deprivation-induced and injury/ischemia-induced cortical plasticity during the critical period (CP) and in adulthood. N.R. = No reports of significant effects; PPI = paired-pulse inhibition.

Time After Deprivation, Injury or Ischemia			
	1 day	2 – 4 days	≥ 7 days
= Anatomy/Molecular = Cellular Physiology = Circuit Behavior			
MD-Induced Plasticity			
CP	N.R. ↓FS interneuron firing rate _{1,2} N.R.	↓TC synapse density (L4) ₁₀ ↑FS → Pyr mEPSC amplitude and LTPi (L4) _{11,23,24,25} ↓Pyramidal cell mEPSC amplitude (L2/3) _{1,26} ↓Spine Density (L2/3 and 5) _{12,13,14} ↓TC to L4 EPSC ₂₂ ↑FS → Pyr mEPSC amplitude and LTPi (L4) _{11,23,24,25} ↓Deprived-eye responses lead to OD shift (2-3d) _{30,31,32,33,34} ↑TC to V1 LTD _{26,27,28}	↑Open and Deprived eye responses (mice/rat), lead to OD shift _{30,31} Recovery of Pyramidal cell mEPSCs to baseline (L2/3) ₂₆ Permanent reduction in acuity ₄₀ Excitatory firing rate returns to baseline ₁
Adult	N.R.	↑Spine Density (or no change) _{14,15} ↓Inhibitory dendrite length and synapses (L1 and 2/3) _{16,17}	↑Open-eye responses (mice/rat), lead to ~50% (vs. CP) OD shift _{32,33,35,38,41} Recovery of acuity possible ₄₀
Injury-Induced Plasticity			
Adult	↓PPI ₃ ↓GABA _A Rs _{7,8,9} +shift in E _{GABA} _{4,5} ↑Excitatory firing rate _{6,7} N.R.	↓Excitatory synaptic spine and bouton density _{18,19} ↑GAP-43 expression (3-14d) _{19,20,21} ↑Theta-burst LTP ₂₉	↑Receptive field size ₆ ↑Excitatory firing rate _{7,36} ↑Excitatory synaptic spine and bouton density ₁₉ N.R. Excitatory cell firing rate returns to baseline _{7,36}

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