Please cite this article in press as: Nahmani M, Turrigiano GG. Adult cortical plasticity following injury: Recapitulation of critical period mechanisms? Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.04.029

Neuroscience xxx (2014) xxx–xxx

REVIEW

ADULT CORTICAL PLASTICITY FOLLOWING INJURY: RECAPITULATION OF CRITICAL PERIOD MECHANISMS?

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Abstract—A primary goal of research on developmental critical periods (CPs) 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 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.

This article is part of a Special Issue entitled: Brain Compensation. For Good?

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INTRODUCTION

Critical periods (CPs) 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 CPs is the recapitulation of a juvenile-like state of malleability in 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' CP 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 CP 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

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Abbreviations: CP, critical period; FS, fast-spiking; LTD, long-term depression; LTP, long-term potentiation; MD, monocular deprivation; MHC1, major histocompatibility complex class 1; NMDA, *N*-methyl-D-aspartate; ODP, ocular dominance plasticity; PirB, paired-immunoglobulin-like receptor B; TC, thalamocortical; TNFα, tumor necrosis factor-alpha; VEPs, visually evoked potentials.

http://dx.doi.org/10.1016/j.neuroscience.2014.04.029
0306-4522/

privileged event, where a brain is either capable of altering its physiology and connectivity or is not, depending on the 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 the 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 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 Nikolich, 2006; Cramer, 2008; Murphy and Corbett, 2009; Overman and Carmichael, 2014).

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 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 (ODP) during the CP

Following the landmark studies by Hubel and Wiesel in kittens and adult cats that first delineated the notion of developmental CPs in the sensory cortex (Hubel and Wiesel, 1963, 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 ODP (Hubel and Wiesel, 1963). Although they will not be discussed at length here, MD and activity-dependent processes also regulate distinct CPs 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 CPs 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 7 d 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

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